Newborn Screening for Cystic Fibrosis: Report and Recommendations

Hawaii Cystic Fibrosis Newborn Screening Task Force

August 2006

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Executive Summary

Cystic Fibrosis (CF) is the second most common life-shortening, childhood-onset inherited disorder after sickle cell disease in the United States. It is a lethal genetic disorder that occurs in one of every 3,700 births in the U.S with approximately 1000 persons diagnosed with CF each year.

The diagnosis and treatment of CF are often delayed for months or years because CF symptoms are easily mistaken for other diseases. During this period, the disease can progress unchecked in infants and young children. Sufficient evidence exists to suggest CF detected at birth improves prognosis and overall health. Current technology can detect babies born with CF by using blood samples already collected for other newborn screening purposes. Several national organizations and the federal government have recommended that serious consideration be given for CF screening of all newborns.

Oregon State Public Health Laboratory performs newborn screening tests for Hawaii's infants as well as for the other northwest regional states including Alaska, Idaho, Nevada, and Oregon. In May 2005, a decision was made by the Oregon Cystic Fibrosis Newborn Screening Task Force to add cystic fibrosis (CF) to their list of disorders. This provided Hawaii with an opportunity to screen newborns for cystic fibrosis.

The Hawaii Cystic Fibrosis Newborn Screening Task Force was created in 2006 to assess this opportunity. After considering benefits, risks, costs, program models, national trends and recommendations, local statistics and services, and policy issues, the CF Task Force recommended the following:

- Implementation of a comprehensive newborn screening program for CF, integrated into the existing program for metabolic, endocrine, and hemoglobin disorders
- Immediate follow-up and tracking of infants with abnormal screening results, and assurance of adequate diagnostic evaluation
- Genetic counseling offered to families of all infants receiving sweat chloride testing
- Expert medical consultation available to infant's primary care provider, as well as for program and policy decisions
- Parent and practitioner education
- Quality assurance of all program elements
- Self-funding of CF screening activities from newborn screening fees

Newborn Screening for Cystic Fibrosis: Report and Recommendations

Introduction and Background

Introduction

The Hawaii Newborn Metabolic Screening Program (NBMSP) currently screens for 31 different disorders. The Oregon State Public Health Laboratory (OSPHL) performs newborn screening tests for Hawaii's infants as well as for the other northwest regional states including Alaska, Idaho, Nevada, and Oregon. In May 2005, a decision was made by the Oregon Cystic Fibrosis Newborn Screening Task Force to add cystic fibrosis (CF) to their list of disorders. This provided Hawaii with an opportunity to screen newborns for cystic fibrosis.

The Hawaii Cystic Fibrosis Newborn Screening Task Force was created in January 2006 to assess this opportunity. They were charged with the task of recommending whether newborn screening for CF should be implemented for Hawaii's infants, and if so, define the critical components of the system for screening, diagnosis, referral, follow-up and counseling. Task Force members were asked to: 1) review and consider a wide range of information; 2) discuss the benefits, risks, limitations, and state specific issues surrounding this endeavor; and 3) make recommendations to the Newborn Metabolic Screening Program Advisory Committee. Task Force members represented private and public health providers and laboratories, consumers, and community, state and federal agencies (Appendix A). The Task Force held two meetings between January and June 2006.

This report covers information that was considered in developing recommendations to the Hawaii NBMSP Advisory Committee about whether to adopt newborn screening for cystic fibrosis. The information includes the collection of local data on the statistics of CF in Hawaii and CF services; and benefits, risks, program models, national trends and recommendations, and policy issues based on publications by federal and state workgroups on this topic.

Background

Cystic Fibrosis (CF) is the second most common life-shortening, childhood-onset inherited disorder after sickle cell disease in the United States. It is a lethal genetic disorder that occurs in one of every 3,700 births in the U.S with approximately 1000 persons diagnosed with CF each year.

The diagnosis and treatment of CF are often delayed for months or years because CF symptoms are easily mistaken for other diseases. During this period, the disease can progress unchecked in infants and young children. Sufficient evidence exists to suggest CF detected at birth improves prognosis and overall health. Current technology can detect babies born with CF by using blood samples already collected for other newborn screening purposes. Several national organizations and the federal government have recommended that serious consideration be given for CF screening of all newborns. Twenty states currently have a NBS program for cystic fibrosis. Many more states have formed task forces which are reviewing the feasibility of adding CF to the newborn screening (NBS) testing panel.

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Overview of Cystic Fibrosis

Inheritance [1, 2]

Cystic Fibrosis is caused by an inherited defect in the normally occurring cystic fibrosis transmembrane regulator (CFTR) gene, which codes for a protein that regulates transport of salts across cellular membranes. This defect leads to excessively thick, viscous secretions that cause blocked glands, chronic respiratory obstruction, and infection.

Cystic Fibrosis has autosomal recessive inheritance. For a child to have CF, both parents must carry a CFTR gene with a CF mutation, and the child must inherit a CF mutation from each parent. However, the molecular diagnosis of CF is complex because there are more than 1,000 different mutations of the CFTR gene. The most commonly recognized mutations cause serious disease, while some of the rare mutations cause less severe health problems.

In the U.S., at least 70% of CF cases are the result of one mutation (ΔF508), and another 25% of cases can result from any of approximately 40 other mutations. On average, one in 32 people in the U.S. carry a single CF mutation. These "carriers" do not have CF and will not develop it. One in 3,700 newborns has two CF mutations, and therefore will develop CF. The frequency of disease varies by race/ethnicity, as shown below.

Group	CF Cases/Live Births
Caucasians	1/2,500-3,000
Hispanics	1/4,000-10,000
African Americans	1/15,000-20,000
Asians	1/30,000

Cystic fibrosis is the most common lethal genetic disease in Caucasians, but CF can occur in any racial or ethnic group. Since CF mutations are specific to certain racial and ethnic populations, the demographics of the state should be considered if a genetic marker panel for CF is used for newborn screening.

Clinical Features [1, 2]

Cystic Fibrosis usually manifests in infancy but it is often difficult to recognize. The most common early symptoms are recurrent cough, wheezing, abdominal pain, loose stools, and failure to thrive. Pancreatic insufficiency leads to malnutrition and severe growth problems. Respiratory infections increase in frequency and severity with age, in association with progressive decrease in lung function. Respiratory failure is the cause of death in more than 90% of persons with CF.

Over the years, treatment has dramatically improved the life span of patients from 14 to 33 years of age. Now, most persons with CF survive into adulthood.

A small portion of infants with CF are diagnosed during pregnancy by prenatal testing. Another 15-20% of infants have meconium ileus or complete intestinal obstruction that is diagnostic of CF. The rest of the infants with CF often go undiagnosed for some time. The reason is most CF symptoms are not specific to CF and many affected children are misdiagnosed

as having food allergies, celiac disease, asthma, or bronchitis before CF is finally recognized. This delay increases health care costs associated with CF. Misdiagnosis also leads to "diagnostic odyssey" of multiple visits, diagnostic tests, and hospitalizations that can have an emotional and economic toll on the family. Families are often left with feelings of distrust and anger toward health care professionals. The child's health is also compromised by delays in diagnosis including severe malnutrition which results in vitamin deficiencies that can affect future cognitive function [3].

Compared to a clinical diagnosis, newborn screening for CF is expected to shorten the median age at diagnosis from 14.5 months to 2 weeks.

Diagnosis, Treatment and Genetic Counseling [1, 2]

Diagnosis

The diagnosis of CF is made on the basis of the presence of one or more of the following:

- One or more clinical findings suggestive of CF
- A history of CF in a sibling
- A positive newborn screening test

PLUS one or more of the following:

- Sweat chloride level $\geq$ 60 mEq/L performed by experienced personnel using standardized methodology
- Characteristic ion transport defects in nasal tissue
- Two CF-causing mutations

In approximately 2% of patients, there is a nonclassic or atypical type of CF where persons have mild CFTR function, and often receive a diagnosis as adolescents or adults. Nonclassic or atypical CF is defined by having sweat chloride test levels below 60 mEq/L, milder clinical features, and 2 identified CFTR mutations with at least one that is associated with less severe disease.

Some infants with classic CF often have initial sweat values of 30-59 mEq/L. Accuracy of the test can be made in most infants at age 2-3 weeks but not all infants with CF have sufficient quantities of sweat for reliable testing. Therefore, sweat chloride levels in infants of 30-59 mEq/L are ambiguous, because the child can have classic or non-classic CF or not get diagnosed. More research is needed in managing those infants with borderline sweat chloride levels.

Treatment

Early treatment of CF is meant to minimize long term consequences of lung involvement and malnutrition. Treatment varies depending on the stage of the disease and organ systems involvement. Once the diagnosis is confirmed, treatment is focused on preventive and maintenance care, with acute care when needed. Pulmonary-specific treatment includes chest physiotherapy at least twice a day to keep the airway clear, and inhaled medications to improve lung function and combat infection. Pancreatic insufficiency results in mal-absorption and malnutrition. Treatments include oral pancreatic enzymes with every meal, oral or tube feedings with high-caloric supplements, and repletion of essential vitamins. Promising new therapies are currently under investigation including those that directly target the underlying mechanism of CF by improving salt transport across membranes.

The Centers for Disease Control and Prevention (CDC) recommends children with CF be evaluated at specialized CF centers that offer a comprehensive, multidisciplinary approach to CF care that can closely monitor the development of respiratory infections and provide nutritional and psychosocial support. The national Cystic Fibrosis Foundation (CFF) accredits such centers, publishes clinical practice guidelines, and convenes consensus panels on CF care.

Genetic Counseling

Genetic counseling answers questions about how CF is inherited, reproductive risks and discusses what testing may be available to the families. This is often offered to parents of children with CF, persons with CF, or known carriers of CF. Decisions regarding genetic testing are highly individual and genetic counselors provide non-directive information and support in keeping with the patient or family member's beliefs and values. Available literature suggests that without adequate counseling, misconceptions about how CF is inherited and the implications of identified CFTR mutations in the family can lead to increased worry, anxiety and overprotection.

Through newborn screening, many more children with CF may be identified. Ensuring families access to expert care and resources in accordance with national standards are needed for including CF in the state NBS program. Elements that should be considered include:

- Integrating a NBS program for CF into the existing metabolic, endocrine, and hemoglobin disorders
- Protocol for diagnosis and follow-up of those who screen positive
- Timely and comprehensive medical consultation and counseling
- Parent and practitioner education
- Quality assurance of program including collection of data, and rigorous practice guidelines to minimize risks to families during screening, diagnosis, treatment, and follow-up
- Cost and self-funding of CF related activities through newborn screening fees

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Newborn Screening for Cystic Fibrosis

National Recommendations

In 1997, CDC convened a workshop that reviewed the state and scientific evidence on newborn screening and found sufficient evidence of nutritional benefit to recommend that states develop "demonstration programs". Furthermore, research was needed on:

1) the consequences of delayed diagnosis
2) cognitive development caused by malnutrition
3) pulmonary benefits
4) cost-effectiveness of early detection through screening

In 2003, CDC reconvened a workshop, in cooperation with CFF, to follow-up on these issues. The objectives of this workshop were 1) to disseminate information about models and best practices for states that choose to adopt newborn screening for CF; 2) to review and evaluate the scientific evidence on benefits and risks of newborn screening for CF; and 3) to review screening, diagnostics, and follow-up concerns in CF newborn screening decision making.

The workgroup concluded "On the basis of a preponderance of evidence, the health benefits to children with CF outweigh the risk of harm and justify screening for CF…. As a result, CDC believes that including screening for CF in state newborn screening programs is justified. The evidence of clinical benefits from newborn screening for CF is based on an extensive body of research, including two randomized clinical trials and multiple prospective cohort studies….The net balance of benefits and risks is contingent on how newborn screening for CF is implemented. Consequently, newborn screening programs for CF, if initiated, should be of high quality and carefully monitored to ensure consistent quality and effectiveness."

Additional recommendations included:

- Consider state priorities and national guidelines regarding CF screening, diagnosis, and treatment
- Collect follow-up data for use in monitoring and improving CF newborn screening
- Implement rigorous infection control policies to minimize the risk of person-to-person transmission of pulmonary infection
- Ensure effective and timely communication between the newborn screening laboratory, parents, and primary care providers to facilitate prompt referral to diagnosis centers. CF centers should be skilled in diagnostic testing and should provide effective education and genetic counseling

A detailed description of the workgroup methodology and discussion can be found in Morbidity and Mortality Weekly Report (MMWR), October 2004 [1].

The March of Dimes also recently added CF newborn screening to its core panel of standard newborn screening tests recommended for implementation in all states [2].

Lastly, the federal Health Resources and Services Administration commissioned the American College of Medical Genetics to evaluate the overall effectiveness of newborn screening, and to make recommendations, including a uniform panel of conditions for implementation across all

states. The report published in March 2005 included cystic fibrosis as one of 29 disorders recommended for inclusion in this uniform panel [4].

State-based Newborn CF Screening Programs and Cystic Fibrosis Screening Strategies [1, 2]

The National NBS Status Report dated August 15, 2006 by the National Newborn Screening and Genetic Resource Center (http://genes-r-us.uthscsa.edu/index.htm) lists 20 states that test all newborns for CF by law; 3 states conduct it in certain hospitals or in selected populations; 6 states report testing for CF is required but not yet implemented and 1 state where it is universally offered but not yet required by law (Appendix 4).

The screening strategies for cystic fibrosis are shown in Table 1. Cystic Fibrosis newborn screening can be performed using the same dried blood spot sample collected for other newborn screening tests. With IRT-repeat IRT, samples are first tested for immunoreactive trypsinogen (IRT), an indication of pancreatic obstruction that is present at birth in most newborns who have CF. The IRT test is then repeated for infants whose initial IRT value is elevated. Those with repeatedly elevated IRT values are referred for diagnostic sweat chloride testing. Testing for specific CF mutations in the infant's DNA is not performed as part of this screening process.

For IRT-DNA testing protocol, all samples with elevated IRT levels are tested for one or more specific mutations in the CFTR gene. Some states test for only the most common mutation (ΔF508), while others test for a panel of up to 40 different CFTR mutations. A few states also test sequentially resorting to the mutation panel when only one ΔF508 mutation is detected.

Representatives from 12 programs that existed in 2003 were interviewed for the purpose of understanding their policy decision to include CF, the approaches to offering testing to the population, the testing strategy, and the approach to communication and follow-up. Conclusions were made about the importance of balancing the detection of as many patients as possible with minimizing the number of false-positives. Moreover, they emphasized that benefits, risks and costs vary depending on how screening is conducted and that those who will decide whether CF is added to a NBS program should pay special attention to this.

In May 2005, the Oregon Cystic Fibrosis Newborn Screening Task Force recommended implementing a comprehensive newborn screening program for CF for Oregon infants. Hawaii contracts with Oregon State Public Health Laboratory (OSPHL) to perform newborn screening specimens for all infants born in this state. If Hawaii were to pursue newborn screening for CF, the screening protocol used relies on OSPHL's screening approach. The Oregon Task Force decided on the IRT/IRT screening strategy due to cost and lower false positives. See Table 2 for a comparison between the IRT-DNA vs IRT-IRT screening protocols.

Table 1. Screening Strategies for Cystic Fibrosis

(**Source:** Grosse, S.D., et al., Newborn screening for cystic fibrosis: evaluation of benefits and risks and recommendations for state newborn screening programs. *MMWR Recomm Rep, 2004; **53**(RR-13): p. 1-36)*.

Protocol	specimen	specimen	Action	specimen	Action	specimen	Action
IRT-repeat IRT	Test 2nd specimen for IRT					Exceeds cutoff	Refer to sweat test
IRT-DNA (ΔF508)	DNA assay for ΔF508 alleles	1–2 mutations detected	Refer to sweat test				
		No mutation detected				Exceeds cutoff	Refer to sweat test
IRT-DNA (multiple mutations)	DNA assay for multiple mutations	1–2 mutations detected	Refer to sweat test				
IRT-DNA (ΔF508, multiple mutations)	DNA assay for ΔF508 alleles	2 mutations detected	Refer to sweat test or treatment	2 mutations detected	Refer to sweat test or treatment		
		1 mutation detected	DNA assay for multiple mutations	1 mutation detected	Inconclusive result reported		

* Immunoreactive trypsinogen.

Table 2. IRT-DNA vs IRT-repeat IRT FOR CF SCREENING OF OREGON NEWBORNS[1]

(**Source:** Personal communications with Michael Skeels, Administrator of OSPHL, *May 2006*)

Function	IRT-DNA	IRT-repeat IRT
Detects carriers	Yes	No
Identifies specific CF allele(s)	Yes	No
Provides families with genetic information about risk of CF in future infants	Yes	No
Requires/allows genetic counseling for families of carriers	Yes	No
CF cases detected per year (estimate)	13	13
False negatives per year	0.3	0.3
False positives[2] per year	177	22
Carriers detected per year	130	0
Sweat chloride tests per year	227	42
Percent of infants receiving sweat tests who will have CF	5.7% (13/227)	31.0% (13/42)
Genetic counselings per year	190	35
Cost per infant	$8	$6
No. samples required per infant	1	2[3]

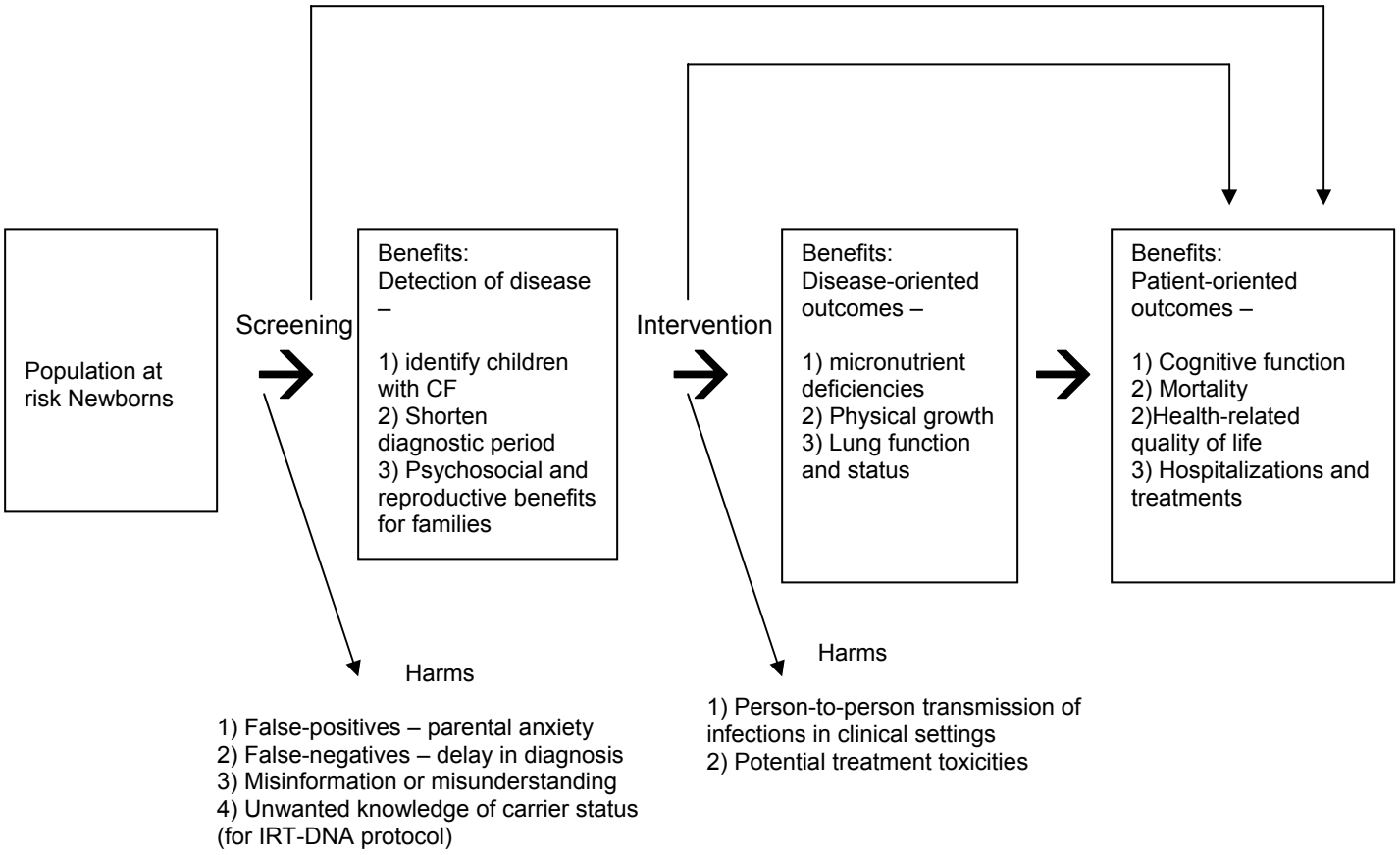
Draft 2-8-06

[1]Based on 46,000 Oregon births per year
[2]Defined as infants who have positive (abnormal) screening results by IRT/DNA or IRT/IRT but have negative sweat chloride tests
[3]Accomplished by two routine samples per infant or by collecting a second sample from those infants with elevated IRT on first sample

Benefits, Risks, and Limitations of Newborn Cystic Fibrosis Screening

The decision to implement CF into NBS is a challenging one as the balance of benefits and risks is not tipped dramatically toward one direction. Two papers published by Wilfond et al. in the Journal of Pediatrics September 2005 supplementary edition [5, 6] re-emphasize CDC and CFF's recommendations about NBS for CF that although screening is justified, it needs to be made in the context of state resources and priorities and with attention to proper planning and implementation to ensure that program benefits offset risks and costs. The figure on the next page summarizes some of the potential benefits and harms of newborn screening for cystic fibrosis. This is followed by a description of the scientific evidence available that support these claims.

Figure 1. Potential benefits and harms of newborn screening for cystic fibrosis (CF)
(**Source:** Grosse, S.D., et al., Newborn screening for cystic fibrosis: evaluation of benefits and risks and recommendations for state newborn screening programs. *MMWR Recomm Rep, 2004;* ***53****(RR-13): p. 1-36)*



Evidence of Benefit

The 1997 and 2003 workshop found that peer-reviewed scientific evidence supports the utility of newborn screening tests in identifying newborns with CF (see Appendix 2). Some of the major benefits include [1, 7]:

- Improved growth (by preventing or minimizing malnutrition)
- Improved cognitive development
- Reduced hospitalization
- Improved survival
- More rapid diagnosis

- Genetic counseling for family planning
- Reduction of psychosocial stress

Evidence of Risks and Limitations

Potential harms exist for CF patients and their families, children who have false-positive or false-negative newborn screens, and for the health care system as a whole [1]. They are described below:

- Infants with CF who are identified through newborn screening could acquire serious lung infections earlier than they would have otherwise, through exposure to other patients during follow-up of a positive newborn screening test, or while receiving preventive treatments. Procedures that isolate screen-positive and affected infants from older CF patients can minimize this risk.

- Parent-child relationships could be altered when a parent learns, via a newborn screening result, that an apparently healthy child may have a serious illness. However, the available research data do not suggest that early identification of CF negatively affects parent-child relationships.

- Although detecting CF carriers is not the primary purpose of CF newborn screening, the IRT-DNA screening process will detect approximately 10% of carriers. Theoretically, families of infants identified as carriers might feel uncomfortable with this information, fear discrimination, or feel stigmatized. However, research has actually shown the opposite that most families consider carrier identification to be a useful by-product of newborn screening because it provides helpful information for future decisions about health care and reproduction.

- As a part of newborn screening for CF, some infants who do not actually have CF will have a positive screening test result, and will undergo a diagnostic evaluation. Many of these "false positive" babies may be carriers for CF, while others will not. The parents of a baby with a false-positive test may experience distress and anxiety while waiting for the results of a confirmatory sweat chloride test. Usually, these feelings resolve once the sweat chloride test is complete and the child is found not to have CF or to be a carrier.

- The genetics of CF are easily misunderstood and the implications are complex for the parents of infants with CF as well as the parents of carriers. In both situations, future children may be at risk of having CF. In addition, many parents of children who are carriers of a single CF mutation may not understand that a single copy of a CF gene will not cause disease. Consequently, it is essential that a CF newborn screening program offers genetic counseling to parents of all infants who have CF or are identified as carriers through screening. Educational materials must also be available to parents, both before and after screening.

- As with any screening test, false-negative test results (negative newborn screening results in infants who have CF) are possible. A well-designed and implemented CF newborn screening program should miss an average of less than one baby per year. Ironically, the implementation of a CF newborn screening program might decrease the index of clinical suspicion among health care providers who assume that all CF cases will be detected at birth. This could delay the diagnosis of the small number of infants with CF who are not detected by newborn screening. Practitioner education efforts should address this issue.

- Newborn screening for CF poses a risk to the health care system as a whole. The increased need for sweat testing and genetic counseling may exceed the capacity of existing health care resources. Therefore, implementing a newborn screening system carries associated opportunity costs if health care resources are diverted away from other potential uses.

Assessing the Implementation of Newborn Cystic Fibrosis Screening in Hawaii

The Task Force reviewed the clinical services in Hawaii. Task Force members felt the main issues that needed to be addressed prior to implementing NBS for CF include diagnosis of newborns detected with CF; follow-up and management of affected individuals; and newborn screening fee.

Cystic Fibrosis in Hawaii

Data was collected on the number of individuals affected with CF in Hawaii, their ethnic background, and the distribution of CFTR disease causing mutations. CF patients in the state were ascertained through pulmonologists and we found there were at least 31 individuals with CF in Hawaii. Affected individuals who were not utilizing CF clinical services at the time this data was collected were not identified. The genetic mutations were known for 27 patients. Twenty six of these individuals carried the ΔF508 gene mutation in combination with another allele that is included in the clinically available mutation panels that range from testing 25 to 97 mutations. Most were Caucasian and seven individuals had Japanese, African American, Hawaiian, Asian or mixed ancestry.

It is anticipated that newborn screening for cystic fibrosis will identify more cases of CF in the population. Our data suggest that CF affects Hawaii's diverse ethnic population and is not affecting families of Caucasian descent only.

Cystic Fibrosis Services in Hawaii

Three agencies manage the care of children with CF in the state of Hawaii: Tripler Army Medical Center, Kapiolani Medical Center and Kaiser Permanente. Table 3 summarizes the services families receive with each agency. The CF services in Hawaii are currently not standardized across the state.

Table 3. Summary of the Diagnosis and Follow-up of Cystic Fibrosis in Hawaii
[Source: CF Task Force Members including Bojanowski, J. (Kaiser Genetic Counselor), Cheng, L. (Queen's Genetic Counselor), Griffith, J. (Kaiser Pulmonologist), Johnson, H. (Kaiser Medical Center Genetic Counselor), Matthews, W. (Kapiolani Medical Center Pulmonologist), Mulreany, L. (Tripler Army Medical Center Pulmonologist), and Staumbaugh, T. (Fetal Diagnostic Institute of the Pacific Genetic Counselor)**]**

Health Agency	Sweat Testing	Management and Follow-Up	Genetic Counseling	Prenatal Screening and Care
Kaiser Permanente	Sweat Conductivity Testing	Independent visits to necessary specialist evaluations within the agency	Provided by a genetic counselor	Provided by a genetic counselor
Kapiolani Medical Center	Sweat Conductivity Testing	Independent visits to necessary specialist evaluations within the agency	Provided by a pulmonologist	Provided by a genetic counselor**
Tripler Army Medical Center	Sweat Chloride Testing	Cystic Fibrosis Foundation accredited Care Center	Provided by a pulmonologist or Tripler genetics consultation	Provided by Tripler prenatal services

** In addition to Kapiolani, Queen's Medical Center and Fetal Diagnostic Institute of the Pacific provide prenatal genetic services.

Diagnosis of Screened Positive Newborns for CF

Sweat chloride testing is currently not offered to non-military families in Hawaii. Several possibilities to address this issue were explored as shown in Table 4. Cost and a laborious administrative process to send families to another state were limitations to working with CHLA or Stanford. The sweat conductivity method was unfavorable because it is not recognized by CFF as a diagnostic standard [8]. Therefore, Task Force members felt that the best option was to perform sweat chloride testing on children locally and contract with Tripler for such services.

Table 4. Cost Analysis of options for Newborn CF screening and testing for Hawaii

[Source: Hawaii DOH Staff including Au, S. (DOH State Genetics Coordinator), Hasegawa-Evans, L. (DOH Genetic Counselor), and Matsumoto, C. (NBMSP Coordinator)**]**

	Sweat Chloride at Tripler		Sweat Chloride and Consult at CHLA [a]		Sweat Chloride and Consult at Stanford [b]		Sweat Conductivity and DNA
	With DNA	Without DNA	With DNA	Without DNA	With DNA	Without DNA	
18,000 newborns screened via initial IRT ($3/specimen)	$54,000	$54,000	$54,000	$54,000	$54,000	$54,000	$54,000
188 newborns will need repeat IRT ($3/specimen)	$564	$564	$564	$564	$564	$564	$564
9 newborns with positive IRT/IRT			$18,657 [c]	$18,657 [c]	$30,015 [d]	$30,015 [d]	$855 [e]
DNA sequencing [f]	$4,440 [g]	N/A	$4,440 [g]	N/A	$4,440 [g]	N/A	$9,990 [h]
Follow-up costs [i]	$10,457	$10,457	$10,457	$10,457	$10,457	$10,457	$10,457
Total Cost			$88,118	$83,678	$99,476	$95,036	$75,866
Total cost per newborn			**$4.90**	**$4.65**	**$5.53**	**$5.28**	**$4.21**

[a] With travel expenses covered by NBS program and participation in a CF clinic.
[b] With travel expenses covered by NBS program and participation in a CF clinic.
[c] 9 newborns are sent to CHLA for sweat chloride testing only at cost of $800 (two roundtrip tickets to CA at $400; newborn is lap child) + $300 (hotel for two nights) + $150 (ground transportation) + $270 (per diem at $45/day/person) + $293 (sweat chloride testing) + $260 (initial consult with pulmonologist and CF team).
[d] 9 newborns are sent to Stanford for sweat chloride testing and CF consult at cost of $800 (two roundtrip tickets to CA at $400; newborn is lap child) + $300 (hotel for two nights) + $150 (ground transportation) + $270 (per diem at $45/day/person) + $1,115 (sweat chloride testing) + $700 (initial consult with pulmonologist).
[e] Sweat conductivity at CLH is $95/specimen.
[f] The cost of DNA sequencing is $1,110 (based on $1,085 institution price charged by Ambry Genetics and $25 blood draw and shipping fee charged by CLH).
[g] 4 newborns will have positive IRT/IRT and sweat chloride results and need DNA.
[h] 9 newborns will have positive IRT/IRT results and need DNA regardless of sweat conductivity results.
[i] Based on $2,000 (yearly cost for EMR) + $8,457 for a 0.25 FTE clerical position ($6,200 + 36.4% fringe).

Follow-up and Management of Cystic Fibrosis in Hawaii

The importance of children detected by newborn screening and cared for by a CFF accredited comprehensive CF center was recognized by the Task Force. Although the current status of clinical services varies depending on the insurance plan of the family, the Task Force members were aware of the benefits and limitations each agency offered.

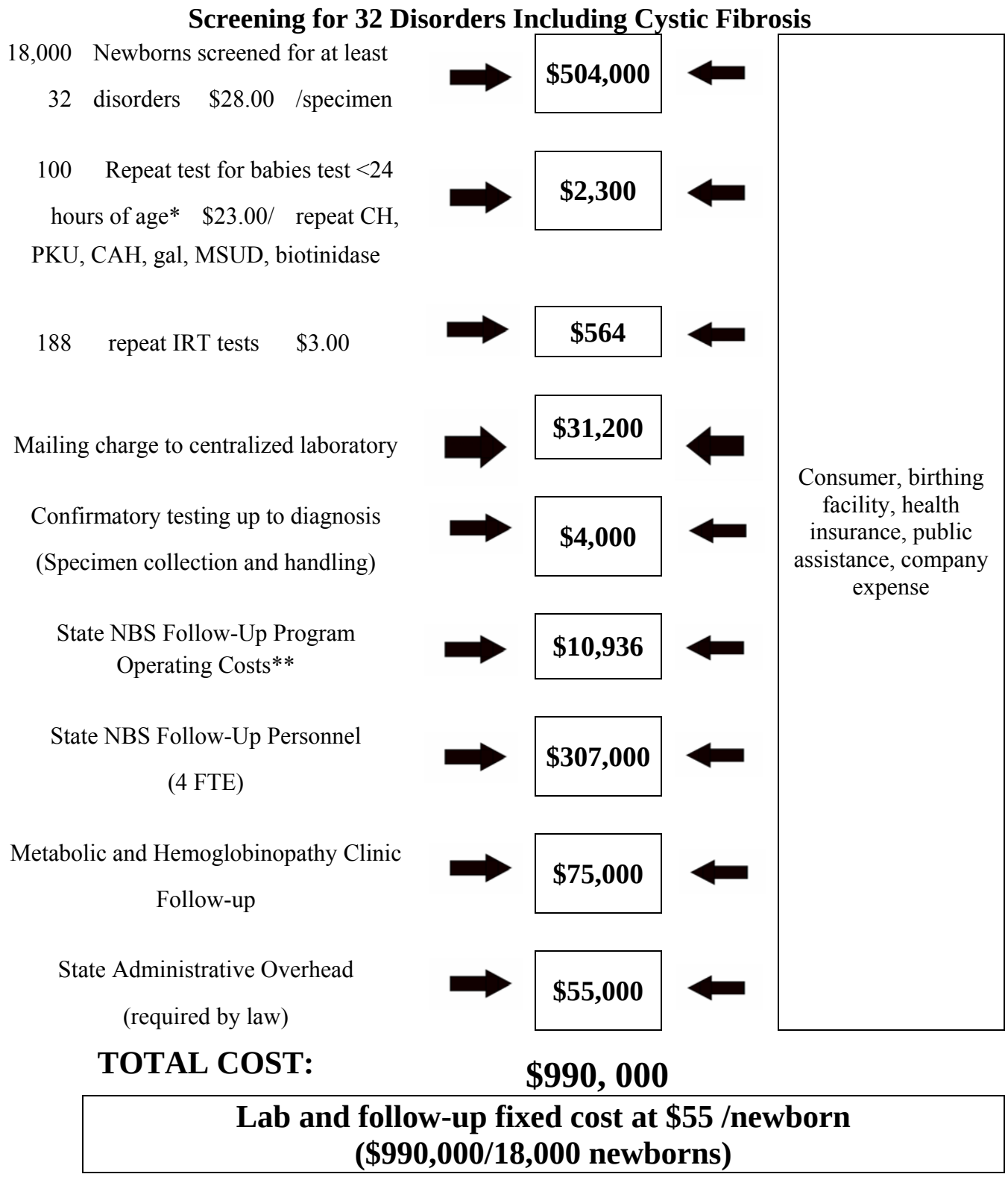
CFF accreditation criteria states a minimum of 50 patients need to be seen at the center [8]. There are currently 30 plus patients identified to have CF in Hawaii. Unless one CF center is formed through the collaboration of Tripler, Kaiser, Kapiolani, and Queen's Medical Center, none of the major health entities alone could meet minimum criteria for CFF accreditation. Representatives from each agency agreed that communication and education of patient, parent, and health provider in ensuring appropriate follow-up care would need to be enforced in the meantime. The Task Force recommended that another workgroup convene to address the issues surrounding standardization and follow-up of individuals diagnosed with CF.

Newborn Screening Fee

The newborn screening fees across the nation ranges from $0 to $140 (Appendix 3). This is likely due to different activities and administrative duties performed within each state. Hawaii's newborn screening fee is currently $47. The Task Force reviewed the information on the prevalence and estimated number of CF cases in Hawaii, the newborn screening method via IRT/IRT, the diagnostic method of sweat chloride testing, and the administrative costs to derive an estimated increase of $4-5 if CF is added to Hawaii's newborn screening panel. In addition, a nursing position will need to be added to the Newborn Metabolic Screening Program (4 FTE) to perform tracking, follow-up, and service coordination, necessitating increase of the newborn screening fee to $55 per newborn. Table 5 summarizes the cost components and how this fee is derived.

Table 5 Cost analysis for CF screening and 31 disorders through Hawaii's Newborn Metabolic Screening Program

[Source: CF Task Force Members including Au, S. (DOH State Genetics Coordinator), and Matsumoto, C. (NBMSP Coordinator)**]**



* American Academy of Pediatrics guidelines and ASTPHLD/CORN Committee recommend repeat tests for newborns tested <24 hours of age.

** Includes professional/community education and testing for uninsured/indigent patients.

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Recommendations

The CF Task Force recommends implementing newborn screening for CF for Hawaii infants, provided all necessary program elements are available and in place at the time the screening program is implemented. These elements include:

- Cystic Fibrosis screening of newborns integrated into the existing newborn screening program for metabolic, endocrine, and hemoglobin disorders
- Laboratory screening of dried blood spots for immunoreactive trypsinogen (IRT)
- Immediate follow-up and tracking of infants with abnormal screening results
- Assurance of an adequate diagnostic evaluation
- Confirmatory testing by a sweat chloride method approved by the Clinical and Laboratory Standards Institute
- Referral of infants with a positive sweat chloride test to appropriate and comprehensive clinical services
- Genetic counseling offered to families of all infants receiving sweat chloride testing
- Expert medical consultation available to infant's primary care provider, as well as for program and policy decisions
- Parent and practitioner education
- Quality assurance of all program elements

The costs of CF newborn screening will be paid from newborn screening fees deposited into the Newborn Metabolic Screening Special Fund. It is recommended that the newborn screening fee be raised to $55 to allow for CF screening, tracking, and follow-up. Program funds will pay for sweat chloride testing and genetic counseling for those infants who are not covered by public or private health insurance (Table 5).

Should the Newborn Metabolic Screening Advisory Committee accept these recommendations, CF screening will be targeted to begin on September 1, 2007, pending approval of the revised contract with the Oregon State Public Health Laboratory. The Hawaii Administrative Rules, Chapter 11-143, will also be amended to include CF screening and the revised newborn screening fee. These changes, which do not require legislative approval, will go through the Administrative Rules process before they are adopted.

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Appendix 1 August 2006

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Appendix 2

(**Source:** Grosse, S.D. et al., Newborn Screening for cystic fibrosis: evaluation of benefits and risks and recommendations for state newborn screening programs. *MMWR Recomm Rep, 2004; **53** (RR-13): p. 1-36)*

unscreened groups measured at same ages

Location	Growth and nutrition	Bacterial colonization	Lung function	Pulmonary scores	Survival	Cognitive function	Care use
Randomized controlled trial							
Wisconsin	Significant differences in height Z-score and percentage low height and weight in favor of screened group* (p<0.01)	Shorter time to infection for screened children seen at one center but not overall†	At age 7 years, 12% of screened, 25% of controls <90% forced expiratory volume in 1 second (FEV_1) n.s.§¶**	Chest radiograph scores significantly worse at age 12 years in screened group, but no significant difference after controlling for infections**		Insignificant difference of 5 points on Cognitive Skills Index; for subset with vitamin E deficiency, significant difference of 12.5 points†† (p<0.05)	Hospital use by 51% in screened group and 34% of control group; no control for confounding by genotype or infections§§
Wales and West Midlands	No significant difference in weight or height¶¶			No difference at ages 1–4 years¶¶	Four CF-related deaths in 71 unscreened children versus 0/71 among screened cohort (p<0.05)***		Screened cohort spent 19.2 days in hospital in first year of life versus 27.0 days for unscreened children (p<0.01)¶¶
Cohort study							
Australia	Difference in height in favor of screened group significant at ages 1 and 5 years†††		Significant difference in FEV_1 in favor of screened group at ages 5, 10, and 15 years (p<0.01)†††§§§	Significant difference in chest radiographs in favor of screened group at age 15 years (p<0.05)§§§	Death rate 47% lower among screened cohort, n.s.¶¶¶		Screened cohort spent 4 days in hospital during first 2 years of life versus 27 days for unscreened cohort¶¶¶
France	Differences in height Z-scores of 0.3–0.6 in favor of screened group significant at ages 1, 3, and 5 years (p<0.05)****	No difference****	No difference****	Better chest radiograph and clinical scores for screened children (p<0.05)****	3 CF-related deaths in 36 unscreened children versus 0/77 in screened cohort (p<0.05)****		Hospitalizations among 49% of screened and 86% of unscreened cohort (p<0.0001)****
Italy — geographic controls (Sicily)	Differences in height in favor of screened group significant at ages 0–2 years through ages 14–16 years (p<0.01)††††				18 deaths in 152 unscreened children versus 2/126 in screened cohort (p<0.001)††††		
Italy — within-region controls	Differences in height in favor of screened group significant at ages 6–8 years through ages 14–16 years (p<0.01)††††				No difference in mortality at age <10 years††††§§§§		

Appendix 2

(**Source:** Grosse, S.D. et al., Newborn Screening for cystic fibrosis: evaluation of benefits and risks and recommendations for state newborn screening programs. *MMWR Recomm Rep, 2004; **53** (RR-13): p. 1-36)*

screened and unscreened groups measured at same ages

Location	Growth and nutrition	Bacterial colonization	Lung function	Pulmonary scores	Survival	Cognitive function	Care use
Cohort study							
Netherlands — contemporaneous controls	Height Z-score greater by 0.42 for screened group, n.s.¶¶¶¶		Higher scores in screened group, n.s.¶¶¶¶		Adjusted relative risk of dying 57% lower for screened group, n.s.¶¶¶¶*****		
Netherlands Post–screening controls	Height Z-score lower by 0.17 in screened group, n.s.¶¶¶¶		No difference¶¶¶¶		Adjusted relative risk of dying 65% lower for screened group, n.s.¶¶¶¶		
Registry							
United Kingdom Cystic Fibrosis Database	Height Z-score higher by 0.32 in screened group than in clinical diagnosis group ($p<0.005$); controlling for genotype 0.22, n.s.†††††	Lower rates in screened group than in clinical diagnosis group at ages 1–3 years ($p<0.005$) †††††	No difference	Better chest radiograph and clinical scores at ages 1–3 years and ages 7–9 years ($p<0.05$)†††††			–20% lower use of high-cost therapies in screened group than in clinical diagnosis group at ages 1–3 years and ages 4–6 years ($p<0.05$)†††††
United States Cystic Fibrosis Foundation National Patient Registry		No difference§§§§§	No difference§§§§§				No difference among those receiving diagnosis after 1986§§§§§¶¶¶¶¶

* Source: Farrell PM, Kosorok MR, Rock MJ, et al. Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. Pediatrics 2001;107:1–13.

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***** Not statistically significant.

††††† Source: Sims EJ, McCormick J, Mehta G, Mehta A. Neonatal screening for cystic fibrosis is beneficial even in the context of modern treatment. J Pediatr (suppl) (in press).

§§§§§ Source: Lai HJ, Cheng Y, Cho H, Kosorok MR, Farrell PM. Association between initial disease presentation, lung disease outcomes, and survival in patients with cystic fibrosis. Am J Epidemiol 2004;159:537–46.

¶¶¶¶¶ Source: Lai HJ, Cheng Y, Farrell PM. The survival advantage of cystic fibrosis patients diagnosed through neonatal screening: evidence from the U.S. Cystic Fibrosis Foundation Registry data. J Pediatr (suppl) (in press).

Appendix 3

(**Source:** National Newborn Screening Information System (NNSIS) database hosted by the National Newborn Screening and Genetics Resource Center (NNSGRC). URL: www2.uthscsa.edu/nnsis/ReportFee.cfm)

State/ Territory	Amount of fee	Program components covered by fee	Last update
Alabama	$ 139.33	Laboratory	7/18/2006
Alaska	$ 55.00	Laboratory, Program administration/follow-up	1/27/2006
Arizona	$ 30.00	Laboratory, Program administration/follow-up, Treatment, Specialist consultation, physicians, and community health nurses	5/16/2006
Arkansas	$ 14.83	Laboratory	4/13/2006
California	$ 78.00	Laboratory, Program administration/follow-up	1/27/2006
Colorado	$ 59.00	Laboratory, Program administration/follow-up, Treatment, Genetic counseling	6/27/2006
Connecticut	$ 28.00	Laboratory	1/27/2006
Delaware	$ 78.00	Laboratory, Program administration/follow-up, Medical genetics consultant	6/27/2006
District of Columbia	No Fee		1/27/2006
Florida	$ 15.00	Laboratory, Program administration/follow-up, Treatment	1/27/2006
Georgia	No Fee		1/27/2006
Hawaii	$ 47.00	Laboratory, Program administration/follow-up, Treatment, Education, Fed Ex Courier	6/27/2006
Idaho	$ 25.00	Laboratory, Program administration/follow-up, $48 for double kits if screened prior to 24 hrs.	6/27/2006
Illinois	$ 47.00	Laboratory, Program administration/follow-up, Treatment	3/1/2006
Indiana	$ 74.50	Laboratory, Program administration/follow-up, Treatment	7/5/2006
Iowa	$ 77.00	Laboratory, Program administration/follow-up, Medical Consultants, Metabolic formula, Short-term and Long-term follow-up, 7-day/ same-day courier, Developmental fund.	7/5/2006
Kansas	No Fee		1/27/2006
Kentucky	$ 53.50	Laboratory, Program administration/follow-up	6/27/2006
Louisiana	$ 18.00	Laboratory, Treatment, Evaluation and Education	6/27/2006
Maine	$ 52.00	Laboratory, Program administration/follow-up, Education	6/27/2006
Maryland	$ 42.00	Laboratory, Covers reagents only	6/27/2006
Massachusetts	$ 54.75	Laboratory, Program administration/follow-up	1/27/2006
Michigan	$ 56.83	Laboratory, Program administration/follow-up	1/27/2006
Minnesota	$ 61.00	Laboratory, Program administration/follow-up	1/27/2006
Mississippi	$ 70.00	Laboratory, Program administration/follow-up	6/27/2006
Missouri	$ 50.00	Laboratory	1/27/2006

Appendix 3

(**Source:** National Newborn Screening Information System (NNSIS) database hosted by the National Newborn Screening and Genetics Resource Center (NNSGRC). URL: www2.uthscsa.edu/nnsis/ReportFee.cfm)

State/ Territory	Amount of fee	Program components covered by fee	Last update
Montana	$ 42.70	Laboratory	6/27/2006
Nebraska	$ 35.75	Laboratory, Treatment	7/27/2006
Nevada	$ 60.00	Laboratory, Program covers up to confirmatory diagnosis then transferred to CSHCNP.	1/27/2006
New Hampshire	$ 40.00	Laboratory	6/27/2006
New Jersey	$ 71.00	Laboratory, Program administration/follow-up, Treatment, Education, Genetic services, Formula.	6/27/2006
New Mexico	$ 32.00	Laboratory, Program administration/follow-up, Treatment, Education and Genetic services.	6/27/2006
New York	No Fee		7/25/2006
North Carolina	$ 14.00	Laboratory	6/27/2006
North Dakota	$ 42.50	Laboratory	2/27/2006
Ohio	$ 45.15	Laboratory, Program administration/follow-up	6/27/2006
Oklahoma	$ 10.50	Laboratory	1/27/2006
Oregon	$ 54.00	Laboratory, Program administration/follow-up, Treatment	1/27/2006
Pennsylvania	No Fee		1/27/2006
Rhode Island	$ 110.00	Laboratory, Program administration/follow-up, Specialty formulas.	6/27/2006
South Carolina	$ 42.00	Laboratory, Program administration/follow-up	6/27/2006
South Dakota	$ 99.16	Fee collected by the contract laboratory for testing only.	6/27/2006
Tennessee	$ 47.50	Laboratory, Program administration/follow-up	6/27/2006
Texas	$ 19.50	Laboratory	1/27/2006
Utah	$ 65.00	Laboratory, Program administration/follow-up	6/27/2006
Vermont	$ 33.30	Laboratory, Program administration/follow-up	1/27/2006
Virginia	$ 53.00	Laboratory, Program administration/follow-up, Treatment, Metabolic formula	6/27/2006
Washington	$ 67.50	Laboratory, Program administration/follow-up, Treatment, Program evaluation and Education.	6/27/2006
West Virginia	No Fee		1/27/2006
Wisconsin	$ 69.50	Laboratory, Program administration/follow-up, Treatment, Genetic counseling.	6/27/2006
Wyoming	$ 70.00	Laboratory	6/30/2006
Puerto Rico			
Virgin Islands	No Fee		1/27/2006
American Samoa			
Northern Marianas			

Appendix 3

(**Source:** National Newborn Screening Information System (NNSIS) database hosted by the National Newborn Screening and Genetics Resource Center (NNSGRC). URL: www2.uthscsa.edu/nnsis/ReportFee.cfm)

State/ Territory	Amount of fee	Program components covered by fee	Last update
Guam			

Appendix 4

Source: National Newborn Screening and Genetic Resource Center (http://genes-r-us.uthscsa.edu/index.htm)

National Newborn Screening Status Report

Updated 08/15/06

The U.S. National Screening Status Report lists the status of newborn screening in the United States.

Dot "●" indicates that screening for the condition is universally required by Law or Rule and fully implemented
A = universally offered but not yet required, **B** = offered to select populations, or by request, **C** = testing required but not yet implemented
D = likely to be detected (and reported) as a by-product of MRM screening (MS/MS) targeted by Law or Rule

STATE	Core[1] Conditions									Additional Conditions Included in Screening Panel (universally required unless otherwise indicated)
	Hearing	Endocrine		Hemoglobin			Other			
	HEAR	CH	CAH	Hb S/S	Hb S/A	Hb S/C	BIO	GALT	CF	
Alabama	A	●	●	●	●	●	●	●		
Alaska	●	●	●	●	●	●	●	●		
Arizona	A	●	●	●	●	●	●	●	C	
Arkansas	●	●		●	●	●		●		
California	B	●	●	●	●	●	C	●	C	HHH; PRO; EMA
Colorado	●	●	●	●	●	●	●	●	●	
Connecticut	●	●	●	●	●	●	●	●	B	HHH; HIV [2]; NKH
D.C.	●	●	●	●	●	●	●	●	●	G6PD
Delaware	●	●	●	●	●	●	●	●	●	
Florida	●	●	●	●	●	●	●	●	C	
Georgia	A	●	●	●	●	●	●	●		
Hawaii	●	●	●	●	●	●	●	●		
Idaho	A	●	●	●	●	●	●	●		
Illinois	●	●	●	●	●	●	●	●		5-OXO, HIV [2]
Indiana	●	●	●	●	●	●	●	●		
Iowa	●	●	●	●	●	●	●	●	●	HHH; NKH
Kansas	●	●		●	●	●		●		
Kentucky	A	●	●	●	●	●	●	●	●	
Louisiana	●	●	●	●	●	●	●	●		
Maine	A	●	●	●	●	●	●	●		HHH; CPS (D)
Maryland	●	●	●	●	●	●	●	●	●	
Massachusetts	●	●	●	●	●	●	●	●	A	TOXO; HHH (A); CPS (D)
Michigan	A	●	●	●	●	●	●	●		
Minnesota	A	●	●	●	●	●	●	●	●	
Mississippi	●	●	●	●	●	●	●	●	●	5-OXO; CPS; HHH
Missouri	●	●	●	●	●	●	C	●	C	
Montana	A	●	B	●	●	●	B	●	B	
Nebraska	A	●	●	●	●	●	●	●	●	5-OXO; HHH; NKH (A)
Nevada	A	●	●	●	●	●	●	●		
New Hampshire	A	●	●	●	●	●	●	●	●	TOXO
New Jersey	●	●	●	●	●	●	●	●	●	
New Mexico	●	●	●	●	●	●	●	●	C	
New York	●	●	●	●	●	●	●	●	●	HIV; HHH
North Carolina	●	●	●	●	●	●	●	●		
North Dakota	A	●	●	●	●	●	●	●	●	HHH; NKH
Ohio	●	●	●	●	●	●	●	●	C	
Oklahoma	●	●	●	●	●	●		●	●	
Oregon	A	●	●	●	●	●	●	●		
Pennsylvania	●	●	●	●	●	●	B	●	B	5-OXO; CPS; G6PD; HHH; NKH (B)
Rhode Island	●	●	●	●	●	●	●	●	●	
South Carolina	A	●	●	●	●	●	●	●	●	
South Dakota	A	●	●	●	●	●	●	●	A	5-OXO; EMA; HHH; NKH
Tennessee	A	●	●	●	●	●	●	●		5-OXO; HHH; NKH
Texas	B	●	●	●	●	●	C	●		
Utah	●	●	●	●	●	●	●	●		
Vermont	●	●	●	●	●	●	●	●		CPS
Virginia	●	●	●	●	●	●	●	●	●	
Washington	A	●	●	●	●	●	●	●	●	
West Virginia	●	●		●	●	●		●		
Wisconsin	A	●	●	●	●	●	●	●	●	
Wyoming	●	●	●	●	●	●	●	●	●	

[1]Terminology consistent with ACMG report - Newborn Screening: Towards a Uniform Screening Panel and System. Genet Med. 2006; 8(5) Suppl: S12-S252

[2]Newborn screened for HIV only if mother was not screened during pregnancy

Additional Conditions/Abbreviations and Names

BIO	Biotinidase	**CF**	Cystic fibrosis	**GALT**	Transferase deficient galactosemia (Classical)	**HB S/C**	Sickle – C disease	**HEAR**	Hearing screening
CAH	Congenital adrenal hyperplasia	**CH**	Congenital hypothyroidism	**HB S/S**	Sickle cell disease	**HB S/A**	S-βeta thalassemia		

Other Disorders

5-OXO	5-oxoprolinuria (pyroglutamic aciduria)	**G6PD**	Glucose 6 phosphate dehydrogenase	**NKH**	Nonketotic hyperglycinemia
CPS	Carbamoylphosphate synthetase	**HHH**	Hyperammonemia/ornithinemia/ citrullinemia (Ornithine transporter defect)	**PRO**	Prolinemia
EMA	Ethylmalonic encephalopathy	**HIV**	Human immunodeficiency virus	**TOXO**	Toxoplasmosis