State of Wisconsin

LEGISLATIVE REFERENCE BUREAU

☞Appendix A

LRB BILL HISTORY RESEARCH APPENDIX

☞

2013 LRB–3697 (AB 654)

RESEARCH APPENDIX -

PLEASE KEEP WITH THE DRAFTING FILE

The attached was included in the drafting file ... because of its size it was removed from the "guts" and a included here as a separate "Appendix".

Report to the Secretary of the Wisconsin Department of Health Services

Newborn Screening Task Force

June 2013

Table of Contents

I. Introduction and Background 1
A. Introduction 1
B. Background 2

II. The Advisory Process 5

III. Criteria for Adding/Deleting Tests 7
A. Characteristics of the specific disorder, including disease incidence, morbidity, and mortality (DHS 115.06(1)) 8
B. The availability of effective therapy and potential for successful treatment (DHS 115.06(2)) 9
C. Characteristics of the test, including sensitivity, specificity, and feasibility for mass screening (DHS 115.06(3)) 11
D. The availability of mechanisms for determining the effectiveness of test procedures (DHS 115.06(4)) 13
E. The ability to collect and analyze specimens reliably and promptly, the ability to report test results quickly and accurately, and the existence of adequate follow-up and management programs (DHS 115.06(5)) 13
F. The mechanism of funding the testing and treatment should be identified (DHS 115.06(6)) 15
G. Adventitious findings (DHS 115.06(6)) 16
H. Consent (DHS 115.06(6)) 18
i. General considerations 18
ii. Consent to testing vs. consent to disclosure of results 19
iii. Opting in vs. opting out 20
iv. Proven vs. unproven tests and treatments 20
v. Frequency and severity of disease; effectiveness of treatment 21
vi. Practical considerations 21

IV. References 23

V. Appendices 26
Appendix A: Summary of recommendations 26
Appendix B: Conditions currently screened and treated in Wisconsin 28
Appendix C: Composition of the Umbrella Committee 30
Appendix D: Wisconsin newborn screening program advisory committee structure 31
Appendix E: Charge of the Ad Hoc Umbrella Committee Task Force (TF1) 32
Appendix F: Charge of the Wisconsin Newborn Screening Task Force 33
Appendix G: Members of the Wisconsin Newborn Screening Task Force 34

I. Introduction and Background

A. Introduction

State-sponsored newborn screening is performed on nearly all of the more than 4 million infants born in the United States annually. It ensures that infants are screened for certain serious conditions at birth, and for infants that have one of these conditions, screening allows physicians to start treatment before harmful effects occur. In general, these are rare conditions that can cause major disability or death if treatment is not started early in life.

Traditionally tests for these conditions have been performed on dried spots of blood collected from a small heel stick. In recent years, point-of-care testing, performed at the birth site (hospital, home), has been included—e.g., to detect congenital hearing loss[1] and critical congenital heart disease.[2] About 1 in 500 infants will have a serious condition detectable through newborn blood spot screening (or 1 in 300 when point-of-care tests are included). Most of these infants benefit greatly by early detection from this program.

Which tests are offered or performed vary by state. In 1966, Wisconsin started screening newborns for phenylketonuria (PKU). Wisconsin currently includes testing for 44 conditions. Two of the current screening tests used across the nation—tests for cystic fibrosis (CF) and for severe combined immunodeficiency (SCID)—were first developed by the Wisconsin program. Additionally, some other states and countries contract with Wisconsin's laboratory to perform their newborn blood spot screening.

In 2012, 66,591 babies underwent newborn (blood spot) screening in Wisconsin. Of these, approximately 130 had serious conditions identified that led to beneficial early intervention (1 in 513). **Table 1** summarizes the cumulative number of children identified for the most common conditions. **Appendix B** summarizes the conditions that are currently screened and treated.

TABLE 1: WISCONSIN NEWBORN SCREENING PROGRAM STATISTICS, SELECTED CONDITIONS (2012)

Test	Cumulative Since	Number Identified
Cong. Hypothyroidism	1978	978
Cong. Adrenal Hyperplasia	1993	84
Cystic Fibrosis	1994	290
PKU	1978	214
Galactosemia	1978	43
Fatty Acid Oxidation Defects	2000	59
Organic Acidemias	2000	75
Sickle Cell / Sickle C	1988	472
SCID	2010	3

Advances in testing have made it possible to identify many additional disorders beyond those currently screened for in Wisconsin. Evolving technology will make it possible to test for thousands of disorders from blood spots, creating unprecedented challenges in deciding when,

whether, and how to incorporate this information into the screening program. Many disorders have a constituency including: families; professional and consumer organizations; health care providers; corporations that make testing equipment and reagents; drug, formula, and food companies; researchers; and others who vigorously advocate for the early identification of their disorder. Some of these groups turn to legislators to get a condition added to a state newborn screening panel. There is concern that without a well-designed framework for considering the addition and deletion of disorders, tests may be added without regard to the complex medical, ethical, legal, economic, and social issues of balancing (1) benefit to the children with conditions detected by screening, (2) risks of false positives in children without these conditions, (3) cost, and (4) availability of treatment and follow-up. This Task Force was formed by the Secretary of the Wisconsin Department of Health Services (DHS) to address this concern by proposing a framework for making addition and deletion decisions by scientifically attempting to weigh all of the evidence and removing the bias of some of the aforementioned groups.

B. Background

In 1960, the development of an inexpensive test for phenylketonuria (PKU), along with an affordable and palatable diet (Lofenalac) stimulated the passage of state laws requiring newborn screening.[3]

Although there were initial problems—including false positives leading to unnecessary and potentially harmful treatment of some children with clinically significant mild hyperphenylalanemia, as well as incomplete understanding of dietary treatment with resultant tyrosine deficiency—PKU screening and treatment have prevented intellectual disability in thousands of children in the United States. PKU provides an example of the potential benefit of newborn screening, but the pitfalls that were encountered earlier in the history of the program illustrate the importance of fully understanding the test characteristics (sensitivity, specificity, false positive, false negatives), natural history, and safety and efficacy of treatment before implementing screening for a new disorder.

The PKU program was started through direct appeals to state legislatures without careful assessments by scientific experts and state health departments. In 1965 the American Academy of Pediatrics Committee on Nutrition, in a letter to the Secretary of the U.S. Department of Health, Education and Welfare (now the U.S. Department of Health and Human Services (DHHS)), recommended that the mandatory program be stopped pending clarification of the scientific issues. Although screening was never stopped, this eventually led to congressional hearings and formation of a committee by the National Academy of Sciences – National Research Council, whose report in 1975 reviewed the problems of the PKU program and suggested guidelines for future screening programs.[4] The PKU story illustrates the hazards of implementing programs directly through legislatures. Today, the PKU screening program is one of the most successful public health programs in the United States.

In subsequent decades, as technology has provided the opportunity for major expansion in newborn screening, the issues raised by the PKU program have been revisited repeatedly, with a parallel expansion in scholarship and debate about the ethical, legal, and social issues of genetic

screening in general, and newborn screening[1] in particular.[5 6 7 8] One response to these issues has been the development of newborn screening advisory committees in most (but not all) states.

Oversight of the Wisconsin newborn screening program is by the Secretary of the Department of Health Services (DHS). Blood spot testing is performed by the State Lab of Hygiene. Interpretation and communication of all test results is under the direction of an advisory committee. Wisconsin has had an advisory committee structure since 1992. The present structure consists of an Umbrella Committee, composed of the chairs of 7 subcommittees and an approximately equal number of members from a variety of constituencies (see **Appendix C**). While this process has generally been well-received, the number and complexity of scientific, ethical, legal, social, and economic issues—including concerns about conflicts of interest—has led to questions about whether the advisory process might be improved, and whether the criteria for adding and deleting tests, presently defined by state administrative rule (WIS. ADMIN. CODE § DHS 115.06), should be revisited.

In November 2011, an Ad Hoc Umbrella Committee Task Force (henceforth TF1) was appointed by the State Health Officer with the charge of addressing issues involving the growing costs of the newborn screening program, including testing and treatment components (see **Appendix E**). TF1 also considered criteria for adding and deleting tests. In October 2012, before this group had submitted their final report, the Secretary of the Wisconsin DHS appointed an advisory committee (henceforth "Task Force"). The Task Force was charged with two assignments:

(1) to "make recommendations to the Secretary on a permanent organization structure for advising the Secretary on additions, deletions, costs, funding, informed consent and retention/use of blood samples, and other issues related to NBS tests"; and
(2) "make recommendations to the Secretary on … criteria, if any, (in addition to the six criteria in state statute) the state should consider when making recommendations about additions to and deletions from the mandated newborn screening tests."
(see **Appendix F**)

The Task Force included members with expertise in genetics, genetic counseling, metabolic disorders, general pediatrics, health law, bioethics, health policy, and a parent of a child with PKU (see **Appendix G**).

The Task Force was not asked to comment on or make recommendations regarding specific tests or disorders, though it inevitably considered specific examples as illustrations of general principles and problems. Similarly, the Task Force was not asked to comment on a number of specific issues, such as payment issues, public readiness for complex information, availability of therapeutic services, and the emerging use of genome-wide technology, but these issues inevitably arose in the course of discussing general criteria for adding or deleting tests.

The Task Force had seven in-person monthly meetings of four hours each, and two teleconferences of two hours each, from December 2012 through June 2013. Literature representing diverse views on newborn screening was made available through a website. All in-person meetings were held at the State Laboratory of Hygiene in Madison, except for the March 2013 meeting which was held at the University of Wisconsin-Milwaukee Zilber School of Public

[1] Not all newborn screening programs involve genetic conditions (e.g.,hypothyroidism), nor are all tests genetic tests.

Health with the primary purpose of hearing public comments. The December 2012 meeting included a joint session with the Umbrella Committee. The April meeting included two leading experts in newborn screening, selected by the Task Force: Dr. Scott Grosse of the Center for Disease Control, and Dr. Jeffrey Botkin of the University of Utah. All Task Force meetings were conducted under Wisconsin's open meetings law and all were attended by 9-11 members. Task Force members were asked to disclose financial conflicts of interest at the December meeting and none was considered sufficient to preclude full participation in the group's work.

II. The Advisory Process

The present Wisconsin advisory process relies on 7 subcommittees, with a wide range of expertise (see **Appendix D**). The chairs of these subcommittees serve on an "Umbrella Committee," joined by individuals representing various areas of expertise and stakeholders (see **Appendix C**).

The present process generally has worked well, but the Umbrella Committee, which has responsibility for final recommendations to the Secretary, does not always have adequate time to discuss the complexities of adding or deleting specific tests, and may not have the relevant expertise to review all proposed new conditions. The Umbrella Committee meets twice a year and has to address operational issues. Review of ongoing tests, as well as proposals for additions and deletions, are discussed in more detail at the subcommittee meetings. There is inconsistency across subcommittees, as some, but not all, may have members with special understanding of ethical, legal, and social issues.

There have also been concerns about unavoidable conflicts of interests among Umbrella Committee members. These include institutional, regional, professional, and financial interests, as well as advocacy for specific tests or programs.

The Task Force reviewed a range of newborn screening advisory structures and processes including state and federal agencies, professional societies, and other countries, as well as guidelines for newborn screening proposed by various groups and individuals. Contributors to these activities include various lay and professional interest groups and numerous areas of expertise, including various medical specialties, law, ethics, nursing, and economics.

Comparisons were noted with Institutional Review Boards (IRBs)—the committees that review research involving human subjects—and Hospital Ethics Committees, which consult and advise on complex clinical ethical dilemmas. These structures have significantly reduced the incidence of decisions that were subsequently deemed to be ethically problematic. They rely on a model in which a decision-making body, which does not necessarily contain all the relevant expertise, receives scientific information and expert opinion from multiple sources.

Ethics committees were modeled on a concept that ethically optimal decisions are those which can be approved by an ideal ethical observer with the qualities of: (1) having access to all the relevant facts; (2) carefully considering the perspectives and interests of key stakeholders; (3) being collectively disinterested, meaning minimization of undue influence by personal interests in the outcome; (4) maintaining a dispassionate approach, meaning maintenance of civil discourse; and (5) being consistent, meaning similar cases have similar outcomes.[9]

The Task Force concluded that the advisory process could be improved by modifying the present structure and process in a way that (1) retains the benefit of the extraordinary contributions of numerous unpaid experts serving on the current umbrella and subcommittees; (2) adds further expertise in ethical, legal and social issues, including economic considerations; and (3) allows time for integrating the scientific issues and ethical, legal and social issues.

The Task Force noted the distinction between the operational functions of the present Umbrella Committee and its role in making recommendations to the Secretary regarding decisions about additions and deletions or other important policy matters. The operational functions clearly require the involvement of individuals engaged in the operational work of the screening program, including physicians, nurses, hospital administrators, consumers, laboratory personnel, and so on. The present Umbrella Committee seems well-constituted to perform these duties and needs to meet regularly to maintain the system. An advisory committee, in contrast, need only convene when there are decisions to be made. If decisions about additions and deletions are infrequent, as has been the case (notwithstanding expanding technologies), an advisory committee could meet on an ad hoc basis, unconstrained by the Umbrella Committee's present six-month schedule, and could devote more time to major decisions than has been feasible for the Umbrella Committee because of its wider and time-consuming agenda.

The Task Force endorsed continuation of the transparency of the present system—with open meetings of the umbrella committee, subcommittees, and the advisory committee—and a process that welcomes input from the public and professions.

Recommendation 1: The Task Force recommends the formation of a new committee to advise the Secretary on additions and deletions.

- **(a) This body should make final recommendations to the Secretary of the Department of Health Services, who has decision-making authority.**
- **(b) This body should be constituted of individuals whose areas of expertise and experience include medicine and science; statistics and epidemiology; ethical, legal, social and policy analysis; laboratory medicine; and should include representation from practicing physicians, the newborn screening program, and individuals with target conditions or their parents.**
- **(c) This advisory committee would hear testimony from the Umbrella Committee, subcommittees, and other individuals with relevant information or who can speak for important constituencies.**

III. Criteria for Adding/Deleting Tests

As required in its charge, the Task Force used the criteria for adding and deleting tests listed in the Wisconsin Administrative Rules as the starting point for its discussions, and focused on whether these criteria should be supplemented or clarified. Since there has been remarkable consistency in most of the guidelines on ethical principles for newborn screening during the past 40 years, the Task Force used the areas of consensus as the starting point of its discussions.

The criteria in the Wisconsin Administrative Rules are as follows:

> **DHS 115.06 Criteria for adding or deleting conditions.** In determining which disorders are to be added or deleted from s. DHS 115.04, the department shall seek the advice and guidance of medical consultants, staff of the state laboratory and other persons who have expertise and experience in dealing with congenital and metabolic disorders. Criteria to be considered in adding or deleting disorders shall include all of the following:
>
> **(1)** Characteristics of the specific disorder, including disease incidence, morbidity and mortality.
>
> **(2)** The availability of effective therapy and potential for successful treatment.
>
> **(3)** Characteristics of the test, including sensitivity, specificity, feasibility for mass screening and cost.
>
> **(4)** The availability of mechanisms for determining the effectiveness of test procedures.
>
> **(5)** Characteristics of the screening program, including the ability to collect and analyze specimens reliably and promptly, the ability to report test results quickly and accurately and the existence of adequate follow-up and management programs.
>
> **(6)** The expected benefits to children and society in relation to the risks and costs associated with testing for the specific condition.
>
> History: Cr. Register, May, 1993, No. 449, eff. 6-1-93; am. (intro.) and (1) to (5), Register, December, 1999, No. 528, eff. 1-1-00.

The Task Force considered all of these criteria necessary but not sufficient for decisions to add or delete conditions. The Task Force also noted that these criteria have not been consistently followed in decisions to add conditions. The advent of tandem mass spectroscopy technology (also known as "MS/MS"), for example, stimulated the addition of dozens of disorders, including some whose characteristics were not understood (criterion #1); disorders for which effective therapy had not been established (criterion #2); and disorders for which the test had unknown sensitivity and specificity (criterion #3).

This section of our report, therefore, will seek to clarify and expand upon important aspects of the addition and deletion criteria specified by state administrative rule, with recommendations for interpretation and implementation of these criteria.

Several reasons exist for having detailed criteria for screening. First, it is important to ensure that children who are identified as having a disorder truly have that disorder. If a healthy child is falsely identified as having a disorder, several adverse consequences can occur:

(1) Parents may treat a well child as if s/he is ill, over months or years, with adverse psychosocial consequences—the so-called "vulnerable child syndrome," in which unfounded parental anxiety about the health of a child results in disturbances of the parent-child interaction.[10]
(2) Parents may change their reproductive plans based on the false belief that they have a child with a serious illness and are at risk for having another.[11 12]
(3) A healthy child may be exposed to an intervention with risks, causing suffering, disability, or death.[3 13 14 15]

Second, it is important that children who are correctly identified as having a disorder are treated with interventions that are safe, effective, and available. Most interventions have risks, and the general duty not to cause harm requires that exposing a child to risk of harm should be balanced by the prospect of benefit.

Historically, many screening programs have been implemented on broad populations on the assumption that the tests were accurate and the interventions were safe and effective, only to be shown years (and sometimes decades) later that some people were being harmed by the program. The purpose of these criteria is to reduce the risk of that happening.

A. Characteristics of the specific disorder, including disease incidence, morbidity, and mortality (DHS 115.06(1))

State-mandated newborn screening has historically been based on concerns that individual children would suffer preventable death or serious disability unless pre-symptomatic recognition allowed diagnosis and initiation of treatment. Thus, mandated screening was justified on the basis of serious health consequences that could not be avoided in any other way. The early targets of mandatory screening—PKU, hypothyroidism, sickle disease—meet these criteria.

With the expansion of testing technology, particularly MS/MS, it not only became possible, but in some cases unavoidable, to detect abnormalities that did not meet the threshold of "life-threatening" or causing "serious disability," or disorders for which there were no clear, safe and effective interventions. Indeed, the economics of testing has led to the use of multi-phasic testing that automatically reveals abnormalities beyond the targeted conditions. The imminent expansion of multi-array molecular testing ,which may have utility in newborn screening, will vastly expand testing for conditions that do not meet the standards thought to be necessary to justify overriding traditional standards for consent.

The most notable recent example of this was the discovery of 26 cases of 2-methylbutyryl CoA dehydrogenase deficiency 2-MBCDD (sometimes referred to as 2MBADD), a genetic variant among children who initially screened positive for isovaleric acidemia.[16] While isovaleric acidemia is a serious disease whose characteristics are fairly well understood and for which treatment is lifesaving, 2-MBCDD was largely unknown prior to the use of tandem mass spectroscopy (MS/MS) for newborn screening. By analogy to other organic acid disorders, and

based on the clinical presentation of the first Wisconsin case, 2-MBCDD was assumed to be a disease requiring treatment. The families of the children diagnosed through newborn screening, almost all of whom were of Hmong ancestry, were advised to treat their children with protein restriction and supplemental carnitine. Subsequently many untreated older siblings of the screened children were found to be healthy, even though they also had biochemical evidence of 2-MBCDD. 2-MBCDD is now recognized as a disorder that does not meet criteria for newborn screening or intervention. Although detection of 2-MBCDD is an unavoidable consequence of screening for isovaleric acidemia, this condition is no longer targeted as a disorder on the newborn screening panel in Wisconsin. This example highlights the importance of understanding the natural history of a condition to avoid needlessly alarming families by recommending unnecessary treatment, but the resolution of the problem by ceasing to report 2-MBCDD illustrates the importance of incorporating new knowledge to change newborn screening by essentially deleting a disorder for which screening turns out to be inappropriate.

The Wisconsin administrative rule requires "consideration" of disease incidence, morbidity, and mortality, but does not require any substantive criteria or threshold. Thus, a decision-maker could theoretically approve mandatory testing for a mild and rare condition with no known treatment and assert that s/he had "considered" the stated criteria, but thought they were outweighed by other considerations. This is problematic, because the testing is functionally mandatory. Mandatory testing should be limited to situations where there is a compelling interest of the child that is unlikely to be met in any other way, justifying bypassing and overriding traditional ethical and legal standards for consent.

Applying this analysis to decisions about whether to add or delete a test requires scientific evidence of the disorder, including its natural history and variations in natural history based on different mutations. "Cystic fibrosis," for example, is now understood to encompass not one condition, but a spectrum of related disorders, caused by a large number of mutations in the CFTR gene. Most cause serious disease in childhood, but some are associated with symptoms that only emerge in adulthood (such as male infertility); and in rare cases, there are mutations in the CFTR gene that have no apparent clinical manifestations.[17] Whether or not newborn testing can accommodate these distinctions and report only disorders that cause serious health risks in childhood will be based on a variety of factors.

<u>Recommendation 2</u>: Mandated testing should be limited to conditions that cause serious health risks in childhood that are unlikely to be detected and prevented in the absence of newborn screening.

<u>Recommendation 3</u>: For each condition, there should be information about the incidence, morbidity and mortality, and the natural history of the disorder.

B. The availability of effective therapy and potential for successful treatment (DHS 115.06(2))

As noted above, the unusual intervention of the state in mandating health care should be predicated on the ability to prevent or ameliorate a serious threat to the health of children.

Screening and labeling a child is not in itself a benefit to that child. Thus, mandatory screening should be limited to serious health conditions for which there is an effective intervention.

An example of what some consider premature addition of a test involved Krabbe disease, a severe degenerative disease of the nervous system. Encouraged by pressure from a parent advocacy group, the state of New York initiated newborn screening for Krabbe disease in 2006 in the hope that stem cell transplant prior to onset of symptoms might ameliorate the disease. Stem cell transplant has significant risk (1 of the first 3 infants treated after detection on newborn screening died from transplant complications) and benefit remains uncertain. Following stem cell transplant, children with Krabbe still have significant disability and some experience progressive neurologic deterioration despite early treatment. Parents have played a critical role in advances in newborn screening. The Krabbe disease example illustrates the importance of advocacy being tempered with attention to other criteria necessary for the successful implementation of screening.

"Effective," as defined here, means determined by well-designed scientific studies. The standards for what constitutes "effective" are generally procedural standards. For new drugs and devices, approval by the Food and Drug Administration (FDA) is required. The FDA relies on panels and internal employees, including experts in science, trial design, and ethical issues. The U.S. Preventive Services Task Force, which reviews some screening tests (e.g., mammography), relies on published criteria for reviewing and evaluating the literature. The US DHHS Secretary's Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (SDACHDNC) has its own criteria.[18]

There is no uniformly accepted algorithm for establishing the safety and effectiveness of proposed newborn screening interventions. Even when treatment for a rare disorder is well-established as effective, initiation of newborn screening may nevertheless uncover mild variants which were previously unrecognized and may or may not require treatment. While one prospective randomized clinical trial (the "gold standard" for evaluating medical interventions) has been conducted to explore newborn screening—the Wisconsin cystic fibrosis study[19 20 21]—most disorders will be sufficiently rare that prospective trials will be impractical. Botkin has reviewed the challenges and opportunities for developing scientific evidence in this area.[22 23]

Thus, conclusions about the adequacy of scientific evidence will inevitably depend on multiple sources, including: review of the literature; local expert opinion; conclusions by other expert committees in the United States and other countries; and so on.

In addition to evidence that proposed interventions meet acceptable standards of safety and efficacy, it is important that treatments be reasonably available to the screened population. Availability will depend on such factors as cost, coverage by third-party payers, and geographic proximity of willing providers. "Availability," therefore, should be understood to include not just the theoretical availability of an effective treatment, but the likelihood that affected children will actually have access to such treatment.

<u>Recommendation 4</u>: Conditions identified by newborn screening should be linked with interventions that have been shown in well-designed studies to

be safe and effective in preventing serious health consequences.

<u>Recommendation 5</u>: The interventions should be reasonably available to affected newborns.

<u>Recommendation 6</u>: Appropriate follow-up should be available for newborns that have a false positive newborn screen.

C. Characteristics of the test, including sensitivity, specificity, and feasibility for mass screening (DHS 115.06(3))

The sensitivity (i.e., proportion of affected babies who screen positive) and specificity (i.e., proportion of unaffected babies who screen negative) of a screen must be considered prior to implementation because these attributes influence the number of babies that will be falsely identified as either having (i.e., false positive) or not having (i.e., false negative) a particular condition. Newborn screening programs commonly select screening platforms and algorithms that minimize the number of affected babies who are missed, and consequently identification of false positives is oftentimes unavoidable. False positive screens are typically resolved upon further diagnostic testing; however, in some cases, children are labeled as having a serious condition that is, in fact, clinically insignificant. This may be due to heterogeneity of the disorder, which is well-illustrated by CF. Many CFTR mutations have been identified, of which some cause serious disease in all patients, some cause serious disease in a subset of patients, some cause a milder form of CF, and others likely have no effect and no association with CF.[17]

Children have also been incorrectly labeled because our understanding of a particular condition, specifically within the context of newborn screening, was not well understood at time of implementation. As noted earlier, 2-MBCDD was added to Wisconsin's screening panel through the availability of affordable MS/MS technology, resulting in false positive labeling of 26 children with chemical abnormalities that resembled a serious disease but were eventually found to be due to a different genetic mutation not associated with life-threatening symptoms.

Concerns about adverse psychosocial effects of false positive tests are illustrated by the Wisconsin experience with CF. During the early years of CF newborn screening, some families with infants confirmed to have a false positive test maintained the belief that their child was ill. In the Wisconsin newborn screening study for CF, 8% of the parents of children with false positive results were not sure whether or not their child had CF one year later; 5% said they thought about the results "often or constantly;" and 70% of those who received genetic counseling did not fully understand their reproductive risk.[11] These results prompted improved follow-up and counseling following false positive CF results, and the situation has improved. By 11-14 years after testing, 100% of parents of children with false positive results knew their child did not have CF and none perceived their child as vulnerable unless s/he actually had serious health issues unrelated to CF. Parents who had received genetic counseling had significantly better understanding of reproductive risks than those who had not, although both groups still had misconceptions about the actual risk associated with being a CF carrier.[24] These experiences illustrate the importance of genetic counseling for helping people understand test results, and

illustrate that newborn screening is not just a matter of performing tests; it includes an array of services.

The sensitivity and specificity of a test can also vary in specific newborn subpopulations. For example, the administration of antibiotics to newborns prior to blood collection may cause a false positive screen for isovaleric acidemia. Blood transfusions, early specimen collection (e.g., before 24 hours of age), or prematurity can cause false positive or negative screens for some conditions. These challenges are inherent to newborn screening and are not always well understood prior to implementation of a new screen. However, they illustrate the importance of ongoing monitoring and quality improvement efforts by the newborn screening program (e.g., adjustment of cut-offs, modification of follow-up protocols, adoption of new screening platforms).

Advocates for screening for a particular disorder naturally focus on the benefits and risks for affected children—particularly the risks of having the disorder cause harm before the diagnosis is made and treatment instituted. This advocacy is often related to personal experiences with a known affected child. Those who urge caution[15 23 25] focus on the unaffected children who may be harmed by being falsely labeled as having a serious disorder,[16] and by adverse effects of unnecessary treatment. The risks for unaffected children can be psychosocial, such as the "vulnerable child syndrome,"[10] or medical, such as overtreatment of children with mild disorders. It is important to remain cognizant of the cases of malnutrition and death that were described in the early days of the PKU program,[3] and aim not to repeat these mistakes.

An example of the complexity of testing is illustrated by Pompe disease. Infantile Pompe disease begins soon after birth with profound weakness and cardiomyopathy, and if untreated will cause death before one year of age. Enzyme replacement, if started early, ameliorates the disease and dramatically prolongs the life expectancy of severely affected infants. Mild or late onset forms may not require treatment in infancy. Because the enzyme levels in milder cases may be only slighter higher than in the severe infantile cases, newborn screening detects not only severely affected infants, but also those destined to develop later onset Pompe disease. Confirmatory enzyme testing on skin fibroblasts, which is necessary to distinguish cases requiring treatment, can take weeks, resulting in prolonged anxiety for families of children who turn out to be at risk for later childhood or adult onset disease.

Some tests may meet strict standards for sensitivity and specificity, but be prohibitively expensive or impractical. For example, routine hip ultrasounds on all newborns could detect some cases of congenital dislocation of the hip which would be missed by clinical exam, but with unacceptable costs.

The costs of adding a test will of course include not only the cost of the test itself, but also the costs of treatment. This is addressed in section F.

Recommendation 7: The characteristics of mandated tests in the newborn population should be known, including specificity, sensitivity, and predictive value.

D. The availability of mechanisms for determining the effectiveness of test procedures (DHS 115.06(4))

Even when a new technology has been subjected to rigorous scientific investigation prior to being implemented on the general public, the numbers of patients studied will usually be insufficient to detect uncommon or rare adverse effects. Thus, drugs approved by the FDA commonly undergo "Phase IV" testing after they are approved, to look for adverse effects that were too infrequent to be noted in the pre-marketing studies. The FDA also encourages reports of adverse effects to add to the body of knowledge about a drug.

The same principles should apply to newborn screening, including the effectiveness of the test as well as the safety and effectiveness of interventions for affected infants. This kind of quality control should be an essential component of a newborn screening program, with periodic review of all elements of the program, including the performance of the test. The Wisconsin 2-MBCDD experience again provides an excellent example of the value of such review, as the detailed studies of Durkin et al.[16] revealed the unanticipated false positive results, and provided the basis for a decision to delete that disorder from the screening program.

Recommendation 8: Disorders on the testing panel should be reviewed at appropriate specified intervals. A new test might require review more frequently than a long-established test.

E. The ability to collect and analyze specimens reliably and promptly, the ability to report test results quickly and accurately, and the existence of adequate follow-up and management programs (DHS 115.06(5))

The Wisconsin State Statute section 253.13 has limited the tests for congenital disorders to blood and urine specimens. Testing has been done through a central laboratory with consistent analysis and reporting of results for every baby tested. The central laboratory has allowed establishment of a consistent and reliable mechanism of follow-up for positive results. This system works well when all the blood spots are sent to the same laboratory.

The addition of a new test to the newborn screening program requires the ability to collect the appropriate sample in a reliable and timely manner. Under the current system, for blood spot testing, this means that it must be possible to test for the disorder using the blood spots that are currently collected. If a new sample collection system were to be proposed for a new test, reliability and timeliness of sample collection would need to be demonstrated.

The addition of a new test also requires the ability to analyze the specimen and report results early enough in the natural time course of the disorder to make a difference in the treatment course. Timely reporting of results depends on a number of factors, including the age of infant at time of specimen collection, the length of time between specimen collection and pick-up by courier service, courier service transit time, specimen processing time, and the time between availability of lab results and their communication to the provider. With the current testing panel, some results may not be returned until the baby is 6 days old. It is not effective to add a disorder

to the screening panel if irreversible damage occurs before the test result is reported. Accuracy is essential for reducing false negatives, as discussed above.

Most disorders identified by newborn screening are rare, and it is likely that the primary care provider receiving the result has never dealt with that disorder before. Therefore, the provider will need instructions on how to proceed. Usually these involve immediate evaluation of the infant, telephone consultation with a specialist, and either additional testing locally or transfer to a pediatric specialty center (depending on the disorder). Before a test is added to the panel, the details of these processes must be completely delineated, including: development of standard instructions, identification of consultants, and identification of appropriate referral centers throughout the state/region.

The Department has been approached about adding point-of-care newborn screening for congenital hearing loss and critical congenital heart defects (CCHD). Since the statute does not include point-of-care testing, neither of these were able to be reviewed through the existing Newborn Screening Program. The legislature was approached to add a separate statute to address the specific disorders. The statute for congenital hearing loss was passed in 1999 (WIS. STAT. § 253.115). Senate Bill 104 and Assembly Bill 111 were introduced this year to screen all babies for CCHD.

Universal point-of-care testing may be done on infants based on current standards of care delivery and supported by clinical guidelines. It becomes a public health newborn screening program only if the public health system is providing oversight for universal access to follow-up diagnosis and treatment.[26] Point-of-care newborn screening does present challenges, as testing is done at each birthing facility; this can result in inconsistent analysis and reporting of results. Follow-up for positive results can be inconsistent, as has been seen with congenital hearing loss screening across the United States.

The U.S. Secretary of Health and Human Services Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) has identified four criteria for public health point-of-care newborn screening:

(1) Urgent treatment of the condition is required earlier than the feasible turnaround time for a public health laboratory.
(2) The screening is based on physiologic testing that requires the presence of the newborn at the time the results are generated.
(3) The public health impact of screening for early diagnosis and treatment is of sufficient importance.
(4) Universal screening and/or follow-up and treatment for the condition are not currently performed under standard clinical practice.[26]

Recommendation 9: If a new sample collection system is needed to add a disorder, reliability and timeliness of sample collection must be demonstrated.

Recommendation 10: Before a test is added to the panel, the details of reporting, follow-up, and management must be completely delineated, including development of standard instructions, identification of consultants, and identification of appropriate referral centers throughout the state/region.

Recommendation 11: Adding point-of-care testing to the congenital disorders statute would allow point-of-care newborn screening to be reviewed under the criteria set forth by the administrative rule and not require legislation for each disorder.

F. The mechanism of funding the testing and treatment should be identified (DHS 115.06(6))

Currently the Wisconsin Newborn Screening Program is funded by the collection of a $109 fee for each blood spot card. The revenue from these fees covers the cost of blood cards, sample transportation, performance of the actual tests in the State Laboratory of Hygiene, communication of results, and the lifetime provision of special formulas for those patients diagnosed with conditions requiring treatment with these formulas. In most cases the fees are paid by the birth hospitals, which in turn bill insurance. In 2010 the fee was increased by $45 to cover the increased costs of special formulas and testing. Because Medical Assistance did not increase the payment for screening, and because roughly half of Wisconsin newborns are covered by Medical Assistance, the state's hospitals absorbed a significant portion of the fee increase.

Historically, blood spot testing has been performed at the State Laboratory of Hygiene. The advent of point-of-care screening—including newborn hearing screening and pulse oximetry screening for critical congenital heart disease—has shifted even more costs to hospitals and patients, as these tests are done entirely by hospital personnel using hospital equipment.

The costs of medical evaluation of infants identified by newborn screening are borne by the infant's insurance and/or parents. For those disorders requiring special dietary formulas, the costs of the formulas are covered by the Newborn Screening Program for the lifetime of the patient. All other medical costs, including medications, surgeries, hospitalizations, and other treatments, are borne by the infant's insurance and/or parents.

Questions often arise about the relative costs and benefits of a particular test or treatment. While a test that reduces costs, due to avoidance of the costs of a burdensome illness, has added value for that reason, a reduction in cost should not be the sole criterion for including a test. Prevention and amelioration of disease and disability, and prevention of premature death, have value that is difficult to measure in monetary terms. Traditional measures of costs and benefits, using such

metrics as quality adjusted life years (QALYs) are increasingly used for cost effectiveness assessments, which refer to comparisons of different interventions.

Thus, while cost benefit analysis and cost effectiveness studies cannot by themselves provide a rationale for adding or deleting a test, they are an important element in deciding how the state should allocate limited funds.

Recommendation 12: Recommendations and decisions should include consideration of the costs of the screening test, confirmatory testing, accompanying treatment, counseling, and the consequences of false positives. The mechanism of funding those costs should be identified. Expertise in economic factors should be available to those responsible for recommendations and decisions.

G. Adventitious findings (DHS 115.06(6))

The rationale for newborn screening, generally without explicit consent from a parent, has been the concern that an infant will suffer premature death or serious disability if screening is not done. If a test does not meet the criteria for mandated screening—i.e., if the results of a proposed test do not meet accepted criteria—then it should not matter whether the test result was deliberately obtained, or became available as an unavoidable consequence of testing technology.

Modern technology increasingly relies on multiphasic systems which make it economically more efficient to test for many abnormalities, rather than use a separate system for each condition or test. This can result in the unintended discovery of abnormalities whose clinical significance is unknown, or for which proven effective interventions are not available. It can also result in the unintended discovery of carrier status (i.e., an infant who has only one copy of a gene mutation, when two mutations are required to cause disease). Such an infant would have an increased risk of having a child with the disorder when s/he reached reproductive age, but this potential benefit does not meet other traditional criteria for newborn screening.

Discovery of an infant's carrier status offers a potential benefit to parents, as a signal that one (or both) is a carrier for the mutation, allowing them to make more informed reproductive decisions regarding future children. This does not constitute a direct medical benefit to the screened infant, which has long been a basic criterion for newborn screening.

The discovery of an infant's or parent's status may also have harmful consequences, such as uncovering nonpaternity (i.e., the likelihood that the infant's father was someone other than the presumed father). This possibility suggests that women should have the opportunity to decide whether such information should be disclosed.

The discovery of unintended, adventitious findings has been a phenomenon of clinical laboratories for 50 years or more, and the general practice is that results that were not specifically sought or requested are not returned to the physician or patient unless they meet certain criteria. The central criterion for managing this problem in clinical laboratories has been

to disclose only those results which exceed what are called "critical values," or what are sometimes called "actionable"—meaning the result signifies a condition which could cause serious harm to the patient, and for which a reasonable patient and physician would generally want to take action.

The criteria for returning these "adventitious" or "incidental" findings has been the subject of extensive debate and discussion in the research arena, where imaging procedures predictably reveal unanticipated findings, often of uncertain clinical significance.[27] The debate has intensified because of the imminent expansion of multi-array molecular testing, which will make it possible to test for 1,000 or more mutations on a single blood sample at an affordable cost. This unprecedented deluge of laboratory information requires criteria for deciding which results should be returned.

While there currently are no consistent guidelines on this issue, the Task Force believes there is an emerging consensus, which it supports, that the criteria for disclosing results in the context of newborn screening should be the same, regardless of the provenance of that result. Thus, if an adventitious finding does not meet the criteria enumerated elsewhere, there is no clear rationale for disclosing it, nor is there a duty to disclose.

Because the issue of returning adventitious results was not thoroughly analyzed and discussed decades ago, in part because it was less common, practices have developed which created expectations among some patients and physicians that adventitious findings would be returned. A common example is the unavoidable detection of carrier status for the sickle gene—so-called sickle cell trait—that occurs in the search for infants with sickle cell disease. The disease is a life-threatening disorder for which effective preventive treatment exists. The major importance of carrier status is its implication for reproductive decisions. While there are some health consequences for individuals with sickle trait, they do not meet the criteria identified elsewhere in this report and which are found in virtually all guidelines on newborn screening.[28]

The Task Force has not been charged with making recommendations on any specific test or condition, but only to identify the criteria by which decisions to add or delete tests should be made. Individuals charged with the responsibility for actually making decisions, whether as part of an advisory group, or someone with decision-making authority, might decide to deviate from the criteria for any particular condition or test, weighing policy considerations, historic facts, or other variables. The task Force recommends adhering to the criteria based on evidence-based scientific rationales.

<u>Recommendation 13</u>: Reporting of test results should be subjected to the same criteria, regardless of whether it is a requested or targeted test, or an unintended or unavoidable byproduct of the testing technology.

H. Consent (DHS 115.06(6))

i. General considerations

Before embarking on a detailed discussion of addition/deletion criteria, the Task Force asked Karen McKeown, Administrator of the Division of Public Health, whether the complex issue of consent should be considered part of the group's charge. Ms. McKeown abstained from offering any opinion on the substantive question of whether or not consent should be required for newborn screening, but stated that it was a possible criterion in deciding whether a test should be performed, and therefore an appropriate part of the charge.

Newborn screening, as practiced in the United States, constitutes a departure from the traditional health care system, which is organized around a doctor-patient (or parent) relationship in which decisions are made in a collaborative manner, typically including the informed consent of the patient. Exceptions have been typically limited to emergencies or conditions that expose third parties to risks (e.g., mandatory immunizations to prevent spread of contagious diseases, or mandatory treatment of patients with tuberculosis).

The rationale for mandatory testing of PKU in the 1960s was the assumption that the technology of testing (the Guthrie test) and treatment (Lofenalac) had progressed to the point where the consequences of the disease could be eradicated in nearly all cases, but that too many children would be missed if testing depended on individual physicians. The rationale for the involuntary nature of the program was the state's *parens patriae* duty to protect children from serious harm when there was no other apparent alternative.

This rationale has provided the justification for state-mandated screening over the ensuing decades. It is at the heart of the other criteria for adding tests addressed in this report, and the numerous other proposals for guidelines for newborn screening; namely, bypassing the usual authority of parents to make decisions about their child's health care (absent reasons to suggest neglect), required strict standards for the reliability of the test, and the availability of safe and effective treatment.

The rationale therefore loses its force if screening is required for a condition that is not clearly serious; if the intervention is of uncertain value; if the test is of uncertain reliability; or if the condition is one which does not affect the individual until adulthood, when s/he can make his/her own decisions about whether or not to pursue treatment.

The Task Force spent considerable time across several meetings on the issue of consent, which has been a central element of American health care, and embedded in statutes and court decisions for a century of more.[29 30 31] Requirements for informed consent are most stringent for interventions that are part of a research study, and subject to state and federal regulations, usually with oversight by an institutional review board (IRB).[32]

With regard to newborn screening, consent has been a requirement of many guidelines, including the National Academy of Sciences – Institute of Medicine 1975 report;[4] the World Health Organization;[7] The UK's Nuffield Council;[33] the American Academy of Pediatrics;[34] and most recently, a joint statement by the American Academy of Pediatrics and the American College of

Medical Genetics.[8 35] While most guidelines for newborn screening emphasize the importance of informed consent, this requirement is typically not implemented in actual screening programs.

Wisconsin statutes allow parents to opt out of newborn screening for religious reasons (WIS. STAT. § 253.13(3)), but it is unclear how many are informed sufficiently of the pros and cons of screening in general, or for any particular test, to allow an informed choice of whether or not to opt out. Nonetheless, some are uncertain if consent should play any role in newborn screening and believe that tests which meet accepted criteria should be mandated.

ii. Consent to testing vs. consent to disclosure of results

Questions of consent also require consideration of the distinction between consent to testing and consent to disclosure of the results of testing. Current screening includes technology which unavoidably produces results beyond the primary target of testing. Tandem mass spectroscopy provides an inexpensive method for testing for conditions such as phenylketonuria (PKU), now widely accepted as a successful program, but unavoidably produces results of uncertain clinical significance, or disorders for which there are no known effective interventions. Similarly, emerging multi-array molecular technology will make it possible to test for disorders with safe and effective interventions, but inevitably will yield results of uncertain significance; conditions without effective treatment; or conditions whose onset occurs later in adulthood. The examples of 2-MBCDD and Krabbe disease have been mentioned.

Thus, one could take the position that testing for PKU should not require consent—i.e. a parent should not have the option of refusing PKU testing—but maintain that disclosure of other results of that test should be optional and require informed consent.

Another approach to this problem is to authorize testing and disclosure of results of proven known clinical value, but require the testing laboratory to destroy or withhold results of uncertain value. Thus, identification of sickle cell disease and other sickle hemoglobinopathies and intervention with prophylactic antibiotics was shown to be an effective program,[36] but the value of disclosing carrier status is of uncertain value to the newborn infant.[28] Thus arguments can be made for requiring sickle testing with low standards for consent, but not reporting carrier status, or at least requiring high standards of consent for such disclosure.

Another approach to reducing the likelihood that unintended results are discovered may be to adjust the testing methodology. For example, the MS/MS technology used to screen for numerous metabolic disorders can be implemented in either a full-scan mode or a multiple reaction monitoring mode. The latter measures only specified analytes that are needed to screen for conditions on the required panel. In states that exclude some or all secondary MS/MS target conditions from the core panel (e.g., Washington[37]), this avoids the unintended detection of conditions that do not share a marker with a primary target condition (e.g., Short-chain acyl-CoA dehydrogenase (SCAD) deficiency, "SCAD"). Secondary target conditions that share a marker with a primary target condition are nonetheless likely to be detected upon follow-up diagnostic testing for the core target condition (e.g., medium-chain acyl-CoA dehydrogenase deficiency, "MCAD," and glutaric academia type II, "GA-II").

In addition, distinctions should be made between tests that have established scientific merit—i.e., high levels of sensitivity and specificity, low incidence of false positives and false negatives, and accurately identify a serious disorder—but with no effective treatment for the disorder. Examples would include disorders such as Huntington disease and Tay Sachs disease. In such cases, arguments for involuntary testing or disclosure of results are less compelling than disorders which have a highly effective treatment, and standards for consent might be higher.

iii. Opting in vs. opting out

Consent can be an active, explicit process with the default position being "no testing" or "no disclosure," requiring an affirmative decision by the patient/parent ("opt in"), or a passive, implicit process, in which the default position is to test or inform unless the parent specifically declines testing or disclosure ("opt out").In either form, ethically meaningful consent requires the parent to be sufficiently aware of, and to understand, the key issues as to be able to make an informed choice of whether to opt in or opt out.

In some clinical situations—when the need for intervention is very clear, when the benefits and risks of intervention are favorable and evidence-based, and when intervention is widely accepted as standard of care—the requirements for obtaining consent are less stringent and detailed communication to ensure high standards of understanding and agreement is not done (i.e., consent is presumed), unless the idiosyncratic patient expressly refuses the intervention. Newborn screening has typically followed this model in which parents have opportunities to learn about the pros and cons of various tests, most commonly through a brochure distributed after delivery, but many if not most are unaware of the details and do not give meaningful informed consent.

Wisconsin statutes allow an opt-out for both newborn blood spot screening and newborn hearing screening based on religious reason, but not personal conviction (WIS. STAT. §§ 253.115(6a), 253.15(3)). The statutes also allow for immunization refusal on the basis of religious reason or personal conviction (WIS. STAT. § 252.04). For antibiotic treatment to prevent newborn eye infection no opt-out is allowed, and a physician is subject to a fine if the treatment is not carried out (WIS. STAT. § 253.11). Such differences confuse practitioners, who are faced most commonly with vaccine refusal. In practice this confusion has led some practitioners to allow opt-out of newborn screening and eye prophylaxis on the basis of personal conviction, believing that all are handled legally the same way.

The Task Force agreed that if there were a cogent ethical basis for allowing parents to opt out of a particular test, it should not be restricted to those with religious reasons, but should be allowed for personal conviction. In addition, the Task Force recognizes that there is value in having uniform opt-out rules.

iv. Proven vs. unproven tests and treatments

Some tests have been evaluated in well-designed scientific studies, establishing the accuracy of the test and the safety and efficacy of an intervention (e.g., sickle cell disease). Other tests and treatments are in an early stage of development, with uncertain test characteristics and uncertain safety and effectiveness of a proposed intervention.

It is axiomatic in the US that new drugs and devices should be tested in well-designed clinical studies, and approved by the FDA, before being implemented on a population-wide basis. Newborn screening technologies, including testing and in some cases therapies, such as special diets, or innovative uses of approved drugs, do not require such approval, and may cause harm before an unfavorable risk/benefit profile is appreciated. Commercial formulas are FDA approved as medical foods, but approved products can be used for unapproved purposes. This has been a more common problem with newborn screening tests and treatments that become standard of care outside of the aegis of state-sponsored programs.[38 39]

The 1975 IOM report, and most subsequent guidelines, includes recommendations for well-designed studies, with high standards for consent, before new screening tests are implemented.[6 4 33 8]

v. Frequency and severity of disease; effectiveness of treatment

Some disorders are so rare that routine testing might not be cost effective, or the benefits of intervention uncertain because of inadequate clinical experience. In addition, the risk of false positives rises as a condition becomes rarer. Tests in this category might be included in an optional "opt-in" list, for families with special concerns about a disorder, with or without different payment requirements.

Other disorders might be more common but not sufficiently severe to warrant mandatory testing with no opportunity to refuse. Alternatively, the disorder may be severe, but the benefit of early intervention may be unclear (e.g., spinal muscular atrophy, or Duchenne muscular dystrophy). The original rationale for the earliest mandatory newborn screening tests—PKU, hypothyroidism, sickle cell disease—was the high likelihood of death or profound brain damage, with an intervention that was thought to be safe and highly effective. As the consequences of foregoing testing decline, the rationale for involuntary testing diminishes, and the rationale for high standards of consent increases.[40]

vi. Practical considerations

Recognizing the central role of informed consent in the American health care system, consent for complex and rare disorders which are poorly understood by the general public, as well as many primary care providers, can be a time-consuming process. Meaningful opt-in informed consent, involving traditional person-to-person conversation and opportunities for discussion, for the current array of newborn tests is not practical. There is general agreement that the perinatal period is particularly impractical, and that meaningful consent, if it is to occur at all, should be initiated in prenatal settings.[41]

Printed materials and interactive computer programs[42 43] have been shown to be as or more effective, and clearly more efficient, than skilled professionals in helping patients understand the basic information needed to make informed choices about testing.

Concerns have been expressed about logistic problems for clinical laboratories performing screening tests, if they had to individualize what tests to do on which samples, or which results to

return based on parental choices. Others thought that deviations from routine practices were likely to be uncommon, but that might not be the case if more and more tests of uncertain value are added to the testing panel.

Recommendation 14: Research to advance knowledge about the incidence or natural history of poorly understood disorders, or for the purpose of identifying potential subjects for clinical trials, should be conducted in compliance with existing ethical and legal guidelines, including review by an institutional review board (IRB).

Recommendation 15: The Task Force believes that all children should be screened. However, parents should maintain the opportunity to opt-out of newborn screening, after receiving appropriate information about the testing program, on the basis of personal conviction (and not just for religious reasons). Information should be presented in the prenatal period, to allow time for questions and consulting with medical advisors.

Recommendation 16: There should be high standards for consent for tests which are of unproven value, or tests linked to treatments of unproven value. Such tests and treatments should be instituted on a research basis, with review by an IRB, and in general, with traditional opt-in consent. Some studies might qualify for exempt status, not requiring IRB oversight, or meet criteria for waiver of informed consent.

IV. References

[1] American Academy of Pediatrics Joint Committee on Infant Hearing. Year 2007 position statement: principles and guidelines for early hearing detection and intervention programs. Pediatrics. 2007;120:898-921. Available from: http://pediatrics.aappublications.org/content/120/4/898.full.pdf.

[2] Beissel DJ, Goetz EM, Hokanson JS. Pulse oximetry screening in Wisconsin. Congenital Heart Disease. 2012;7:460-5.

[3] Paul DB. The history of newborn phenylketonuria screening in the U.S. In: Holtzman NA, Watson MS. Promoting safe and effective genetic testing in the United States: final report of the task force on genetic testing. Bethesda, Maryland: National Institutes of Health; 1997. Appendix 5. Available from: http://biotech.law.lsu.edu/research/fed/ tfgt/appendix5.htm.

[4] National Research Council (U.S.) – Committee for the Study of Inborn Errors of Metabolism. Genetic screening: programs, principles, and research. Washington, D.C.: National Academy of Sciences; 1975.

[5] Committee on Assessing Genetic Risks, Institute of Medicine. Assessing genetic risks: implications for health and social policy. Andrews LB, Fullarton JE, Holtzman NA, Motulsky AG, eds. Washington, D.C.: National Academies Press; 1994.

[6] Wilson JMG, Junger G. Principles and practice of screening for disease. Geneva: World Health Organization; 1968. Available from: http://whqlibdoc.who.int/php/WHO_PHP_34.pdf.

[7] Andermann A, Ingeborg B, Beauchamp S, Déry V. Revisiting Wilson and Junger in the genomic age: a review of screening criteria over the past 40 years. Bulletin of the World Health Organization. 2008 April;86(4):317-9.

[8] American Academy of Pediatrics Committee on Bioethics, American Academy of Pediatrics Committee on Genetics, American College of Medical Genetics, Genomics Social, Ethical and Legal Issues Committee. Policy statement: ethical and policy issues in genetic testing and screening of children. Pediatrics. 2013;131:620-2. Available from: http://www.pediatrics.org/cgi/doi/10.1542/peds.2012-3680.

[9] Fost N. Infant care review committees in the aftermath of Baby Doe. In: Caplan AL, Blank RH, Merrick JC, eds. Compelled compassion. New Jersey: Humana Press; 1992.

[10] Kokotos F. The vulnerable child syndrome. Pediatr Rev. 2009 May;30(5):193-4.

[11] Tluczek, Orland KM, Cavanagh L. Psychosocial consequences of false-positive newborn screens for cystic fibrosis. Qualitative Health Research. 2011 Feb;21:174-86.

[12] Mischler EH, Wilfond BS, Fost N, Laxova A, Reiser C, Sauer CM, et al. Cystic fibrosis newborn screening: impact on reproductive behavior and implications for genetic counseling. Pediatrics. 1998;102(1):44-52.

[13] Welch HG, Schwartz LM, Woloshin S. Overdiagnosed: making people sick in the pursuit of health. Boston: Beacon Press; 2011.

[14] Paul DB. PKU screening: competing agendas, converging stories. In: Paul DB. The politics of heredity: essays on eugenics, biomedicine, and the nature-nurture debate. Albany: State University of New York Press; 1998. p. 173-86.

[15] Holtzman NA. Proceed with caution: producing genetic risks in the recombinant DNA era. Baltimore: The Johns Hopkins University Press; 1989.

[16] Van Calcar SC, Gleason LA, Lindh H, Hoffman G, Rhead W, Cockley G, Wolff JA, Durkin MS. 2-Methylbutyryl-CoA dehydrogenase deficiency in Hmong infants identified by expanded newborn screen. Wisconsin Medical Journal. 2007;106(1):12-5.
[17] Clinical and Functional Translation of CFTR (CFTR2) Website. Available from: http://www.cftr2.org/.
[18] Calonge N, Green NS, Rinaldo P, Lloyd-Puryear M, Dougherty D, Boyle C, et al; Advisory Committee on Heritable Disorders in Newborns and Children. Committee report: method for evaluating conditions nominated for population-based screening of newborns and children. Genetics in Medicine. 2010;12:153-9. Available from: http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/reportsrecommendations/reports/methodforevaluating.pdf.
[19] Farrell PM, Kosorok MR, Laxova A, Green CG, Collins J, Slaingard ML. Bronchopulmonary disease in children with cystic fibrosis after early or delayed diagnosis. American Journal of Respiratory and Critical Care Medicine. 2003;168(9):1100-8.
[20] Fost N, Farrell PM. A prospective randomized trial of early diagnosis and treatment of cystic fibrosis: a unique ethical dilemma. Clin Res. 1989;37:495-500.
[21] Farrell PM. Improving the health of patients with cystic fibrosis through newborn screening. Adv Pediatr. 2000;47:79-115.
[22] Botkin JR. Research for newborn screening: developing a national framework. Pediatrics. 2005 October;116(4):862-71.
[23] Botkin JR, Clayton EW, Fost NC, Burke W, Murray TH, Baily MA. Newborn screening technology: proceed with caution. Pediatrics. 2006 May;117(5):1793-9.
[24] Cavanagh L, Compton CJ, Tluczek A, Brown RL, Farrell PM. Long-term evaluation of genetic counseling following false-positive newborn screen for cystic fibrosis. Journal of Genetic Counseling. 2010;19:199-210.
[25] Holtzman NA. Expanding newborn screening: how good is the evidence? Journal of the American Medical Association. 2003;290(19):2606-8.
[26] Kemper AR, Kus CA, Ostrander RJ, Comeau AM, Boyle CA, Dougherty D, Mann MY, Botkin JR, Green NS, United States Secretary of Health and Human Services Advisory Committee. A framework for key considerations regarding point-of-care screening of newborns. Genetics in Medicine. 2012;14(12):951-4.
[27] Wolf SM, Paradise J, Nelson CA, Kahn JP, Lawrenz F, eds. Symposium on "incidental findings in human subjects research: from imaging to genomics." Journal of Law, Medicine & Ethics. 2008;36(2):216-383.
[28] Oliver S, Dezateux C, Kavanagh J, Lempert T, Stewart R. Disclosing to parents newborn carrier status identified by routine blood spot screening. Cochrane Database System Review. 2004 Oct;18(4):CD003859.
[29] Schloendorff v. Society of New York Hospital, 211 NY 125, 129-30, NE 92, 93 (1914).
[30] Information on alternate modes of treatment. WIS. STAT. § 448.30.
[31] Scaria v. St. Paul Fire & Marine Insurance Co., 227 N.W. 2d 647, 68 Wis. 2d 1 (1975).
[32] U.S. Department of Health & Human Services [Internet]. Federal policy for the protection of human subjects ("common rule") [cited 2013 June 12]. Available from: http://www.hhs.gov/ohrp/humansubjects/commonrule/.

[33] Nuffield Council on Bioethics. Genetic screening: ethical issues. London: Nuffield Council on Bioethics; 1997. Available from: http://www.nuffieldbioethics.org/sites/default/files/Genetic_screening_report.pdf.
[34] American Academy of Pediatrics Committee on Bioethics. Ethical issues with genetic testing in pediatrics. Pediatrics. 2001;107(6):1451-5. Available from: http://aappolicy.aappublications.org/cgi/content/full/pediatrics;107/6/1451.
[35] Ross LF, Sal HM, David KL, Anderson RR, American Academy of Pediatrics, American College of Medical Genetics and Genomics. Technical report: ethical and policy issues in genetic testing and screening of children. Genetics in Medicine. 2013;15(3):234-45.
[36] Pearson HA. Neonatal testing for sickle cell diseases—a historical and personal review. Pediatrics 1989;83(5):815-18.
[37] National Newborn Screening and Genetics Resource Center. National newborn screening status report, updated 01/06/13. Available from: http://genes-r-us.uthscsa.edu/sites/genes-r-us/files/nbsdisorders.pdf.
[38] Odell G. Therapeutic misadventures in neonatal care. In: Gluck, ed. Modern perinatal medicine. Chicago: Year Book Medical; 1974.
[39] Simmons MA, Adcock EW, Bard H et al. Hypernatremia and intracranial hemorrhage in neonates. The New England Journal of Medicine. 1974;291:6-10.
[40] President's Council on Bioethics. The changing moral focus of newborn screening. Washington, D.C.: Government Printing Office; 2008.
[41] American College of Obstetricians and Gynecologists, Committee on Genetics. Committee opinion no. 481: newborn screening. Obstet Gynecol. 2011;117(3):762-5.
[42] Clayton EW, Hannig VL, Pfotenhauer JP, Parker RA, Campbell PW, Phillips JA. Teaching about cystic fibrosis carrier screening by using written and video information. American Journal of Human Genetics. 1995;57:171-81.
[43] Green MJ, Peterson SK, Baker MW, et al. Effect of a computer-based decision aid on knowledge, perceptions, and intentions about genetic testing for breast cancer susceptibility: a randomized controlled trial. Journal of the American Medical Association. 2004;292:442-52.

V. Appendices

Appendix A: Summary of recommendations

Recommendation 1 The Task Force recommends the formation of a new committee to advise the Secretary on additions and deletions.

(a) This body should make final recommendations to the Secretary of the Department of Health Services, who has decision-making authority.

(b) This body should be constituted of individuals whose areas of expertise and experience include medicine and science; statistics and epidemiology; ethical, legal, social and policy analysis; laboratory medicine; and should include representation from practicing physicians, the newborn screening program, and individuals with target conditions or their parents.

(c) This advisory committee would hear testimony from the Umbrella Committee, subcommittees, and other individuals with relevant information or who can speak for important constituencies.

Recommendation 2 Mandated testing should be limited to conditions that cause serious health risks in childhood that are unlikely to be detected and prevented in the absence of newborn screening.

Recommendation 3 For each condition, there should be information about the incidence, morbidity and mortality, and the natural history of the disorder.

Recommendation 4 Conditions identified by newborn screening should be linked with interventions that have been shown in well-designed studies to be safe and effective in preventing serious health consequences.

Recommendation 5 The interventions should be reasonably available to affected newborns.

Recommendation 6 Appropriate follow-up should be available for newborns that have a false positive newborn screen.

Recommendation 7 The characteristics of mandated tests in the newborn population should be known, including specificity, sensitivity, and predictive value.

Recommendation 8 Disorders on the testing panel should be reviewed at appropriate specified intervals. A new test might require review more frequently than a long-established test.

Recommendation 9 If a new sample collection system is needed to add a disorder, reliability and timeliness of sample collection must be demonstrated.

Recommendation 10 Before a test is added to the panel, the details of reporting, follow-up, and management must be completely delineated, including development of standard instructions, identification of consultants, and identification of appropriate referral centers throughout the state/region.

Recommendation 11 Adding point of care testing to the congenital disorders statute would allow point of care newborn screening to be reviewed under the criteria set forth by the administrative rule and not require legislation for each disorder.

Recommendation 12 Recommendations and decisions should include consideration of the costs of the screening test, confirmatory testing, accompanying treatment, counseling, and the consequences of false positives. The mechanism of funding those costs should be identified. Expertise in economic factors should be available to those responsible for recommendations and decisions.

Recommendation 13 Reporting of test results should be subjected to the same criteria, regardless of whether it is a requested or targeted test, or an unintended or unavoidable byproduct of the testing technology.

Recommendation 14 Research to advance knowledge about the incidence or natural history of poorly understood disorders, or for the purpose of identifying potential subjects for clinical trials, should be conducted in compliance with existing ethical and legal guidelines, including review by an institutional review board (IRB).

Recommendation 15 The Task Force believes that all children should be screened. However, parents should maintain the opportunity to opt-out of newborn screening, after receiving appropriate information about the testing program, on the basis of personal conviction (and not just for religious reasons). Information should be presented in the prenatal period, to allow time for questions and consulting with medical advisors.

Recommendation 16 There should be high standards for consent for tests which are of unproven value, or tests linked to treatments of unproven value. Such tests and treatments should be instituted on a research basis, with review by an IRB, and in general, with traditional opt-in consent. Some studies might qualify for exempt status, not requiring IRB oversight, or meet criteria for waiver of informed consent.

Appendix B: Conditions currently screened and treated in Wisconsin

Wisconsin newborns are currently screened for:

- Argininosuccinic Acidemia (ASA)
- Biotinidase Deficiency
- Citrullinemia (Type I & II)
- Congenital Adrenal Hyperplasia
- Congenital Hypothyroidism
- Cystic Fibrosis
- Fatty Acid Oxidation (11):
  - Medium Chain Acyl-CoA Dehydrogenase Deficiency
  - Long Chain 3-Hydroxyacyl CoA Dehydrogenase Deficiency
  - Trifunctional Protein Deficiency
  - Very Long Chain Acyl-CoA Dehydrogenase Deficiency
  - Carnitine Palmitoyltransferase Deficiency Type II
  - Carnitine/Acylcarnitine Translocase Deficiency
  - Glutaric Acidemia Type II
  - 2,4 Dienoyl-CoA Reductase Deficiency
  - Carnitine Uptake Defect
  - Medium/Short Chain Hydroxylacyl CoA Dehydrogenase
  - Medium Chain 3-Ketoacyl CoA Thiolase Deficiency
- Galactosemia
- Congenital Hearing Loss
- Hemoglobin S-Beta Thalassemia
- Hemoglobin S/C Disease
- Hemoglobin Variants
- Homocystinuria
- Hypermethioninemia
- Hyperphenylalaninemia
- Maple Syrup Urine Disease
- Organic Acidemia (12):
  - Glutaryl CoA Dehydrogenase Deficiency Type I
  - Propionyl CoA Carboxylase Deficiency
  - Methylmalonic Acidemia:
    - mutase
    - Clb A & B
    - Clb C & D
  - Isovaleryl CoA Dehydrogenase Deficiency
  - 3-Methylcrontonyl CoA Carboxylase Deficiency
  - Multiple CoA Carboxylase Deficiency
  - 3 Methylglutaconyl CoA Hydratase Deficiency
  - Mitochondrial Acetoacetyl CoA Thiolase Deficiency
  - 2-Methyl-3-Hydroxybutyryl CoA Dehydrogenase
  - 3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency

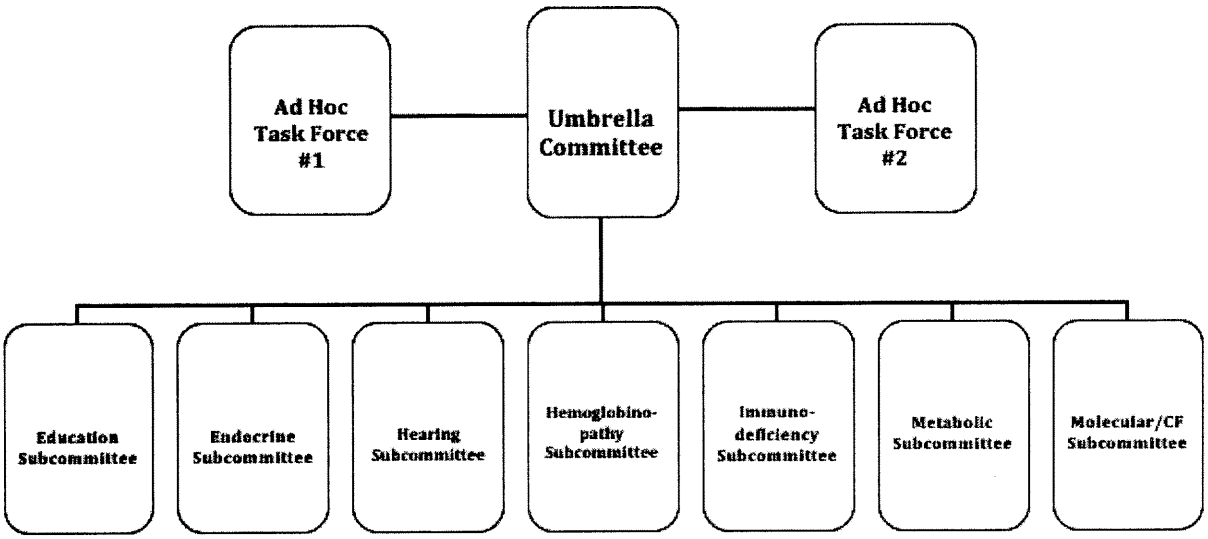
Phenylketonuria
Severe Combined Immune Deficiency (SCID)
Sickle Cell Disease
Tyrosinemia (Type I, II & III)

Appendix C: Composition of the Umbrella Committee

WISCONSIN NEWBORN SCREENING UMBRELLA COMMITTEE *(as of June 2013)*

Position	Vote
Chair: Chief Medical Officer for Bureau of Community Health Promotion (DHS)	1 DHS consensus vote
Newborn Screening Coordinator (DHS)	
State Genetic Coordinator (DHS)	
Director State Laboratory of Hygiene (SLH)	1 SLH consensus vote
Co-Directors of Newborn Screening Laboratory (SLH)	
Education Subcommittee Chair	1 vote
Endocrine Subcommittee Chair	1 vote
Hearing Subcommittee Chair	1 vote
Hemoglobinopathy Subcommittee Chair	1 vote
Immunodeficiency Subcommittee Chair	1 vote
Metabolic Subcommittee Chair	1 vote
Molecular Cystic Fibrosis Subcommittee Chair	1 vote
WI Chapter American Academy of Pediatrics Representative	1 vote
Ethics Representative	1 vote
Local Health Department Representative	1 vote
Consumer/Parent Representative	1 vote
Registered Nurse Representative	1 vote
Certified Genetic Counselor Representative	1 vote
Registered Dietitian Representative	1 vote
Advocacy Organization (March of Dimes)	1 vote
Wisconsin Hospital Association	1 vote

Appendix D: Wisconsin newborn screening program advisory committee structure



This image originally appeared in the Ad Hoc Umbrella Committee Task Force (TF1) Report (as "Appendix A").

Appendix E: Charge of the Ad Hoc Umbrella Committee Task Force (TF1)

TF1 (which was a different entity from the Task Force authoring this Report) met 3 times in 2011 with the following charges:

(1) Review factors affecting fiscal status of the NBS Program. Develop recommendations to promote its financial sustainability.

(2) Review existing programmatic requirements and processes identified in state statute and administrative rule. Develop recommendations to modify the process for adding and/or deleting tests from the NBS panel, while considering ethical and cost/funding implications.

(3) Review process of fee setting of the fee for NBS tests, and recommend alternatives.

Appendix F: Charge of the Wisconsin Newborn Screening Task Force

In 2012, the Secretary of the Wisconsin Department of Health Services established the Wisconsin Newborn Screening Task Force (i.e., the author of this report) to carry out the following charges:

> "[T]he Task Force shall make recommendations to the Secretary on a permanent organization structure for advising the Secretary on additions, deletions, costs, funding, informed consent and retention, use of blood samples, and other issues related to NBS tests. This report shall include the composition of the structure, as well as criteria, if any, (in addition to the six criteria in state statute) the state should consider when making recommendations about additions to and deletions from the mandated newborn screening tests."

Appendix G: Members of the Wisconsin Newborn Screening Task Force

Norman Fost (chair), MD, MPH, FAAP, University of Wisconsin – Madison
Jeffrey Britton, MD, FAAP, Aurora Medical Group
Christine S. Brown, MS, parent of two children with PKU
Arthur Derse, MD, JD, FACEP, Medical College of Wisconsin
David Dimmock, MD, Children's Hospital of Wisconsin
Kevin Josephson, MS, CGC, Gundersen Health System
Murray L. Katcher, MD, PhD, FAAP, Wisconsin Department of Health Services
Steven Leuthner, MD, MA, FAAP, Medical College of Wisconsin /
Children's Hospital Milwaukee
Elizabeth McPherson, MD, FAAP, FACMG, Marshfield Clinic
Joseph J. Piccione, SThD, JD, OSF Healthcare System
Jessica Seay, MPH, Wisconsin Department of Health Services

This Report was approved unanimously by the voting members. David Dimmock was unavailable at the time of the vote; his vote will be recorded when available.