Proposed Performance Measures for the Newborn Screening System

Evidence Summary Report
MAY 2009

Texas Newborn Screening Performance Measures Project

Copyright © 2009 Texas Department of State Health Services

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior permission of the copyright owner.

The findings and conclusions in this document are those of the author(s), who are responsible for its content, and do not necessarily represent the views of the Texas Department of State Health Services (DSHS). No statement in this report should be construed as an official position of the Texas DSHS or of the Texas Health and Human Services Commission.

The information in this report is intended to provide a summary of scientific evidence that lends support to the proposed performance measures for the Texas Newborn Screening Performance Measures Project (TNSPMP). The stakeholders participating in TNSPMP will use the evidence summary for refining and prioritizing the proposed performance. Measures that are most likely to have a significant impact (subject to feasibility) on the newborn screening system will be selected for pilot testing in the final phase of the project (2009–2010).

Suggested Citation:

Tiwana S, Douglass M, Freedenberg D, Washington P, Patta AM, Shaw C, Williams D, Newcomb-Kase S, Martinez D, Johnson D, Guerin P, Borgfeld L, Hunt P, Tanksley S. *Texas Newborn Screening Program Summary of Evidence to Support Proposed Performance Measures for the Newborn Screening System April 2009*. Austin: Texas Department of State Health Services. Available at http://www.dshs.state.tx.us/lab/tnspmpResources.shtm.

The work presented in this report was made possible through funding provided by the Centers for Disease Control and Prevention (CDC), grant number (CDC-CI07-710).

A special thanks to TNSPMP system stakeholders for their input, guidance, and generous contribution to this report. Members include Sandra Billings; George R. Buchanan, MD; Donna Claeys, BSN, RN; Robert Crumb, MD; L. Margaret Drummond-Borg, MD; Kari Casas, MD, Alice K. Gong, MD; Jose L. Gonzalez, MD; Charleta Guillory, MD; Cheryl Hermerath, MBA, DLM; Scott McLean, MD; Javier Ramirez; John Saito, MD; Stuart K. Shapira, MD, PhD; Eileen Sheridan-Shayeb, MD; Reid Sutton, MD; Larry Sweetman, PhD; Brad Therrell, PhD, Colleen Buechner; Lois Taylor, BSN, CPM; Sister Mary Nicholas Vincelli, RN, MA; Morgan Walthall, MSW; Don P. Wilson, MD, and Jerald L. Zarin, MD.

CDC personnel also contributing to this report include Susan Snyder PhD, MBA, Lisa Kalman, PhD, Scott Grosse, PhD, Stuart Shapira, MD, Malaika P. Washington, MSPH, Abrienne M. Patta, MPH, and Colleen Shaw, MPH.

Thank you to DSHS leadership for supporting this project. Members on the leadership team include Susan Neill, PhD, MBA, Jann Melton-Kissel, RN, MBA, Margaret Bruch, LCSW, Sherry Clay, MA, and Eldridge Hutcheson, PhD.

Table of Contents

1 Acronym and Initialism List 1

2 Texas Newborn Screening Performance Measures Project 5

2.1 Background Information 5

2.2 Department of State Health Services Texas Newborn Screening Program 5

2.3 Performance Measures 5

2.4 Methods 5

3 Summary of Literature on Proposed Performance Measures for Congenital Adrenal Hyperplasia 9

3.1 Introduction to Congenital Adrenal Hyperplasia 9

3.2 Nomenclature and Disease Variants for Congenital Adrenal Hyperplasia 9

3.3 Incidence and Screening for Congenital Adrenal Hyperplasia 9

3.4 Laboratory Testing, Follow-up, and Diagnosis for Congenital Adrenal Hyperplasia .. 9

3.5 Disease Characteristics and Suggested Treatment for Congenital Adrenal Hyperplasia 10

3.6 Objectives of the Literature Review 10

3.7 Candidate Performance Measures for Congenital Adrenal Hyperplasia 11

3.8 Methodology 11

3.9 Results 11

3.10 Discussion 12

3.11 Conclusion 12

3.12 Limitations 13

4 Evidence Supporting Candidate Measures for Congenital Adrenal Hyperplasia 15

4.1 Time to Initiate Treatment for Salt Wasting CAH 15

4.2 Time to Initiate Treatment for SW and SV CAH: Male versus Female 16

4.3 Time to Gender Assignment for CAH 17

4.4 Frequency of Medical Evaluations that Assess Growth Through Age 18 for SW CAH 18

5 Summary of Literature on Proposed Performance Measures for Galactosemia 21

5.1 Introduction to Galactosemia 21

5.2 Nomenclature and Disease Variants for Galactosemia 21

5.3 Incidence and Screening for Galactosemia 21

5.4 Laboratory Testing, Follow-up, and Diagnosis for Galactosemia 22
5.5 Disease Characteristics and Suggested Treatment for Galactosemia[23] 22
5.6 Objectives of the Literature Review 23
5.7 Candidate Performance Measures for Galactosemia 23
5.8 Methodology 23
5.9 Results 24
5.10 Discussion 24
5.11 Conclusion 24
5.12 Limitations 25

6 Evidence Supporting Candidate Measures for Galactosemia 27
6.1 Time to Initiate Treatment for Galactosemia 27
6.2 Dietary Compliance in Galactosemia 31

7 Summary of Literature on Proposed Performance Measures for Medium Chain Acyl CoA Dehydrogenase Deficiency 33
7.1 Introduction to Medium Chain Acyl CoA Dehydrogenase Deficiency 33
7.2 Nomenclature and Disease Variants for Medium Chain Acyl CoA Dehydrogenase Deficiency 33
7.3 Incidence and Screening for Medium Chain Acyl CoA Dehydrogenase Deficiciency 33
7.4 Laboratory Testing, Follow-up, and Diagnosis for Medium Chain Acyl CoA Dehydrogenase Deficiency 33
7.5 Disease Characteristics and Suggested Treatment for Medium Chain Acyl CoA Dehydrogenase Deficiency 34
7.6 Objectives of the Literature Review 35
7.7 Candidate Performance Measures for Medium Chain Acyl CoA Dehydrogenase Deficiency 35
7.8 Methodology 36
7.9 Results 36
7.10 Discussion 36
7.11 Conclusion 37
7.12 Limitations 37

8 Evidence Supporting Candidate Measures for Medium-chain acyl-CoA Dehydrogenase Deficiency 39
8.1 Time to a Confirmed Diagnosis for MCADD 39

8.2 Hospitalization for Severe Episodes Related to MCADD 39
8.3 Parent Understanding of Condition Post Physician Notification of MCADD 40
8.4 Adherence to Dietary Treatment for MCADD (Avoidance of Fasting) 40
8.5 Screening/Diagnosis of At-Risk Family Members of MCADD Patients 41
8.6 Normal Developmental and Cognitive Outcome at Age 4 for MCADD..... 42

9 Summary of Literature on Proposed Performance Measures for Congenital Hypothyroidism..... 43

9.1 Introduction to Congenital Hypothyroidism 43
9.2 Nomenclature and Disease Variants for Congenital Hypothyroidism..... 43
9.3 Incidence and Screening for Congenital Hypothyroidism 43
9.4 Laboratory Testing, Follow-up, and Diagnosis for Congenital Hypothyroidism..... 43
9.5 Disease Characteristics and Suggested Treatment for Congenital Hypothyroidism .. 44
9.6 Objectives of the Literature Review 44
9.7 Candidate Performance Measures for Congenital Hypothyroidism 44
9.8 Methodology 45
9.9 Results..... 45
9.10 Discussion 45
9.11 Conclusion 46
9.12 Limitations 47

10 Evidence Supporting Candidate Measures for Congenital Hypothyroidism..... 49

10.1 Time to Initiate Treatment for CH 49
10.2 Initial Dosage of L-Thyroxine 54
10.3 Normalization of TSH, T4, and FT4 Concentration within One Month of Treatment59
10.4 Evaluation for Transient CH by Age 4 60

11 Summary of Literature on Proposed Performance Measures for Maple Syrup Urine Disease..... 63

11.1 Introduction to Maple Syrup Urine Disease 63
11.2 Nomenclature and Disease Variants for Maple Syrup Urine Disease[66] 63
11.3 Incidence and Screening for Maple Syrup Urine Disease 63
11.4 Laboratory Testing, Follow-up, and Diagnosis for Maple Syrup Urine Disease 64
11.5 Disease Characteristics and Suggested Treatment[66] 64
11.6 Objectives of the Literature Review 64

11.7 Candidate Performance Measures for Maple Syrup Urine Disease 65
11.8 Methodology 65
11.9 Results 65
11.10 Discussion 65
11.11 Conclusion 66
11.12 Limitations 66

12 Evidence Supporting Candidate Measures for Maple Syrup Urine Disease 69
12.1 Time To Initiate Treatment for MSUD 69
12.2 Time to Reduce Plasma Leucine Concentration Levels for MSUD 71
12.3 Mean Annual Leucine Levels for Long-Term Metabolic Control in MSUD 73

13 Summary of Literature on Proposed Performance Measures for Sickle Cell Disease. 75
13.1 Introduction to Sickle Cell Disease 75
13.2 Nomenclature and Disease Variants for Sickle Cell Disease 75
13.3 Incidence and Screening for Sickle Cell Disease 75
13.4 Laboratory Testing, Follow-up, and Diagnosis for Sickle Cell Disease 75
13.5 Disease Characteristics and Suggested Treatment for Sickle Cell Disease [79, 80] 76
13.6 Objectives of the Literature Review 77
13.7 Candidate Performance Measures for Sickle Cell Disease 77
13.8 Methodology 78
13.9 Results 78
13.10 Discussion 78
13.11 Conclusion 79
13.12 Limitations 79

14 Candidate Measures for Sickle Cell Disease with References 81
14.1 Time to Initiate Penicillin Treatment for HbSS 81
14.2 Compliance with Twice Daily Oral Prophylactic Prescription of Penicillin Through Age 5 for HbSS 82
14.3 Age at Time of First Prevnar Immunization for SCD 84
14.4 Clinical Evaluation at Age 5 for Disease Management Decisions for SCD 87
14.5 Parent Education on Assessing Enlarged Spleen and Monitoring Episodes of Febrile Illness in SCD 89
14.6 Genetic Counseling on SCD for Parents 91

15 Summary of Literature on Proposed Performance Measures for Phenylketonuria 93
15.1 Introduction to Phenylketonuria 93
15.2 Nomenclature and Disease Variants for Phenylketonuria 93
15.3 Incidence and Screening for Phenylketonuria 93
15.4 Laboratory Testing, Follow-up, and Diagnosis for Phenylketonuria 93
15.5 Disease Characteristics and Suggested Treatment for Phenylketonuria 94
15.6 Objectives of the Literature Review 94
15.7 Candidate Performance Measures for Phenylketonuria 95
15.8 Methodology 95
15.9 Results 95
15.10 Discussion 95
15.11 Conclusion 96
15.12 Limitations 96

16 Evidence Supporting Candidate Measures for Phenylketonuria 97
16.1 Time to Initiate Treatment for PKU 97
16.2 Dietary Compliance for PKU 98
16.3 Monitoring Phenylalanine Levels for Metabolic Control 102
16.4 Age-Appropriate Frequency of Monitoring Phenylalanine Levels 104

17 Universal Performance Measures 105
17.1 Introduction to System-Wide Universal Measures 105
17.2 Universal Measures Related to Specimen Collection and Specimen Quality 107

18 Limitations of Evidence 109
18.1 Unpublished versus Published Evidence 109
18.2 Available Evidence within Pediatric Research 109
18.3 Lack of Statistical Significance 109
18.4 Lack of Consensus within the Available Evidence 109
18.5 Generalizability to Texas 109

19 References 111

1 Acronym and Initialism List

Acronym and Initialism List	
Acronym or Initialism	Expanded
µmol	Micromoles
17-OHP	17-Hydroxyprogesterone
21-OH	21-Hydroxylase Deficiency
95% CI	95% Confidence Interval
AAP	American Academy of Pediatrics
ACS	Acute Chest Syndrome
ACTH	Adrenocorticotropic Hormone
ADD	Attention Deficient Disorder
APC	Acute Pain Crisis
ASSC	Acute Splenic Sequestration Crisis
BCAA	Branched-chain Amino Acids
BCKAD	Branched-chain Alpha-ketoacid Dehydrogenase Complex
BH4	Tetrahydrobiopterin
CAH	Congenital Adrenal Hyperplasia
CDC	Centers for Disease Control and Prevention
CH	Congenital Hypothyroidism
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COG	Committee on Genetics
CSSCD	Cooperative Study of Sickle Cell Disease
D/G	Duarte Galactosemia
dL	Deciliter
DNA	Deoxyribonucleic Acid
DOB	Date of Birth
DOC	Date of Collection
DQ	Developmental Quotient
DSHS	Department of State Health Services
ECI	Early Childhood Intervention
et al.	and others

Acronym and Initialism List	
Acronym or Initialism	Expanded
FSIQ	Full Scale Intelligence Quotient
FT4	Free Thyroxine
G/G	Classical Galactosemia
GAL	Galactosemia
GALE	Galactose-4-epimerase Deficiency
GALK	Galactokinase Deficiency
GALT	Galactose-1-phosphate uridyl transferase
gm	Gram
Hb	Hemoglobin
HBB	Hemoglobin Beta Gene
HbS	Abnormal Hemoglobin S
$HbS\beta^+$	Hemoglobin S/beta Thalassemia
$HbS\beta^0$	Hemoglobin S/beta-zero Thalassemia
HbSC	Hemoglobin SC Disease
HbSS	Hemoglobin SS Disease (Sickle Cell Anemia)
HIV	Human Immunodeficiency Virus
HPA	Hyperphenylalaninemia
IEF	Isoelectric Focusing
IQ	Intelligence Quotient
kg	Kilogram
L	Liter
LT4	L-Thyroxine
MCADD	Medium Chain acyl CoA Dehydrogenase Deficiency
mcg	Microgram
MDI	Mental Development Index
mg	Milligram
mmol	Millimole
MS/MS	Tandem Mass Spectrometry
MSUD	Maple Syrup Urine Disease
N	Number of Participants
NBS	Newborn Screening

Acronym and Initialism List	
Acronym or Initialism	Expanded
ng	Nanogram
NICU	Neonatal Intensive Care Unit
OVID	Medical Database
PAH	Phenylalanine Hydroxylase
PCP	Primary Care Physician
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PCV-7	7-Valent Pneumococcal Conjugate Vaccine
Phe	Phenylalanine
PKU	Phenylketonuria
PROPS	Prophylactic Penicillin Study
PS-23/23PS	Polysaccharide Vaccine (Pneumovax)
r	correlation coefficient
RFLP	Restriction Fragment Length Polymorphism
SCD	Sickle Cell Disease
SD	Standard Deviation
SIDS	Sudden Infant Death Syndrome
SV	Simple Virilizing
SW	Salt Wasting
T3	Triiodothyronine
T4	Thyroxine
TAC	Texas Administrative Code
TNSP	Texas Newborn Screening Program
TNSPMP	Texas Newborn Screening Performance Measures Project
TOMI	Test of Motor Intelligence
TRH	Thyrotropin Releasing Hormone
TSH	Thyroid Stimulating Hormone
TYR	Tyrosine
UDP	Uridine Diphosphate
WHO	World Health Organization
WSIC	Wechsler Intelligence Scale for Children

2 Texas Newborn Screening Performance Measures Project

2.1 Background Information

In September 2007, the Texas Newborn Screening Program (TNSP) and the Centers for Disease Control and Prevention (CDC) entered a cooperative agreement to develop evidence-based performance measures for the pre- and post-analytical phases of newborn screening (NBS). The three-year project is entitled Texas Newborn Screening Performance Measures Project (TNSPMP) and involves participation from stakeholders representing various aspects of the Texas newborn screening system.

This report documents candidate performance measures for the newborn screening system and provides corresponding evidence where available. The report is intended as a resource to assist system stakeholders in making informed decisions on the selection of evidence-based performance measures that will be piloted in the third year of the project (2009–2010).

2.2 Department of State Health Services Texas Newborn Screening Program

The Department of State Health Services Texas Newborn Screening Program (DSHS TNSP) is a program consisting of two organizational areas (Newborn Screening Laboratory and Newborn Screening Case Management) within the Department of State Health Services.

The Newborn Screening Laboratory is a part of the Division of Prevention and Preparedness Services, and Newborn Screening Case Management is a part of the Division for Family and Community Health Services.

2.3 Performance Measures

According to the American Heritage Dictionary 1991, a performance measure is “the specific quantitative representation of a capacity, process, or outcome deemed relevant to the assessment of performance.” By monitoring performance of the newborn screening system, opportunities for improvement can be identified and necessary interventions can be implemented.

The proposed performance measures listed in this document are accompanied by a working, conceptual definition. If considered for piloting, these performance measures will be further refined using clearly defined terms. Several factors that may influence the definition of these measures include the reporting method, the available sample size, state rules, and/or TNSP protocols.

2.4 Methods

Disorders on the original TNSP screening panel and two of the disorders added in late 2006 were selected as focal points for the literature review process. A list of the disorders included is provided in section 2.4.1. Candidate performance measures for each disorder were collected through a combination of activities including examining existing measures, soliciting expert opinion from TNSPMP system stakeholders, and conducting targeted literature reviews to identify evidence for specific measures.

With respect to literature reviews, two approaches were used to obtain pertinent literature. In the first approach, the review was undertaken to synthesize the body of knowledge of varying clinical outcomes of patients with newborn screening disorders to support a single performance measure variable: the timing of care (i.e., time to treatment or time to diagnosis). In this case, the literature searches were limited to the disorder name and a handful of search terms related to timeliness (time to treatment, time to diagnosis, age at therapy, etc.). In the second approach, subject matter experts were asked about potential performance measures based on their clinical experience in a particular newborn screening disorder. These suggestions provided additional search terms, in addition to time to treatment, which allowed comprehensive literature searches on several variables related to clinical outcomes.

The evidence review process was instrumental in refining the list of disorder specific performance measures to include only those with supporting literature.

2.4.1 Disorder-Specific Performance Measures

The literature review summaries found in this report include general information about each of the chosen disorders, a list of candidate performance measures, and discussion that synthesizes the available evidence for each of the measures. The review was not intended to provide a comprehensive study of the disorder, but rather to provide evidence to substantiate the proposed performance measures. The literature summaries are followed by a section in which each of the candidate measures are listed in tabular format with supporting information from the published material reviewed.

- Congenital Adrenal Hyperplasia (CAH)
  - Time to initiate treatment for salt wasting CAH
  - Time to initiate treatment for salt wasting and simple virilizing CAH: male versus female
  - Time to gender assignment for salt wasting CAH
  - Frequency of medical evaluations that assess growth through age 18 for salt wasting CAH
- Galactosemia (GAL)
  - Time to initiate treatment
  - Dietary compliance
- Medium Chain acyl CoA Dehydrogenase Deficiency (MCADD)
  - Time to a confirmed diagnosis
  - Hospitalization for severe episodes related to MCADD
  - Parent understanding of condition post physician notification
  - Adherence to dietary treatment (avoidance of fasting)
  - Screening/Diagnosis for at-risk family members
  - Normal developmental and cognitive outcome at age 4
- Congenital Hypothyroidism (CH)
  - Time to initiate treatment
  - Initial dosage of L-thyroxine (LT4)

  - Normalization of serum TSH, T4, and FT4 concentrations within 1 month of treatment
  - Evaluation for transient CH by age 4
- Maple Syrup Urine Disease (MSUD)
  - Time to initiate treatment
  - Time to reduce plasma leucine concentration levels
  - Mean annual leucine levels for long-term metabolic control
- Sickle Cell Disease (SCD)
  - Time to initiate penicillin treatment for HbSS
  - Compliance with twice daily oral prophylactic penicillin through age 5 for HbSS
  - Age at the time of first Prevnar® vaccination (PCV-7) for SCD
  - Clinical evaluation at age 5 for disease management decisions for SCD
  - Parent education on assessing enlarged spleen/monitoring episodes of febrile illness in SCD
  - Genetic counseling on SCD for parents
- Phenylketonuria (PKU)
  - Time to initiate treatment
  - Dietary compliance
  - Monitoring phenylalanine (Phe) levels for metabolic control
  - Age-appropriate frequency of monitoring Phe levels

2.4.2 Universal Performance Measures Related to Time to Initiate Treatment and Specimen Quality

Timely disease management is a shared variable of interest among each of the disorders listed above. For the majority of the conditions discussed in this report, time to treatment is chosen over time to diagnosis as an indicator of the efficiency of disease management processes. Although it may be assumed that treatment will be initiated after a confirmed diagnosis, there may be several exceptions. For example, if it is suspected that a patient has galactosemia, physicians typically prescribe a lactose-free diet (treatment) even before a diagnosis is confirmed. Time to treatment serves as a comprehensive performance measure that includes several parameters such as prompt communication between the TNSP, the physician, and the family and actions taken to prevent immediate morbidity and mortality. Time to treatment may not be a valid indicator of timely disease management in some disorders such as MCADD. It is important to note that treatment typically refers to a specific procedure or therapy given to ameliorate or prevent an adverse patient outcome; however, patients with MCADD appear normal and healthy until an event of prolonged fasting leads to metabolic crisis. Many MCADD patients may remain asymptomatic for extended periods of time. Avoidance of fasting is the first line of treatment that is prescribed for patients diagnosed with MCADD. For this reason, MCADD is the only condition included in the current report that utilizes “time to a confirmed diagnosis” as the preferred performance measure for timely disease management.

The universal performance measures in this report address the collective processes needed for timely disease management. They are "universal" in that they are applicable to all newborn screening disorders. Examples of measures found in this category are time from birth to specimen collection, time from specimen collection to receipt in the laboratory, time from abnormal screen to patient contact, and time to initiation of treatment. Examples of other process-related measures associated with timely treatment discussed in this section include percentage of specimens deemed unsatisfactory for testing, timing of specimen collections, and percentage of specimens missing demographic fields found on the blood collection cards.

Many of the disorders have evidence lending support to timely treatment; yet no direct evidence was found in the literature to explicitly support universal performance measures in this category. Thus, in lieu of a literature review summary, the last section of the report provides a brief discussion of the proposed measures relating to timeliness and their importance to the screening process.

2.4.3 Performance Measures Not Considered in this Report

TNSPMP team members and system stakeholders proposed a list of approximately 50 evidence-based performance measures. Many more were considered, but based on the above-mentioned literature search strategies, there was insufficient evidence to support them. The following are some examples of measures that were not further considered for inclusion in this report:

- Cost of noncompliance
- Time to dietary counseling
- Time to referral to Early Child Intervention (ECI) services
- Initiation of treatment prior to receipt of screening results
- Accessibility to a dietician
- Quality of parent education of newborn screening
- Physician adherence to protocol
- Psychosocial stress factor through a specified age
- Frequency of specialist center visits
- Specialist adherence to protocol
- Specialist patient ratio per health region
- Missing technician's initials
- Missing total demographic fields

2.4.4 Limitations of Evidence

The final section titled Limitations of Evidence discusses issues such as the availability of evidence to support proposed performance measures, the quality of available evidence, and the generalizability of the available evidence to the TNSP.

3 Summary of Literature on Proposed Performance Measures for Congenital Adrenal Hyperplasia

3.1 Introduction to Congenital Adrenal Hyperplasia

Congenital Adrenal Hyperplasia (CAH) is a group of inherited autosomal recessive disorders characterized by a deficiency of one or more enzymes involved in cortisol biosynthesis. Most cases of CAH (90%–95%) can be attributed to 21-hydroxylase (21-OH) deficiency.[1] This deficiency can lead to increased blood levels of Adrenocorticotropic hormone (ACTH) and a subsequent over production of androgens. Excess androgens may cause virilization in an affected individual.[2] Classical CAH includes salt wasting and simple virilization forms. Although virilization at birth can be seen in either form of the disease, salt wasting crisis is only seen in the salt wasting form of the disease during the first few weeks of life. Other symptoms include virilization at birth among female patients, virilization in childhood in male patients, and precocious puberty.

3.2 Nomenclature and Disease Variants for Congenital Adrenal Hyperplasia

There are three primary forms of CAH:

- **Salt wasting (SW) form**—Characterized by neonatal onset of symptoms such as virilization, salt crisis, and serum concentration of 17-hydroxyprogesterone (17-OHP) that may be greater than 20,000 ng/dL.
- **Simple virilizing (SV) form**—Characterized by various degrees of virilization and the absence of salt crisis.
- **Non-classical form**—Characterized by premature adrenarche (changes due to puberty as a result of increased secretion of adrenocortical hormones), acne, menstrual disturbances, and excessive hair (hirsutism).

3.3 Incidence and Screening for Congenital Adrenal Hyperplasia

The national incidence of CAH (with SW and SV combined) is reported as greater than 1 in 16,000.[3] Salt wasting CAH (SW CAH) is more frequent than the SV form (2.7:1).[4]

Newborn screening for CAH began in Texas in 1989.[4] In 2007, approximately 4,968 specimens were identified as presumptive positive for this condition. Of the infants with presumptive positive results, 15 were diagnosed with SW CAH, and 5 infants were diagnosed with SV CAH. Based on these numbers (for a birth rate of 414,000[i]), the incidence of SW CAH and SV CAH in Texas for 2007 is estimated at 1:27,600 and 1:82,800 respectively.

3.4 Laboratory Testing, Follow-up, and Diagnosis for Congenital Adrenal Hyperplasia

TNSP conducts testing for CAH using a fluoro-immunoassay for 17-OHP, which is a precursor of cortisol. A 17-OHP test result in the upper 3% of an assay run causes the specimen to be re-analyzed in duplicate before a final determination is made. Confirmatory testing includes serum 17-OHP and serum electrolyte levels, specifically sodium and potassium. If the serum 17-OHP

concentration is high, the pediatric endocrinologist may have an ACTH stimulation test performed to determine the risk for salt wasting CAH.

For infants with presumptive positive results, TNSP immediately contacts the PCP or the attending physician to suggest a follow-up protocol. TNSP continues to track or follow the clinical status of the infant until diagnosis or until the infant is confirmed not to have the condition.

3.5 Disease Characteristics and Suggested Treatment for Congenital Adrenal Hyperplasia

The following elaborates on commonly encountered disease characteristics of patients with CAH.

- **Prenatal virilization**—Because of the exposure to excess androgens, females with classical CAH may be born with various degrees of virilization, which include an enlarged clitoris, fused labia, and formation of a urogenital sinus.
- **Postnatal virilization**—Both males and females are at a risk of virilization and precocious puberty. If not treated adequately, classical CAH can cause premature development of axillary and pubic hair as well as acne. Males may experience penile enlargement coupled with poorly developed testes. Females may experience clitoral enlargement, menstrual abnormalities, hirsutism, and infertility.
- **Salt wasting**—Infants born with SW CAH can experience life-threatening emergencies because of severe salt imbalance.
- **Cortisol deficiency**—Cortisol deficiency is reported in almost all the individuals with untreated classical CAH but is reportedly rare in the non-classical form.

Cortisone treatment for CAH first became available in the 1950's.[5] Over the years, carefully monitored glucocorticoid therapy has become the standard of care for addressing steroid deficiency, virilization, and infertility among CAH patients. Poor compliance with this therapy may result in compromised adult height as well as virilization.[6] Mineralocorticoid treatment and sodium chloride supplementation (especially in infants) are also crucial for optimal patient outcomes. Prenatal treatment of an affected female fetus with CAH is available.[7] Due to the complex nature of the disease, collaborative care by specialists from endocrinology, urology, surgery, genetics, and psychology has been deemed optimal.[8] Many institutions have developed interdisciplinary teams to evaluate and treat these patients.

3.6 Objectives of the Literature Review

The primary objective of this review is to describe findings from the literature on timeliness of treatment of CAH and its impact on patient outcomes. In addition, the review is also intended to provide a general understanding of the disease characteristics and treatment options. Evidence from the literature will be used to provide support to the proposed performance measures. Candidate measures may potentially be piloted in the third year of the TNSPMP which begins in September 2009.

3.7 Candidate Performance Measures for Congenital Adrenal Hyperplasia

The candidate performance measures listed below are general in nature. If considered for piloting in the third year of the project, these working conceptual definitions will be further developed and refined into clearly defined terms.

- **Time to initiate treatment for SW CAH**
  Measuring the time it takes from birth to initiate treatment for an infant with SW CAH.
- **Time to initiate treatment for SW and SV CAH: male versus female**
  Measuring the time it takes from birth to initiate treatment for an infant with CAH, where the outcome measure is stratified by gender.
- **Time to gender assignment for SW CAH**
  Measuring the time it takes from birth to assign a definitive gender for an infant with SW CAH.
- **Frequency of medical evaluations that assess growth through age 18 for SW CAH**
  Measuring the number of times a patient with SW CAH visits a specialist center for growth and development assessment purposes through the age of 18 years. (TNSP follows patients with CAH through 18 years of age.)

3.8 Methodology

The literature review was undertaken to synthesize the body of knowledge surrounding associations between timing of treatment and clinical outcomes of patients with congenital adrenal hyperplasia.

3.8.1 Keywords

Prominent scientific databases were searched for relevant articles. Keywords used for the literature search included the disorder name and one or more of the following: time to treatment, time to diagnosis, age at therapy, and start of therapy.

3.8.2 Inclusion/Exclusion Criteria

Only the articles written in English language were considered. In addition, articles discussing long-term clinical outcomes in adulthood were included only if the literature established a correlation between early treatment variables and long-term outcomes.

3.9 Results

The literature search generated 42 relevant articles. Studies from 17 countries published between 1966 and 2008 were included in the review. Some of the studies were case reports while others were population-based studies. The tables in the next section provide a detailed account of each of the studies and their relevance to the proposed performance indicators.

3.10 Discussion

The majority of SW patients may become symptomatic within the first two months after birth. A significant number of patients develop symptoms during the first weeks of life. Evidence in the literature that indicates that earliest physiological signs of salt wasting may occur at an average age of 7.6 days.[9] Often the patients present with symptoms before confirmatory test results are available.[10] Time to treatment has a major impact on mortality, especially for SW CAH patients. More than one study supports treatment initiation for SW CAH within 10 days of life.[10 11]

The incidence of CAH is the same in both males and females. Affected females may present with clinical findings at birth. Based on the findings in the literature, female infants tend to be diagnosed earlier because of their ambiguous genitalia while males may not be diagnosed until they exhibit signs of SW CAH.[12 13] Early treatment impacts their outcomes. While timely treatment of CAH is a very important parameter for measuring the performance of the newborn screening system, the assessment of timeliness may need to be stratified by gender.[14, 15]

The primary focus of early detection and treatment of CAH is to avoid mortality and incorrect gender assignment. Screening does not solve the problem of misclassification; however, it may result in quicker resolution of incorrect gender assignment.[16 17]

Several studies have examined the long-term implications of timely therapy as it relates to growth. Although in untreated CAH patients, the final adult height is decreased, and in childhood there is early rapid growth with premature fusion of the growth plates. Several researchers have reported that timely treatment allows CAH patients to reach normal or near normal height. Patients receiving delayed treatment may have a growth pattern similar to that of the untreated patients. It is important to note that “timely” treatment in older studies may not necessarily be seen as “timely” in the more recent investigations. For example, Bergstand et al. compared the growth curves of patients who received early and adequate treatment with the growth curves of patients who received late treatment. Treatment was initiated between three and eight weeks of age for the early group and between five and six years of age in the late group. The early group included at least four SW CAH patients and achieved better height than the late treatment group. Growth potential of the late treatment group was similar to that of the untreated group.[18-22]

Review of the literature suggests that CAH patients need to be monitored closely as they go through different phases of growth and maturity. After the initial critical period of infancy where preventing mortality is the principal concern, other outcomes such as final height also become important considerations. Periodic evaluations of the patient are another important component of optimal patient care in CAH disease management.

3.11 Conclusion

CAH is a complex disorder affecting both males and females. In most developed countries, population-wide screening of CAH has been undertaken. The primary goal of screening is to prevent mortality (in case of SW CAH), and to avoid gender misclassification. Newborn screening for CAH has made it possible to identify individuals affected with non-classical CAH as well. There is sufficient evidence in the literature that the earliest symptoms of salt-wasting CAH may appear within the first week of life. It is essential to streamline the pre- and post-

analytical phases of newborn screening to avoid any delays in timely identification of this vulnerable group of infants. Overall, time to treatment for SW CAH (analyzed separately for male and female patients), time to gender assignment, and the frequency of medical evaluations to assess growth of patients are all valid performance measures for CAH disease management.

3.12 Limitations

The type of CAH (SW, SV, or non-classical) was not always specified in the studies reviewed.

4 Evidence Supporting Candidate Measures for Congenital Adrenal Hyperplasia

4.1 Time to Initiate Treatment for Salt Wasting CAH

Time to Initiate Treatment for Salt Wasting CAH		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Bajpai, A et al. (2004)[11] Type of Study – Cohort study on patients seen at the Pediatric Endocrine Clinic between 1990 and 2002 for clinical features, laboratory profile, and pointers to diagnosis of 21-OH deficiency Location – New Delhi, India	N = 94 patients with CAH; 46 with SW form, 25 males and 21 females; 44 with SV form, 10 males and 34 females; 4 with NC form, 4 females	Some of the patients were symptomatic within the first week of life. Patients were diagnosed on the basis of various clinical features, laboratory results on 17-OHP levels, and family history. A statistically significant difference was noted in the average age of diagnosis between patients with SW and SV form of the disease ($p<0.001$). SW CAH patients were diagnosed at an age of 1 day to 18 months with an average age at diagnosis of 1.8 months (95% CI 0.9 – 2.7 months). Authors emphasized the importance of prompt clinical diagnosis and disease management in settings where universal screening for CH is unavailable.
Reference – Steigert M, et al. (2002)[9] Type of Study – Retrospective study between 1993 and 2001 to evaluate the efficiency of the Zurich University Children's Hospital Screening program which screens approximately 50% of Switzerland's infant population Location – Switzerland	N = 30 patients with SW CAH, 1 with 11beta-hydroxylase deficiency	Average time to therapy was reported as 6.7 days. There were 60 cases of recall because of suspected CAH of which 30 were later confirmed. Five patients (one female and four males) were already exhibiting laboratory signs of salt wasting at the time of recall and therefore benefited from timely treatment (6–9 days, mean 7.6 days)
Reference – Cutfield WS, Webster D (1995)[10] Type of Study – Retrospective study from December 1984 to December 1993 on infants diagnosed with CAH within 6 weeks of life Location – New Zealand	N = 23 patients with classical CAH; 20 with SW form, 3 with SV form	Vomiting, poor feeding, and shock were common after day 10 of life in SW CAH infants. Two of 10 infants showed symptoms before day 10 and 8 of 8 showed symptoms between day 11 and 16. Authors recommended that treatment should start before the age of 10 days.

4.2 Time to Initiate Treatment for SW and SV CAH: Male versus Female

Time to Initiate Treatment for SW and SV CAH: Male versus Female		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Török D, et al. (2003)[12] Type of Study – Retrospective study from 1978 to 1998 examining the efficacy of identifying CAH patients Location – Hungary	N = 185 patients with various forms of CAH; 110 with SW form, 45 with SV form, 27 with non-classical form, and 3 with 11beta-hydroxylase deficiency	SW CAH males were typically diagnosed two weeks later than SW CAH females. (Median age of diagnosis in males is 25 days versus 7 days in females). For SV CAH, diagnosis was made at similar age in both males and females (2–2.5 years).
Reference – Frisch H, et al. (2002)[13] Type of Study – Retrospective study between 1969 and 1998 on epidemiological data, growth data, and genotypes on CAH patients Location – Austria; Czech Republic; Hungary; Slovenia; Slovakia	N = 484 patients diagnosed with classical CAH; 387 with SW form, 211 with SV form	Data showed there were 43% males and 57% females with classical CAH. Diagnosis was established later in males than in females in both SW and SV forms. Mortality in CAH patients was reported to be significantly higher than in the general population (11.3% versus 2.2%).
Reference – Kovács J, et al. (2001)[15] Type of Study – Retrospective study from 1969 to 1998 examining the time elapsed before diagnosis is made for CAH patients Location – Middle Europe	N = 484 patients with classical CAH; 313 with SW form, 171 with SV form	It took 26 days to establish a diagnosis of SW CAH in males versus 13 days in females. SW CAH survivors were diagnosed at median age 16.5 days, SW CAH non-survivors were diagnosed at median age of 22 days.
Reference – Gasparini N, et al. (1997)[14] Type of Study – Longitudinal study of growth patterns in CAH infants during the first 36 months of life Location – Italy	N = 24 patients with classical CAH; Form of CAH not specified; 7 male, 17 female	At diagnosis, female population was younger at 15 ± 14 days while the male population was older at 45 ± 16 days.

4.3 Time to Gender Assignment for CAH

Time to Gender Assignment for CAH		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Thilén A, et al. (1998)[16] Type of Study – Prospective follow-up study with patients diagnosed with CAH between January 1989 and December 1994. The results of this analysis were compared with that of a retrospective study performed on patients diagnosed between 1969 and 1986 (when newborn screening was not in place). Location – Sweden	N = 73 patients with classical CAH; 56 with SW form, 17 with SV form	Screening does not solve the problem of misclassification; however, it may result in quicker resolution of such errors. Screening prevented deaths since infants with SW CAH were treated in a timely manner. Although the main aim of screening is to identify newborns with classical CAH, patients with non-classical CAH also benefit from earlier therapy. Benefits of early therapy may include decreased virilization, normalized growth and puberty, and improved psychosocial outcomes.
Reference – Listernick R, et al. (1992)[17] Type of Study – Descriptive case studies of infants identified with CAH between January 1989 and March 1991 who failed to receive medical attention in a timely fashion Location – Illinois, USA	N = 3 patients with classical CAH; All with SW form	Despite early identification by a state neonatal program, authors noted breakdown in follow-up of screens. In one case, timely diagnosis was performed but corrective surgery was needed for a female infant that was classified as male.

4.4 Frequency of Medical Evaluations that Assess Growth Through Age 18 for SW CAH

Frequency of Medical Evaluations that Assess Growth Through Age 18 for SW CAH		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Merke DP, Bornstein SR. (2005)[21] Type of Study – Review article on the epidemiology, genetics, pathophysiology, diagnosis, and management of CAH Location – Not Applicable	Not Applicable	Highest rate of classic CAH was found in Yupic Eskimos in the US, which was 1 out of 280. Incidence of classical CAH was lower in African Americans than in Caucasians. (1 in 42,000 vs. 1 in 15,500). Mean adult height of patients with classical CAH is 10cm below the population mean.
Reference – Manoli I, et al. (2002)[20] Type of Study – Retrospective study of linear growth pattern and body mass index on CAH patients seen at a single hospital Location – Athens, Greece	N = 48 patients with CAH; 17 with SW form, 21 with SV form and 6 with non-classical form	Patients with SV CAH tended to be diagnosed later (mean age 3.9 years) leading to advanced bone age and precocious puberty. This in turn resulted in poor adult height. Monitoring treatment especially in first two years may lead to better outcome.
Reference – Van der Kamp HJ, et al. (2002)[22] Type of Study – Retrospective longitudinal study on growth and puberty with CAH patients treated with hydrocortisone and fludrocortisone (in case of salt wasting) Location – Netherlands	N = 60 patients; 34 with SW form, 26 with non-SW form	In SW CAH patients, poor sodium levels and excess glucocorticoid treatment may result in poor adult height. Short stature was also reported in SV CAH patient who were diagnosed late.
Reference – Eugster EA, et al. (2001)[19] Type of Study – Meta-analysis of CAH patients older than 5 years of age who were followed from 1978 to 1998 at a single hospital. A meta-analysis of 18 studies with a combined sample size of 561 patients was also conducted. Location – Indianapolis, IN, USA	N = 65 patients with classical CAH; Form of CAH not specified	Diagnosis at an early age (<1 year) and “good compliance” (based on subjective view of provider) may contribute to better adult height in patients with 21-OH deficiency

Frequency of Medical Evaluations that Assess Growth Through Age 18 for SW CAH		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Bergstand CG (1966)[18] Type of Study – Prospective follow-up evaluating linear growth of patients with various forms of CAH Location – Sweden	N = 28 patients; 14 males, 14 females; age ranging from 8–26 years	The study compared the growth curves of patients who received early and adequate treatment with the growth curves of patients who received late treatment. Treatment was initiated between 3 and 8 weeks of age for the early group and between 5 and 6 years of age in the late group. The early group included at least 4 SW CAH patients and achieved better height than the late treatment group. Growth potential of the late treatment group was similar to that of the untreated group.

5 Summary of Literature on Proposed Performance Measures for Galactosemia

5.1 Introduction to Galactosemia

Galactosemia is an autosomal recessive disorder characterized by an inability to metabolize a simple sugar called galactose. Galactose is a major component of the milk sugar lactose, which is present in all dairy products. Traces of these sugars are found in a variety of food products. Individuals affected with classical galactosemia lack the enzyme galactose-1-phosphate uridyl transferase (GALT) and therefore cannot use galactose for their energy needs. This enzyme is responsible for the conversion of galactose-1-phosphate and uridine diphosphate (UDP) glucose to UDP galactose and glucose-1-phosphate. Presenting symptoms include vomiting, diarrhea, poor feeding, symptoms related to hepatocellular damage (e.g., jaundice), failure to thrive, lethargy, and sepsis. A small percentage of patients may also suffer from seizures.[23] Experts agree that timely treatment (before the age of 10 days) can lead to improved prognosis especially in the short run. Lapses in treatment can lead to adverse outcomes such as developmental delay and mental retardation.[24]

5.2 Nomenclature and Disease Variants for Galactosemia

Nomenclature and disease variants for galactosemia follow.

- **Classical Galactosemia (G/G)**—G/G is characterized by very little or no activity of GALT (less than 5% of control values). Affected infants are unable to metabolize the milk sugar galactose.
- **Duarte Galactosemia (D/G)**—D/G is a milder variant of the disease. Although the TNSP does not actively screen for this condition, a number of cases of Duarte galactosemia are still picked up each year. Individuals with Duarte galactosemia have compromised enzyme function, but it is not as severe as in classical galactosemia. Activity of GALT in cases of Duarte galactosemia may be 5%–20% of control values, although occasionally it may be higher.[24]
- **Galactokinase Deficiency (GALK) and UDP galactose-4-epimerase deficiency (GALE)**—GALK and UDP GALE are also conditions that involve the metabolism of galactose but are caused by mutations in different genes. Currently, the TNSP does not screen for these conditions.

5.3 Incidence and Screening for Galactosemia

The national incidence of classical galactosemia is reported as greater than 1 in 47,000.[3] There is no significant difference in incidence between males and females although the manifestations of the disease may vary by gender.

Newborn screening for galactosemia began in Texas in 1979.[25] The TNSP initially utilized total galactose levels to screen for galactosemia. In September 2004, the program switched from measuring total galactose levels to measuring only GALT levels. In 2007, approximately 565 specimens were identified as presumptive positive for galactosemia. Of the presumptive positives, 7 infants were diagnosed with the classical form of galactosemia and 87 with the

Duarte form of galactosemia. Based on these numbers (for a birth rate of 414,000[i]), the incidence of classical galactosemia in Texas for 2007 is estimated at 1 in 59,000.

5.4 Laboratory Testing, Follow-up, and Diagnosis for Galactosemia

TNSP conducts testing for classical galactosemia using a fluorometric assay that detects the amount of GALT in a dried blood spot specimen. In addition, TNSP performs reflex DNA testing on specimens with a low GALT level.

For infants with presumptive positive results, TNSP immediately contacts the PCP or the attending physician to suggest follow-up protocol. TNSP continues to track or follow the clinical status of the infant until diagnosis or until the infant is confirmed not to have the condition.

5.5 Disease Characteristics and Suggested Treatment for Galactosemia[23]

The following elaborates on commonly encountered disease characteristics of patients with galactosemia.

- **Mental retardation**—Mental retardation affects a large number of untreated galactosemic patients. As the patient grows older, even with treatment, there may be a progressive decline in IQ.
- **Speech disorders (verbal dyspraxia)**—Verbal dyspraxia is a motor speech disorder. Affected individuals may be slow in speech development, are unable to pronounce words correctly, and have a short verbal memory span. This condition is seen in greater than 50% of galactosemics who are older than three years of age and may include treated as well as untreated patients.
- **Compromised motor function**—In approximately one-fifth of patients, impaired motor function may be seen. Patients exhibit fine motor tremors, poor coordination, unstable gait, and poor balance. A small number of patients may have ataxia (very poor coordination of muscular movements).
- **Ovarian failure (in females)**—The majority of females with galactosemia experience some degree of ovarian failure. Most common manifestations are oligomenorrhea (infrequent menstruation) and secondary amenorrhea (cessation in menstrual cycles). The incidence of ovarian failure depends largely on the genotype. Females who are homozygous for the Q188R mutation are more likely to have ovarian failure.
- **Impaired growth**—Impaired growth is characterized by delays in growth, especially during early childhood and early adolescence.
- **Cataracts**—Mild to severe cataracts are observed in as many as one third of patients. Evidence shows that the presence of cataracts regresses with treatment.
- **Hepatic Dysfunction**—Patients often present with a variety of symptoms associated with varying degrees of liver dysfunction. Examples include jaundice, hepatomegaly, abnormal liver function, and coagulation disorders.
- **Sepsis**—Sepsis is characterized by a systematic inflammatory response to infection, in which there is fever or hyperthermia, tachycardia, tachypnea, and evidence of inadequate blood flow to internal organs.

The standard treatment for an infant diagnosed with galactosemia includes immediate cessation of any lactose-based diet (breast milk or conventional infant formula). The family is instructed to change the baby's diet to soy formula. When babies are switched from breast milk or conventional formula to a soy-based diet, they show dramatic improvement. There is considerable debate on whether small amounts of galactose can be given to children with some level of GALT activity. In the long-term, calcium supplements, routine biochemical assessment for accumulation of toxic substances, eye exams, and speech assessments are recommended.[24]

5.6 Objectives of the Literature Review

The main objective of this review is to present evidence from the literature that supports performance measures related to galactosemia disease management. As mentioned in the introductory section, there are variant forms of galactosemia. This review focuses on the most severe form of the condition, classical galactosemia. In addition, the review is intended to provide a general understanding of the disease characteristics and treatment options. Evidence from the literature will be used to provide support to the proposed performance measures listed in the following section. Candidate measures may potentially be piloted in the third year of the TNSPMP which begins in September 2009.

5.7 Candidate Performance Measures for Galactosemia

The candidate performance measures listed below are general in nature. If considered for piloting, these working conceptual definitions will be further refined into operational definitions. Performance goals shown in *italics* are tentative and may change during the refinement phase.

- **Time to initiate treatment**
  Monitoring the number of newborns in which a soy-based diet has been initiated in the *first 7 days of life*.
- **Dietary compliance**
  Monitoring adherence to a soy-based diet of galactosemic patients *in the first 12 months of life*. Milk and dairy products are the primary source of energy for infants during this time period.

5.8 Methodology

The literature review was undertaken to synthesize the body of knowledge surrounding associations between clinical outcomes and timing of treatment for patients with galactosemia.

5.8.1 Keywords

Prominent scientific databases were searched for relevant articles. The main keywords used for the literature search included the disorder name and one or more of the following: treatment, diagnosis, age at therapy, and start of therapy.

5.8.2 Inclusion/Exclusion Criteria

The primary treatment variable of interest was the time to initiation of dietary restriction in galactosemia. Other relevant variables were compliance with restricted diet and frequency of

specialist center visits. In addition, articles discussing long-term clinical outcomes in adulthood were included only if the literature established a correlation between early treatment variables and long-term outcomes. Although case studies are a weak form of scientific evidence, they were included in the review if they supported the performance measure(s).

Studies done on animal subjects or written in languages other than English were not included.

5.9 Results

The tables in the next section provide a list of these performance measures along with a synopsis of specific studies from the literature that lend evidence in support of each performance measure.

5.10 Discussion

The majority of infants with classical galactosemia experience symptoms within the first two months of life. There is mixed evidence regarding the impact of early treatment on patient outcomes. It appears that mortality, developmental delay, and incidence of cataracts are affected by the timeliness of treatment. Several studies provide evidence that if treated early, patients do well with respect to these outcomes.[23, 26-28]

Findings from the literature also show that patients treated early tend to do well primarily in the early years. As they grow older, patients experience subtle deterioration in IQ and verbal abilities. Consequently, school performance among galactosemic children is often suboptimal.[26, 27] Time to initial treatment also seems unrelated to premature ovarian failure among female patients.[23, 26, 29] It is unclear why individuals with galactosemia suffer from adverse long-term outcomes despite adequate treatment.[28, 30, 31] Some researchers believe that these patients suffer considerable damage during the prenatal period, which is why post-natal treatment is often insufficient.[32]

The literature review suggests that metabolic control (indicative of dietary compliance) in galactosemia is directly related to patient outcomes. Poor metabolic control has been especially linked to cataract formation.[33, 34] At least one case study reports complete reversal of liver damage upon initiation of dietary restriction in a galactosemia patient.[35] Good dietary control may be linked to optimal physical growth and an IQ that is within the normal range; however, speech problems were reported despite good dietary compliance.[32]

5.11 Conclusion

Galactosemia is a complex disorder, and there is minimal clear-cut correlation between treatment practices and many of the long-term outcomes. Despite mixed evidence on the efficacy of early treatment in preventing long-term complications in galactosemic patients, timeliness of treatment may be important at least in the immediate period following birth. Based on the evidence provided in the literature, timely treatment does address immediate concerns of neonatal morbidity. Further, compliance with soy-based diet is life saving in the neonatal period and affords better metabolic control in the period thereafter. Sufficient evidence supports that some of the long-term outcomes for galactosemia patients may be linked to metabolic control. Therefore, timeliness of treatment and dietary compliance are both important considerations for developing potential performance measures.

5.12 Limitations

Many of the studies included in this review were based on a relatively small sample size. Literature search produced a large number of case studies. Only one case study that provided a direct association between one of the performance measures of interest was included.

6 Evidence Supporting Candidate Measures for Galactosemia

6.1 Time to Initiate Treatment for Galactosemia

Time to Initiate Treatment for Galactosemia		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Schweitzer-Krantz S (2003)[30] Type of Study – Retrospective cross sectional study to evaluate outcomes in patients with galactosemia Location – Germany	N = 148 patients, with classical form, born between 1955 and1995; 81 males, 67 females	Screening leads to early treatment (dietary restriction) of newborns with galactosemia. Only one death was recorded after Germany's screening program was initiated in 1978; whereas prior to the program, twenty of the 148 patients died. There was no significant correlation between time to treatment and long-term cognitive outcome except in those cases where dietary restriction was started after the 8th week. The intelligence quotient and developmental quotients for patients treated within the first 8 weeks of life was not significantly different.
Reference – Guerrero NV, et al. (2000)[29] Type of Study – Retrospective cross sectional study to evaluate ovarian function in galactosemic females Location – Atlanta Georgia; Philadelphia, Pennsylvania; Portland, Oregon	N = 53 patients with classical form, studied over 1 year of age	Genotype was an important risk factor that predicted ovarian failure. Median age at initiation of dietary restriction was 7 days. No significant association between premature ovarian failure in female patients and age at start of dietary restriction could be established. Females who were homozygous for Q188R had a much higher risk (16 times higher) of premature ovarian failure. These results can not be generalized to those who were not homozygous for Q188R.
Reference – Brazeal TJ, J.E. F. (1999)[27] Type of Study – Case study of a 7-year-old child with galactosemia. Study describes disease progression over a period of 41 months. Location – Missouri, USA	Male patient with classical form, studied at 7 years of age	A child was diagnosed in the neonatal period when he presented with lethargy, vomiting, and poor feeding at the age of 9 days. With dietary intervention, immediate improvement was seen, and the child achieved early developmental milestones. However, cognitive function was reportedly progressively deteriorating since the child entered kindergarten.

Time to Initiate Treatment for Galactosemia		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Badawi N, et al. (1996)[26] Type of Study – Retrospective study of patients screened for galactosemia between 1972 and 1992 Location – Ireland	N = 62 patients; 55 classical form; 7 Duarte form	Time to positive screen was associated with mortality. A total of 9 deaths occurred among the 62 who were diagnosed. A difference was noted in survival when patients were categorized by average age of the screen. Average age of positive screen was 11 days in those who died, while the average age of positive screen was 7.5 days among the survivors. High-risk infants, who had a prior family history of the disease, were diagnosed at an average age of 2.5 days as compared to 6.9 days for those who were screened routinely. Long-term follow-up data were available for 32 patients, all of whom had the classical form of the disease. On an average, restricted diet was initiated at an average age of 7.6 days. Nineteen of the 32 patients experienced one or more complications of galactosemia. These complications included cataracts (13/32 with varying degrees of lens opacity); speech disorders (7/32, 3/7 severely affected); poor gonadal function (12/17 female patients); mental retardation (5/32); and recurring bacterial infections (3/32).
Reference – Schweitzer S, et al. (1993)[28] Type of Study – Cross sectional evaluation of physical and neurological status of galactosemic patients. Location – Germany	N = 134 patients, classical form (screening introduced in 1978); 31 patients in history group /retrospective analysis; 83 patients participated in clinical evaluation	It is unclear as to why well-treated patients continue to experience poor long-term outcomes; however, mortality may be related to time of treatment initiation. Twenty deaths were reported in the study population where all but one patient died by 9 weeks of age. No significant correlation between the declining IQ and onset of therapy was noted except when dietary restrictions were initiated after the 8th week of life.

<table>
<tr><th colspan="3">Time to Initiate Treatment for Galactosemia</th></tr>
<tr><th>Reference</th><th>Study Population</th><th>Main Finding(s)
As it relates to the performance measure</th></tr>
<tr><td>Reference – Waggoner DD, et al. (1990)[23]
Type of Study – Cross sectional survey aimed at describing the long-term outcomes of galactosemia and their correlation with treatment variables (e.g., age at treatment initiation, dietary compliance, etc.)
Location – USA and Europe</td><td>N = 750 questionnaires, 371 responses, Age range from 2 weeks to 37 years; average age is 9.5 years; targeting patients with classical galactosemia</td><td>Early clinical symptoms such as liver damage, food intolerance, failure to thrive, lethargy, seizures, and sepsis were associated with the age at initiation of dietary treatment.
Patients beginning dietary treatment on the first day of life did not show symptoms. The table shows the percentage of patients who were symptomatic based on the initiation of dietary restriction.
<table>
<tr><th>Age Diet Began</th><th>n</th><th>% Symptomatic</th></tr>
<tr><td>0 days</td><td>37</td><td>0%</td></tr>
<tr><td>2–14 days</td><td>182</td><td>30%</td></tr>
<tr><td>15–64 days</td><td>87</td><td>64%</td></tr>
<tr><td>65 days to 3 years</td><td>42</td><td>100%</td></tr>
</table>
Long-term outcomes such as cataracts and developmental delay could be traced back to initiation of dietary restrictions. Patients with cataracts (n=92) had received dietary treatment at an average age of 77 days, whereas the group without cataracts (n=220) had received dietary restrictions before 20 days.
Further, there was a greater incidence of developmental delay in infants for whom dietary restrictions were initiated after two months of age, yet speech problems were found in more than half the cases regardless of early treatment. This also includes 52% of 33 cases that had IQ greater than 90, which is in the normal range.
IQ and ovarian function do not differ significantly based on time to treatment.</td></tr>
<tr><td>Reference – Burke JP, et al. (1988)[34]
Type of Study – Cross sectional evaluation of lens abnormalities in galactosemic children. Results of ophthalmic evaluation were correlated with historical data such as age at diagnosis and the level of biochemical control among these patients.
Location – Dublin, Ireland</td><td>N = 18 children, classical form</td><td>Age at diagnosis may be related to occurrence of lens abnormalities in galactosemic patients. There was a higher incidence of lens opacities observed in patients who were diagnosed late.
Patients in group 1 (n=11) with no lens opacities began a restricted diet at an average age of 5.8 days (range 1–11 days). In comparison, patients in group 2 (n=7) received restricted diet at an average age of12.7 days (range 1–46 days). All 7 patients in this group experienced lens opacities.</td></tr>
</table>

Time to Initiate Treatment for Galactosemia		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Sardharwalla IB, Wraith JE (1987)[31] Type of Study – Retrospective study on management of classical galactosemia at Willink Biochemical Genetics Unit (single hospital study) Location – England	N = 18 patients, classical form, the oldest patient was 36 years of age at time of study	Long-term outcomes for cognitive development in galactosemic patients were poor; however, there was no significant difference if the child was diagnosed at two weeks of age or before six weeks of age. Outcomes were worse for infants who were diagnosed very late (13 months). All patients showed normal physical growth.
Reference – Waisbren SE, et al. (1983)[32] Type of Study – Cross sectional study aimed at evaluating speech and language ability in patients diagnosed with galactosemia Location – Massachusetts, USA	N = 8 children, classical form; 6 male, 2 female; Age range from 3.6–11.6 years	Patients (n=8) in this study had normal physical development and decent full-scale intelligence quotients; however, they all experienced speech related difficulties early in life. The average age when dietary restrictions began was 5.25 days (with a range of 1–15 days). The mean full scale IQ (FSIQ) of the study sample was 97. Speech difficulties were reported in all patients included in this study. The prevalence of speech difficulties in the general population was reported as approximately 1%; therefore, the study subjects experienced a disproportionately high rate of speech problems. Authors speculated that occurrence of speech problems in galactosemia could be due to prenatal effect because galactose-1-phosphate accumulation was found in cord blood of affected children.

6.2 Dietary Compliance in Galactosemia

Dietary Compliance in Galactosemia		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Beigi B, et al. (1993)[33] Type of Study – Prospective study examining cataract formation in galactosemic patients Location – Dublin, Ireland	N = 33 children, classical form; 15 male, 18 female; observed for average of 8.5 years	Acute early signs were reported between 1 and 7 days. Poor dietary control may be strongly related to cataract formation in galactosemic patients.
Reference – Waisbren SE, et al. (1983)[32] Type of Study – Prospective study examining speech and language abilities of galactosemic patients Location – Massachusetts, USA	N = 8 children, classical form; 6 male, 2 female; age range from 3.6–11.6 years	Good metabolic control (which is indicative of good dietary compliance) was reported for all patients in this study. As mentioned earlier, patients (n=8) had normal physical development and intelligence quotient within the normal range. However, they all experienced speech related difficulties early in life. Biochemical monitoring began four to five days after treatment began, during which time there was no detectable galactose in blood or urine and blood galactose-1-phosphate concentrations were less than 2mg/dl.
Reference – Applebaum MN, Thaler MM (1975)[35] Type of Study – Case report Location – San Francisco, California, USA	Female patient, evaluated at 28 days of age Classical form assumed	An infant presented with severe symptoms of liver damage, which developed at the age of 1 month. Dietary management with galactose-free diet resulted in complete reversal of liver damage.

7 Summary of Literature on Proposed Performance Measures for Medium Chain Acyl CoA Dehydrogenase Deficiency

7.1 Introduction to Medium Chain Acyl CoA Dehydrogenase Deficiency

Medium Chain Acyl CoA Dehydrogenase Deficiency (MCADD) is an autosomal recessive disorder of fatty acid oxidation. Medium chain acyl CoA dehydrogenase is an enzyme that is responsible for the breakdown of medium chain fatty acids in the liver cells. With prolonged fasting, the breakdown of fatty acids followed by the production of ketone bodies occurs in response to low glucose levels. Individuals affected with MCADD are unable to utilize their body's energy reserves via fatty acid oxidation and typically present with one or more of the following symptoms: hypoglycemia, lethargy, seizures, acute liver disease, and coma. Some of the symptoms such as brain damage and liver damage may also be experienced by individuals affected by Reye Syndrome, which has led to misdiagnosis in some cases. Often, the first acute episode is observed before the age of two years, although there are instances of presentation in adulthood. An illness, prolonged fasting, or events of metabolic stress such as surgery may precede clinical decompensation. MCADD is cited as a rare cause of sudden infant death syndrome (SIDS).[36]

7.2 Nomenclature and Disease Variants for Medium Chain Acyl CoA Dehydrogenase Deficiency

It is estimated that about half of the infants detected via newborn screening are homozygous for a common allele K304E. This is a relatively common allele in individuals of northern European descent. The remaining cases detected by newborn screening are compound heterozygotes with either K304E or a large variety of other rare alleles. Individuals who are homozygous for K304E or compound heterozygotes with other mutant alleles are classified as cases of classical MCADD.[36]

7.3 Incidence and Screening for Medium Chain Acyl CoA Dehydrogenase Deficiciency

According to the American College of Medical Genetics, the national incidence of MCADD is reported as greater than 1 in 25,000.[37]

Newborn screening for MCADD in Texas began in late 2006 with the expansion of the testing panel from 7 to 27 disorders. In 2007, approximately 161 specimens were identified as presumptive positive for this condition. Of the infants with presumptive positive results, 24 were diagnosed with MCADD. Based on these numbers (for a birth rate of 414,000[i]), the incidence of MCADD in Texas for 2007 is estimated at 1 in 17,250.

7.4 Laboratory Testing, Follow-up, and Diagnosis for Medium Chain Acyl CoA Dehydrogenase Deficiency

TNSP currently performs screening for MCADD by tandem mass spectrometry (MS/MS). MS/MS screening detects elevated concentrations of medium chain acylcarnitines and also evaluates their relationship with each other. These measurements provide analyte concentration

profiles that can aid in the detection of several fatty acid disorders. Confirmatory testing includes obtaining a plasma acylcarnitine profile, measuring urine acylglycines, urine organic acids, and plasma carnitine levels.

For infants with presumptive positive results, TNSP immediately contacts the PCP or the attending physician to suggest a follow-up protocol. TNSP continues to track or follow the clinical status of the infant until diagnosis or until the infant is confirmed not to have the condition.

Method development and validation is underway for DNA testing of mutations of the MCADD gene commonly found in Texas patients.

7.5 Disease Characteristics and Suggested Treatment for Medium Chain Acyl CoA Dehydrogenase Deficiency

The following elaborates on commonly encountered disease characteristics of patients with MCADD based on a retrospective study of 120 MCADD patients who were diagnosed based on clinical symptoms. Children who have been diagnosed by newborn screening and treated adequately often do not experience these symptoms. These disease characteristics have been adapted from their findings.[38]

- **Hepatomegaly**—Nearly 44% of the patients presented with an enlarged liver.
- **Chronic Muscle Weakness**—Chronic muscle weakness was reported in 16% of the cases. Delayed diagnosis had a significant correlation with the occurrence of chronic muscle weakness. Overall, patients with a complaint of chronic muscle weakness were diagnosed only after the age of three years. Such patients also experienced more clinical events and hospitalizations as compared to those who did not have muscle weakness.
- **Mental Retardation and Cerebral Palsy**—Approximately 9% of the study population suffered from cerebral palsy. Overall, it is estimated that at least 9% of surviving patients suffer from some form of disability such as cerebral palsy, mental retardation, or both.[39]
- **Attention Deficit Disorder (ADD)**—A diagnosis of ADD may be established when the child's behavior is significantly less attentive than that of the child's peers. In the Iafolla study, ADD was observed in 11% of the patients. The number of female patients with ADD was 7 times that of the number of male patients with ADD. Occurrence of seizures, encephalopathy (generalized brain dysfunction), hyperammonemia (excessive ammonia in blood), and episodes of clinical illness were all statistically significant predictors of ADD. A subset of the study subjects was diagnosed before symptoms appeared because of family history. It was noted that the risk of ADD was minimal among patients who were diagnosed before the onset of symptoms.
- **Developmental Delay**—The authors obtained psychodevelopmental information from 73 patients. Each of these patients was older than 2 years. Twenty-nine of 73 patients had abnormal developmental screen results. Of these, 23 patients tested abnormal on the psychodevelopmental scale. Twelve patients were diagnosed with global disability, and 7 had a diagnosis of behavioral disability. Four patients had a combined diagnosis of developmental as well as behavioral disability.

- **Aphasia**—Lack of speech due to injury or damage to specific areas of the brain was observed in 22% of the surviving patients (2 years old or older).
- **Sudden Death**—It was reported that 19% of the patients had died before any concrete diagnosis could be established. Among one-third of the symptomatic patients, there was a family history of a sibling with a pre-established diagnosis of MCADD or a sibling who suffered sudden unexplained death. Overall, the risk of death after a clinical episode (prior to diagnosis) was 20% in this study population.

To prevent the primary manifestations of MCADD, frequent feedings, low-fat diet, and avoidance of fasting are recommended. Uncooked cornstarch is sometimes utilized to help control the hypoglycemia. In case of suspected hypoglycemia, the patient should be given intravenous glucose. Many treatment centers in Europe differ from the US centers on their prescription of Carnitine as an additional treatment for MCADD. Carnitine supplementation is a common practice in the US.[40]

7.6 Objectives of the Literature Review

This review focuses on classical MCADD only. The main objective of this review is to describe findings from the literature on critical aspects of MCADD disease management (including timeliness of treatment) and their impact on patient outcomes. In addition, the review is intended to provide a general understanding of the disease characteristics and treatment options. Evidence from the literature will be used to provide support to the proposed performance measures. Candidate measures may potentially be piloted in the third year of the TNSPMP which begins in September 2009.

7.7 Candidate Performance Measures for Medium Chain Acyl CoA Dehydrogenase Deficiency

The candidate performance measures listed below are general in nature. If considered for piloting, these working conceptual definitions will be further refined into operational definitions.

- **Time to a confirmed diagnosis**
  Measuring the time it takes from birth to a confirmed diagnosis for an infant with MCADD.
- **Hospitalization for severe episodes related to MCADD**
  Monitoring the number of times an infant with MCADD is hospitalized with a severe episode in the first 4 years of life. A severe episode is tentatively defined as an emergency admission with the need for intravenous therapy, and not simply prophylactic therapy. TNSP follows patients with MCADD through 4 years of age.
- **Parent understanding of condition post physician notification**
  Assessing parent understanding of MCADD after receiving a confirmed diagnosis from a specialist.
- **Adherence to dietary treatment (avoidance of fasting)**
  Monitoring the rate of adherence to a frequent feeding regimen specified for an MCADD newborn.

- **Screening/Diagnosis for at-risk family members**
  Measuring how often at-risk family members of an MCADD-positive infant identified by NBS are tested for MCADD.
- **Normal developmental and cognitive outcome at age 4**
  Determining whether cognitive outcome is normal at the age of 4 years for a patient with MCADD. TNSP follows patients with MCADD through 4 years of age.

7.8 Methodology

The literature review was undertaken to synthesize the body of knowledge surrounding associations between clinical outcomes and timing of treatment for patients with MCADD.

7.8.1 Keywords

Prominent scientific databases were searched for relevant articles. Keywords used for the literature search included the disorder name and one or more of the following: SIDS, treatment, diagnosis, age at therapy, and start of therapy.

7.8.2 Inclusion/Exclusion Criteria

Only the articles written in English language were considered. In addition, articles discussing long-term clinical outcomes in older patients were included only if the literature established a correlation between early treatment variables and long-term outcomes.

7.9 Results

The tables in the next section provide a list of the above mentioned performance measures along with a synopsis of specific studies from the literature that lend evidence in support of each performance measure.

7.10 Discussion

In the absence of screening, MCADD patients may remain asymptomatic and therefore undiagnosed for years. Screening is instrumental in providing timely diagnosis and reducing the incidence of life-threatening adverse outcomes. The risk of death and other negative health outcomes is more pronounced in the unscreened patients (as compared to screened patients who are diagnosed earlier).[41]

Although screened patients also require hospitalization during illnesses (especially during early childhood), the incidence of hospitalizations is lower among the screened children. Further, the length of stay has been shown to be shorter among screened patients.[41]

Little evidence directly links parent education of newborn screening disorders and patient outcomes. Literature does note that physician-parent communication is often poor.[42] As pointed out during discussion with clinical experts at TNSPMP stakeholder meetings, parents' understanding of their child's health status can be an extremely critical aspect of MCADD

disease management as the child may be asymptomatic between hypoglycemic episodes. Avoidance of fasting and adherence to the prescribed dietary regimen is the first line of treatment recommended for infants testing positive for MCADD.[43] Therefore, if parents have incomplete understanding of the importance of proper feeding of their child, the results can be catastrophic.

Screening of siblings is recommended to diagnose asymptomatic/pre-symptomatic individuals with MCADD. As MCADD is an autosomal recessive disease, there is a 25% chance that unscreened siblings will be affected with MCADD.[38, 40] This is especially germane at the present time, since universal screening for MCADD was introduced in Texas in 2007.

Early childhood is a critical developmental period for all children. Survival among MCADD patients has improved greatly since the implementation of screening. If MCADD is poorly controlled, the sequelae of hypoglycemia, including developmental delay, may persist. Seizures, developmental delay, verbal disabilities, and ADD have been reported in untreated MCADD patients.[38, 40, 44] These potential negative effects highlight the importance of periodic developmental evaluations.

7.11 Conclusion

MCADD is a relatively common metabolic disorder with a good disease prognosis. Timely treatment, hospital use, compliance with treatment, parental understanding of patient care, periodic patient evaluation, and screening of other siblings all constitute important components of comprehensive patient care. Therefore, evaluation of the Texas newborn screening system utilizing these proposed measures can be useful in identifying potential lapses in effective treatment.

7.12 Limitations

Although there is abundant literature on disease management and patient outcomes for MCADD, evidence may not clearly support some of the proposed measures. Some of the variables of interest in MCADD were the subject of scientific studies but were not adequately supported by statistically significant evidence. Some of the studies included in this review include only short-term data.

Many of the studies on MCADD are based on the outcomes of unscreened populations. If timely diagnosis and treatment are provided, the outcomes for MCADD patients are very positive. Therefore, the findings of studies based on clinically diagnosed cases may represent a much worse disease prognosis.

8 Evidence Supporting Candidate Measures for Medium-chain acyl-CoA Dehydrogenase Deficiency

8.1 Time to a Confirmed Diagnosis for MCADD

Time to a Confirmed Diagnosis for MCADD		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Wilcken B, et al. (2007)[41] Type of Study – Population-based cohort study of babies born in Australia in the 10-year period from 1994–2004. Data from MCADD patients diagnosed clinically were compared with that of MCADD patients diagnosed via newborn screening. Location – Australia	N = 59 patients with MCADD for cohort study	Study results showed that the screened patients were diagnosed much earlier than those diagnosed clinically. Median age of diagnosis for screened patients was 0.5 months in contrast to 16 months for the unscreened patients. Earlier diagnosis translated into better outcomes for the screened patients. Screened patients had an absolute risk of death or severe adverse event of 5% by the age of two years. The same risk was about 55% in the unscreened patients who were diagnosed clinically. The relative risk of an adverse event (such as metabolic decompensation and death) in screened versus unscreened patients was 0.44 (95% CI 0.13–1.45).

8.2 Hospitalization for Severe Episodes Related to MCADD

Hospitalization for Severe Episodes Related to MCADD		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Wilcken B, et al. (2007)[41] Type of Study – Population-based cohort study of babies born in Australia in the 10-year period from 1994 to 2004. Data from MCADD patients diagnosed clinically were compared with that of MCADD patients diagnosed via newborn screening. Location – Australia	N = 59 patients with MCADD for cohort study	Hospital admissions were tracked and compared between screened (n=24) and unscreened (n=35) group of MCADD patients. The rate of admission for screened group was lower at 1.8 admissions per child as compared to 2.1 admissions per child for the unscreened group. Further, the average length of hospital stay was 2.35 days versus 2.95 days for the screened versus unscreened group.

8.3 Parent Understanding of Condition Post Physician Notification of MCADD

Parent Understanding of Condition Post Physician Notification of MCADD		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Farrell MH, Kuruvilla P (2008)[42] Type of Study – Explicit criteria abstraction. 32 pediatric residents were asked to participate in an experiment involving audio taped conversations about newborn screening. Physicians were to communicate with parents after a positive screen result. Location – Wisconsin, USA	N = 59 transcripts from 32 pediatric resident physicians	In a simulated patient-physician communication, only 3 out of 59 transcripts met the criteria for open-ended questions. None of the transcripts had a "teach-back" type of communication (teach-back is considered the ideal). This indicates that resident physicians performed poorly in terms of asking questions that assessed parental understanding of the healthcare information. This study provides evidence that physician communication with parents of an affected infant may not be optimal; however, it does not provide any direct evidence that poor communication may lead to poor patient outcomes.

8.4 Adherence to Dietary Treatment for MCADD (Avoidance of Fasting)

Adherence to Dietary Treatment for MCADD (Avoidance of Fasting)		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Derks TG, et al. (2007)[43] Type of Study – Combination of literature review from 1996 to 2005 and a retrospective study examining fasting studies performed on MCADD patients Location – Netherlands	N = 22 patients with MCADD; 25 reports on fasting tests;* 14 from the literature, 11 from hospital database *some patients had more than one record of fasting	The duration of safe fasting for children with MCADD varies with age. Babies aged 6 months to 1 year should not fast for more than 8 hours. Fasting for more than 10 hours may be unsafe for children aged 1–2 years. After the age of 2 years, fasting for more than 12 hours may be rendered unsafe.
Reference – Wilson CJ, et al. (1999)[40] Type of Study – Retrospective study of patients treated at a single hospital for MCADD related complications. Data from 1993–1997 were utilized in the study. Location – London, UK	N = 41 patients with MCADD	37 patients were treated *without* Carnitine supplementation. Data are inconclusive about the three patients who received Carnitine supplementation.

8.5 Screening/Diagnosis of At-Risk Family Members of MCADD Patients

Screening/Diagnosis of At-Risk Family Members of MCADD Patients		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Wilson CJ, et al. (1999)[40] Type of Study – Retrospective study of MCADD patients seen either acutely or as an outpatient between September 1993 and September 1997 in a single hospital Location – London, UK	N = 41 patients with MCADD	20% of the study population had a history of prior sibling death.
Reference – Iafolla AK, et al. (1994)[38] Type of Study – Hospital-based retrospective study to compile clinical outcomes of MCADD patients used to inform families on morbidity and mortality Location – North Carolina, USA	N = 120 patients with a diagnosis of MCADD	32% of the 120 infants studied had a history of an older sibling with a known diagnosis of MCADD or an older sibling who had experienced sudden, unexpected death.

8.6 Normal Developmental and Cognitive Outcome at Age 4 for MCADD

Normal Developmental and Cognitive Outcome at Age 4 for MCADD		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Wilson CJ, et al. (1999)[40] Type of Study – Retrospective study of MCADD patients seen either acutely, or as an outpatient between September 1993 and September 1997 in a single hospital Location – London, UK	N = 41 patients with MCADD	In the study group, five patients suffered from mild to severe cognitive impairment in an evaluation conducted three months after their discharge from the hospital. Patients' age at the time of evaluation is unclear. In the long run, four patients suffered from complications such as mild hemiparesis, temporary vision loss, severe feeding problems, and severe behavioral problems.
Reference – Iafolla AK, et al. (1994)[38] Type of Study – Hospital-based retrospective study (chart review) to compile clinical outcomes of MCADD patients used to inform families on morbidity and mortality Location – North Carolina, USA	N = 120 patients with a diagnosis of MCADD	Patients who had suffered seizures or encephalopathy between the ages of 12 and 18 months were more likely to have speech disability after the age of 2. Episodes of clinical illness and late diagnosis were also correlated with incidence of ADD.
Reference – Wilcken B, et al. (1994)[44] Type of Study – Retrospective chart review to investigate overall effectiveness of neonatal screening for MCADD (Study included follow-up phone interviews of affected child's parents) Location – Sydney, Australia	N = 20 patients diagnosed with MCADD between 1976 and 1993	The study reported the death of 5 of 20 patients. Of the 15 survivors, 8 patients showed normal development. Of these 8 patients, six were younger than 7 years of age. Four patients (aged 9–17 years) showed mild intellectual handicap. 1 of 15 survivors had severe handicap characterized by epilepsy, significant developmental delay, and loss of speech after a single severe episode. At the time of the study, this patient was younger than 7 years. Two patients were lost to follow-up.

9 Summary of Literature on Proposed Performance Measures for Congenital Hypothyroidism

9.1 Introduction to Congenital Hypothyroidism

Congenital hypothyroidism (CH) is a condition caused by partial or complete absence of thyroid function. The thyroid gland produces iodine-based hormones that are instrumental in controlling key functions such as growth regulation, brain development, and metabolic rate. The hormones involved in these functions include thyroxine (T4), and its unbound form, free thyroxine (FT4), triiodothyronine (T3), and thyroid stimulating hormone (TSH). Complete absence, abnormal location, or severely diminished size of thyroid gland lead to a majority (80%–85%) of CH cases. In other cases, an anatomically normal or enlarged thyroid gland is present; yet, the production of thyroid hormones is sub-optimal. Symptoms of CH may not be evident at the time of birth. Severely affected infants may have a characteristic appearance with a puffy face, low hairline, and a thick and protruding tongue. Other symptoms include abnormally enlarged fontanelles (soft spots in the skull), decreased muscle tone, jaundice, poor feeding, and sluggishness. If untreated, congenital hypothyroidism can lead to mental retardation and poor physical growth. Universal newborn screening for CH is routinely conducted in the United States and many other countries. If treatment begins in the neonatal period, normal growth and development can be expected.

9.2 Nomenclature and Disease Variants for Congenital Hypothyroidism

Of the common forms, dysgenesis of thyroid gland is the most common form of the disease. It is characterized by agenesis (complete absence) or ectopy (lingual or sublingual location). Dyshormonogenesis, characterized by unresponsiveness to TSH or an inability to uptake iodine is also common. A deficiency in TSH or thyrotropin releasing hormone (TRH) can also potentially lead to CH. Overall, Ectopic thyroid and thyroid agenesis each account for 20%–50% of all cases of CH. Dyshormogenesis is reported in 4%–15% of the cases and Hypothalamic-pituitary dysfunction is found in another 10%–15% patients. Transient form of CH occurs in 5%–10% of all reported cases of the condition.

9.3 Incidence and Screening for Congenital Hypothyroidism

The national incidence of CH is reported as greater than 1 in 3,000 to 1 in 4,000.[3] CH is known to affect twice as many females than males. Infants with Down syndrome are also at a higher risk for developing the condition.[45]

Newborn screening for CH began in Texas in 1980.[25] In 2007, approximately 7,850 specimens were identified as presumptive positive for this condition. Of these, 197 infants were diagnosed with primary CH and 2 with secondary CH. Based on these numbers (for a birth rate for 414,000[i]), the incidence of primary CH in Texas for 2007 is estimated at 1 in 2,100.

9.4 Laboratory Testing, Follow-up, and Diagnosis for Congenital Hypothyroidism

TNSP tests for CH using an immunofluorometric microtiter assay to detect T4. Specimens whose T4 value falls in the lowest 10% of the day's run are retested in duplicate for T4 and TSH determinations. Newborns with both T4 and TSH outside of normal limits, especially those with an excessively elevated TSH, are considered highly suspect for congenital hypothyroidism and therefore require immediate serum follow-up testing.

For infants with presumptive positive results, TNSP immediately contacts the PCP or the attending physician to suggest follow-up protocol. TNSP continues to track or follow the clinical status of the infant until diagnosis or until the infant is confirmed not to have the condition.

Diagnostic tests should include serum free T4, T4, and TSH. The consultant may also recommend total T4 along with an ultra sound of the thyroid.

9.5 Disease Characteristics and Suggested Treatment for Congenital Hypothyroidism

The following elaborates on commonly encountered disease characteristics of patients with CH.

- **Mental retardation**—In the absence of appropriate treatment, mental retardation is the most likely outcome for children with CH. Researchers have studied various aspects of cognitive development and reported that CH may impact specific abilities of a child. In some patients, performance IQ and verbal IQ are impacted.
- **Poor growth**—Poor physical development is also commonly found among CH patients in the absence of treatment. Failure to achieve developmental milestones, poor motor skills, and disproportionate growth are frequently seen.

Infants diagnosed with primary CH are treated with thyroid hormone replacement therapy.

9.6 Objectives of the Literature Review

The main objective of this review is to describe findings from the literature on some critical aspects of CH disease management (including timeliness of treatment) and their impact on patient outcomes. In addition, the review is intended to provide a general understanding of the disease characteristics and treatment options. Evidence from the literature will be used to provide support to the proposed performance measures. Candidate measures may potentially be piloted in the third year of the TNSPMP which begins in September 2009.

9.7 Candidate Performance Measures for Congenital Hypothyroidism

The candidate performance measures listed below are general in nature. If considered for piloting in the third year of the project, these working conceptual definitions will be further developed and refined into clearly defined terms.

- **Time to initiate treatment**
  Measuring the time it takes from birth to begin initial treatment for an infant with CH.
- **Initial dosage of L-thyroxine**
  Monitoring the number of newborns with CH receiving 10 to 15 mcg / kg / dose of L-thyroxine within one month of birth.

- **Normalization of serum TSH, T4 and FT4 concentration within one month of treatment**
  Monitoring the number of newborns with normal serum TSH, T4, FT4 concentrations within one month of treatment (based upon ranges provided by the reference laboratory used by the endocrinologist).
- **Evaluation for transient CH by age 4**
  Monitoring the number of patients who received an evaluation for transient CH by age 4.. TNSP follows patients with CH through 4 years of age.

9.8 Methodology

In 2006, the American Academy of Pediatrics published an update on newborn screening and therapy for CH. This report covers many aspects of CH disease management including screening methods, disease variants, treatment, follow-up, and developmental outcomes. This report served as the primary resource for development of proposed performance parameters. Targeted literature searches were then conducted to further substantiate the parameters suggested in the AAP report. Evidence from the literature was presented to the TNSPMP stakeholders. Detailed discussions on the presented evidence led to further refinement of the proposed measures.

9.8.1 Keywords

Several literature searches were performed in a variety of databases including PubMed, Web of Knowledge, OVID, CINAHL, Cochrane Library, and the National Guideline Clearinghouse. Specific terms provided for the search included congenital hypothyroidism; treatment time; early T4 treatment; treatment guidelines; time to therapy; start of therapy; frequency of follow-up; and treatment initiation.

9.8.2 Inclusion/Exclusion Criteria

Peer-review articles were excluded if they did not meet the following criteria: provided a measurable outcome; related to timeliness in diagnosis or treatment; written recently (1982–2008); and provided in the English language. In addition, articles discussing long-term clinical outcomes in older patients were included when the literature established a correlation between early treatment variables and long-term outcomes.

9.9 Results

The tables in the next section provide a list of the above mentioned performance measures along with a synopsis of specific studies from the literature that lend evidence in support of each performance measure.

9.10 Discussion

Based on the findings from the literature, several treatment factors such as disease severity, timely therapy, initial dosage, patient compliance, and socioeconomic factors play an important role in disease management. These factors are often interdependent and patient outcomes may be impacted by a number of these variables. Clinical experts agree that disease severity can be a very important predictor of long-term outcomes in CH. Evidence suggests that despite early and

adequate treatment, infants with severe CH may be at an elevated risk of poor cognitive development. It is speculated that low levels of hormone during prenatal development and during early days of life (before treatment initiation) contribute to some irreversible damage. Within the group of patients with severe CH, long-term outcomes may also depend on social variables. There is evidence that CH patients with severe CH are at a risk of poorer cognitive outcomes (as compared to their peers with severe CH) if they belong to families with low socioeconomic status. Risk of late entry into sixth grade among CH patients was reportedly higher for students who had adverse social and family circumstances.[46-52] Disease severity should be taken into consideration when evaluating clinical outcomes associated with timely treatment, initial dosage of L-thyroxine, and serum hormone levels.

Timely treatment coupled with the recommended dosage of L-thyroxine is supported by numerous studies. The dosage that is most commonly recommended is from 10–15 µg/kg/day. Many researchers advocate timely treatment, but early treatment with inadequate dosage may not be sufficient for optimal outcomes. Studies show that infants treated early have the potential of achieving normal or near normal neurocognitive outcomes. CH is known to affect many aspects of IQ. Timely treatment results in significant improvements in verbal performance and global IQ scores. Even when infants were on thyroxin treatment within the first few weeks of life, outcomes were less than ideal if the dosage of the drug was not optimal. Conversely, normal IQ was observed in patients with severe CH at diagnosis if they had received 10–15 µg/kg dose of T4. Initial dose of T4 is also correlated with co-morbidities like hearing loss, poor intellectual development, and poor psychosocial outcomes.[48-61]

Prolonged periods with low levels of thyroid hormones can also be detrimental to the cognitive development. With prompt normalization of thyroid hormone levels, neurocognitive outcomes like visual memory, attention, and arithmetic may all improve.[58, 62, 63]

While timely and appropriate treatment is very important for the true cases of CH, thyroid hormone replacement treatment may be unnecessary for those who have only the transient form of the disease.[64] If a patient has low thyroid hormone level but has an otherwise well developed thyroid gland at birth, he/she may be experiencing a transient deficiency in hormone levels. After the critical period of early childhood is over, the need for continued therapy may have to be re-evaluated. Unnecessary treatment or over treatment with thyroid hormone supplements may result in behavioral problems.[64, 65]

9.11 Conclusion

CH has long been recognized as a treatable condition (subject to initial disease severity) where timely and adequate treatment can have a dramatic impact on long–term patient outcomes. Successful disease management depends on several interdependent treatment variables. Some of these variables are within the control of the healthcare provider while others, like disease severity, are harder for care providers to impact. Maintaining serum TSH, T4, and FT4 levels within the normal range should be an important goal of therapy. This goal can be achieved by careful and periodic monitoring of physiological levels of these hormones. While experts agree that laboratory values are a good surrogate marker for treatment compliance, patient's growth and cognition should be the ultimate consideration. Treatment can often be complicated by factors such as the socio-economic variables. Parent education on treatment compliance and the

importance of periodic laboratory evaluations can address this issue to some extent. Unnecessary treatment to those affected by the transient form can be avoided if detailed evaluation is conducted when the patient turns 3 years of age.

9.12 Limitations

Evidence provided by some of the older studies was not exactly consistent with the findings of some of the newer studies. Treatment variables that have been the subject of more recent literature were included in the review. Long-term outcomes in CH are almost always subject to disease severity at the time of diagnosis. Abundant evidence in the literature supports the impact of disease severity on patient outcomes in CH. Patients with severe CH have been shown to perform poorly on cognitive assessments despite having received timely and adequate treatment. However, because there is little control over severity at the time of diagnosis, it was not possible to develop a performance measure based on severity alone. For data analysis purposes, disease severity is an important consideration, especially while establishing correlation between treatment variables and outcomes.

10 Evidence Supporting Candidate Measures for Congenital Hypothyroidism

10.1 Time to Initiate Treatment for CH

Time to Initiate Treatment for CH		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Dimitropoulos A, et al. (2009)[54] Type of Study – Prospective study to assess long-term intellectual outcomes in CH patients. All patients had received early treatment with high dose of levothyroxine. Location – Zurich, Switzerland	N = 63 children with CH; type of CH not specified; 49 females, 14 males; born between 1978 and 1991; aged 14 years	Wechsler Intelligence Scale scores were compared with 175 children from the control group. On an average, CH patients received 14.7 µg/kg/day (range 9.9–23.6 µg/kg/day). There was a significant correlation between lower initial dose of l-thyroxine (LT4) and IQ ($r=0.27$, $p<0.04$). There was also a significant interaction for socioeconomic status and IQ ($p=0.03$). In other words, the negative effect of low initial dose of LT4 was more pronounced in patients who belonged to families with poor socioeconomic status. However, treatment in early years of life did not guarantee good intellectual outcomes at age 14.
Reference – Kempers MJ, et al. (2007)[56] Type of Study – Cohort study to compare the effect of age at treatment initiation on cognitive and motor variables in 10 year old patients. Outcomes of CH patients receiving earlier treatment (median age 20 days) were compared with the outcomes of those who received slightly later treatment (median age 28 days). Location – Netherlands	N = 82 patients with thyroidal CH; 41 with severe form; 41 with mild and moderate form; median age of treatment initiation was 22 days (2–73 days). The average age of the study subjects was 10.5 years (9.6–11.4 years)	When the outcomes of 1992-93 cohort (median age at treatment initiation = 20 days) were compared with the outcomes of a 1981-82 cohort, (median age at treatment initiation = 28 days), there was no significant difference. Patients with severe CH were reported to have poor IQ on verbal, performance and full scale measures. Similar assessments in the mild CH group showed that their scores were comparable to those of the normative population. Therefore, earlier treatment initiation did not necessarily translate into better cognitive outcomes.

Time to Initiate Treatment for CH		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Kempers MJ, et al. (2006)[48] Type of Study – Cohort study of young adults with CH who were diagnosed via newborn screening. Primary objective of the study was to study the effect of disease severity and age at treatment initiation on cognitive and motor outcomes. Location – Netherlands	N = 70 patients with CH; 35 with severe form; 16 moderate form; and 19 with mild form; mean age was 21.5 years; median age at treatment was 28 days	Long-term cognitive outcome depends on the severity of CH. Severity of CH was based on an initial FT4 concentration where severe CH was described as an FT4 concentration of 0.3 ng/dl. Cognitive and motor deficits were prevalent among young adults with CH despite receiving early diagnosis and timely treatment. Both IQ and motor deficits correlated with severity of disease. Authors could not find a correlation between cognitive and motor outcomes and the timing of treatment. They acknowledged that time to treatment was closely related to the severity of the underlying disease and also that there was very little variation in the range of age at treatment initiation.
Reference – Oerbeck B, et al. (2003)[50] Type of Study – Case control study of individuals with CH followed from infancy to young adulthood (20 years) with a sibling control group. Among several objectives, the study looked at long-term outcomes and how they may be impacted by severity of hypothyroidism, and serum T4 levels during the first years of life. Location – Norway	N = 49 children with CH; 41 sibling control subjects, mean age at time of study was 20 years and 21 years respectively; mean age at diagnosis was 17.3 (± 8.3 days); age at start of treatment was 24.4 (± 29.2 days)	Early treatment variables studied included age at start of treatment, LT4 starting dose, and mean serum T4 values. Of these treatment variables, mean serum T4 values for children aged 1–2 years showed a significant correlation to verbal IQ, verbal fluency, reading abilities, and arithmetic. Serum T4 at diagnosis, a measure of the severity of hypothyroidism, showed to be correlated to motor performance particularly with the Finger tapping test. Age at start of treatment showed to have a low or moderate correlation between IQ, motor function, and school-associated performance. However, none of these correlations was reported as statistically significant. Neuropsychological outcome at 20 years of age was associated with both severity of hypothyroidism and early treatment variables. Multiple regression analysis was conducted to study the impact of background variables, CH severity, and CH treatment variables on intellectual and school associated outcomes. A significant amount of variance in verbal IQ was attributed to initial LT4 dose and mean serum T4 level in the second year of life. On the other hand, arithmetic ability in school-aged children was predicted by average serum T4 level in the second year of life.

Time to Initiate Treatment for CH		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Rovet J, Daneman D (2003)[58] Type of Study – Review article to investigate the impact of disease related factors (etiology and severity of CH) and treatment related factors (age at the time of treatment, initial dosage and compliance) on CH patient outcomes. Location – Not applicable	Not applicable	Review article that combined the findings of other authors with some of their own findings for various variables of treatment linked to outcomes. For "age at onset of therapy" as a treatment variable, a broad range of abilities such as visuomotor abilities and language skills was seen. For "starting dosage" as a treatment variable, patients receiving higher dosage tend to perform better but are also prone to mild abnormalities with social skills and attention span. For "time to achieve normalization" as a treatment variable, poor language skills, poor motor skills, and poor auditory skills were reported as more common among patients who took longer to achieve normal hormone levels.
Reference – Salerno M, et al.(2002)[59] Type of Study – Longitudinal study to examine the correlation between initial dosage of levothyroxine and growth and intellectual development in patients with CH. Location – Naples, Italy	N = 83 patients with CH; 20 with severe form; 20 males, 63 females, followed through 4 years of age,	Patients were divided into three groups based on their age at treatment and the initial dosage of LT4. Patients treated with a high dose of LT4 (13.4 µg/kg/day) by the age of 21 days (± 6 days) showed to have a FSIQ score significantly higher than the other two groups who received later treatment with lower dosage of LT4. FSIQ at age 4 had a positive correlation with starting dosage of LT4 ($r=0.27$, $p<0.02$) and negative correlation with age at treatment initiation ($r= -0.26$, $p < 0.02$). However, there was no significant difference in verbal IQ scores for each of the three groups. Further, groups receiving high dose achieved normal thyroid hormone levels in a month's time. Normalized hormone levels within three months of age predicted better intellectual outcome but only for patients who received high initial dose of LT4.
Reference – Leger J, et al. (2001)[57] Type of Study – Population-based cohort study to compare school achievement in CH patients with that in the national population. Factors that may contribute to poor school performance in CH patients were also investigated Location – France	N = 682 patients with CH with a known age for enrollment in 6th grade; with a treatment initiated at an age of less than 40 days	All the patients included in the study had received early treatment. The factors that were related to late entry into 6th grade were: disease severity; delayed bone maturation; poor compliance; poor socioeconomic status; having a mother with no professional activity; having a single mother; and having one of the parents as born out of France. However, as long as treatment was initiated within the first 40 days of life, there was no incremental risk of late entry into 6th grade.

Time to Initiate Treatment for CH		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Bongers-Schokking JJ, et al. (2000)[53] Type of Study – Cross sectional survey-based study to examine the effect of timing and initial dosage of treatment on cognitive outcomes in CH patients. Treatment variable data were obtained from past medical records Location – Netherlands	N = 61 patients with CH; 27 with severe form, 34 with mild CH; 19 male, 42 female; born between 1993 and 1996; mean age at testing was 21.7 ± 5.3 months.	A sample of 61 patients was separated into 4 groups depending on early versus late treatment (before or after 13 days of age) and on high or low initial dosage of Levothyroxine (less than 9.5 µg/kg/d or greater than or equal to 9.5 µg/kg/d). On an average, significantly lower mental development index (MDI) scores were reported for the patients with severe CH (as compared to the mild CH group). Severely affected patients who had received early treatment with high dosage of LT4 had an average MDI score of 124 ± 16, which was similar to the score for mild CH group as well as for the reference group. Developmental outcomes in both mild and severe cases of CH were similar to that of the reference group if the patients received early, high dose treatment. Late treatment with low dose of LT4 was associated with suboptimal development even when the patients had mild CH. Authors concluded that it is important to achieve normal thyroid levels by the 3rd week of life. Early treatment with a high dose of medication can be instrumental in achieving this goal.
Reference – Heyerdahl S, et al. (1997)[55] Type of Study – Longitudinal cohort study of patients with CH (described previously) to study the effect of treatment variables on linear growth Location – Norway, Sweden	N = 103 CH patients; 34 having a more severe CH; 49 from Norway born between 1979 and 1981, 67 from Sweden born from 1980 to 1982; 47 males, 56 females.	The correlation between growth and treatment variables such as mean serum T4 at various ages and the age at start of treatment was described in this study. Change in height (from birth) was correlated with these treatment variables: serum T4 at 1 year of age; Mean serum T4 from 1–2 years of age; Mean serum T4 from 2–4 years of age. In case of patients with severe CH (pretreatment serum T4 <40 nmol/L) there was a significant inverse correlation between initial dosage of LT4 and age at onset of childhood component of growth. This correlation was more enhanced in female patients. Initial dosage of LT4 was not significantly correlated with the onset of childhood component of growth in patients with less severe CH. A significant correlation was reported for age of treatment initiation and onset of childhood component of growth in less severe cases of CH.

Time to Initiate Treatment for CH		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Kooistra L, et al. (1994)[49] Type of Study – Case control study to examine the effect of etiology, disease severity, and age at the start of therapy on motor and cognitive outcomes in children with CH. Location – Netherlands	N = 72 children with permanent CH; mean age 7.9 years (range 7–8.75 years), born between 1981 and 1982	The comparison group consisted of 72 children (mean age 7.9 years range 7–8.75 years) with permanent CH diagnosed as a result of newborn screening. The control group included 35 healthy children who were comparable to the patient group in terms of their age, sex, and socioeconomic variables. Patients were grouped by the level of initial T4 levels. There were 48 patients with low t4 levels at the time of screening (T4<50 nmol/L, mean 25 nmol/L; range 0–49 nmol/L). There were 23 patients with intermediate T4 at the time of diagnosis (T4 ≥50 nmol/L; mean 86 nmol/L; range 51–140 nmol/L). It was reported that at the time of the study, the total and verbal intelligence scores were significantly lower for the low T4 group as compared to the control group. Scores for fine motor assessments were significantly lower among the intermediate T4 patients as compared to the control group. Time to treatment and its impact on motor and intelligence scores was also studied. In patients identified with thyroid agenesis (mean T 4 level 19 nmol/L; average age of treatment initiation 23 days), time to therapy was significantly correlated with test of motor intelligence (TOMI) scores at age 7.5 years (r=0.45; p=0.03). For the same group of patients, the Wechsler intelligence scale for children – revised (WSIC) performance IQ was also significantly related to the time to therapy (r= -0.34; p = 0.004).
Reference – Tillotson SL, et al. (1994)[52] Type of Study – Case-control study to examine the relationship between early treatment and intellectual outcomes in of CH patients Location – England, Wales, Northern Ireland	N = 361 children with CH; 198 with the more severe form of disease; born between 1982 and 1984; age at time of testing was 5 years.	Early diagnosis and treatment may reduce, but does not eliminate, neurological damage for affected children with CH at age 5. IQ was not influenced by early treatment measures including age at start of treatment (1–173 days), average T4 dose (12.76 mug in the first year), average T4 concentration during treatment (79–234 nmol/L in the first year), and T4 concentration less than 103 nmol/L at least once during the first year influenced IQ at age 5. However, higher initial T4 values and non-manual class were significantly associated with higher IQs. The data showed that children were divided into two distinct groups by severity of disease; those with plasma T4 concentrations of less than 42.8 nmol/L at diagnosis who showed a global deficit in mean IQ of 10 points and those with less severe hypothyroidism who showed no deficit.

10.2 Initial Dosage of L-Thyroxine

Initial Dosage of L-Thyroxine		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Dimitropoulos A, et al. (2009)[54] Type of Study – Prospective study to determine predictors of long-term intellectual outcome in adolescents with early high-dose treated congenital hypothyroidism Location – Zurich, Switzerland	N = 63 children with CH; type of CH not specified; 49 females, 14 males; born between 1978 and 1991; aged 14 years	WIS scores were compared with 175 children from the control group. On an average, CH patients received 14.7 µg/kg/day (range 9.9–23.6 µg/kg/day). There was a significant correlation between lower initial dose of LT4 and IQ ($r=0.27$, $p<0.04$). There was also a significant interaction for socioeconomic status and IQ ($p=0.03$). In other words, the negative effect of low initial dose of LT4 was more pronounced in patients who belonged to families with poor socioeconomic status. However, treatment in early years of life did not guarantee good intellectual outcomes at age 14.
Reference – Bongers-Schokking JJ, de Muinck Keizer-Schrama SM (2005)[47] Type of Study – Case study to evaluate the impact of initial and post-initial treatment factors on cognitive, psychomotor, and psychological parameters in children with CH Location – Netherlands	N = 45 patients with CH, 19 with severe CH and 26 with mild CH; Patients were from the ages of 5.5–7 years born between 1993 and 1996; control group of 37	The authors observed verbal, visuomotor, and attention deficits in CH patients. It was noted that while insufficient early treatment can influence early developmental measures, it does not affect IQ and visuomotor scores of children at ages 5–7. Mild over treatment (high dosage of LT4), on the other hand can potentially lead to higher-than normal IQ, which also can be problematic in the long run. Prolonged exposure to high concentrations of thyroid hormones can cause abnormalities in neuronal development and consequently lead to behavior problems. Therefore, it is important to keep the thyroid levels within the normal range by avoiding over- and under-treatment.

Initial Dosage of L-Thyroxine		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Selva KA, et al. (2005)[60] Type of Study – Case control study to compare neuro developmental outcomes in patients with varying L-thyroxine dosage and with varying degrees of disease severity, varying L-thyroxine dosage and by disease severity Location – USA	N = 31 patients with CH; 13 with severe form, 18 with moderate form; age range from 21 months to 8 years, 1 month	Various types of neurodevelopmental assessments (for cognition, academic achievement, and attention/behavior) were conducted on a group of 31 subjects with CH. Patients were divided in three treatment groups: Group 1: 10.9 µg/kg/day; Group 2: 14.5 µg/kg/day; and Group 3: 17.7 µg/kg/day for three days. At the end of three days, each group was placed on an L-Thryroxine dosage of 10.6 µg/kg/day. It was reported that subjects who received a low dose had a FSIQ score that was 11 points lower than those who received a high dose (14.5 µg/kg/day). The three treatment groups did not differ much on verbal and performance IQ scores. It was also reported that disease severity played an important role in cognitive outcomes. Patients with severe CH, despite receiving high treatment dose had lower FSIQ when compared with the ones with moderate form of the disease. When compared on time to achievement of normal thyroid function, patients who attained normal function in the first week of life had normal FSIQ scores (100 points). Those who took 2 weeks to attain normal thyroid levels had significantly lower FSIQ scores (79.75 points, $p<0.05$).

Initial Dosage of L-Thyroxine		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Oerbeck B, et al. (2003)[50] Type of Study – Case control study of individuals with CH followed from infancy to young adulthood (20 years) with a sibling control group. Among several objectives, the study looked at long-term outcome and how they may be impacted by severity of hypothyroidism, and serum T4 levels during the first years of life. Location – Norway	N = 49 children with CH; 41 sibling control subjects, mean age at time of study was 20 years and 21 years respectively; mean age at diagnosis was 17.3 (± 8.3 days); age at start of treatment was 24.4 (± 29.2 days)	Early treatment variables studied included age at start of treatment, LT4 starting dose, and mean serum T4 values. Of these treatment variables, mean serum T4 values for children aged 1–2 years showed a significant correlation to verbal IQ, verbal fluency, reading abilities, and arithmetic. Serum T4 at diagnosis, a measure of the severity of hypothyroidism, showed to be correlated to motor performance particularly with the Finger tapping test. Age at start of treatment showed to have a low or moderate correlation between IQ, motor function, and school-associated performance. However, none of these correlations were reported as statistically significant. Neuropsychological outcome at 20 years of age was associated with both severity of hypothyroidism and early treatment variables. Multiple regression analysis was conducted to study the impact of background variables, CH severity, and CH treatment variables on intellectual and school associated outcomes. A significant amount of variance in verbal IQ was attributed to initial LT4 dose and mean serum T4 level in the second year of life. On the other hand, arithmetic ability in school-aged children was predicted by average serum T4 level in the second year of life.
Reference – Rovet J, Daneman D (2003)[58] Type of Study – Review article to investigate the impact of disease related factors (etiology and severity of CH) and treatment related factors (age at the time of treatment, initial dosage and compliance) on CH patient outcomes. Location – Not applicable	Not applicable	Review article that combined the findings of other authors with some of their own findings for various variables of treatment linked to outcomes. For "age at onset of therapy" as a treatment variable, a broad range of abilities such as visuomotor abilities and language skills was seen. For "starting dosage" as a treatment variable, patients receiving higher dosage tend to perform better but are also prone to mild abnormalities with social skills and attention span. For "time to achieve normalization" as a treatment variable poor language skills, poor motor skills, and poor auditory skills were reported as more common among patients who took longer to achieve normal hormone levels.

Initial Dosage of L-Thyroxine		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Salerno M, et al. (2002)[59] Type of Study – Longitudinal cohort study to examine the growth and intellectual outcome measures were affected by LT4 dosage and the age at time of treatment initiation Location – Naples, Italy	N = 83 patients with CH; 20 with severe form; 20 males, 63 females, followed through 4 years of age	A sample of 83 four-year-old patients with CH was evaluated for longitudinal growth and intellectual outcomes and whether these measures were affected by LT4 dosage and the age at treatment initiation. Patients were divided into three groups based on their age at treatment and the initial dosage of LT4. Results showed that for patients treated with a high dose of LT4 (13.4 µg/kg/day) by the age of 21 days, (± 6 days), FSIQ was significantly higher than the other two groups who received later treatment with lower dosage of LT4. FSIQ at age 4 had a positive correlation with starting dosage of LT4 ($r=0.27$, $p<0.02$) and negative correlation with age at treatment initiation ($r= -0.26$, $p < 0.02$). However, there was no significant difference in verbal IQ scores for each of the three groups. Further, groups receiving high dose achieved normal thyroid hormone levels in a month's time. Normalized hormone levels within three months of age predicted better intellectual outcome but only for patients who received high initial dose of LT4.
Reference – Bongers-Schokking JJ, et al. (2000)[53] Type of Study – Cross sectional survey-based study to examine the effect of timing and initial dosage of treatment on cognitive outcomes in CH patients. Treatment variable data were obtained from past medical records Location – Netherlands	N = 61 patients with CH; 27 with severe form, 34 with mild CH; 19 male, 42 female; born between 1993 and 1996; mean age at testing was 21.7 ± 5.3 months	A sample of 61 patients was separated into 4 groups depending on early versus late treatment (before or after 13 days of age) and on high or low initial dosage of Levothyroxine (less than 9.5 µg/kg/d or greater than or equal to 9.5 µg/kg/d). Twenty-seven of the 61 patients had severe CH. On an average, significantly lower MDI scores were reported for the patients with severe CH (as compared to the mild CH group). Severely affected patients who had received early treatment with high dosage of LT4 had an average MDI score of 124 ± 16 which was similar to the score for mild CH group as well as for the reference group. Developmental outcomes in both mild and severe cases of CH were similar to that of the reference group if the patients received early, high dose treatment. Late treatment with low dose of LT4 was associated with suboptimal development even when the patients had mild CH. Authors concluded that it is important to achieve normal thyroid levels by the 3rd week of life. Early treatment with a high dose of medication can be instrumental in achieving this goal.

Initial Dosage of L-Thyroxine		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Van Vliet G (1999)[61] Type of Study – Review article to describe findings on disease severity and outcomes; treatment factors and patient outcomes; and the potential side effects of high dose treatment with L-Thyroxine in CH patients. Location – Not applicable	Not applicable	This review article highlights the importance of appropriate dosage of LT4 in CH patients. Early treatment with high dose of LT4 (10–15 µg/kg/day) is recommended by many researchers and also by the AAP. Inadequate treatment is associated with high concentrations of plasma TSH. Elevated plasma TSH over a period of time may be associated with delayed bone maturation and poor developmental outcomes. It is also noted that over treatment with LT4 has potential side effects like behavioral problems. Disease severity is also reported as a crucial risk factor for negative outcomes in the long run.
Reference – Heyerdahl S, et al. (1997)[55] Type of Study – Longitudinal cohort study of patients with CH to study the effect of treatment variables on linear growth Location – Norway (1979 to 1982); Sweden (7/1980 to 6/1982)	N = 103 CH patients, 47 males, 56 females	The correlation between many of the treatment variables and growth was demonstrated in this study. Change in height (from birth) was correlated with these treatment variables: serum T4 at 1 year of age; Mean serum T4 from 1–2 years of age; Mean serum T4 from 2–4 years of age. In case of patients with severe CH (pretreatment serum T4 <40 nmol/L), there was a significant inverse correlation between initial dosage of LT4 and age at onset of childhood component of growth. This correlation was more enhanced in female patients. Initial dosage of LT4 was not significantly correlated with the onset of childhood component of growth in patients with less severe CH. A significant correlation was reported for age of treatment initiation and onset of childhood component of growth in less severe cases of CH.

Initial Dosage of L-Thyroxine		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Tillotson SL, et al. (1994)[52] Type of Study – Case-control study to examine the relationship between early treatment and intellectual outcomes in CH patients Location – England, Wales, Northern Ireland	N = 361 children with CH; 198 with the more severe form of disease; born between 1982 and 1984; age at time of testing was 5 years.	Early diagnosis and treatment may reduce, but does not eliminate neurological damage for affected children with CH at age 5. IQ was not influenced by early treatment measures including age at start of treatment (1–173 days), average T4 dose (12.76 mug in the first year), average T4 concentration during treatment (79–234 nmol/l in the first year), and T4 concentration less than 103 nmol/L at least once during the first year influenced IQ at age 5. However, higher initial T4 values and non-manual class were significantly associated with higher IQs. The data showed that children were divided into two distinct groups by severity of disease; those with plasma T4 concentrations of less than 42.8 nmol/l at diagnosis who showed a global deficit in mean IQ of 10 points, and those with less severe hypothyroidism who showed no deficit.

10.3 Normalization of TSH, T4, and FT4 Concentration within One Month of Treatment

Normalization of TSH, T4, and FT4 Concentration within One Month of Treatment		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Heyerdahl S, Oerbeck B (2003)[62] Type of Study – Review article to compare outcomes in CH patients with outcomes in control group. Similar comparisons were also made between severe and mild cases of CH. The correlation between treatment variables and developmental outcomes was also reported. Location – Not applicable	Not applicable	This review discusses the association between levothyroxine treatment variables and developmental outcomes. Disease management of CH using higher initial dosage of LT4 was supported by this review. Authors also noted the lack of sufficient long-term data that study the negative effects of treatment with high dose of LT4. Based on the information available at the time of the review, it is suggested an association between high dose treatment and behavior problems. The authors also emphasized the need for good quality multi-center studies.

Normalization of TSH, T4, and FT4 Concentration within One Month of Treatment		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Rovet J, Daneman D (2003)[58] Type of Study – Review article to investigate clinical outcomes of CH patients who were diagnosed by screening and were treated early Location – Not applicable	Not applicable	This review article combined the findings of other authors with some of their own findings for various variables of treatment linked to outcomes. For "age at onset of therapy" as a treatment variable, a broad range of abilities such as visuomotor abilities and language skills was seen. For "starting dosage" as a treatment variable, patients receiving higher dosage tend to perform better but are also prone to mild abnormalities with social skills and attention span. For "time to achieve normalization" as a treatment variable, poor language skills, poor motor skills, and poor auditory skills were reported as more common among patients who took longer to achieve normal hormone levels.
Reference – Ilicki A, Larsson A (1991)[63] Type of Study – Case control study to evaluate psychological development of children with permanent CH Location – Sweden	N = 60 children with permanent CH; tests performed at ages 6.5–7.5 years; two age groups evaluated 78–83 months and 84–89 months of age; sexes analyzed separately because the female control group scored significantly higher than male control group	There were 68 patients in this study who were evaluated for their psychological development at age 6.5–7.5 years using Griffith's test. This study results disagree with the findings of some other studies. It is reported that delayed normalization of serum TSH levels does not necessarily predict poor psychological outcomes in school age children with CH. Thirteen patients with delayed normalization of TSH had Griffith's scores that were comparable to the reference population. The need for early treatment was emphasized, and the ideal replacement dosage of LT4 was recommended at 6–11 µg/kg/day.

10.4 Evaluation for Transient CH by Age 4

Evaluation for Transient CH by Age 4		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Yang RL, et al. (2005)[65] Type of Study – Prospective study to determine treatment needs of children aged 2–3 years with suspected transient CH Location – China	N = 57 patients with transient CH; 34 males, 23 females	This study advocates lower dose of CH especially for patients with transient CH. Patients in the study were on a LT4 dose of 3.21–5.81 µg/kg/day. Treatment was provided for an average of 28.09 months (± 9.56 months). Treatment was discontinued after 2–3 years when the patients showed normal thyroid function and normal physical and mental growth.

Evaluation for Transient CH by Age 4		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Eugster EA, et al. (2004)[64] Type of Study – Prospective study to determine treatment needs of children older than 3 years with suspected transient CH Location – USA	N = 33 children with CH; 17 males, 16 females	Children participating in this study were at least 3 years of age. Children with an anatomically normal thyroid gland, those with historically mild biochemical abnormalities (even with a diagnosis of severe CH), and those without a prior thyroid imaging study were included in this study. If a cause for permanent CH (such as an absent or ectopic thyroid gland) was already established, the patient was not included in this study. It was reported that 12/33 (36%) of the patients were able to maintain normal thyroid hormone levels even after the withdrawal of therapy. Therefore, these patients had the transient form of the disease. Authors recommended that a standardized protocol should be established so that patients experiencing transient CH can be assessed and unnecessary medication can be avoided, especially beyond the period of early childhood.

11 Summary of Literature on Proposed Performance Measures for Maple Syrup Urine Disease

11.1 Introduction to Maple Syrup Urine Disease

Maple Syrup Urine Disease (MSUD) is an autosomal recessive disorder characterized by the inability to metabolize branched chain keto-acids, due to a deficiency of branched-chain alpha-ketoacid dehydrogenase complex (BCKAD). The impaired branched-chain keto-acid metabolism results in a secondary elevation of corresponding branched-chain amino acids (BCAAs). The amino acids leucine, isoleucine, alloisoleucine, and valine are included in BCAAs. Infants affected by the severe form of this disease become symptomatic soon after birth and can suffer rapid deterioration within the first week or ten days of life. A maple syrup odor in the cerumen (secretions from the ear) and in the urine is the hallmark of this disease. Other presenting symptoms include poor feeding, lethargy, intermittent apnea (lack of breathing), opisthotonus (arching of back with spasms), ketonuria (presence of ketone bodies in urine), and signs of deepening encephalopathy including stereotype movements such as fencing and bicycling.[66]

11.2 Nomenclature and Disease Variants for Maple Syrup Urine Disease[66]

The nomenclature and disease variants for MSUD follow.

- **Classical**—This form of the disease presents in the neonatal period. Activity of the enzyme BCKAD is typically less than 3% of unaffected individuals. Biochemical signs include elevated BCAAs in plasma, elevated plasma allo-isoleucine, and elevated branched chain keto acids in urine.
- **Intermediate**—The age of disease onset is variable. Enzyme activity may be between 3% and 30%. Biochemical features are similar but less severe as compared to the classic form.
- **Intermittent**—The onset of intermittent MSUD may also be variable. Typically, the patient has normal levels of BCAAs. During an illness, BCAA levels may become elevated and therefore look similar to that of a patient with classic MSUD.
- **Thiamine responsive**—Clinical features of this type of MSUD are similar to that of the intermittent form; however, when treated with thiamine, patients show a positive response. Their laboratory values of BCAAs improve, and they also exhibit greater tolerance for leucine.

11.3 Incidence and Screening for Maple Syrup Urine Disease

The national incidence of MSUD is reported as less than 1 in 185,000.[3] Incidence is much higher (1 in 200 – 400) in the Mennonite populations of Pennsylvania, Kentucky, New York, Indiana, Wisconsin, Michigan, Iowa, and Missouri.[67]

Newborn screening for MSUD began in Texas in late 2006 with the expansion of the testing panel from 7 to 27 disorders. In 2007, approximately 80 specimens were identified as presumptive positives for this condition. From the presumptive positives, one infant was

diagnosed with classical MSUD. Based on the national estimates, it was expected that 2 to 3 cases of MSUD would be diagnosed in Texas each year. Based on these numbers, the incidence of classical MSUD in Texas for 2007 is estimated as 1 in 414,000[i]. It is expected that over time the incidence will be closer to the national average.

11.4 Laboratory Testing, Follow-up, and Diagnosis for Maple Syrup Urine Disease

TNSP currently screens for MSUD using MS/MS. MS/MS screening detects elevated concentrations of amino acids and also evaluates their relationship with each other. These measurements provide analyte concentration profiles that can aid in the detection of several metabolic disorders. Confirmatory testing includes plasma quantitative amino acids analysis for elevations of leucine, isoleucine, alloleucine, and valine and urine organic acids analysis for abnormal branched-chain hydroxyl- and ketoacids.

For infants with presumptive positive results, TNSP immediately contacts the PCP or the attending physician to suggest a follow-up protocol. TNSP continues to track or follow the clinical status of the infant until diagnosis or until the infant is confirmed not to have the condition.

11.5 Disease Characteristics and Suggested Treatment[66]

The following elaborates on commonly encountered disease characteristics of patients with MSUD.

- **Metabolic Decompensation**—Metabolic decomposition is characterized by lethargy, behavior changes, emesis (vomiting), and loss of cognitive function that may be triggered by an infectious illness.
- **Developmental Delay**—Developmental delay is characterized by failure to meet developmental milestones, poor physical growth.
- **Coma and Central Respiratory Failure**—Coma and central respiratory failure are characterized by episodes of altered consciousness with inadequate respiratory effort.
- **Anxiety and Depression**—Anxiety and depression are characterized by feelings of sadness, irritability, and inability to cope with stress.

Management of MSUD is multi-faceted. Chronic care involves the regular use of a diet that is low in BCAAs. Acute care may employ: nutritional restriction of BCAAs; adequate caloric intake to promote anabolism; hemodialysis; intensive care therapy; and, rarely, liver transplantation.

11.6 Objectives of the Literature Review

This review focuses on classical MSUD only. The main objective is to describe findings from the literature on some critical aspects of MSUD treatment (especially in regard to timeliness of treatment) and their impact on patient outcomes. In addition, the review is also intended to provide a general understanding of the disease characteristics and treatment options. Evidence from the literature will be used to provide support to the proposed performance measures.

Candidate measures may potentially be piloted in the third year of the TNSPMP which begins in September 2009.

11.7 Candidate Performance Measures for Maple Syrup Urine Disease

The candidate performance measures listed below are general. If considered for piloting in the third year of the project, these working conceptual definitions will be further developed and refined into clearly defined terms.

- **Time to initiate treatment**
  Measuring the time it takes from birth to begin treatment for an infant with MSUD.
- **Time to reduce plasma leucine concentration levels**
  Measuring the time from birth to reduce plasma leucine concentration to normal levels in newborns with MSUD.
- **Mean annual leucine levels for long-term metabolic control**
  Monitoring mean leucine levels in patients with MSUD through the age of 4 years. TNSP follows patients with MSUD through 4 years of age.

11.8 Methodology

The literature review was undertaken to synthesize the body of knowledge surrounding associations between timing of treatment and clinical outcomes of patients with MSUD.

11.8.1 Keywords

Prominent scientific databases were searched for relevant articles. Various combinations of the following key words were used for the literature search: MSUD, maple syrup urine disease, time to treatment, and time to diagnosis.

11.8.2 Inclusion/Exclusion Criteria

Only the articles written in the English language were considered.

11.9 Results

The tables in the next section provide a list of these performance measures along with a synopsis of specific studies from the literature that lend evidence in support of each performance measure.

11.10 Discussion

Prompt diagnosis and treatment are critical in MSUD management. Due to rapid deterioration within the first few days of life, any delay in treatment can result in irreparable neurological and intellectual damage or death. In certain ethnic populations with a high incidence (Mennonite populations), physicians have been able to identify high-risk newborns based on their family history and other pre-disposing factors. When such newborns were placed on treatment on the first day of life, their overall prognosis was very good. With prompt intervention, the incidence of seizures and metabolic decompensation was small in this group.[67] Many researchers have demonstrated either a direct correlation or a suggestive trend between developmental progress and time to diagnosis.[68-71] Snyderman et al. suggest initiating treatment by 10 days of age since normal IQ was observed only in patients diagnosed prior to this age.[71] An increased incidence of long-term neurological abnormalities is also associated with delayed treatment initiation.[67-71]

Yoshino et al. reported poor neurological outcomes for patients who had experienced either a pretreatment leucine level of >40mg/dl or a period of altered level of alertness that lasted longer than 10 days.[72]

A number of studies report their findings on time to reduce plasma leucine concentrations.[68, 70-74] At least one study reports a statistically significant correlation between IQ and the period after birth for which leucine level was elevated.[68] In general, it seems that prolonged exposure to high levels of plasma leucine is a predictor of poor cognitive outcome. One of the studies did not find an association between cognitive outcome and the time to reduce plasma leucine levels. Patients in this study did not do well intellectually or neurologically. It is important to note, however, that this study was conducted before newborn screening of MSUD was routinely conducted. Patients in this particular study had extremely high initial leucine levels (ranging from 2400 to 6400 umol/L). Patients in the Kaplan study, in contrast, were diagnosed via screening. The initial plasma leucine levels in these study subjects were much lower (ranging from 250 to 5300 umol/L). Findings of this study showed a significant association between cognitive function and time to reduce plasma leucine levels. It is likely that earlier diagnosis and treatment may be helpful in preventing the able to accumulation of plasma leucine to extremely high levels.

Several studies support monitoring of mean annual leucine levels in the neonatal period through the first few years of life.[68, 73, 75] Study designs varied on the frequency of monitoring mean annual leucine levels depending on the age of the child, yet each had similar outcomes. Leucine levels within the low range (189 ± 82 μ, mol/L) are known to predict better developmental outcomes.[75] It is especially important to maintain leucine levels within the normal range during childhood. For every 100 μmol/L increase in plasma leucine level, a corresponding decrease of 10 points in IQ may be seen.[68, 75]

11.11 Conclusion

The prognosis for classical MSUD, which was once considered a deadly metabolic disorder, has improved in recent years. Research on populations with high incidence of MSUD has greatly contributed to the understanding of disease progression and long-term outcomes. Based on the evidence presented in the literature, there is a consensus that early diagnosis and treatment prompt restoration of normal plasma leucine levels, and monitoring mean annual leucine levels are of strong interest for MSUD disease management. Performance measures based on these parameters can provide valuable insights into quality of care for MSUD patients.

11.12 Limitations

Prominent studies on MSUD have been conducted at a single clinic in Pennsylvania.[67] This clinic receives a lot of MSUD cases from the Amish community. Healthcare providers in this clinic have been able to identify MSUD cases based on prior family history, and the time to treatment has been very short. This has been possible, in part, because of the concentrated clinical expertise and the relatively large volume of MSUD patients seen at this clinic. The findings of such studies may not be applicable to Texas where the incidence of MSUD is not as high. Some of the studies included in this review do not specify the exact length of time taken to normalize plasma leucine levels from a specified time (i.e., from birth and from diagnosis). Thus, it is not clear how long the infants were exposed to elevated levels of leucine. Prolonged

exposure to elevated levels of leucine can be a significant predictor of long-term outcomes in MSUD.

12 Evidence Supporting Candidate Measures for Maple Syrup Urine Disease

12.1 Time To Initiate Treatment for MSUD

Time To Initiate Treatment for MSUD		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – le Roux C, et al. (2006)[69] Type of Study – Retrospective cohort study of adults with MSUD to examine time to diagnosis as a predictor of intelligence quotient Location – UK	N = 14 adults with MSUD; 11 with classical form, 3 with intermediate form; age at mental evaluation ranged from 20–43 years	Intelligence quotient (IQ) was higher for adult patients with classical MSUD who were diagnosed earlier (r=+0.75, p=0.08). Nine patients of whom 6 had the classical form underwent mental evaluation. The mean age at diagnosis for the classical group was 10.5 days ranging from 5–21 days. The mean performance IQ for the classical group was 75.7 (range 54–108) and mean verbal IQ was 75.6 (range 55–102). Other classical MSUD patients were not tested because they were too neurologically damaged to conduct IQ tests. Patients diagnosed less than 9 days had better outcomes: performance IQ from 74–108 and verbal IQ from 78–102. In contrast, patients diagnosed between 14 and 21 days had poorer intellectual outcome: performance IQ of 55–68 and verbal IQ from 54–57.
Reference – Morton DH, et al. (2002)[67] Type of Study – Retrospective cohort study of patients with classical MSUD to evaluate the outcome of patients where a specific treatment protocol was utilized. The protocol approach utilizes protein anabolism and dietary correction of imbalances in plasma amino acids rather than removal of leucine by dialysis or hemofiltration. Location – Pennsylvania, USA	N = 36 patients with classical MSUD; 18 of 36 patients were at high-risk; 30 of 36 patients were diagnosed, treated, and followed in a single clinic.	Patients diagnosed earlier experienced fewer neurological complications than those diagnosed later. Age at diagnosis ranged from 1–16 days. High-risk MSUD patients diagnosed on day 1 (n=18) did not develop seizures, and only 1 of the 18 high-risk patients suffered from lethargy, poor feeding, and dystonia. Non high-risk MSUD patients who were diagnosed between 3 and 16 days (n=12) were lethargic and irritable at diagnosis. Of the twelve, 11 had dystonia, and 2 had seizures.

Time To Initiate Treatment for MSUD		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Nord A, et al. (1991)[70] Type of Study – Longitudinal cohort study of patients with classical MSUD to review developmental patterns. Patients were given dietary treatments to maintain plasma leucine levels between 100 and 400 umol/L. Location – Denver, Colorado, USA	N = 9 patients with classical MSUD (one possible variant); age at mental evaluation ranged from 6–15 years	The study reported that earlier diagnosis is associated with a less severe neonatal course, and the severity of neonatal course is linked with IQ and required special education. For this study, the severity of neonatal course was classified as asymptomatic, mild, moderate, or severe where the severity level was defined on clinical variables including lethargy, feeding difficulties, muscle tone, need for intravenous therapy, neurological status, need for dialysis, and ventilator assistance. Patients classified under the asymptomatic/mild severity had a median Verbal IQ of 96, mean performance IQ of 77, and a mean FSIQ of 87. While patients classified as moderate/severe had a median verbal IQ of 74, performance IQ of 63, and mean FSIQ of 69. Three of the 4 children classified in the asymptomatic/mild neonatal course group required no or a few years of special education, while the remaining 5 patients in the moderate/severe groups required special education throughout their school years.
Reference – Kaplan P, et al. (1991)[68] Type of Study – Prospective cohort study of MSUD patients comparing the intellectual outcome of children diagnosed after the onset of symptoms from the children diagnosed before the onset of symptoms Location – Lancaster County, Pennsylvania, USA	N = 16 patients with MSUD; 13 with classical form, 3 with variant form; 8 of the 16 patients from the Mennonite community; age at mental evaluation ranged from 1.1–8.1 years	Early and diligent treatment can result in normal intellectual outcomes. Mean age at diagnosis was 25 days ranging from 1–240 days. Children with normal IQ scores were diagnosed at a mean age of 3.5 ± 3 days and within 8 days of birth. Children with below normal IQ were diagnosed at mean age of 10 ± 4 days. The mean IQ score of the five children whose MSUD was treated within 5 days was significantly higher than those diagnosed at 6 days or later. The study also statistically shows using multiple regression analysis that the age at diagnosis along with long-term leucine concentrations are statistically significant predictors of IQ ($p<0.05$).

Time To Initiate Treatment for MSUD		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Snyderman SE (1988)[71] Type of Study – Retrospective cohort study of MSUD patients to evaluate age of diagnosis on treatment outcome Location – New York, USA	N = 18 patients with MSUD; forms of MSUD were not specified; age at mental evaluation ranged from 0.8–28 years	The study reported a relationship between age at diagnosis and IQ. Author stresses early diagnosis and treatment before 10 days of age to prevent mental impairment. Age at diagnosis ranged from 0.75–52 days. Patients diagnosed before 13 days of life had an IQ ranging from 95–130. In contrast, patients diagnosed from 16–52 days of life had an IQ ranging from 40–68. No neurological abnormalities were noted for 13 of the 18 patients that were diagnosed at 17 days of life or less. One patient died at age 13 from a relapse caused by a common illness.

12.2 Time to Reduce Plasma Leucine Concentration Levels for MSUD

Time to Reduce Plasma Leucine Concentration Levels for MSUD		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Yoshino M, et al. (1999)[72] Type of Study – Prospective study to investigate therapeutic measures to control episodes of metabolic decompensation in MSUD and the factors that may affect outcome. 13 of 42 patients with complete medical records responded to survey. Deaths from metabolic decompensation were not included in the study. Location – Japan	N = 13 surviving patients; 2 with classic form, 4 with intermediate form, 6 with intermittent form, and 1 with thiamine-responsive type disease; aged 2–17 years at time of survey. Response rate from survey was 33% from 42 total patients.	Asymptomatic patients who are treated have a better neurological outcome than those who develop signs of the disease during the neonatal period. Each patient with a plasma leucine level greater than 40 mg/100mL before the initiation of treatment or experiencing altered level of alertness longer than 10 days had some neurological sequelae. The authors recommended improving neurological outcome of MSUD patients by shortening the duration of altered level of alertness and by reducing plasma leucine concentrations as much as possible. Post-natal time period that plasma remained elevated is not specified.
Reference – Hilliges C, et al. (1993)[73] Type of Study – Prospective cohort study comparing intellectual performance of MSUD patients with PKU patients and normal subjects (controls) Location – Germany	N = 22 patients with MSUD; 16 with classical form, 3 with severe variant form, 3 mild variant form; age at time of mental evaluation ranged from 3–16 years	The mean IQ score of the MSUD patients was far below the lower limit of normal intelligence. The study shows an inverse correlation between IQ of patients and the post-natal time period in which patient's leucine levels were greater than 1 mmol/L. Duration of elevated levels ranged from 1–67 days. (r=0.57: P=0.019 for all MSUD patients, and r=0.51: P=0.049 for classical MSUD patients.) Post-natal time period that plasma remained elevated is not specified.

Time to Reduce Plasma Leucine Concentration Levels for MSUD		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Nord A, et al. (1991)[70] Type of Study – Longitudinal cohort study of patients with classical MSUD to review developmental patterns. Patients were given dietary treatments to maintain plasma leucine levels between 100 and 400 umol/L. Location – Denver, Colorado, USA	N = 9 patients with classical MSUD (one possible variant); age at mental evaluation ranged from 6–15 years	No association between initial levels of BCAA and the outcome measures are reported. Post-natal time period that plasma remained elevated is not specified.
Reference – Naughten ER, et al. (1982)[74] Type of Study – Retrospective study to evaluate the progress of patients with classical MSUD treated in a single hospital and to examine factors of outcomes Location – London, UK	N = 12 patients with classical MSUD; age at mental evaluation ranged from 1 year to 11.5 years; median time to diagnosis was 7 days (1day to 9 months)	The time taken for leucine to fall below 1000umol/L did not appear to influence outcomes. The median time to reduce leucine levels below 1000 umol/L from day of diagnosis was 6 days ranging from 2–16 days. At age 2 years, the mean leucine intake was 3.5 mmol/day ranging from 1.6–4.7 mmol/day. Patients in this study had extreme levels of leucine at the time of diagnosis (2420 umol/L to 6450 umol/L).Only one of the 12 patients has an IQ greater than 90 and has a normal neurological status. All other patients have an IQ of 90 or less and experience some degree of abnormal neurological signs such as brisk tendon reflexes, hypotonia, ataxia, & spastic quadriplegia.
Reference – Snyderman SE (1988)[71] Type of Study – Retrospective cohort study of MSUD patients to evaluate age of diagnosis on treatment outcome Location – New York, USA	N = 18 patients with MSUD; forms of MSUD were not specified; age at mental evaluation ranged from 0.8–28 years	Author recommends a cutoff date of 10 days of age since normal IQ was observed only in patients diagnosed before this age.

12.3 Mean Annual Leucine Levels for Long-Term Metabolic Control in MSUD

Mean Annual Leucine Levels for Long-Term Metabolic Control (MSUD)		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Hoffmann B, et al. (2006)[75] Type of Study – Longitudinal cohort study of MSUD patients to examine the relationship between plasma leucine levels and IQ Location – Germany; Austria; Switzerland	N = 24 patients with classical MSUD; age at mental evaluation ranged from 4–13 years, patients treated with BCAA-restricted diet	Long-term metabolic control of mean plasma leucine levels influences intellectual outcome for classical MSUD patients. Profiles of the first 6 years of life were grouped by cluster analysis into 3 clusters based on leucine levels: a low level (n=8) at 189 ± 82 umol/L; an intermediate level (n=13) at 379 ± 147umol/L; and a high level (n=3) at 572 ± 147 umol/L. Differences of the IQ scores between the 3 clusters were statistically significant. ($p<0.05$). Children with moderate and poor metabolic control had more severe metabolic decompensations than patents with excellent long-term control. Based on laboratory data for leucine levels collected over a course of 6 years, each patient underwent an average of 32 ± 14 analyses per year.
Reference – Hilliges C, et al. (1993)[73] Type of Study – Prospective cohort study comparing intellectual performance of MSUD patients with PKU patients and normal subjects (controls) Location – Germany	N = 22 patients with MSUD; 16 with classical form, 3 with severe variant form, 3 mild variant form; age at time of mental evaluation ranged from 3–16 years	Long-term metabolic control of plasma leucine levels (means of semi-annual medians) in the first year of life ($p=0.032$) and in the first 3 years of life ($p=0.043$) for classical MSUD patents was predictive of IQ. Based on the mean leucine concentrations recorded biannually over the course of 3 years, the regression slope indicated a decrease in 10 IQ points for each 0.1mmol/L average increase in plasma leucine level.
Reference – Kaplan P, et al. (1991)[68] Type of Study – Prospective cohort study of MSUD patients comparing the intellectual outcome of children diagnosed after the onset of symptoms from the children diagnosed before the onset of symptoms Location – Lancaster County, Pennsylvania, USA	N = 16 patients with MSUD; 13 with classical form, 3 with variant form; 8 of the 16 patients from the Mennonite community; age at mental evaluation ranged from 1.1–8.1 years	Study shows an inverse correlation between IQ and annual plasma leucine levels (for the year prior to receiving the IQ test). ($p = 0.06$, $p = 0.02$ excluding an outlier patient). Multiple regression analysis showed both age at diagnosis and long-term leucine concentration were statistically significant predictors of IQ ($p<0.05$) in a model containing both variables. The mean number of measurements taken was 5 per year per patient before psychometric testing was conducted. Measurements taken ranged from 2–10 per year and the mean plasma leucine level was 379 ± 227 umol/L.

13 Summary of Literature on Proposed Performance Measures for Sickle Cell Disease

13.1 Introduction to Sickle Cell Disease

Sickle cell disease (SCD) encompasses a group of conditions that affects the red blood cells and is defined by the presence of hemoglobin S due to a mutation in the beta globin gene (HBB), which is responsible for making hemoglobin beta chains. Individuals affected with SCD are unable to produce normal hemoglobin. In SCD, the shape of red blood cells changes from round to sickle or crescent shaped. Due to their abnormal shape, sickled red blood cells cannot pass easily through the blood vessels. Infants born with SCD are normal at birth but begin to show symptoms as their levels of fetal hemoglobin decrease and abnormal hemoglobin (HbS) levels increase. Presenting symptoms include dactylitis (painful swelling of hands and feet), pallor, jaundice, pneumococcal sepsis (severe bacterial infection), meningitis (infection in the protective membranes of the brain), severe anemia, acute splenic sequestration (enlarged and damaged spleen) and acute chest syndrome (ACS). Outcomes for affected infants have been shown to improve (especially in early childhood) with prompt diagnosis and treatment.[76]

13.2 Nomenclature and Disease Variants for Sickle Cell Disease

SCD includes HbSS, HbSßº Thalassemia, HbSβ$^+$ Thalassemia, Hemoglobin SC (HbSC) and a variety of other sickling hemoglobinopathies. Approximately 60%–70% of the cases of SCD in the US are due to the presence of HbSS. Other disease variants result from the co-inheritance of HbS with other abnormal beta chain variants. These disease variants differ in severity and therefore may require different disease management strategies.[37] The majority of the literature on SCD includes research on more severe forms of the disease, i.e., HbSS and HbSßº Thalassemia.

13.3 Incidence and Screening for Sickle Cell Disease

The national incidence of SCD is reported as greater than 1 in 2000 to 2,500.[3] Incidence within the African American population is much higher (1 in 250 to 600).[77]

Newborn screening for SCD in Texas began in November 1983.[78] In 2007, approximately 184 specimens were identified as presumptive positive for HbSS, 83 for HbSC , 20 HbSβ$^{+,}$ and 5 for HbSßº Thalassemia. Of the presumptive positives, 91 infants were diagnosed with HbSS, 42 for HbSC, 10 for HbSβ$^{+,}$ and 2 infant with HbSßº Thalassemia. Based on these numbers (for a birth rate of 414,000), the estimated incidence in Texas is 1:4,549 for HbSS, 1:9,857 for HbSC, 1:41,400 for HbSβ$^+$, and 1:207,000 for HbSßº Thalassemia for a combined incidence of 1:2,855.

13.4 Laboratory Testing, Follow-up, and Diagnosis for Sickle Cell Disease

TNSP screens for SCD by isoelectric focusing (IEF) of a hemolysate prepared from a dried blood spot. Hemoglobin bands are identified by their migration in an electric field. Confirmatory DNA testing by polymerase chain reaction—restriction fragment length polymorphism (PCR-RFLP)—allows the confirmation of hemoglobin type at birth in most cases. In Texas, PCR-

RFLP is performed as a second tier test on the abnormal specimens with clinically significant hemoglobinopathies.

For infants with presumptive positive results, TNSP immediately contacts the PCP or the attending physician to suggest a follow-up protocol. TNSP continues to track or follow the clinical status of the infant until diagnosis or until the infant is confirmed not to have the condition. Further, program staff also notifies parents, by mail, when their children are confirmed with sickle cell trait.

13.5 Disease Characteristics and Suggested Treatment for Sickle Cell Disease [79, 80]

SCD is a complex disorder and can manifest itself in a variety of ways. Some of the common symptoms exhibited by patients with SCD include: bacterial infections, ACS, acute splenic sequestration, acute pain crisis (APC), and stroke.

- **Bacterial Infections**—Due to splenic dysfunction, which can develop as early as 3 months of age, children affected with SCD are at high risk of bacterial infections. *Streptococcus pneumoniae* is the most frequent etiology of bacteremia and meningitis among SCD patients. Other encapsulated bacteria may also cause infections. Younger patients are especially prone to these infections since their immune systems are not yet developed and the spleen (which provides protection from infections) has compromised functional capacity. A significant proportion of patients may follow the fulminant course of infection where death can occur within 12 hours of fever onset. In recent years, a multi-step disease management approach has helped greatly in reducing the rate of invasive infections and therefore improving survival among patients with severe hemoglobinopathies.
- **Acute Chest Syndrome (ACS**)—ACS is triggered by a variety of factors such as infection, blocked blood vessels (due to sickling of blood cells), and insufficient oxygen inhalation. It is diagnosed via a chest X-ray that shows a new infiltrate in the lungs, combined with low blood oxygen levels. Other symptoms include fever, chest pain, cough, and troubled breathing. ACS is one of the leading causes of hospitalization among patients and also accounts for a significant number of premature deaths. Treatment approaches of ACS include: adequate pain management, antibiotics to cure infection, supplemental oxygen, transfusions, respiratory therapy, and hydration with abundant fluids.
- **Acute Splenic Sequestration Crisis (ASSC**)—ASSC is a serious complication characterized by an acutely enlarged spleen and a hemoglobin (Hb) level of 2 gm/dL or more below patient's baseline value. Other symptoms include pale skin, lethargy and a distended abdomen. ASSC is observed in 10%–30% of children with SCD, commonly between the ages of 6 months and 3 years. In some cases, an enlarged spleen may be observed in infants as young as 2 months old. In a Jamaican study that included patients from 1973 to 1981, as many as 23% of the patients with HbSS (homozygous for the sickle cell allele) had suffered from ASSC by the age of 2 years. Cases of ASSC may be treated with transfusions. Occasionally, surgical intervention (splenectomy) may be required. Deaths due to ASSC have decreased as disease management has improved.

Parent education to recognize early symptoms of ASSC has helped to decrease the mortality.

- **Acute Pain Crisis (APC)**—APC is a common feature of SCD. Patients complain of sharp or throbbing pain most commonly in the lower back, extremities and joints, chest, and abdomen. APC may be triggered by a variety of factors such as low temperature, dehydration, infection, physical exertion, and psychological stress. Patients with uncomplicated episodes of pain may be treated at home using oral hydration and oral analgesics. More severe episodes of pain require hospitalization with parenteral analgesics.
- **Stroke**—Various kinds of stroke may occur at any time during the life span of an SCD patient. The highest incidence of stroke is between the ages of 2 and 9 years, with an additional peak observed in older individuals. Silent infarctions (neurocognitive changes without a recognized acute event) are reported in an additional 17% of patients. Transfusions, neurologic monitoring, and management of seizures are some of the common treatment options.

13.6 Objectives of the Literature Review

As a part of the TNSPMP, clinical experts were asked to provide their input on critical steps in disease management of an infant born with SCD. A list of performance measures was proposed based on their input. The primary objective of this review is to explore scientific evidence that lends support to the proposed performance measures. Candidate measures may potentially be piloted in the third year of the TNSPMP which begins in September 2009.

13.7 Candidate Performance Measures for Sickle Cell Disease

The candidate performance measures listed below are general in nature. If considered for piloting in the third year of the project, these working conceptual definitions will be further developed and refined into clearly defined terms.

- **Time to penicillin treatment for patients with HbSS**
  Measuring the time it takes from birth to initiate twice daily oral prophylactic penicillin treatment for an infant with HbSS.
- **Compliance with twice daily oral prophylactic prescription of penicillin through age 5 for HbSS**
  Monitoring the compliance of administering twice daily oral prophylactic penicillin to patients with HbSS through the age of five years.
- **Age at the time of first Prevnar® vaccination (PCV-7) for SCD**
  Measuring the age of when the first Prevnar vaccination was administered to patients with SCD.
- **Clinical evaluation at age 5 for disease management decisions for SCD** Measuring the number of infants with SCD receiving a detailed assessment and consultation at age 5 years. This includes administration of the second dose of 23-valent pneumococcal polysaccharide and parent consultation about discontinuation of penicillin therapy.

- **Parent education on assessing enlarged spleen/monitoring episodes of febrile illness in SCD**
  Monitoring the number of parents having children with SCD who receive education within the first three months of the infant's birth on both assessing for an enlarged spleen and for monitoring episodes of fever.
- **Genetic counseling on SCD for parents**
  Monitoring the number of parents having a child with SCD who have received genetic counseling within the first three months of the infant's life.

13.8 Methodology

Subject matter experts were requested to provide a list of performance measures that would be the most critical to assessing infant patient care in the assessment of the Texas newborn screening system with respect to SCD.

13.8.1 Keywords

Based on their input, various combinations of the following key words were used to search PubMed for potentially relevant articles: SCD, sickle cell anemia, time to treatment, age at diagnosis, compliance, prophylactic penicillin, enlarged spleen, splenomegaly, and genetic counseling.

13.8.2 Inclusion/Exclusion

Only the articles written in English language were considered.

13.9 Results

The tables in the next section provide a list of these performance measures along with a synopsis of specific studies from the literature that lend evidence in support of each performance measure.

13.10 Discussion

Based on the review of the articles, timely treatment for SCD is correlated with improved clinical outcomes including reduced mortality and morbidity including occurrence of bacterial infections, painful crises, and episodes of ASSC.[81]

Prophylactic penicillin therapy is recommended for newborns with SCD by the age of three months.[82] The benefits of prophylactic therapy with oral penicillin have been highlighted by a number of studies. Compliance with this treatment has been shown to result in reduced mortality and greater longevity. Episodes of pneumococcal infections in patients below the age of 5 years are also significantly reduced by penicillin prophylaxis.[83-85]

Compliance with oral administration of prophylactic penicillin can be a challenge for many patients.[86, 87] A rigorous vaccination schedule throughout the early years of life provides additional protection although the immunogenicity provided by the vaccinations is not as broad as that provided by the oral penicillin.[79, 88-92] Widespread use of these interventions has resulted in a significant reduction of invasive pneumococcal infections in children with SCD.[88]

Prophylactic penicillin may not be indicated beyond the age of 5 years (PROPS II and some follow-up studies). After early childhood, the patient's own immune system is competent enough to fight bacterial infections. Evidence in the literature also suggests that long-term use of antibiotics may be associated with the development of drug resistant strains of bacteria. A comprehensive evaluation of the child's clinical status is recommended at the age of 5 years. Depending on the results of the evaluation, penicillin may be discontinued (except when the patient may have specific health issues that indicate prolonged use).[85, 93, 94]

Cases of ASSC are no longer a leading cause of mortality among SCD patients. This has been possible in part due to parent education on symptoms of ASSC. Specifically, parent education on the early recognition of an acutely enlarged spleen and febrile illnesses has contributed to timely treatment. Assessment of parent education may provide an insight into the current practices related to SCD management.[95-97]

Genetic counseling of couples with a child affected with SCD was also recommended as one of the potential measures. Based on the evidence in the literature, health behaviors of such couples (e.g., informed reproductive decisions) may be influenced by having an SCD-affected child.[98, 99]

13.11 Conclusion

Timely initiation and compliance with penicillin therapy are important for successful management of SCD. It may be useful to assess whether caregivers and families of patients younger than 5 years of age follow oral penicillin regimen and vaccination schedule closely. Parent education on assessing enlarged spleen/monitoring episodes of fever, clinical evaluation at age 5, and genetic counseling of parents are meaningful performance parameters supported by evidence in the literature.

13.12 Limitations

In most of the guidelines on clinical practice for SCD, children with HbSC are not distinguished from children with HbSS. This may be due to a paucity of research studies that include HbSC as a separate disease category. Treatment recommendations for HbSS may not necessarily apply to patients with HbSC. Further, with the current screening techniques, it is not always possible to distinguish between H beta zero thalassemia and beta plus thalassemia. Additional testing is required to test for the type of thalassemia. The TNSP has in-house facilities for DNA testing. However, other programs may have to outsource this type of testing. The additional time required for supplemental testing should be factored in while assessing the timeliness of treatment.

14 Candidate Measures for Sickle Cell Disease with References

14.1 Time to Initiate Penicillin Treatment for HbSS

Time to Initiate Penicillin Treatment for HbSS		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Tefler P, et al. (2007)[82] Type of Study – Prospective study on infants diagnosed with SCD to evaluate the risk of pneumococcal sepsis, overt stroke, and death Location – UK – London	N = 252 children; 180 with HbSS, 64 with HbSC, 8 with HbSßº Thalassemia	Study results showed that mortality was considerably lower (compared to previous reports) in patients with HbSS. For patients with HbSC and HbSßº Thalassemia, incidence of death, strokes, or pneumococcal sepsis was negligible. Children enrolled received oral penicillin starting at 3 months of age and continued indefinitely. Vaccination schedules included 23-Valent polysaccharide vaccine (Pneumovax) from 1993, conjugate vaccine for Haemophilius influenza type B from 1993, conjugate meningitis C vaccine from 2000, and Prevenar from 2002.
Reference – Bardakdjian-Michau J, et al. (2002)[81] Type of Study – Cohort study to compare complications of patients with homozygous sickle cell diagnosed at birth via screening with patients diagnosed without screening Location – France	N = 38 patients with HbSS; aged more than two years at last medical consultation	Of the common complications, painful crisis, and splenic sequestration were significantly reduced in the screened cohort compared with the non-screened cohort. Patients in the screened cohort (n=38) were diagnosed at birth, while the patients in the control group (n=67) had a mean age of diagnosis of 23.6 months (SD 14.2). Splenic sequestration was defined as at least 2 cm increase in spleen size associated with a drop of at least 2g/dL in Hb levels. Painful crisis was defined as pain in the extremities, back, abdomen, chest, or head for which no other explanation could be found.

14.2 Compliance with Twice Daily Oral Prophylactic Prescription of Penicillin Through Age 5 for HbSS

Compliance with Twice Daily Oral Prophylactic Prescription of Penicillin Through Age 5 for HbSS		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Tefler P, et al. (2007)[82] Type of Study – Prospective study on infants diagnosed with SCD to evaluate the risk of pneumococcal sepsis, overt stroke, and death Location – UK – London	N = 252 children; 180 with HbSS, 64 with HbSC, 8 with HbSßº Thalassemia	Study results showed that mortality was considerably lower (compared to previous reports) in patients with HbSS. For patients with HbSC and HbSßº Thalassemia, incidence of death, strokes, or pneumococcal sepsis was negligible. Children enrolled received oral penicillin starting at 3 months of age and continued indefinitely. Vaccination schedules included: 23-Valent polysaccharide vaccine (Pneumovax) from 1993; conjugate vaccine for Haemophilius influenza type B from 1993; conjugate meningitis C vaccine from 2000; and Prevenar from 2002.
Reference – Quinn CT, et al. (2004)[84] Type of Study – Prospective cohort study of patients to record incidence of death, stroke, and overall survival related to SCD Location – USA	N = 711 children with SCD; born in Texas on or after Nov 1, 1983; prophylactic Penicillin was prescribed for all patients with HbSS or HbSßº Thalassemia; followed from 1983 to 2002	Results from Dallas Newborn Cohort were compared with those of the Cooperative Study of Sickle Cell Disease (CSSCD) and the Jamaican study. Percent of death caused by infection in the Dallas study was 20%, as compared to 28% in Jamaica and 50% in CSSCD. The age of death had also improved in the Dallas cohort (4-6 years as compared to 0.5–1 in Jamaica and 1–3 years in CSSCD). The Dallas cohort recorded decreased death rate, decreased number of fatal infections, and increased age at death. All these factors point to the effectiveness of wide spread use of prophylactic penicillin.

Compliance with Twice Daily Oral Prophylactic Prescription of Penicillin Through Age 5 for HbSS		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Hord J, et al. (2002)[83] Type of Study – Observational study to determine age-related risks, disease-specific risks, and incidence of pneumococcal infections using data from three pediatric sickle cell control programs Location – Eastern United States	N = 5,885 patients with a diagnosis of HbSS or HbSC aged 1–21 years	Throughout the study period (Jan 1992 to May 1998), a total of 47 episodes of pneumococcal infection were observed among 40 patients. The majority of the infections (40/47) were observed in HbSS patients. Most of the episodes (37/47) were observed in patients younger than 5 years of age. The overall rate of infections among HbSS patients below the age of 5 years was 2.4 events per 100 patient years. The rate was lower among the HbSC patients younger than 5 years of age (at 1.3 events per 100 patient years). The authors concluded that the observed rates of infection were lower than those observed in similar patient populations before the widespread use of penicillin prophylaxis. Therefore, the study results support the penicillin prophylaxis regimen up to the age of 5 years. The benefit of penicillin among older children was reported as unclear.
Reference – Hirst C, Owusu-Ofori S (2002)[85] Type of Study – Systematic review of randomized or quasi randomized controlled trials Location – Jamaica, West Indies (1 study); USA (2 studies)	Results from three trials were included. John 1984: 242 children with HbSS in Jamaica, West Indies (IM injection monthly), PROPS 1986 (Gaston et al. 1990): 215 children with HbSS in USA (125 mg twice daily oral or placebo), PROPS II:400 children with HbSS or HbSß° Thalassemia in USA (250 mg twice daily or identical placebo tablet)	Data support that penicillin given preventatively reduces the rate of pneumococcal infections in children with SCD less than five years of age. All three trials showed a reduced rate of infection in children with SCD receiving penicillin preventatively. Two trials looked at effectiveness of treatment; the third followed on from one of the earlier trials and looked at when it was safe to stop treatment. The follow-on trial did not show a significant increase in risk when penicillin was halted at five years old.
Reference – Gaston MH, Verter J (1990)[87] Type of Study – Multi-center randomized double blind placebo controlled trial to assess the effectiveness of twice daily oral penicillin in preventing severe bacterial infections in HbSS patients younger than 3 years of age Location – USA	N = 216 patients with HbSS; 108 patients each in the treatment and placebo group	After eight months of the trial period, a total of 15 cases of pneumococcal septicaemia were reported. Of these, 13/15 cases were from the placebo group and 2/15 were from the treatment group. The difference in rate of infection was statistically significant (p=.0025). Three deaths were reported for the placebo group (as compared to no deaths in the treatment group).

Compliance with Twice Daily Oral Prophylactic Prescription of Penicillin Through Age 5 for HbSS		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Babiker MA (1986)[86] Type of Study – Observational study on compliance with Penicillin prophylaxis comparing groups of patients who chose either the oral or the intramuscular method of penicillin prophylaxis (September 1983 to April 1994) Location – Saudi Arabia	N = 42 SCD children with impaired splenic function; 32 with HbSS, 10 with HbSß° Thalassemia	Group A included 24 children (of which 22 were hemozygotes for SCD) who had opted for the oral regimen. Group B included 18 children (of which 10 were hemozygotes for sickle cell) who opted for the intramuscular injection regimen. Clinic attendance was above 90% for both patient groups, however, after examining 178 urine samples for group A, only 78 (44%) were found to be positive for antibacterial activity, where antibacterial activity would indicate compliance with penicillin regimen. On the other hand, 100% of the 188 urine samples collected from group B were positive for antibacterial activity. Results show that compliance with oral regimen of penicillin is poor. Authors speculated that the educational efforts were helpful in improving general understanding of the disease but were not necessarily effective in improving compliance with the medication.

14.3 Age at Time of First Prevnar Immunization for SCD

Age at Time of First Prevnar Immunization for SCD		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Adamkiewicz TV, et al. (2008)[88] Type of Study – Pre-and post-comparison of the incidence of invasive *S pneumoniae* in children less than 10 years old before and after licensure of PCV vaccine Location – USA	N = 1247 children with SCD; born after 1983	Incidence of invasive *S pneumoniae* infections in children with SCD declined in a 3-year period after PCV vaccine licensure compared to a 5-year period before PCV licensure. Authors support vaccinating high-risk children at ages 2–5 years and recommend “catch up” vaccinations for children with SCD beyond the age of 4 years. (40% of study patients received a first dose of PCV after the age of 4.)

Age at Time of First Prevnar Immunization for SCD		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Reinert P, et al. (2007)[92] Type of Study – Open label multi-center study that included 2-month old SCD patients who were vaccinated with PCV-7 at 2, 3, and 4 months of age followed by a booster dose of PS-23 at 15–18 months of age Location – France	N = 51 infants with SCD; age at study enrollment was 2 months.	Study results showed that after the series of vaccinations, at least 95% of the infants had antibody titers ≥ 0.35 µg/ml. This level is considered to provide sufficient protection according to the World Health Organization (WHO). Further, after the booster dose of PS-23 was given at 15–18 months of age, the antibody titers increased dramatically (titers had declined after the third dose). These results show that the primary series of PCV-7 vaccinations along with the booster dose result in a good immune response in children with SCD. Further, the safety and immunogenicity of PCV-7 at 2, 3, and 4 months was reportedly similar to the 2, 4, 6 month schedule typical in US clinical practice. This study also observed fewer cases of local and febrile reactions when the PS-23 was given at 15–18 months (as compared to reports in the literature for PS-23 at 24 months).
Reference – Center KJ (2007)[89] Type of Study – Review article Location – Not applicable	Not applicable	Study comments on the reduction in rates of Pneumococcal infections after the initiation of routine administration of Prevnar vaccination. When invasive pneumococcal disease rates were compared for 2003 and 1998–1999, a 94% decline was observed in children younger than 5 years of age.
Reference – Davies EG, et al. (2004)[90] Type of Study – Systematic review of randomized and quasi-randomized controlled trials Location – Not applicable	Results from 5 trials: John 1984: 242 children with HbSS in Jamaica, West Indies, Goldblatt 2000: 150 children with SCD in Ghana (mean age at 13.9 months), Goldblatt 2003: 100 children with SCD (mean age at 2.2 months), Rigau-Perez 1983: 32 participants in USA, aged 3–24 years at entry, Vernacchio 1998: 23 participants with SCD in USA, aged at least 2 years old	Trials compared a polysaccharide or conjugate pneumococcal vaccine (Prevnar/ PCV-7) regime with a different regime or no vaccination in patients with SCD. This review found that conjugate vaccines can increase the immunity to pneumococcal infection in patients with SCD, including infants.

Age at Time of First Prevnar Immunization for SCD		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Overturf GD (2000)[91] Type of Study – Technical report on prevention of pneumococcal infections, including the use of pneumococcal conjugate and polysaccharide vaccines and antibiotic prophylaxis Location – Not applicable	Not applicable	The report highlighted a trial conducted by Vernacchio et al. in 1998 demonstrating the safety and immunogenicity of PCV-7 vaccinations. The trial included 24 children aged 2 years or more. Every child received two doses of PCV-7 separated by an interval of 8 weeks. Then, one group was given a dose of 23PS along with a third dose of PCV-7 and another group was given 23PS alone. It was observed that antibody levels were higher among children who had received the 23PS along with the third dose of PCV-7 as compared to the group who received 23PS alone.
Reference – AAP (2000)[79] Type of Study – AAP recommendations for pneumococcal conjugate vaccine (Prevnar), pneumococcal polysaccharide vaccination, and antibiotic prophylaxis Location – Not applicable	Not applicable	Routine administration of PCV-7 vaccine is advised for infants under the age of 23 months. Recommendations include four doses at 2, 4, 6, and 12–15 months. However, additional doses are recommended for children at a high risk of infections (including children with SCD and HIV). The schedule is listed as follows: 1. A dose of 23PS vaccine at the age of 24 months. 2. Second dose of 23PS at 3–5 years after the first dose of 23PS. For children who have not followed the above schedule of four doses of PCV-7 vaccine by age 24 months, along with additional doses of PCV-7, several catch-up regimens were recommended based on the number of missed doses.

14.4 Clinical Evaluation at Age 5 for Disease Management Decisions for SCD

Clinical Evaluation at Age 5 for Disease Management Decisions for SCD		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Falletta JM, et al. (1995)[93] Type of Study – Randomized, double blind, placebo controlled study (PROPS II) to evaluate the use of twice daily prophylactic penicillin therapy in SCD patients older than 5 years of age Location – Eighteen teaching hospitals across the United States	N = 400 children with a HbSS or HbSß° Thalassemia with a history of penicillin prophylaxis treatment for a continuous period of at least 2 years before the age of 5 years. Average age of study population was 5.1 years at the time of enrollment for both treatment and placebo groups. For both groups, first pneumococcal vaccine was given at 1.9 years, and the last pneumococcal vaccine was given at the age of 4.9 years. Patients from each group had been on prophylactic penicillin for about 4 years.	The two groups were compared for rates of pneumococcal infection or meningitis. Results showed that in the penicillin group, the rate of infection was 0.33 per 100 patient years; for the placebo group, this rate was 0.67 per 100 patient years. It was concluded that after the age of five years, it might be safe to discontinue the use of prophylactic penicillin in children affected with SCD. Other factors to consider before discontinuing therapy include: 1. Patient preference 2. Cost of medication 3. Patient tolerance of the medication The authors also supported the avoidance of prolonged use of Penicillin among patients older than 5 years due to the occurrence of antibiotic resistant strains of bacteria isolated from the study population (one third of the S. pneumonia isolates were found to be at least intermediately resistant to penicillin, and 15% were found to be resistant to a number of antibiotics)
Reference – Pai VB, Nahata MC (2000)[94] Type of Study – Review article on penicillin prophylaxis in patients with HbSS Location – Not Applicable	Not Applicable	Review article supports the discontinuation of penicillin prophylaxis after the age of 5 years in patients with HbSS. Authors point to the trend in the increase of penicillin-resistant organisms in North America. This number was at 5% in 1989. By 1997 it had increased to 35%. Other factors that may support discontinuation of penicillin after 5 years of age include: 1. Lack of evidence of additional benefit 2. Poor compliance 3. Overall reduced risk of getting bacterial infections after age 5 4. Increasing population of penicillin resistant strains of bacteria across the world *Overall, results support the recommendations of PROPS II.*

Clinical Evaluation at Age 5 for Disease Management Decisions for SCD		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Quinn CT, et al. (2004)[84] Type of Study – Prospective cohort study of patients to record incidence of death, stroke, overall survival related to SCD Location – USA	N = 711 children with SCD; born in Texas on or after Nov 1, 1983; prophylactic Penicillin was prescribed for all patients with HbSS or HbSß° Thalassemia; followed from 1983 to 2002	Results from Dallas Newborn Cohort were compared with those of the Cooperative Study of Sickle Cell Disease (CSSCD) and the Jamaican study. Percent of death caused by infection in the Dallas study was 20%, as compared to 28% in Jamaica and 50% in CSSCD. The age of death had also improved in the Dallas cohort (4–6 years as compared to 0.5–1 in Jamaica and 1–3 years in CSSCD). The Dallas cohort recorded decreased death rate, decreased number of fatal infections, and increased age at death. All these factors point to the effectiveness of wide spread use of prophylactic penicillin.
Reference – Hord J, et al. (2002)[83] Type of Study – Observational study to determine age-related risks, disease-specific risks, and incidence of pneumococcal infections using data from three pediatric sickle cell control programs Location – Eastern United States	N = 5,885 patients with a diagnosis of HbSS or HbSC aged 1–21 years	Throughout the study period (Jan 1992 to May 1998), a total of 47 episodes of pneumococcal infection were observed among 40 patients. The majority of the infections (40/47) were observed in HbSS patients. Most of the episodes (37/47) were observed in patients younger than 5 years of age. The overall rate of infections among HbSS patient below the age of 5 years was 2.4 events per 100 patient years. The rate was lower among the HbSC patients younger than 5 years of age (at 1.3 events per 100 patient years). The authors concluded that the observed rates of infection were lower than those observed in similar patient populations before the widespread use of penicillin prophylaxis. Therefore, the study results support the penicillin prophylaxis regimen up to the age of 5 years. The benefit of penicillin among older children was reported as unclear.

Clinical Evaluation at Age 5 for Disease Management Decisions for SCD		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Babiker MA (1986)[86] Type of Study – Observational study on compliance with Penicillin prophylaxis comparing groups of patients who chose either the oral or the intramuscular method of penicillin prophylaxis (September 1983 to April 1994) Location – Saudi Arabia	N = 42 SCD children with impaired splenic function; 32 with HbSS, 10 with HbSß° Thalassemia	Group A included 24 children (of which 22 were hemozygotes for sickle cell disease) who had opted for the oral regimen. Group B included 18 children (of which 10 were hemozygotes for sickle cell) who opted for the intramuscular injection regimen. Clinic attendance was above 90% for both patient groups. However, after examining 178 urine samples for group A, only 78 (44%) were found to be positive for antibacterial activity; where antibacterial activity would indicate compliance with penicillin regimen. On the other hand, 100% of the 188 urine samples collected from group B were positive for antibacterial activity. Results show that compliance with oral regimen of penicillin is poor. Authors speculated that the educational efforts were helpful in improving general understanding of the disease but were not necessarily effective in improving compliance with the medication.

14.5 Parent Education on Assessing Enlarged Spleen and Monitoring Episodes of Febrile Illness in SCD

Parent Education on Assessing Enlarged Spleen and Monitoring Episodes of Febrile Illness in SCD		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Wilson-Okoh DA, et al. (2006)[97] Type of Study – Review article on splenic changes in patients with HbSS Location – Not applicable	Not applicable	In case of children affected with HbSS, the spleen may appear normal at birth; however, by the age of five months, it may become significantly enlarged in most cases. There may be a small chance of an enlarged spleen in children as young as one month of age. Studies were cited where 37% of the patient population had an enlarged spleen by the age of six months, 65% by the age of 12 months, and 77% by the age of 24 months. Authors concluded that it is imperative to have a regular monitoring schedule for splenic changes in sickle cell patients.

Parent Education on Assessing Enlarged Spleen and Monitoring Episodes of Febrile Illness in SCD		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Vichinsky E, et al. (1988)[95] Type of Study – Retrospective study to determine effectiveness of newborn screening over 10 years for SCD patients. Effects of early treatment on long-term mortality and morbidity are reported. Location – California, USA	N = 153 patients with SCD; group one studied (n=89) diagnosed at birth, the control group (n=64) studied were diagnosed after the newborn period where mean age was 21 months	Authors attribute low mortality rate of newborns to early diagnosis and treatment compliance coupled with proper parent education. Parents were given a thermometer and given instruction on use. Parents were informed that a temperature of 101deg F or greater constituted a life threatening emergency. Parents of patients enrolled in their program sought care for their child within six hours of the onset of fever.
Reference – Emond AM, et al. (1985)[96] Type of Study – Cohort study to examine the natural history and disease management of ASSC in patients with HbSS Location – Jamaica, West Indies	N = 308 children with SCD diagnosed at birth	Parents/ guardians were educated on splenic palpation. When pre- and post-educational periods were compared; the post-education period indicated a decrease in mortality (3.1 per 100 events versus 29.4 per 100 events). Improved patient outcomes were attributed to improvement in diagnosis and management.

14.6 Genetic Counseling on SCD for Parents

Genetic Counseling on SCD for Parents		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Dorticos-Balea A, et al. (1997)[98] Type of Study – Cross sectional study to collect information on couples' attitude towards prenatal diagnosis of SCD Location – Cuba	N = 343 couples who were at risk of having a child affected with SCD	Of the 343 couples who responded to the survey, 268/343 (78%) were still living with the same partner while 22% had discontinued their relationship. Only 2% of the separated couples attributed the risk of having a sickle cell affected offspring as the reason for their separation. Among the couples that had stayed together, 168/268 had decided not to have any more children. 45/168 mentioned that the decision was based on their fear of having children affected with SCD. 52/268 couples had gone on to have at least one more pregnancy. 23/52 had voluntarily opted for prenatal testing. The remaining 29/52 had to be counseled. After counseling, 23/29 couples opted for prenatal diagnosis. The remaining six who did not go for prenatal diagnosis did so mainly due to the physical/psychological discomfort associated with amniocentesis (prenatal diagnosis). Only one couple mentioned that they were willing to have a child regardless of the baby's potential sickle cell status.
Reference – Howard RJ, et al. (1993)[99] Type of Study – Cross sectional study to assess the use of contraceptives among women with SCD Location – North London	N = 156 females; 102 with HbSS, 12 with HbSß° Thalassemia, 42 with HbSC	Of the 149 sexually active patients, about one third acknowledged to having received counseling against pregnancy. Only three women said that the counseling was an important factor in their future reproductive decisions. About 50% of the study subjects were aware of antenatal diagnosis. Overall, study results reflect little influence of counseling on reproductive behavior of the study population.

15 Summary of Literature on Proposed Performance Measures for Phenylketonuria

15.1 Introduction to Phenylketonuria

Phenylketonuria (PKU) is an autosomal recessive disorder most commonly characterized by the deficiency of the enzyme called phenylalanine hydroxylase (PAH). This enzyme is necessary to metabolize the amino acid phenylalanine (Phe) to the amino acid tyrosine (Tyr). In the absence of PAH, Phe accumulates in the blood plasma and is converted into phenylpyruvate. Affected infants suffer from problems with brain development and progressive mental retardation. PKU can be treated with a diet low in phenylalanine and high in tyrosine. If left untreated, symptoms begin to appear at 3 to 6 months of age. The infant may present with a peculiar odor to the urine and may have vomiting, eczema, convulsions, and restlessness. Long-term outcomes of untreated PKU include severe mental retardation and numerous other neurological and cognitive defects.

15.2 Nomenclature and Disease Variants for Phenylketonuria

The three forms of this disease follow.

- **Classical Phenylketonuria (PKU)—**PKU is caused by a complete or near-complete deficiency of PAH activity. Patients can have plasma phenylalanine concentration higher than 1000 µmol/L and a dietary Phe tolerance of less than 500 mg/day.
- **Hyperphenylalaninemia (HPA)**—HPA is characterized by plasma phenylalanine concentration between 120 and 1000 µmol/L. Treatment may not be needed in some individuals whose Phe levels are in the lower range.
- **Tetrahydrobiopterin (BH_4) Deficiency**—BH_4 Deficiency is characterized by hyperphenylalaninemia caused by impaired recycling of the cofactor tetrabiopterin. This accounts for approximately two percent of the individuals with HPA.

15.3 Incidence and Screening for Phenylketonuria

The national incidence of PKU is reported as greater than 1 in 13,000 to 19,000.[3]

Newborn screening for PKU was initiated in Texas as a pilot project in 1963 and was universally mandated in 1965.[25] In 2007, the screening method changed from a fluorometric assay to a tandem mass spectrometry platform. In 2007, approximately 142 specimens were identified as presumptive positives for this condition. From the presumptive positives, 13 infants were diagnosed with classical PKU, 1 infant was diagnosed with variant hyperphenylalanemia, and 21 infants were diagnosed with benign persistent hyperphenylalanemia. Based on these numbers (for a birth rate of 414,000[i]), the incidence of classical PKU in Texas for 2007 is estimated at 1 in 31,850.

15.4 Laboratory Testing, Follow-up, and Diagnosis for Phenylketonuria

Screening for PKU is currently performed by MS/MS. MS/MS screening detects elevated concentrations of amino acids and also evaluates their relationship with each other. These measurements provide analyte concentration profiles that can aid in the detection of several

metabolic disorders. Confirmatory testing includes plasma/serum amino acid analysis to detect increased phenylalanine without increased tyrosine (increased phenylalanine to tyrosine ratio).

For infants with presumptive positive results, TNSP immediately contacts the PCP or the attending physician to suggest follow-up protocol. TNSP continues to track or follow the clinical status of the infant until diagnosis or until the infant is confirmed not to have the condition.

TNSP began a PKU dietary monitoring program in 1992. This program provides testing services for Texas children diagnosed with PKU—phenylalanine and tyrosine levels are measured from dried blood spots. The frequency of monitoring varies with the age of the child and the level of metabolic control.

15.5 Disease Characteristics and Suggested Treatment for Phenylketonuria

The following elaborates on commonly encountered disease characteristics of patients with PKU.

- **Low IQ**—Without dietary restriction of phenylalanine, most children with PKU develop profound and irreversible mental retardation. HPA is associated with a lower risk of impaired cognitive development in the absence of treatment.
- **Visual-spatial deficits**—Visual-spatial deficits are characterized by difficulty in performing everyday activities such as recognizing objects and faces and judging distance, depth, and volume.
- **Poor motor skills**—Poor motor skills are often characterized by a lack of coordination.
- **Poor executive function**—Poor executive function is characterized by difficulty with abstract reasoning, problem solving, and sustained attention.
- **Psychiatric problems**—Untreated or inadequately treated PKU patients are prone to psychiatric illnesses like depression and anxiety.
- **Osteopenia**—Abnormal bone density is often observed in adolescents with PKU. Osteopenia may be associated with poor compliance with restricted diet.

Treatment for classic PKU includes a low-protein diet and a phenylalanine free medical formula. Since it is an essential amino acid, individuals on a phenylalanine free diet require controlled amounts of supplemental phenylalanine for growth. The infant needs to be on treatment as soon as possible. The goal of treatment is to bring plasma Phe concentrations down to 120–360 µmol/L. There is no clear consensus on the utility of dietary treatment for patients affected with HPA and with plasma Phe concentrations maintained below 600 µmol/L.[100]

15.6 Objectives of the Literature Review

The main objective of this review is to present evidence from the literature that supports performance measures related to PKU disease management. This review addresses classical PKU only. Milder forms of the disease (HPA) will not be discussed in detail. In addition, the review is also intended to provide a general understanding of the disease characteristics and treatment options. Evidence from the literature will be used to provide support to the proposed performance measures listed in the following section. Candidate measures may potentially be piloted in the third year of the TNSPMP which begins in September 2009.

15.7 Candidate Performance Measures for Phenylketonuria

The candidate performance measures listed below are general in nature. If considered for piloting in the third year of the project, these working conceptual definitions will be further developed and refined into clearly defined terms.

- **Time to initiate treatment**
  Measuring the time it takes from birth to begin treatment for an infant with PKU.
- **Dietary compliance**
  Monitoring the rate of compliance with a prescribed PKU diet.
- **Monitoring Phenylalanine levels for metabolic control**
  Monitoring phenylalanine and tyrosine levels within the target range in a newborn with PKU.
- **Age-Appropriate frequency of monitoring phenylalanine levels**
  Monitoring the number of times (depending on age and phenylalanine levels) an infant with PKU is monitored for phenylalanine levels within a given period.

15.8 Methodology

Subject matter experts were requested to provide suggested performance measures for assessing the quality of PKU patient care. Measures related to timeliness of screening, confirmatory testing, initiation of restricted diet, parent education, and genetic counseling were suggested. Other measures pertaining to frequency of phenylalanine monitoring, dietary compliance, and periodic assessments of growth and development were also suggested.

15.8.1 Keywords

The following key words were used to perform targeted searches to support the suggested performance measures for PKU: Time to treatment, dietary control, metabolic control, phenylalanine levels, and patient compliance.

15.8.2 Inclusion/Exclusion Criteria

Research articles that discussed a direct relationship between one or more proposed performance measures and post-natal clinical outcomes were included. Studies done on animal subjects, or written in languages other than English were not included.

15.9 Results

The tables in the next section provide a list of these performance measures along with a synopsis of specific studies from the literature that lend evidence in support of each performance measure.

15.10 Discussion

Timely treatment has been shown to be important for PKU patients. Early childhood is a critical period for cognitive development, especially for PKU patients. Any lapses in timely treatment can lead to irreversible damage. At least one study has documented that delayed treatment is associated with a progressive decline in IQ. When cognitive assessments were conducted for a

group of 6-year-old PKU patients, those receiving treatment in the first month of life were most likely to have normal IQ. Treatment initiated in the second month of life was correlated with lower IQ (as compared to that for treatment in the first month). IQ for patients who received treatment after the second month was within the abnormal range.[101, 102]

There is abundant literature on the importance of dietary compliance in PKU. Poor compliance leads to high Phe levels, which in turn impact cognitive outcomes like executive function.[103] Patients who strictly follow the low Phe diet had better outcomes than their peers who are on a less strict or relaxed diet. Being on a restricted diet is also correlated with a higher IQ.[104] Unlike many other metabolic disorders, patients may experience varying degrees of improvement in their behavioral outcomes even when they get delayed dietary treatment. A restricted diet has been shown to improve concentration and help with irritability in previously untreated patients.[101-103, 105-107]

The average phenylalanine level (metabolic control) is a strong predictor of long-term cognitive outcome among PKU patients. Waisbren et al. in their recent meta-analysis of Phe levels and clinical outcomes in PKU patients (age group 0 to 12 years) reported a consistent quantitative relationship between average Phe levels and IQ. Results compiled from 64 studies published between 1980 and 2004 showed that for every 100 µmol/L increase in Phe, there was a corresponding decrease of 1.3–4.1 points in IQ. Good metabolic control is critical in early childhood, especially during the first six years of life.[108-111]

Regarding the frequency of monitoring Phe levels in PKU patients, evidence suggests that younger PKU patients are seen regularly at specialty centers. As patients get older, they typically do not need to visit the specialist center as frequently (e.g., every week). However, evidence from the literature indicates that patients tend to become irregular in their age-specific schedule of specialist center visits as they get older. A corresponding increase in their Phe levels has also been documented. Data on patient outcomes after the age of 18 are sparse. There is also concern about lack of uniform standards for monitoring Phe levels as patients become older (after the age of 10 years). Poor compliance and infrequent monitoring may lead to negative outcomes in adolescence or adulthood.[108, 109]

15.11 Conclusion

In conclusion, although PKU is the oldest disorder on state newborn screening panels, issues related to long-term care of patients are still not fully resolved. The primary factor related to poor long-term outcomes (mental retardation and depression anxiety) is poor metabolic control of Phe levels. Phe levels in turn depend on patient compliance. Therefore, a careful assessment of these parameters can provide valuable insights into PKU disease management.

15.12 Limitations

Some of the older studies on PKU report standards of care that may be obsolete at the present time. Although there is awareness among the medical community that there is a greater risk of poor compliance in adolescents with PKU, there is very little documentation of this problem in the literature.

16 Evidence Supporting Candidate Measures for Phenylketonuria

16.1 Time to Initiate Treatment for PKU

Time to Initiate Treatment for PKU		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Gassio R, et al. (2005)[102] Type of Study – Case control study with the objective of studying the relationship between dietary control and cognitive function in patients with PKU. Location – Barcelona, Spain	N = 37 patients with PKU; 17 females and 20 males, mean age 9y 9mo. (Standard deviation [SD] 5y 3mo), range 2y 8mo to 19y 4mo; and 35 individuals with HPA (HPA; 20 females, 15 males, mean age 7y 10mo [SD 3y 2mo], range 2y 8mo to 17y 3mo) compared with 29 healthy controls (14 females and 15 males, mean age 9y 8mo [SD 4y 9mo], range 2y 6mo to 18y 10mo) was performed.	The primary objective of this study was to study the relationship between dietary control and cognitive function in patients with PKU. When individuals with PKU (n=37, mean age 9 year and 9 months) were compared with the individuals in control group (n=29, mean age 9 years, 8 months), a statistically significant difference in intelligence was observed (p=0.001). Patients with PKU had lower scores for measures of intelligence. Index of dietary control showed an association with intelligence particularly up to the age of 6 years. It was concluded that cognitive development in PKU patients can be affected by metabolic control especially during early childhood. Therefore, timely treatment is important.
Reference – Cabalska MB, et al. (1996)[101] Type of Study – Longitudinal study examining correlation between age at treatment initiation and IQ and DQ. Location – Poland	N= 560; total cases of classical PKU, 99 mild HPA and six atypical PKU cases were detected.	IQ and DQ were measured in a group of six year old patients (n=100). An inverse correlation was reported between age at the time of treatment onset and IQ at six years of age. Patients receiving treatment in the first month of life had an average IQ of 101 ± 14.9 as compared to 96 ± 23.0 in the second month and 71 ± 26.0 in the third month. When IQ was measured in the adult patients (19–26 years old) who were no longer on the special diet, good quality control was associated with better outcomes. Average IQ scores were higher (97.2 ± 15.5) in the “very good dietary control group” as compared to the “poor dietary control group” (average IQ 81.0 ± 13.8). No information was provided about the “good dietary control” group.

16.2 Dietary Compliance for PKU

Dietary Compliance for PKU		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Gassio R, et al. (2005)[102] Type of Study – Case control study with the objective of studying the relationship between dietary control and cognitive function in patients with PKU. Location – Barcelona, Spain	N=37; patients with PKU 17 females and 20 males, mean age 9y 9mo. (standard deviation [SD] 5y 3mo), range 2y 8mo to 19y 4mo; and 35 individuals with HPA (HPA; 20 females, 15 males, mean age 7y 10mo [SD 3y 2mo], range 2y 8mo to 17y 3mo) compared with 29 healthy controls (14 females and 15 males, mean age 9y 8mo [SD 4y 9mo], range 2y 6mo to 18y 10mo) was performed.	When individuals with PKU (n=37, mean age 9 year and 9 months) were compared with the individuals in control group (n=29, mean age 9 years, 8 months), a statistically significant difference in intelligence was observed (p=0.001). Patients with PKU had lower scores for measures of intelligence. Index of dietary control showed an association with intelligence particularly up to the age of 6 years. It was concluded that cognitive development in PKU patients can be affected by metabolic control especially during early childhood. Therefore, timely treatment is important.
Reference – VanZutphen KH, et al. (2007)[103] Type of Study – Cross sectional study to investigate effects of dietary adherence, Phe levels, and age on performance and executive function tasks in PKU patients Location – USA	N = 15 patients; age range 8–20 years, mean 13.8 years	Patients were diagnosed by the age of 20 days of life followed by prompt treatment upon diagnosis. Of the 15 patients, 11 were still receiving dietary treatment at the time of the study. Results showed that there was a statistically significant inverse relationship between age and dietary adherence ($r= -0.53$; $p<0.05$). Also, both concurrent and life time phenylalanine levels were inversely related to dietary adherence. This relationship was also statistically significant at $p<0.001$ and $p<0.05$ respectively. It was recommended that PKU patients should be monitored closely, especially as they approach adolescence when there is a greater risk of poor dietary compliance.

Dietary Compliance for PKU		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Fitzgerald B, et al. (2000)[105] Type of Study – Prospective study of severely disabled patients with untreated PKU. This study recorded physical, social and behavioral outcomes after the patients were treated with a Phenylalanine restricted diet Location – Learning Difficulties Service, Chase Farm Hospital, Enfield, UK	N=5; phenylalanine-restricted diet of subjects with severe intellectual disability	There were five subjects in the study with ages ranging from 30 years to 56 years. All these patients were severely disabled at the time of enrollment in the study. Behavior change was observed prospectively in these patients after the initiation of restricted diet. Good dietary compliance was reported for each of the patients. Although the change in patient behavior was not quantified, subjective descriptions of behavior change such as reduced aggression and hyperactivity, fewer episodes of self-injury, and other challenging and embarrassing behaviors were provided in the study results.

Dietary Compliance for PKU		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Koch R, et al. (1999)[106] Type of Study – Retrospective chart review of late –treated patients with PKU to investigate their mental and psychological outcomes. Location – Children's Hospital of Los Angeles, California	N=124; adults with PKU seen in the metabolic service at the Children's Hospital of Los Angeles	Data on 57 subjects were divided into 4 categories. Group I (n=28) included patients who were diagnosed late (average age 8 years, range 3 months to 44 years), started treatment after diagnosis, and were continuously on treatment. Group II (n=8) Included patients who were diagnosed late (average age 0.8 years; range 0.25–1.5 years), received treatment upon diagnosis, then discontinued for a variety of reasons, and started treatment again after many years. Group III (n=15) included patients who were diagnosed late (average age 1.7 years; range 0.25–6 years), received late treatment, and then discontinued treatment without starting again. Group IV (n=6) included patients who were diagnosed late (average age 4.3 years; range 1–9 years). Measures of IQ for this study sample ranged from not measurable to above average. Patients belonging to group I had a broad spectrum of DQ/IQ ranging from non-measurable to 100. A similar range was also seen in group II. The range of DQ/IQ in group III was also very wide from 25–109. The DQ/IQ at diagnosis for patients in group IV was generally poor (12–43) except for one patient who was exceptionally bright with a score of 134. In general, mental retardation was seen in all the late-treated patient groups whether they had received continuous, intermittent or no treatment at all. This finding supports the opinion that there is a greater risk of cognitive damage in the early years of life, and, therefore, PKU treatment should be initiated as soon as possible. However, when patients within group I (patients receiving late but continuous treatment) were segregated by quality of treatment, a clear association was seen between good control and better IQ. Patients with better IQ tended to perform better in academic performance. Therefore, one of the most important variables in PKU treatment, even among patients who are treated late, is good dietary control.

Dietary Compliance for PKU		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Poustie VJ, Rutherford P (1999)[104] Type of Study – Review article to study the impact of dietary restrictions in PKU patients Location – Not applicable	N= 4 studies four studies with a cumulative sample size of 251 patients	It was reported that average Phe levels were lower among patients who were on a restricted diet. Only one of the studies adequately supported the association between IQ and long-term compliance with restricted diet in PKU. Overall the authors pointed to a general lack of good quality, randomized control studies in PKU. However, it was noted that compliance with the restricted diet should be maintained because of the potential risk of mental retardation.
Reference – Cabalska MB, et al. (1996)[101] Type of Study – Longitudinal study examining correlation between age at treatment initiation and IQ and DQ Location – Poland	N= 560 patients with classical PKU, 99 with mild HPA, 6 with atypical PKU	IQ and DQ were measured in a group of six year old patients (n=100). An inverse correlation was reported between age at the time of treatment onset and IQ at six years of age. Patients receiving treatment in the first month of life had an average IQ of 101 ± 14.9 as compared to 96 ± 23.0 in the second month and 71 ± 26.0 in the third month. When IQ was measured in the adult patients (19–26 years old) who were no longer on the special diet, good quality control was associated with better outcomes. Average IQ scores were higher (97.2 ± 15.5) in the "very good dietary control group" as compared to the "poor dietary control group" (average IQ 81.0 ± 13.8). No information was provided about the "good dietary control" group.

16.3 Monitoring Phenylalanine Levels for Metabolic Control

Monitoring Phenylalanine Levels for Metabolic Control		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Waisbren SE, et al. (2007)[110] Type of Study – A systematic literature review and meta-analysis of published trials of PKU to assess the reliability of blood Phe levels as a predictive biomarker of clinical outcomes in the development of treatments for PKU, which included Phe level and neurological and dietary compliance outcome measures Location – Children's Hospital Boston, MA	Results of 40 studies	Phe levels can be a reliable predictor of IQ. When data from various studies are compiled, there is a clear, quantitative relationship between Phe levels and IQ, especially in early childhood (0–12 years). Every 100 µmol/L increase in Phe levels resulted in 1.3 – 4.1 point reduction in IQ.
Reference – Wappner R, et al. (1999)[111] Type of Study – Cross sectional survey of parents of PKU patients, young adults with PKU, and directors of PKU clinics to assess various parameters for developing PKU disease management guidelines Location – Indianapolis, Indiana, USA	Members of the AAP Committee on Genetics (COG) reviewed the literature and conducted surveys of parents of children with PKU, young adults with PKU, and directors of PKU clinics in the United States. A meeting was held at the National Institute of Child Health and Human Development to review the AAP/COG efforts at reviewing the status of PKU management and guideline development in the United States.	Survey participants were asked to respond on questions related to current dietary practice, serum Phe monitoring, costs, and satisfaction with current treatment practices. Treatment was started between the ages of 8–14 days in 53% of the patients. Nearly 5% of the study participants were not on dietary treatment at the time of the survey. Patients between the ages of 6–10 years or 11–15 years were most likely to stop treatment, although it was reported that 90% of the families acknowledged that the clinic had advised them to be on a special diet for life. Serum Phe levels were monitored either monthly or bi monthly in most cases. More than half of the families were unclear about the optimal Phe concentration for their child.

Monitoring Phenylalanine Levels for Metabolic Control		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Fisch RO, et al. (1997)[108] Type of Study – Cross sectional study to assess dietary treatment practices in North America Location – USA and Canada	N= 6,950 PKU patients from 111 centers	The range of patients served by these clinics was very broad. Participating clinics served anywhere from 2–600 PKU patients. Patient follow-up at least to the age of 18 years was reported by all clinics. 18/111 clinics did not have any limit placed on the age of follow-up. The majority of smaller clinics (85%) reported higher frequency of clinic visits (on a monthly basis) as compared to some larger clinics where on 48% reported monthly patient visits. Monitoring of Phe levels in the period between two clinic visits was recommended by 88% of all clinics. The target Phe levels for PKU patients varied by age. Blood Phe levels of less than 5 mg/dL were recommended for infants younger than 1 year by 43% of the clinics while another 51% recommended a less stringent range of 6–10 mg/dL. For ages 1 year to 10 years, most clinics preferred the Phe levels to be within the 6–10 mg/dL range. The same range was still preferred for patients between 11 and 18 years of age and those older than 18 by majority of the clinics. However, nearly 35% of the clinics reported that levels between 10 and 15 mg/dL were also acceptable for older patients.
Reference – Schuler A, et al. (1996)[109] Type of Study – Longitudinal study to analyze Phe levels, physical growth, intellectual development and performance in achievement tests in patients with classical PKU Location – Budapest, Hungary	N=56 patients with classical PKU; between the ages of 3 months and 20.5 years	Fifty six patients aged 3 months to 20 years were monitored for physical growth and intellectual development. The average age of initiation of restricted diet was 16.9 days for these patients (SD 8.8 days). The mean Phe levels before treatment initiation were 1956 µmol/L (SD 864 µmol/L). Authors reported that only 45% of the patients had Phe levels within the recommended range. Poor dietary control (indicated by high Phe levels) was reported for 33% of the patients while 22% had an intermediate level of dietary control. Although it was reported that the study subjects had normal/near normal physical growth and verbal/nonverbal IQ, no correlation was drawn between metabolic control and long-term outcomes.

16.4 Age-Appropriate Frequency of Monitoring Phenylalanine Levels

Age-Appropriate Frequency of Monitoring Phenylalanine Levels		
Reference	Study Population	Main Finding(s) *As it relates to the performance measure*
Reference – Fisch RO, et al. (1997)[108] Type of Study – Cross sectional study to assess dietary treatment practices in North America Location – USA and Canada	N= 6,950 PKU patients from 111 centers	The range of patients served by these clinics was very broad. Participating clinics served anywhere from 2–600 PKU patients. Patient follow-up at least to the age of 18 years was reported by all clinics. 18/111 clinics did not have any limit placed on the age of follow-up. The majority of smaller clinics (85%) reported higher frequency of clinic visits (on a monthly basis) as compared to some larger clinics where on 48% reported monthly patient visits. Monitoring of Phe levels in the period between two clinic visits was recommended by 88% of all clinics. The target Phe levels for PKU patients varied by age. Blood Phe levels of less than 5 mg/dL were recommended for infants younger than 1 year by 43% of the clinics while another 51% recommended a less stringent range of 6–10 mg/dL. For ages 1 year to 10 years, most clinics preferred the Phe levels to be within the 6–10 mg/dL range. The same range was still preferred for patients between 11 and 18 years of age and those older than 18 by majority of the clinics. However, nearly 35% of the clinics reported that levels between 10 and 15 mg/dL were also acceptable for older patients.
Reference – Schuler A, et al. (1996)[109] Type of Study – Longitudinal study to analyze Phe levels, physical growth, intellectual development and performance in achievement tests in patients with classical PKU Location – Budapest, Hungary	N = 56; patients with classical PKU; between the ages of 3 months and 20.5 years	Fifty six patients aged 3 months to 20 years were monitored for physical growth and intellectual development. The average age of initiation of restricted diet was 16.9 days for these patients (SD 8.8 days). The mean Phe levels before treatment initiation were 1956 µmol/L (SD 864 µmol/L). Authors reported that only 45% of the patients had Phe levels within the recommended range. Poor dietary control (indicated by high Phe levels) was reported for 33% of the patients while 22% had an intermediate level of dietary control. Although it was reported that the study subjects had normal/near normal physical growth and verbal/nonverbal IQ, no correlation was drawn between metabolic control and long-term outcomes.

17 Universal Performance Measures

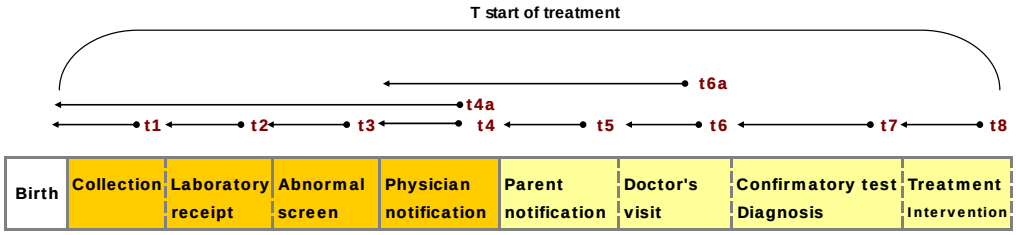
17.1 Introduction to System-Wide Universal Measures

The Texas Newborn Screening system is made up of a number of interdependent entities aimed at providing quality care for affected infants. These interdependent entities include, but are not limited to, primary care providers, birthing facilities, the Texas Newborn Screening Program, specialist centers, and families. Examples of activities and/or processes that occur across the system include: parent and provider education, collection of blood specimens, specimen transport to the laboratory, specimen receipt and preparation, laboratory analysis, case management or follow-up of abnormal screen results to ensure diagnosis/treatment, long-term follow-up, and ongoing program evaluation.

Performance measures discussed in this section address efficiency of discrete system-wide processes in the pre- and post-analytical phases of newborn screening. They are referred to as "universal" performance measures because these processes are essential for detection and treatment of affected infants regardless of the disorder.

17.1.1 Universal Measures Related to Time to Initiate Treatment

The following figure provides an overview of the series of steps that may be followed before appropriate treatment can be initiated for the affected infant. When considered cumulatively, these processes translate into "time to initiate treatment". This is a primary variable of interest for each of the disorders presented in this document (with an exception of MCADD which uses "time to a confirmed diagnosis"). Although the processes are depicted as discrete chronological events, in practice, they may overlap or occur in a different sequence. As an example, infants may be diagnosed immediately at birth or in the Neonatal Intensive Care Unit (NICU) for emergency treatment if life-threatening symptoms are detected. In such cases, treatment may begin before newborn screening results are available.



17.1.1.1 Candidate Performance Measures for Time to Initiate Treatment

The candidate performance measures listed below are general in nature. If considered for piloting, these working conceptual definitions will be further refined into operational definitions. A majority of these universal performance measures are not yet tied to established performance goals (e.g., "within 24 hours"). Performance goals shown in *italics* are tentative and may change during the refinement phase. The first measure listed below has a definitive performance goal of specimen collection between 24 and 48 hours. This goal has been established in accordance with State rules. Per Texas Administrative Code (TAC Title 25; Part 1, Chapter 37 Rule §37.56) an

initial blood specimen is to be obtained from a newborn after 24 hours of age and before 48 hours of age.

- **(t1) Time from Birth to Specimen Collection for the First Screen**

  Determine the percentage of initial blood specimens acceptable for testing that are collected from newborns between 24 to 48 hours of life.
- **(t2) Specimen Transit Time**

  Determine the percentage of newborn blood specimens received by the state public health laboratory *within two* calendar days of the collection date.
- **(t3) Time from Laboratory Abnormal Screen Result To Notifying Case Managers**

  Determine the percentage of abnormal specimens reported to case management *within the one calendar day* of the screen results being finalized.
- **(t4) Time from Abnormal Result Obtained until Physician Notification**

  Determine the percentage of abnormal results reported to the physician by the case manager *within 24 hours* of receipt from the laboratory.
- **(t4a) Time from Birth until Physician Notification**

  Determine the percentage of abnormal results reported to physicians *within 5 days of birth*.
- **(t5) Time from Physician Notification until Parent Notification**

  Determine the time from primary physician notification of an abnormal result to parent notification.
- **(t6) Time from Parent Notification until Physician/Specialist Visit for confirmatory testing**

  Determine time from parent notification of an abnormal result to specialist visit for confirmatory testing.
- **(t6a)Time from Abnormal Screen Result to Time Infant is seen by Physician/Specialist for confirmatory testing**

  Determine time from abnormal result to confirmatory testing (includes t4 through t6).
- **(t7) Time from Physician/Specialist Visit until Receipt of Confirmatory Testing Results**

  Determine time from confirmatory testing to results received.
- **(t8) Time from Receipt of Confirmatory Testing Results until Treatment Initiation**

  Determine time from confirmatory testing to parent notification and treatment initiation.

17.1.2 Discussion

Little or no direct evidence was found to support the universal measures in this section. This could be attributed to the fact that few studies have focused on system-wide processes in public health. However, timely treatment was associated with clinical outcomes in numerous disorder-specific studies. Timely treatment is feasible only if each of the steps in pre- and post-analytical phases of newborn screening is carried out efficiently. Therefore, direct evidence in support of timely treatment lends indirect support to the cumulative steps that precede treatment initiation. These measures are under consideration because they have direct impact on how promptly a

child is identified with a disorder and placed on treatment. For example, evidence in the literature indicates that the earliest signs of salt-wasting in patients with SW CAH may appear at an average age of 7.6 days, and more than one study supports treatment initiation within 10 days of life.[9-11] Since the primary intent of newborn screening is to prevent morbidity and mortality, it is critical to treat each specimen as an assumed positive. Further, based on a recent survey of current practices of reporting quality assurance feedback to specimen submitters, a majority of states (including Texas) report information on" time from birth to specimen collection" and "specimen transit time". Only a few states routinely report information on other aspects of timing. This could be because of a possible lack of infrastructure to collect, synthesize, and report such data on a periodic basis.

17.2 Universal Measures Related to Specimen Collection and Specimen Quality

Performance measures in the pre- analytical phase of newborn screening are related to specimen quality and specimen collection processes. Specimen quality refers to the degree of acceptability of a specimen for testing purposes. Specimen collection processes involve the actual collection, submission and receipt of blood specimen within a specified period of time. In addition, they also involve collection of demographic information on the specimen card.

17.2.1 Candidate Performance Measures Related to Specimen Collection and Specimen Quality

The candidate performance measures listed below are general in nature. If considered for piloting, these working conceptual definitions will be further refined into operational definitions. The goal of the TNSP is for birthing facilities to be error-free in regards to these measures in order to reduce the possibility of negative health effects on infants.

- **Unsatisfactory Specimen Rate**

  Determine the percentage of unsatisfactory specimens received. Unsatisfactory specimens cannot be tested. Therefore, a window of opportunity to identify a child with a disorder may be lost.
- **Percentage Missing Birth Weight**

  Determine the percentage of specimens missing birth weight information. The algorithm for calculating screen results for some disorders takes the weight of baby at birth into consideration, leading to inaccurate results when this information is missing.
- **Percentage Missing Date of Birth (DOB)**

  Determine the percentage of specimens missing the DOB. The algorithm for calculating screen results takes the age of the infant at the time of specimen collection into consideration.
- **Percentage Missing Date of Collection (DOC)**

  Determine the percentage of specimens not tested due to missing the DOC. Due to regulatory requirements, specimens cannot be tested if a DOC is not provided. When attempts to obtain the DOC from the specimen submitter are unsuccessful, the specimen must be rejected.
- **Percentage missing Primary Care Physician (PCP) information**

Determine the percentage of specimens missing PCP information. Case managers need contact information for the PCP to quickly notify then if an infant has a life threatening condition.

- **Percentage with incorrect PCP information**

  Determine the percentage of specimens with incorrect PCP information. Case managers need accurate contact information for the PCP to quickly notify them if an infant has a life threatening condition.

17.2.2 Existing Measures Used by Other State Programs

A newborn screening "report card" is used by many states in the US to provide feedback on specimen quality, collection, and submission practices. The term "report card" is not used in all the states; however, some have similar terms on their feedback reports such as "Quality Assurance Data" or "Practice Profiles."

In response to a telephone request for a copy of the newborn screening report card, 43 of 50 states shared information with TNSP staff members. Of the 43 responders, 13 do not provide feedback to their specimen submitters. The remaining 30 states provide periodic feedback to their submitters on the rate of unsatisfactory specimens received from their facility.

Universal Performance Measure	Number of states utilizing the measure in their feedback to submitters (N=43)
Unsatisfactory Specimen Rate	30
Percentage Missing Birth Weight	6
Percentage Missing DOB	12
Percentage Missing DOC	14
Percentage Missing PCP Information	3
Percentage with Incorrect PCP Information	Not applicable

17.2.3 Discussion

A specimen may be declared unsatisfactory for a number of reasons. An insufficient or excessive amount of blood on the collection card or a damaged, discolored, or contaminated specimen may lead to inaccurate test results. Therefore, any one of these reasons can lead to rejection of a specimen upon receipt in the newborn screening laboratory. Rejected specimens automatically result in the need for repeat screening which ultimately delays the follow-up, diagnosis, and treatment.

Similarly, missing or inaccurate demographic information may also lead to specimen rejection. Missing or inaccurate demographic information can lead to: 1) inaccurate test results and thus missed cases; or 2) delayed follow-up, diagnosis, and treatment. Therefore, measures related to specimen quality are indirectly related to timeliness of screening and diagnosis.

18 Limitations of Evidence

18.1 Unpublished versus Published Evidence

This evidence based review was based on the scientific articles that were available at the time of our search. Many of the proposed measures did not have sound scientific evidence that supported them. Lack of scientific evidence may not automatically indicate a lack of significance. It can also mean that the issue has not yet been the subject of research that is available in the public domain. It is also common to encounter numerous studies on disorders that have been on the screening panels for a long time while the literature on some of the newer conditions is relatively sparse. This disparity in the existing knowledge base is also likely to create bias in favor of performance measures related to better-researched disorders.

18.2 Available Evidence within Pediatric Research

Since the subject of this evidence summary was newborn screening and clinical outcomes associated with it, most of the studies included in the review are related to pediatric subjects. Research on pediatric subjects is inherently difficult because of ethical concerns. Subsequently, randomized controlled studies (which are the gold standard in evidence based research) are very rare in pediatric literature. Most of the studies that we encountered were hospital based studies, with a good number of case studies as well. Therefore the quality of evidence in this review may not be comparable to that of the evidence that is available for some of the more common adult conditions.

18.3 Lack of Statistical Significance

Studies that included the performance measure of interest may not have had the measure as the primary focus of the study. Therefore, some of the evidence was considered weak because the data did not directly support the performance measure of interest. Lack of statistical significance in the available evidence led to the exclusion of some of the potential measures.

18.4 Lack of Consensus within the Available Evidence

A review of the literature also shows that some of the treatment guidelines have evolved over a period of time. For example, “optimal” leucine levels in MSUD disease management have changed significantly over time as specialists have gained better understanding of the disease. Levels that were considered acceptable a few decades ago are considered unacceptably high in some of the more recent studies. Therefore, as new evidence becomes available, some of the older evidence may become obsolete.

18.5 Generalizability to Texas

Because most of the studies that are included in this review were conducted at locations other than Texas, their findings may not be generalizable to the population served by the newborn screening system in Texas. Variations are likely to exist in the demographic characteristics. Also, the size and the geographical location of Texas may also be potential reasons why some of the evidence may not be applicable to this state. Some of the studies were conducted in specialty

centers that receive high volumes of patients with newborn screening disorders. These clinics are better equipped with identifying and treating the patients because of their expertise. It may not be possible to expect a similar level of clinical expertise in some of the smaller clinics that receive very few patients with newborn screening disorders.

Therefore, despite the obvious benefits of this evidence summary, there are inherent limitations as well. Many of these limitations can be attributed to a lack of existing knowledge. Identification of gaps in the current literature may generate an interest in future research activities.

19 References

1. McKusick VA. Adrenal Hyperplasia, Congenital, Due to 21-Hydroxylase Deficiency. *Online Mendelian Inheritance in Man (OMIM)* [http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=201910. Accessed March 12, 2009.
2. Technical report: congenital adrenal hyperplasia. Section on Endocrinology and Committee on Genetics. *Pediatrics.* Dec 2000;106(6):1511-1518.
3. Kaye CI, Accurso F, La Franchi S, et al. Newborn screening fact sheets. *Pediatrics.* Sep 2006;118(3):e934-963.
4. Therrell BL, Jr., Berenbaum SA, Manter-Kapanke V, et al. Results of screening 1.9 million Texas newborns for 21-hydroxylase-deficient congenital adrenal hyperplasia. *Pediatrics.* Apr 1998;101(4 Pt 1):583-590.
5. Brook CG, Zachmann M, Prader A, Murset G. Experience with long-term therapy in congenital adrenal hyperplasia. *J Pediatr.* Jul 1974;85(1):12-19.
6. Hauffa BP, Winter A, Stolecke H. Treatment and disease effects on short-term growth and adult height in children and adolescents with 21-hydroxylase deficiency. *Klin Padiatr.* Mar-Apr 1997;209(2):71-77.
7. Riepe FG, Krone N, Viemann M, Partsch CJ, Sippell WG. Management of congenital adrenal hyperplasia: results of the ESPE questionnaire. *Horm Res.* 2002;58(4):196-205.
8. Hughes IA, Houk C, Ahmed SF, Lee PA. Consensus statement on management of intersex disorders. *Arch Dis Child.* Jul 2006;91(7):554-563.
9. Steigert M, Schoenle EJ, Biason-Lauber A, Torresani T. High reliability of neonatal screening for congenital adrenal hyperplasia in Switzerland. *J Clin Endocrinol Metab.* Sep 2002;87(9):4106-4110.
10. Cutfield WS, Webster D. Newborn screening for congenital adrenal hyperplasia in New Zealand. *J Pediatr.* Jan 1995;126(1):118-121.
11. Bajpai A, Kabra M, Menon PS. 21-Hydroxylase deficiency: clinical features, laboratory profile and pointers to diagnosis in Indian children. *Indian Pediatr.* Dec 2004;41(12):1226-1232.
12. Torok D, Eckhardt G, Solyom J. Twenty years experience in rapid identification of congenital adrenal hyperplasia in Hungary. *Eur J Pediatr.* Dec 2003;162(12):844-849.
13. Frisch H, Waldhauser F, Lebl J, et al. Congenital adrenal hyperplasia: lessons from a multinational study. *Horm Res.* 2002;57 Suppl 2:95-101.
14. Gasparini N, Di Maio S, Salerno M, Argenziano A, Franzese A, Tenore A. Growth pattern during the first 36 months of life in congenital adrenal hyperplasia (21-hydroxylase deficiency). *Horm Res.* 1997;47(1):17-22.
15. Kovacs J, Votava F, Heinze G, et al. Lessons from 30 years of clinical diagnosis and treatment of congenital adrenal hyperplasia in five middle European countries. *J Clin Endocrinol Metab.* Jul 2001;86(7):2958-2964.
16. Thil'en A, Nordenstrom A, Hagenfeldt L, von Dobeln U, Guthenberg C, Larsson A. Benefits of neonatal screening for congenital adrenal hyperplasia (21-hydroxylase deficiency) in Sweden. *Pediatrics.* Apr 1998;101(4):E11.
17. Listernick R, Frisone L, Silverman BL. Delayed diagnosis of infants with abnormal neonatal screens. *JAMA.* Feb 26 1992;267(8):1095-1099.

18. Bergstrand CG. Growth in congenital adrenal hyperplasia. *Acta Paediatr Scand.* Sep 1966;55(5):463-472.

19. Eugster EA, Dimeglio LA, Wright JC, Freidenberg GR, Seshadri R, Pescovitz OH. Height outcome in congenital adrenal hyperplasia caused by 21-hydroxylase deficiency: a meta-analysis. *J Pediatr.* Jan 2001;138(1):26-32.

20. Manoli I, Kanaka-Gantenbein C, Voutetakis A, Maniati-Christidi M, Dacou-Voutetakis C. Early growth, pubertal development, body mass index and final height of patients with congenital adrenal hyperplasia: factors influencing the outcome. *Clin Endocrinol (Oxf).* Nov 2002;57(5):669-676.

21. Merke DP, Bornstein SR. Congenital adrenal hyperplasia. *Lancet.* Jun 18-24 2005;365(9477):2125-2136.

22. Van der Kamp HJ, Otten BJ, Buitenweg N, et al. Longitudinal analysis of growth and puberty in 21-hydroxylase deficiency patients. *Arch Dis Child.* Aug 2002;87(2):139-144.

23. Waggoner DD, Buist NR, Donnell GN. Long-term prognosis in galactosaemia: results of a survey of 350 cases. *J Inherit Metab Dis.* 1990;13(6):802-818.

24. Elsas LJ. Galactosemia. http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=galactosemia. Accessed December 22, 2008.

25. Therrell BL, Jr., Brown LO, Dziuk PE, Peter WP, Jr. The Texas Newborn Screening Program. *Tex Med.* Feb 1983;79(2):44-46.

26. Badawi N, Cahalane SF, McDonald M, et al. Galactosaemia--a controversial disorder. Screening & outcome. Ireland 1972-1992. *Ir Med J.* Jan-Feb 1996;89(1):16-17.

27. Brazeal TJ, J.E. F. Natural course and treatment of neuropsychological deficits in a child with early-treated galactosemia. *Child Neuropsychology.* 1999;5(3):197-209.

28. Schweitzer S, Shin Y, Jakobs C, Brodehl J. Long-term outcome in 134 patients with galactosaemia. *Eur J Pediatr.* Jan 1993;152(1):36-43.

29. Guerrero NV, Singh RH, Manatunga A, Berry GT, Steiner RD, Elsas LJ, 2nd. Risk factors for premature ovarian failure in females with galactosemia. *J Pediatr.* Dec 2000;137(6):833-841.

30. Schweitzer-Krantz S. Early diagnosis of inherited metabolic disorders towards improving outcome: the controversial issue of galactosaemia. *Eur J Pediatr.* Dec 2003;162 Suppl 1:S50-53.

31. Sardharwalla IB, Wraith JE. Galactosaemia. *Nutr Health.* 1987;5(3-4):175-188.

32. Waisbren SE, Norman TR, Schnell RR, Levy HL. Speech and language deficits in early-treated children with galactosemia. *J Pediatr.* Jan 1983;102(1):75-77.

33. Beigi B, O'Keefe M, Bowell R, Naughten E, Badawi N, Lanigan B. Ophthalmic findings in classical galactosaemia--prospective study. *Br J Ophthalmol.* Mar 1993;77(3):162-164.

34. Burke JP, O'Keefe M, Bowell R, Naughten ER. Cataracts in children with classical galactosaemia and in their parents. *J Inherit Metab Dis.* 1988;11 Suppl 2:246-248.

35. Applebaum MN, Thaler MM. Reversibility of extensive liver damage in galactosemia. *Gastroenterology.* Aug 1975;69(2):496-502.

36. Matern D. Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=mcad. Accessed December 28, 2008.

37. American College of Medical Genetics NEWBORN SCREENING ACT SHEETS AND CONFIRMATORY ALGORITHMS.

http://www.acmg.net/resources/policies/ACT/condition-analyte-links.htm. Accessed December 17, 2008.

38. Iafolla AK, Thompson RJ, Jr., Roe CR. Medium-chain acyl-coenzyme A dehydrogenase deficiency: clinical course in 120 affected children. *J Pediatr.* Mar 1994;124(3):409-415.

39. Grosse SD, Khoury MJ, Greene CL, Crider KS, Pollitt RJ. The epidemiology of medium chain acyl-CoA dehydrogenase deficiency: an update. *Genet Med.* Apr 2006;8(4):205-212.

40. Wilson CJ, Champion MP, Collins JE, Clayton PT, Leonard JV. Outcome of medium chain acyl-CoA dehydrogenase deficiency after diagnosis. *Arch Dis Child.* May 1999;80(5):459-462.

41. Wilcken B, Haas M, Joy P, et al. Outcome of neonatal screening for medium-chain acyl-CoA dehydrogenase deficiency in Australia: a cohort study. *Lancet.* Jan 6 2007;369(9555):37-42.

42. Farrell MH, Kuruvilla P. Assessment of parental understanding by pediatric residents during counseling after newborn genetic screening. *Arch Pediatr Adolesc Med.* Mar 2008;162(3):199-204.

43. Derks TG, van Spronsen FJ, Rake JP, van der Hilst CS, Span MM, Smit GP. Safe and unsafe duration of fasting for children with MCAD deficiency. *Eur J Pediatr.* Jan 2007;166(1):5-11.

44. Wilcken B, Hammond J, Silink M. Morbidity and mortality in medium chain acyl coenzyme A dehydrogenase deficiency. *Arch Dis Child.* May 1994;70(5):410-412.

45. Rose SR, Brown RS, Foley T, et al. Update of newborn screening and therapy for congenital hypothyroidism. *Pediatrics.* Jun 2006;117(6):2290-2303.

46. Derksen-Lubsen G, Verkerk PH. Neuropsychologic development in early treated congenital hypothyroidism: analysis of literature data. *Pediatr Res.* Mar 1996;39(3):561-566.

47. Bongers-Schokking JJ, de Muinck Keizer-Schrama SM. Influence of timing and dose of thyroid hormone replacement on mental, psychomotor, and behavioral development in children with congenital hypothyroidism. *J Pediatr.* Dec 2005;147(6):768-774.

48. Kempers MJ, van der Sluijs Veer L, Nijhuis-van der Sanden MW, et al. Intellectual and motor development of young adults with congenital hypothyroidism diagnosed by neonatal screening. *J Clin Endocrinol Metab.* Feb 2006;91(2):418-424.

49. Kooistra L, Laane C, Vulsma T, Schellekens JM, van der Meere JJ, Kalverboer AF. Motor and cognitive development in children with congenital hypothyroidism: a long-term evaluation of the effects of neonatal treatment. *J Pediatr.* Jun 1994;124(6):903-909.

50. Oerbeck B, Sundet K, Kase BF, Heyerdahl S. Congenital hypothyroidism: influence of disease severity and L-thyroxine treatment on intellectual, motor, and school-associated outcomes in young adults. *Pediatrics.* Oct 2003;112(4):923-930.

51. Song SI, Daneman D, Rovet J. The influence of etiology and treatment factors on intellectual outcome in congenital hypothyroidism. *J Dev Behav Pediatr.* Dec 2001;22(6):376-384.

52. Tillotson SL, Fuggle PW, Smith I, Ades AE, Grant DB. Relation between biochemical severity and intelligence in early treated congenital hypothyroidism: a threshold effect. *BMJ.* Aug 13 1994;309(6952):440-445.

53. Bongers-Schokking JJ, Koot HM, Wiersma D, Verkerk PH, de Muinck Keizer-Schrama SM. Influence of timing and dose of thyroid hormone replacement on development in infants with congenital hypothyroidism. *J Pediatr.* Mar 2000;136(3):292-297.

54. Dimitropoulos A, Molinari L, Etter K, et al. Children with congenital hypothyroidism: long-term intellectual outcome after early high-dose treatment. *Pediatr Res.* Feb 2009;65(2):242-248.

55. Heyerdahl S, Ilicki A, Karlberg J, Kase BF, Larsson A. Linear growth in early treated children with congenital hypothyroidism. *Acta Paediatr.* May 1997;86(5):479-483.

56. Kempers MJ, van der Sluijs Veer L, Nijhuis-van der Sanden RW, et al. Neonatal screening for congenital hypothyroidism in the Netherlands: cognitive and motor outcome at 10 years of age. *J Clin Endocrinol Metab.* Mar 2007;92(3):919-924.

57. Leger J, Larroque B, Norton J. Influence of severity of congenital hypothyroidism and adequacy of treatment on school achievement in young adolescents: a population-based cohort study. *Acta Paediatr.* Nov 2001;90(11):1249-1256.

58. Rovet J, Daneman D. Congenital hypothyroidism: a review of current diagnostic and treatment practices in relation to neuropsychologic outcome. *Paediatr Drugs.* 2003;5(3):141-149.

59. Salerno M, Militerni R, Bravaccio C, et al. Effect of different starting doses of levothyroxine on growth and intellectual outcome at four years of age in congenital hypothyroidism. *Thyroid.* Jan 2002;12(1):45-52.

60. Selva KA, Harper A, Downs A, Blasco PA, Lafranchi SH. Neurodevelopmental outcomes in congenital hypothyroidism: comparison of initial T4 dose and time to reach target T4 and TSH. *J Pediatr.* Dec 2005;147(6):775-780.

61. Van Vliet G. Neonatal hypothyroidism: treatment and outcome. *Thyroid.* Jan 1999;9(1):79-84.

62. Heyerdahl S, Oerbeck B. Congenital hypothyroidism: developmental outcome in relation to levothyroxine treatment variables. *Thyroid.* Nov 2003;13(11):1029-1038.

63. Ilicki A, Larsson A. Psychological development at 7 years of age in children with congenital hypothyroidism. Timing and dosage of initial treatment. *Acta Paediatr Scand.* Feb 1991;80(2):199-204.

64. Eugster EA, LeMay D, Zerin JM, Pescovitz OH. Definitive diagnosis in children with congenital hypothyroidism. *J Pediatr.* May 2004;144(5):643-647.

65. Yang RL, Zhu ZW, Zhou XL, Zhao ZY. Treatment and follow-up of children with transient congenital hypothyroidism. *J Zhejiang Univ Sci B.* Dec 2005;6(12):1206-1209.

66. Strauss KA, Peffinberger EG, Morton DH. Maple Syrup Urine Disease. *Gene Reviews* [http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=msud. Accessed January 20th, 2009.

67. Morton DH, Strauss KA, Robinson DL, Puffenberger EG, Kelley RI. Diagnosis and treatment of maple syrup disease: a study of 36 patients. *Pediatrics.* Jun 2002;109(6):999-1008.

68. Kaplan P, Mazur A, Field M, et al. Intellectual outcome in children with maple syrup urine disease. *J Pediatr.* Jul 1991;119(1 (Pt 1)):46-50.

69. le Roux C, Murphy E, Hallam P, Lilburn M, Orlowska D, Lee P. Neuropsychometric outcome predictors for adults with maple syrup urine disease. *J Inherit Metab Dis.* Feb 2006;29(1):201-202.

70. Nord A, van Doorninck WJ, Greene C. Developmental profile of patients with maple syrup urine disease. *J Inherit Metab Dis.* 1991;14(6):881-889.

71. Snyderman SE. Treatment outcome of maple syrup urine disease. *Acta Paediatr Jpn.* Aug 1988;30(4):417-424.

72. Yoshino M, Aoki K, Akeda H, et al. Management of acute metabolic decompensation in maple syrup urine disease: a multi-center study. *Pediatr Int.* Apr 1999;41(2):132-137.

73. Hilliges C, Awiszus D, Wendel U. Intellectual performance of children with maple syrup urine disease. *Eur J Pediatr.* Feb 1993;152(2):144-147.

74. Naughten ER, Jenkins J, Francis DE, Leonard JV. Outcome of maple syrup urine disease. *Arch Dis Child.* Dec 1982;57(12):918-921.

75. Hoffmann B, Helbling C, Schadewaldt P, Wendel U. Impact of longitudinal plasma leucine levels on the intellectual outcome in patients with classic MSUD. *Pediatr Res.* Jan 2006;59(1):17-20.

76. Quinn CT, Thomas K, Rogers ZR, Buchanan GR. Improved Survival of Children and Adolescents with Sickle Cell Disease. *ASH Annual Meeting.* Vol 112; 2008.

77. Vichinsky E, Schlis K. Sickle Cell Disease. *Gene Reviews* [March 7, 2006; http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=sickle. Accessed December 12, 2008.

78. Therrell BL, Jr., Simmank JL, Wilborn M. Experiences with sickle hemoglobin testing in the Texas Newborn Screening Program. *Pediatrics.* May 1989;83(5 Pt 2):864-867.

79. American Academy of Pediatrics. Committee on Infectious Diseases. Policy statement: recommendations for the prevention of pneumococcal infections, including the use of pneumococcal conjugate vaccine (Prevnar), pneumococcal polysaccharide vaccine, and antibiotic prophylaxis. *Pediatrics.* Aug 2000;106(2 Pt 1):362-366.

80. Redding-Lallinger R, Knoll C. Sickle cell disease--pathophysiology and treatment. *Curr Probl Pediatr Adolesc Health Care.* Nov-Dec 2006;36(10):346-376.

81. Bardakdjian-Michau J, Guilloud-Batailie M, Maier-Redelsperger M, et al. Decreased morbidity in homozygous sickle cell disease detected at birth. *Hemoglobin.* Aug 2002;26(3):211-217.

82. Telfer P, Coen P, Chakravorty S, et al. Clinical outcomes in children with sickle cell disease living in England: a neonatal cohort in East London. *Haematologica.* Jul 2007;92(7):905-912.

83. Hord J, Byrd R, Stowe L, Windsor B, Smith-Whitley K. Streptococcus pneumoniae sepsis and meningitis during the penicillin prophylaxis era in children with sickle cell disease. *J Pediatr Hematol Oncol.* Aug-Sep 2002;24(6):470-472.

84. Quinn CT, Rogers ZR, Buchanan GR. Survival of children with sickle cell disease. *Blood.* Jun 1 2004;103(11):4023-4027.

85. Hirst C, Owusu-Ofori S. Prophylactic antibiotics for preventing pneumococcal infection in children with sickle cell disease. *Cochrane Database Syst Rev.* 2002(3).

86. Babiker MA. Compliance with penicillin prophylaxis by children with impaired splenic function. *Trop Geogr Med.* Jun 1986;38(2):119-122.

87. Gaston MH, Verter J. Sickle cell anaemia trial. *Stat Med.* Jan-Feb 1990;9(1-2):45-49; discussion 49-51.

88. Adamkiewicz TV, Silk BJ, Howgate J, et al. Effectiveness of the 7-valent pneumococcal conjugate vaccine in children with sickle cell disease in the first decade of life. *Pediatrics.* Mar 2008;121(3):562-569.

89. Center KJ. Prevenar vaccination: review of the global data, 2006. *Vaccine.* Apr 20 2007;25(16):3085-3089.

90. Davies EG, Riddington C, Lottenberg R, Dower N. Pneumococcal vaccines for sickle cell disease. *Cochrane Database Syst Rev.* 2004(1):CD003885.

91. Overturf GD. American Academy of Pediatrics. Committee on Infectious Diseases. Technical report: prevention of pneumococcal infections, including the use of pneumococcal conjugate and polysaccharide vaccines and antibiotic prophylaxis. *Pediatrics.* Aug 2000;106(2 Pt 1):367-376.

92. Reinert P, Benkerrou M, de Montalembert M, et al. Immunogenicity and safety of a pneumococcal conjugate 7-valent vaccine in infants with sickle cell disease. *Pediatr Infect Dis J.* Dec 2007;26(12):1105-1109.

93. Falletta JM, Woods GM, Verter JI, et al. Discontinuing penicillin prophylaxis in children with sickle cell anemia. Prophylactic Penicillin Study II. *J Pediatr.* Nov 1995;127(5):685-690.

94. Pai VB, Nahata MC. Duration of penicillin prophylaxis in sickle cell anemia: issues and controversies. *Pharmacotherapy.* Jan 2000;20(1):110-117.

95. Vichinsky E, Hurst D, Earles A, Kleman K, Lubin B. Newborn screening for sickle cell disease: effect on mortality. *Pediatrics.* Jun 1988;81(6):749-755.

96. Emond AM, Collis R, Darvill D, Higgs DR, Maude GH, Serjeant GR. Acute splenic sequestration in homozygous sickle cell disease: natural history and management. *J Pediatr.* Aug 1985;107(2):201-206.

97. Wilson-Okoh DA, Nwauche CA, Ejele OA. Splenic changes in sickle cell anaemia. *Niger J Med.* Jan-Mar 2006;15(1):20-23.

98. Dorticos-Balea A, Martin-Ruiz M, Hechevarria-Fernandez P, et al. Reproductive behaviour of couples at risk for sickle cell disease in Cuba: a follow-up study. *Prenat Diagn.* Aug 1997;17(8):737-742.

99. Howard RJ, Lillis C, Tuck SM. Contraceptives, counselling, and pregnancy in women with sickle cell disease. *BMJ.* Jun 26 1993;306(6894):1735-1737.

100. Mitchell J, Scriver C. Phenylalanine Hydroxylase Deficiency. *Gene Reviews* [http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=pku. Accessed March 1, 2009.

101. Cabalska MB, Nowaczewska I, Sendecka E, Zorska K. Longitudinal study on early diagnosis and treatment of phenylketonuria in Poland. *Eur J Pediatr.* Jul 1996;155 Suppl 1:S53-55.

102. Gassio R, Artuch R, Vilaseca MA, et al. Cognitive functions in classic phenylketonuria and mild hyperphenylalaninaemia: experience in a paediatric population. *Dev Med Child Neurol.* Jul 2005;47(7):443-448.

103. VanZutphen KH, Packman W, Sporri L, et al. Executive functioning in children and adolescents with phenylketonuria. *Clin Genet.* Jul 2007;72(1):13-18.

104. Poustie VJ, Rutherford P. Dietary interventions for phenylketonuria. *Cochrane Database Syst Rev.* 1999(2):CD001304.

105. Fitzgerald B, Morgan J, Keene N, Rollinson R, Hodgson A, Dalrymple-Smith J. An investigation into diet treatment for adults with previously untreated phenylketonuria and severe intellectual disability. *J Intellect Disabil Res.* Feb 2000;44 (Pt 1):53-59.

106. Koch R, Moseley K, Ning J, Romstad A, Guldberg P, Guttler F. Long-term beneficial effects of the phenylalanine-restricted diet in late-diagnosed individuals with phenylketonuria. *Mol Genet Metab.* Jun 1999;67(2):148-155.

107. Poustie VJ, Rutherford P. Tyrosine supplementation for phenylketonuria. *Cochrane Database Syst Rev.* 2000(2):CD001507.

108. Fisch RO, Matalon R, Weisberg S, Michals K. Phenylketonuria: current dietary treatment practices in the United States and Canada. *J Am Coll Nutr.* Apr 1997;16(2):147-151.

109. Schuler A, Somogyi C, Toros I, et al. A longitudinal study of phenylketonuria based on the data of the Budapest Screening Center. *Eur J Pediatr.* Jul 1996;155 Suppl 1:S50-52.

110. Waisbren SE, Noel K, Fahrbach K, et al. Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systematic literature review and meta-analysis. *Mol Genet Metab.* Sep-Oct 2007;92(1-2):63-70.

111. Wappner R, Cho S, Kronmal RA, Schuett V, Seashore MR. Management of phenylketonuria for optimal outcome: a review of guidelines for phenylketonuria management and a report of surveys of parents, patients, and clinic directors. *Pediatrics.* Dec 1999;104(6):e68.

---

[i] This Texas birth occurrence for 2007 was provided by the Texas DSHS Bureau of Vital Statistics. The data are provisional and subject to errors/changes.