Arizona Department of Health Services

Meeting Notice

Newborn Screening Advisory Committee
Meeting Notice and Agenda
Monday, December 9, 2013

Pursuant to A.R.S. § 38-431.02, notice is hereby given to the members of the Newborn Screening Advisory Committee (NBSAC) of the Arizona Department of Health Services and to the general public that the NBSAC will hold a meeting open to the public on December 9, 2013 from 3:00 p.m. until 5:00 p.m., at the Arizona State Laboratory, 250 North 17th Avenue, First Floor Igloo Conference Room.

The agenda for the meeting is as follows:

I. Call to Order, Welcome and Introductions (Director Will Humble)
II. Milwaukee Journal Sentinel Report – Update
III. NBS Rulemaking Update
IV. Recent ACMG Panel Additions – Discussion
   a. Critical Congenital Heart Defects (CCHD)
   b. Severe Combined Immune Deficiencies (SCID)
V. Call to Public
   This is the time for the public to comment. Members of the Committee may not discuss items that are not on the agenda. Therefore, action taken as a result of public comment will be limited to directing staff to study the matter or schedule it for further consideration/decision at a later date.
VI. Announcements
VII. Adjournment

A copy of the agenda and background material provided to Committee members will be available for public inspection on the AZ NBS website – www.aznewborn.com.

Persons with a disability may request a reasonable accommodation, such as a sign language interpreter, by contacting Ward Jacox at (602) 364-1409 or toll free at (800) 548-8381 (For the hearing/speech impaired, please call 711 for the AZ Relay Service) Requests should be made as soon as possible to allow time to arrange the accommodation.

Dated this 26th day of November, 2013.

ARIZONA DEPARTMENT OF HEALTH SERVICES

Ward B. Jacox
Chief of the Office of Newborn Screening

Milwaukee Journal Sentinel Report

Newborn Screening Advisory Committee
December 9, 2013

Deadly Delays | Watchdog Update

Hospital, lab associations push for improved newborn testing procedures

March of Dimes calls for 'culture of safety' in screening system

By Ellen Gabler of the Journal Sentinel
Nov. 23, 2013

Hospitals and public health labs across the country are being urged to review their newborn screening policies and procedures in response to a Milwaukee Journal Sentinel investigation that revealed tens of thousands of blood samples from babies across the country are not promptly screened for rare yet deadly disorders.

The American Hospital Association issued a quality advisory last week, asking its nearly 5,000 member-hospitals to check their performance in the Journal Sentinel's analysis and review with hospital staff the proper way to handle newborn screening samples. The Journal Sentinel found that thousands of hospitals throughout the country send babies' blood samples late to state labs that perform the lifesaving tests.

The Association of Public Health Laboratories asked lab directors in all 50 states to read the Journal Sentinel series, which Executive Director Scott Becker said "exposes gaps in the system that could be addressed if handled carefully."

Becker wrote that in an email to lab directors across the country and sent a four-page report outlining how every entity involved in the newborn screening process plays a critical role in how babies are screened for serious genetic disorders.

In an interview, Becker said quality improvement is needed but will require cooperation between hospitals, state health departments, doctors and federal regulators, in addition to public health labs.

"There is not one solution. I think there will be a series of things," Becker said. "The first thing is the recognition that there is a problem, and your report did that. It is going to force the conversation a little bit deeper between public health agencies and hospitals."

The national March of Dimes also issued a statement calling for a "culture of safety" throughout the entire newborn screening system.

About one in every 800 babies is born with a potentially severe or deadly condition that can be treated and managed if the child is properly tested. These babies often appear healthy at birth but can become extremely sick within days. The entire premise of newborn screening is to detect disorders quickly so babies can be treated early, averting death and preventing or limiting brain damage, disability and a lifetime of costly medical care.

Nearly every baby in the country has blood collected within a day or two of birth for the screening. The baby's heel is pricked, and blood is collected on a card. The card is supposed to be sent within 24 hours to a lab for testing.

But a Journal Sentinel analysis of nearly 3 million newborn screening tests found that at least 160,000 blood samples from newborns arrived late at labs throughout the country last year — a conservative calculation, as the

newspaper used five or more days as a standard for lateness; federally backed guidelines recommend blood samples take no more than three days to arrive at labs for testing.

Problems found

The investigation also identified other problems with state-run newborn screening programs:

■Labs in half the country are closed on weekends and holidays, meaning babies born later in the week could have their tests delayed two or three days.

■In nearly three-quarters of the country, hospitals are supposed to send samples using overnight delivery or courier services. Yet it still takes days for hundreds of thousands of samples to arrive at labs for testing. In some cases, hospitals are sending samples through the U.S. mail even when a courier service is arranged and paid for by the state.

■Many hospitals ignore regulations that require them to quickly send babies' blood samples to labs, and suffer no consequences when they're late.

■For nearly 15 years, federal regulators and public health officials have discussed the need to standardize newborn screening systems throughout the country, but little action has been taken beyond increasing the number of conditions tested.

■Lab administrators and public health officials in dozens of states have fought to keep the track records of hospitals hidden.

In June, the Journal Sentinel requested newborn screening data from every U.S. state and the District of Columbia. Twenty-four states and Washington, D.C., would not release information identifying hospital names. Many cited patient privacy, even though children's names and outcomes of tests were not requested. Other states said releasing such information would be adversarial to hospitals or might reveal their business practices. Five states released statewide information only.

For 26 states, the Journal Sentinel published searchable databases showing how long it took blood samples to arrive at testing labs from individual hospitals. Expectant parents in the District of Columbia and the 24 states that refused to release the data have no idea how well the hospital where their baby will be born measures up.

Hospitals vow improvement

Before the investigation was published, hospitals in Wisconsin and across the country thanked the Journal Sentinel for bringing the issue to their attention and pledged to fix the problems. Many hospitals said they were unaware of their performance because state labs had not given them feedback. In Arizona, the hospital association is organizing statewide newborn screening training for its members after learning about its state's poor performance. The Florida Hospital Association outlined a series of specific recommendations, telling its hospitals to review and enforce newborn screening guidelines and develop policies to prevent delays.

Becker, of the public health lab association, said going forward, his group will "encourage as much transparency as possible." However, it is unclear if that means the performance of individual hospitals and all states will ever be made public by state labs or health departments.

The association said it is about to begin collecting about 10 quality indicators from state labs. That includes how long it takes for blood samples to arrive at labs, but at this point, the information will not be made public about individual states. It will be provided to states in a report so they can use it to improve, Becker said. Hospital-specific information will not be collected.

The effort is through a contract with a branch of the U.S. Department of Health and Human Services. In September, a committee of medical and genetics experts that makes recommendations to the U.S. secretary of

health and human services asked the public health lab association to begin collecting the data.

Newborn screening programs are run by states, and the association cannot compel them to participate. The Journal Sentinel found wide differences among newborn screening programs throughout the country. Only Iowa and Delaware, for example, had 99% of blood samples meet the three-day turnaround time recommend by federal guidelines. In Texas, 15% of blood samples took five or more days to arrive at the state lab after they were collected.

Political will needed

Becker and others continue to stress improving the entire system that newborn screening depends on.

State health departments in most states oversee newborn screening, and legislatures determine the programs' funding, which affects factors such as whether labs are open on weekends or whether overnight delivery is included in the cost of newborn screening tests.

"There really needs to be a political will to make changes," Becker said. "The public could also write to their legislators."

Then there are the hospitals, which are often responsible for newborn screening delays for a variety of reasons: New staff doesn't know the protocol; samples are "batched," and held in groups instead of being sent within 24 hours of collection; samples are delayed in the mail room or a hospital's own laboratory.

The American Hospital Association said it will hold a conference call next month to address issues and highlight "best practices" hospitals should follow. In a statement, the association said the Journal Sentinel investigation "presents a good opportunity for everyone involved to work together to examine the entire process and ensure the best outcomes."

Wisconsin's largest hospital chain, Aurora Health Care, made an immediate switch after being told about its delayed samples. The hospital chain's courier now delivers samples to the Wisconsin State Laboratory of Hygiene on Saturdays, which it hadn't done before.

In January, the committee of experts that advises the U.S. secretary of health and human services will meet to address quality issues and review preliminary data collected by the public health lab association, although collection of that data has not yet begun.

The committee chairman, Joseph Bocchini, said several potential solutions will be discussed, including increasing involvement from the federal Health Resources and Services Administration and setting newborn screening standards for hospitals under the Joint Commission, a body that accredits hospitals.

He also said he supports transparency in how states perform.

"The more data that is publicly available about each state, the better it would be for the public and that state. There's no question," said Bocchini, chairman of the pediatrics department at Louisiana State University. "I think we have had considerable success, but obviously we are not where we want to be in creating a system where we identify potentially life-threatening disorders."

U.S. Sen. Kay Hagan (D-N.C.) said the delays "represent a break in a critical link of the newborn screening program" and said she would consider making changes to the Newborn Screening Saves Lives Reauthorization Act, which is pending in Congress.

The bill, originally passed in 2008, funds several programs related to newborn screening, including the secretary's advisory committee, follow-up care for children, education and outreach, quality control in labs, and research on new disorders and treatments.

"Newborn screening saves lives, but the program is only effective if samples are taken and tested in a timely manner," Hagan said.

U.S. Sen. Orrin Hatch (R-Utah), who co-sponsored the bill with Hagan, did not respond for comment. Neither did U.S. Reps. Lucille Roybal-Allard (D-Calif.) and Mike Simpson (R-Idaho), who are sponsoring a related bill in the House.

Twitter: twitter.com/egabler

Find this article at:
http://www.jsonline.com/watchdog/watchdogreports/hospital-lab-associations-push-for-improved-newborn-testing-procedures-b99148031z1-233169401.html

☐ Check the box to include the list of links referenced in the article.

Baby tests require a culture of safety

By Edward R.B. Mccabe and Jennifer L. Howse
Nov. 23, 2013

The nation's newborn screening system touches every one of the nearly 4 million babies born annually in the United States. It prevents death and disability through early identification of and interventions for newborns with numerous, but rare, disorders. This life-saving system requires a culture of safety that recognizes its complexity and proactively addresses its potential weaknesses.

Last week's "Deadly Delays" series of articles in the Journal Sentinel has focused attention on one area of weakness: delay in the transport of these time-critical samples from the hospital where the baby was born to the newborn screening testing laboratory. One reason for these delays was reported to be hospitals waited until they had collected several newborn screening samples over multiple days before sending them to the laboratory as a larger group, a practice known as "batching."

Many of the disorders targeted by newborn screening can strike a child within days of birth, and delays can mean the difference between life and death or lead to long-term disabilities. For this reason, many states require, and at least one professional organization, the Clinical and Laboratory Standards Institute, recommends, that these newborn samples be sent to the laboratory within 24 hours of collection. Delays occur even when insurance or the state would cover more timely delivery.

Errors occur in medicine as they do in other industries because humans are operating in a complex environment and often are unable to see beyond their limited responsibilities. In the case of the nurseries with delays, these may have to do with inadequate orientation, following verbal guidance to save money wherever possible and other perceived reasons. In addition, the disorders identified by newborn screening are rare, and it is unlikely that a nursery will have had experience with a baby screened positive within their recent history.

A culture of safety recognizes the complexity of the system, the absence of total safety, the ever-present vulnerability and the need to be vigilant at all times.

The California newborn screening program has adopted this culture of safety: That state requires a representative from the screening program to visit each hospital every two years and review practices. They identified "batching" as a problem in one hospital, and it was immediately corrected. The culture of safety is enabled by such approaches to continuous quality improvement.

The March of Dimes has been an advocate for newborn screening since it supported the work of researcher Robert Guthrie, who developed the first newborn screening for PKU or phenylketonuria. In recent years, the March of Dimes led a nationwide campaign encouraging all states to screen every newborn for the full panel of recommended conditions.

Today, 44 states and the District of Columbia require screening for at least 29 of the 31 core conditions. We remain vigilant about any inequities in the system, and we have serious concerns about any delay in the newborn screening process.

A delay in screening, diagnosis or treatment can be the difference between life and death for some babies. For other infants, a delay can mean the difference between a healthy life or one with lifelong, serious disabilities and intellectual delays.

Babies should benefit from a system that is one of the most important public health innovations in the last 50

years, but a system like any other that is also vulnerable. Recognizing this vulnerability and adopting a culture of safety for newborn screening is essential to protect our babies.

Edward R.B. McCabe is a pediatrician and geneticist and a member of the federal Discretionary Advisory Committee on Heritable Disorders in Newborns and Children. He has worked in the area of newborn screening since the 1970s. He was the first to show that DNA could be extracted from newborn screening blotters, which is the basis for the use of blotters for molecular genetic diagnosis and forensics, including the DNA dog tag. Jennifer L. Howse is president of the March of Dimes Foundation.

Find this article at:
http://www.jsonline.com/news/opinion/baby-tests-require-a-culture-of-safety-b99147707z1-233091091.html

☐ Check the box to include the list of links referenced in the article.

5 Year Hospital Data Limitations:

Even though considerable effort was made to adhere to the public information request as accurately as possible, there were some limitations to the data that had to be addressed. Four hospitals- Banner Thunderbird Medical Center (BTMC); Banner Page Hospital (BPH or PAGE); Banner Ironwood Medical Center (BIMC); and Cobre Valley Hospital(CVH or COBRE)-have been corrected using the Neometrics data available within NBS. Banner Thunderbird Medical Center was mistakenly identified as “TMC” in the original data capture thus no data was reported for the five year period requested. Banner Page Hospital and Cobre Valley Hospital have two acronyms for the time period requested, but only one was used in the original data capture, thus the numbers had to be updated to include both possibilities. Banner Ironwood Medical Center opened two years into the time period requested, thus the data from the facility was skewed.

Situation: ADHS recently received a public records request from The Milwaukee Journal Sentinel to provide data related to the shipping practices of newborn screening bloodspot specimens from 2008-2013 for each Arizona hospital's initial bloodspot screenings (both valid and unsatisfactory). After establishing our legal obligation to respond to this request, we provided the same data given to the reporter to NBS Points of Contact at Arizona hospitals.

The data had a positive story to tell about Arizona hospitals, though there still remained many opportunities for improvement, especially considering the somewhat limiting constraints on the raw data requested by the reporter. Thereby we performed additional individual and statewide analysis of the data elements provided (See Attached).

Background: The Arizona Newborn Screening Statute (Arizona State Statute §36-694) and Rule (Arizona Administrative Code (R9-13-201) describes the responsibility of the submitting facility regarding the processing of newborn blood samples for congenital disorder testing including: collection, procedures, timing, designee, and reporting requirements. This law also stipulates the responsibilities of the State for Newborn Screening Specimens. Newborn screening success is based on the accuracy of collection, handling, transport and analysis of specimens. This mandate requires a joint effort between the facilities who perform the screens and the ADHS-Office of Newborn Screening (NBS) who is charged with the responsibility of ensuring that the testing for congenital disorders is conducted in an effective and efficient manner.

Assessment: Between 2008 and September 2013, the statewide percentage of total initial screens received at NBS within 4 days of collection-the gold standard- has increased from 68% to 86%. The number of specimens that were received between 5 and 14 days post-collection has decreased from almost 33%(n=27,660) of all initial specimens to less than 20%(n=7,574)to date. More importantly, the number of specimens received outside the legal limit for analysis, i.e. 15 days or more, has dropped from 233 in 2008 to 2 in 2013 thus far, equaling a 99% reduction. The number of unsatisfactory initial bloodspot screenings has decreased significantly over the time period observed from a high of almost 1100 in 2009 to less than 100 in 2013. Attached are your hospital's individual outcomes from the data elements captured in 2008 to September 2013.

Recommendations: The continuation and implementation of current education & outreach activities should be expanded to every Arizona hospital. The activities that are currently being utilized include standardizing transport to the state lab via FedEx for timeliness of receipt; consistently training hospital staff on blood collection; increasing communication with facilities; and actively minimizing the use of expired materials. Continuation and implementation at every Arizona hospital is recommended.

It is recommended that each hospital assess its current standing in comparison to the statewide goal and establish or refine protocols to ensure success in achieving said goal. Ideally, no lab specimens should be received greater than four days post collection, thus the statewide 2015 goal is to reduce the number of specimens received more than 4 days past collection to 10%.

Through continuous quality improvement efforts and shared accountability, the universal newborn screening objective of early identification to allow for better health outcomes that reduce morbidity and mortality is achievable to an even greater number of Arizona newborns.

DRAFT

AZ Statewide
5-Year Submission Report

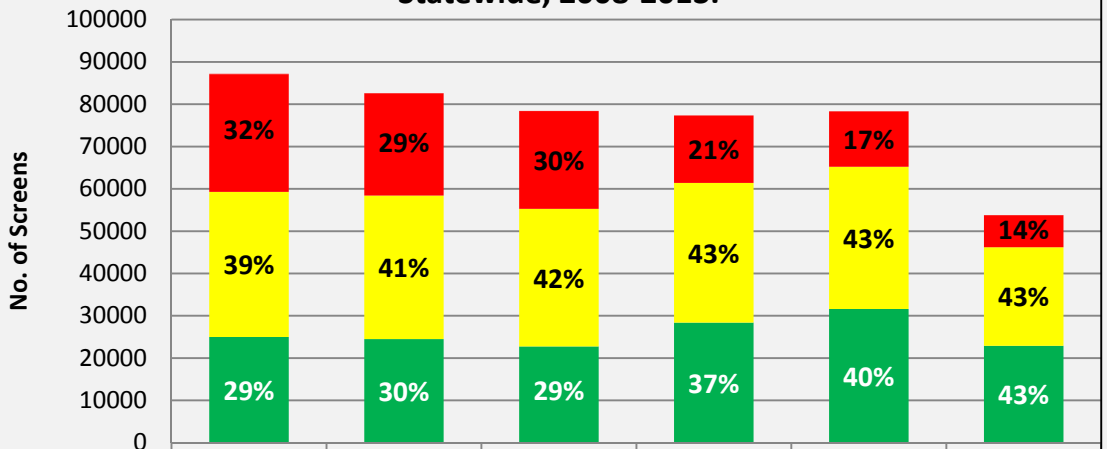
Between 2008 and September 2013, the statewide percentage of initial lab specimens arriving at NBS within 4 days of collection-the gold standard-has increased from 68% of total initial lab specimens received to 86% as illustrated in the blue and gold portions reflecting the highlighted rows in Figure 1. The number of initial lab specimens that were received between 5 and 14 days post-collection has decreased from almost 33%(n=27,660) of all initial lab specimens to less than 20%(n=7,574) in 2013. Most remarkably however, the number of specimens outside the legal limit for analysis*, i.e. 15 days or more, has dropped by 99% to less than 1 in 10,000 initial screenings over the time period presented.

The number of unsatisfactory initial lab specimens has decreased considerably over the time period observed from a high of almost 1100 in 2009 to less than 100 in 2013(Figure 2). Changes to both internal processes and external compliance are the most likely causes for these results. Activities performed to ensure the timeliness and accuracy of initial lab specimens included: standardizing transport to the state lab via FedEx for timeliness of receipt; consistent training of hospital staff on blood collection; increased communication with facilities; actively minimizing the use of expired materials; and increased proficiency/accuracy of identifying unsatisfactory specimens.

For 2013 (YTD), 14 % of initial specimens are received >5 days. Thereby continuing to reduce the number of specimens received outside the best practice timeframe to 10% by 2015 is our next goal. Similar goals should be established for each hospital included in the analysis. Through continuous quality improvement efforts and shared accountability, the universal newborn screening objective of early identification to allow for better health outcomes that reduce morbidity and mortality is achievable to an even greater number of Arizona newborns.

***Arizona State Statute §36-694**

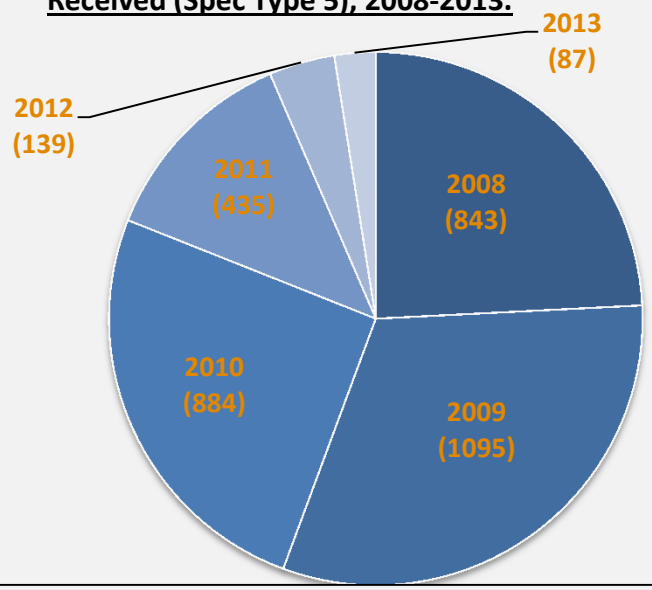
Number of Screenings by Time to Receipt-Statewide, 2008-2013.



	2008	2009	2010	2011	2012	2013
15+ days	233	31	29	16	14	2
5-14 days	27660	24169	23107	15918	13074	7574
3-4 days	34310	33907	32523	33007	33642	23262
≤ 2 days	24984	24501	22762	28390	31596	22920

**** The gold standard of transit time is within 4 days of collection.***

Statewide Unsatisfactory Initial Blood Spot Screens Received (Spec Type 5), 2008-2013.



NBS Rulemaking Update

Newborn Screening Advisory Committee
December 9, 2013

FEE INCREASE PROPOSAL – EXPLANATORY NOTES

Overview

This document contains explanatory notes to accompany the estimates in the Excel spreadsheet used to estimate the fee increase required to restore previous program cuts and sustain the current panel of newborn screening (NBS) disorders. Arizona's NBS program was designed to operate using only the fees collected from screening, which have not changed in over seven years. The legislature annually appropriates a program budget from collected fees deposited in the program's non-lapsing revolving fund. In 2009, due to a statewide budget crisis, the program was subject to a revolving fund sweep, appropriation reduction and personnel sweep amounting to over two million dollars. These sweeps, as well as birth rate declines accompanying the economic downturn, had several far-reaching impacts, including:

- Laboratory instruments could not be replaced according to the manufacturer's schedule
- The creation of an ongoing program budget deficit (reduced fee collections generated insufficient fees to reach our appropriated budget)

In order to meet these challenges, the program and the Department moved aggressively to reduce costs by:

- Realizing vacancy savings through a combination of position eliminations, indefinite holds or refilling with less expensive temporary employees (~11 total positions from 2009 are still vacant)
- Canceling projects intended to optimize processes and reduce costs through technology improvements
    - Implementation of a single program data management system
    - Participation in an external program evaluation
- Changing or retaining cheaper test methods, even if more time-consuming or subjective
- Implementing one-time and ongoing fund transfers (indirect waivers, Title V funds, laboratory general fund, etc.)

To ensure that the program can be sustained, we have proposed the restoration of a limited set of program budget items (described below). We feel the restoration of these budget items strikes an appropriate balance of maintaining the effective delivery of program services while minimizing the magnitude of a fee increase.

Spreadsheet Design

The spreadsheet lists the previously mentioned budget items, their associated costs and a calculation of the fee increase required to meet these costs. A more detailed item by item breakdown follows:

General

- A three year planning horizon was used, including adjustments for inflation to reflect annual increases in the costs of reagents and supplies
- ***Expected revenue –*** included to ensure that the proposed fee matched revenues to costs

Fee Increase Estimate

- ***Annual births –*** estimated based on 2012 births and continuing birth rate declines
- ***2nd screens –*** reflects the number of second screens historically received (as a percentage of firsts)
- ***Revised Fee –*** calculated by averaging the costs over three years and dividing by the number of 2nd screens, the only source of increased revenue

For More Information:
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FEE INCREASE PROPOSAL – EXPLANATORY NOTES

Personnel

- ***Public Health Scientist*** – Cost reductions resulted in a laboratory staff shortage which led to the consolidation of Cystic Fibrosis DNA confirmation testing from daily to twice per week, postponement of an evaluation study of a new tandem mass spectrometry (MSMS) method and the delayed adoption of secondary markers in MSMS testing that would greatly reduce false positive results. This has ultimately increased already heavy workloads while making it more difficult to maintain the delivery of timely results.
- ***Bloodspot Follow-up Specialist*** – Replacing a current temporary employee with a state position will help reduce the turnover inherent with temporary staff while improving continuity of knowledge and delivery of services.
- ***Hearing Follow-up Specialist*** – Replacing a current temporary employee with a state position will help reduce the turnover inherent with temporary staff while improving continuity of knowledge and delivery of services.
- ***Program Educator/Epidemiologist*** – one program educator position was held vacant after a retirement and those duties partially assumed by another employee. The program epidemiologist position was held vacant after a resignation. In order to save costs, we have proposed reinstating only one position by combining the duties of both. We will still ensure our ability to reach hospitals and other providers with critical education messages and also allow for program evaluation and performance measure implementation.
- ***PHS Series Salary Adjustment*** – Two years ago ADOA determined that state laboratory public health scientists were compensated far below prevailing market conditions. Upon final approval, PHS salaries will be adjusted accordingly.

Instate Travel – This will allow the Educator/Epidemiologist to deliver educational training and on-site process evaluation to hospitals.

Other Operating Expenses

- ***Hemoglobin Method*** – In 2009 we were forced to cancel an RFP to replace an antiquated method. We want to replace the antiquated method with a better, more accurate method.
- ***CF IRT*** – Due to cost reductions, we postponed consideration of testing IRTs on the second screen. As a result, initially high IRTs not due to CF (which would typically return to normal levels by the second screen) have instead required diagnostic testing which results in increased stress on families and increased costs to families (and their insurance companies) due to the ultimately unnecessary testing.
- ***MSMS instrument replacement through reagent rental*** – All of the MSMS instruments have exceeded their suggested operating lifetime. Delayed replacement has resulted in additional staff time for maintenance, which delays testing and reduces the time available for quality assurance and other activities. In addition, we are currently unable to reliably test for Tyrosinemia, as elevated tyrosine is no longer considered a reliable indicator for the disorder. The instrument replacement would also allow us to use a different method that detects a more reliable indicator for Tyrosinemia, succinyl acetone. In order to ensure timely equipment replacement, we propose leasing new equipment under a reagent rental contract. This will also allow us to maintain the equipment to current standards due to regular replacement by the vendor.
- ***Education/Outreach Materials*** – As a cost cutting measure we previously transferred some production costs to federal grants. However, these grants are being reduced and can no longer support those costs. These materials

are made available to hospitals, providers and parents and emphasize the importance of NBS to the life and health of affected newborns, timeliness of sample shipment, etc.

Capital Equipment – In 2009 we were forced to cancel the acquisition of a unified program data management system to replace the multiple products that currently support laboratory, follow-up and billing. This system was anticipated to greatly improve overall program efficiency and effectiveness by integrating all activities under a common platform and allowing web-based analytical results access and reporting for submitting agencies and physicians. This electronic reporting will reduce program costs for printing and mailing, and allow faster (and 24 hour) access to critical results.

Current Cash Flow Insolvency – A calculated value used to estimate the program deficit. This value represents increased program costs due to reinstated indirect cost collection and the phase-out of laboratory and other general fund transfers.

For More Information:
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Arizona Department of Health Services
Office of Newborn Screening
November 19, 2013

Fee Increase Estimate

Current Fee/Birth:	$70.00	Annual Births	87,000
Restoration Fee	$24.91	2nd Screens	73,950
New Total Fee	$94.91		

Inflation	Rate	Reinstatement Needs	FY1 Cost Detail	FY1 Total Cost	FY2 Cost Detail	FY2 Total Cost	FY3 Cost Detail	FY3 Total Cost	Three Year Total
		Personnel		$195,000.00		$245,000.00		$245,000.00	$685,000.00
		Public Health Scientist	$60,000.00		$60,000.00		$60,000.00		
0%		*Bloodspot Follow-up Specialist*	$45,000.00		$45,000.00		$45,000.00		
		Hearing Follow-up Specialist	$45,000.00		$45,000.00		$45,000.00		
		Program Epidemiologist/Educator	$0.00		$50,000.00		$50,000.00		
		PHS Series Salary Market Adjustment - Existing Employees (8 + Office Chief)	$45,000.00		$45,000.00		$45,000.00		
	40.5%	**Fringe Benefits**		$78,975.00		$99,225.00		$99,225.00	$277,425.00
		P&O		-$142,644.00		-$142,644.00		-$142,644.00	-$427,932.00
		Public Health Scientist (REMOVAL OF TEMP)	-$47,548.00		-$47,548.00		-$47,548.00		
		Bloodspot Follow-up Specialist (REMOVAL OF TEMP)	-$47,548.00		-$47,548.00		-$47,548.00		
		Hearing Follow-up Specialist (REMOVAL OF TEMP)	-$47,548.00		-$47,548.00		-$47,548.00		
		Instate Travel		$2,500.00		$2,550.00		$2,601.00	$7,651.00
2%		*Provider/stakeholder education and outreach*	$2,500.00		$2,550.00		$2,601.00		
2%		**Out of State Travel**		$0.00		$0.00		$0.00	
		Food		$0.00		$0.00		$0.00	
		Other Operating		$795,000.00		$826,800.00		$859,872.00	$2,481,672.00
		Hemoglobin method - instrument replacement	$200,000.00		$208,000.00		$216,320.00		
4%		*Cystic Fibrosis IRT - 2nd screen testing*	$180,000.00		$187,200.00		$194,688.00		
		MSMS instrument replacement through reagent rental	$410,000.00		$426,400.00		$443,456.00		
		Education/Outreach Materials	$5,000.00		$5,200.00		$5,408.00		
		Non-Capital Equipment		$0.00		$0.00		$0.00	
		Subtotal - Current Gaps		$928,831.00		$1,030,931.00		$1,064,054.00	$3,023,816.00
		Assistance to Others		$0.00		$0.00		$0.00	
		Captial Outlay		$0.00		$0.00		$0.00	
		Capital Equipment		$175,000.00		$175,000.00		$175,000.00	$525,000.00
		Program Data Management System	$175,000.00		$175,000.00		$175,000.00		
	1.05739%	**ITS Direct Charges**		$9,821.37		$10,900.96		$11,251.20	$31,973.53
	28.00%	**Indirect Costs**		$76,713.00		$96,383.00		$96,383.00	$269,479.00
		Current Cash Flow Insolvency (Est. from FY12)		$558,998.00		$558,998.00		$558,998.00	$1,676,994.00
		Reinstated Indirect Costs	$443,018.00		443,018.00		443,018.00		
		Net General Fund Transfers	$115,980.00		115,980.00		115,980.00		
		Grand Total - Current Gaps		$1,749,363.37		$1,872,212.96		$1,905,686.20	$5,527,262.53
		Expected Revenue		$ 1,842,420.84		$ 1,842,420.84		$ 1,842,420.84	$5,527,262.53

CCHD

Newborn Screening Advisory Committee
December 9, 2013

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Cost-Effectiveness of Routine Screening for Critical Congenital Heart Disease in US Newborns

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KEY WORDS
Congenital heart defects, neonatal screening, costs and cost analysis

ABBREVIATION
CCHD—critical congenital heart disease

Dr Peterson led the study design, data analysis, and interpretation of findings; and drafted the initial manuscript. Dr Grosse assisted with the study design, data analysis, and interpretation of findings; and edited the manuscript. Drs Oster and Olney provided clinical oversight, assisted with the interpretation of findings, and edited the manuscript. Dr Cassell assisted with the study design and interpretation of findings, and edited the manuscript. All authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Critical congenital heart disease (CCHD) was recently added to the US Recommended Uniform Screening Panel for newborns.

WHAT THIS STUDY ADDS: Routine screening could cost an estimated additional $6.28 per newborn and $40 385 per life-year gained. The incremental cost of screening might be approximately $0.50 per newborn with reusable sensors. Future analysis of newborn screening programs may help refine these projections.

abstract

OBJECTIVES: Clinical evidence indicates newborn critical congenital heart disease (CCHD) screening through pulse oximetry is lifesaving. In 2011, CCHD was added to the US Recommended Uniform Screening Panel for newborns. Several states have implemented or are considering screening mandates. This study aimed to estimate the cost-effectiveness of routine screening among US newborns unsuspected of having CCHD.

METHODS: We developed a cohort model with a time horizon of infancy to estimate the inpatient medical costs and health benefits of CCHD screening. Model inputs were derived from new estimates of hospital screening costs and inpatient care for infants with late-detected CCHD, defined as no diagnosis at the birth hospital. We estimated the number of newborns with CCHD detected at birth hospitals and life-years saved with routine screening compared with no screening.

RESULTS: Screening was estimated to incur an additional cost of $6.28 per newborn, with incremental costs of $20 862 per newborn with CCHD detected at birth hospitals and $40 385 per life-year gained (2011 US dollars). We estimated 1189 more newborns with CCHD would be identified at birth hospitals and 20 infant deaths averted annually with screening. Another 1975 false-positive results not associated with CCHD were estimated to occur, although these results had a minimal impact on total estimated costs.

CONCLUSIONS: This study provides the first US cost-effectiveness analysis of CCHD screening in the United States could be reasonably cost-effective. We anticipate data from states that have recently approved or initiated CCHD screening will become available over the next few years to refine these projections. *Pediatrics* 2013;132:1–9

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Critical congenital heart disease (CCHD) was added to the US Recommended Uniform Screening Panel for newborns in 2011.[1] Many states before and since have proposed or approved legislation or regulations requiring CCHD screening at birth hospitals.

CCHD is typically diagnosed prenatally or during postnatal clinical examination. However, newborns with CCHD might not present with signs or symptoms of their condition at birth hospitals. If these newborns leave the birth hospital without a diagnosis, they are at risk for cardiovascular collapse or death.[2] Population-based data from California from 1998 to 2004 suggested at least 0.9 infant deaths per 100 000 live births occurred in the United States due to missed CCHD (calculated from unpublished data obtained from study authors),[3,4] although authors suggested the number of infants affected by missed CCHD could be much greater. That estimate is equivalent to 36 infant deaths annually in the current US birth cohort.[5] A retrospective analysis of Florida Birth Defects Registry data from 1998 to 2007 estimated 23% (n = 825 in 3603) of infants with CCHD did not receive a diagnosis during their birth hospitalization, of whom 1.8% died before readmission or upon emergency hospital readmission.[6]

Recent studies in the United States and Europe indicate CCHD screening through pulse oximetry (a test that measures levels of blood oxygen saturation) can detect CCHD in newborns whose condition is otherwise not apparent at the birth hospital.[7] At present, there is no published economic evaluation of costs and outcomes of newborn CCHD screening in the United States.[8] This study aimed to estimate the cost-effectiveness of screening all US newborns unsuspected of having CCHD.

METHODS

Model

We developed a cohort state transition model using TreeAge Pro 2011 (Williamstown, MA) and Excel software based on available estimates from recent US and European studies (Fig 1). The model assessed the number of additional newborns with CCHD detected at birth hospitals, number of lives saved, and number of life-years gained from screening. We did not assess quality-adjusted life-years because of a lack of relevant data. We assessed inpatient medical costs from the perspective of the US health care sector. The model's time horizon was infancy (<1 year of age); therefore, costs were not discounted. All costs are presented as 2011 US dollars. Where necessary, costs were inflated by using annual estimates from the US Producer Price Index for Hospitals.[9] Estimates of life expectancy for the current US birth cohort were discounted at 3%.[10] Model inputs included results from analyses of hospital screening costs in New Jersey in 2012[11] and inpatient costs for infants with CCHD born in Florida from 1998 to 2007,[6] which were undertaken in part to provide information for this analysis (Table 1).

Clinical Case Definition

CCHD has been defined as congenital heart defects that require surgery or catheter intervention within the first

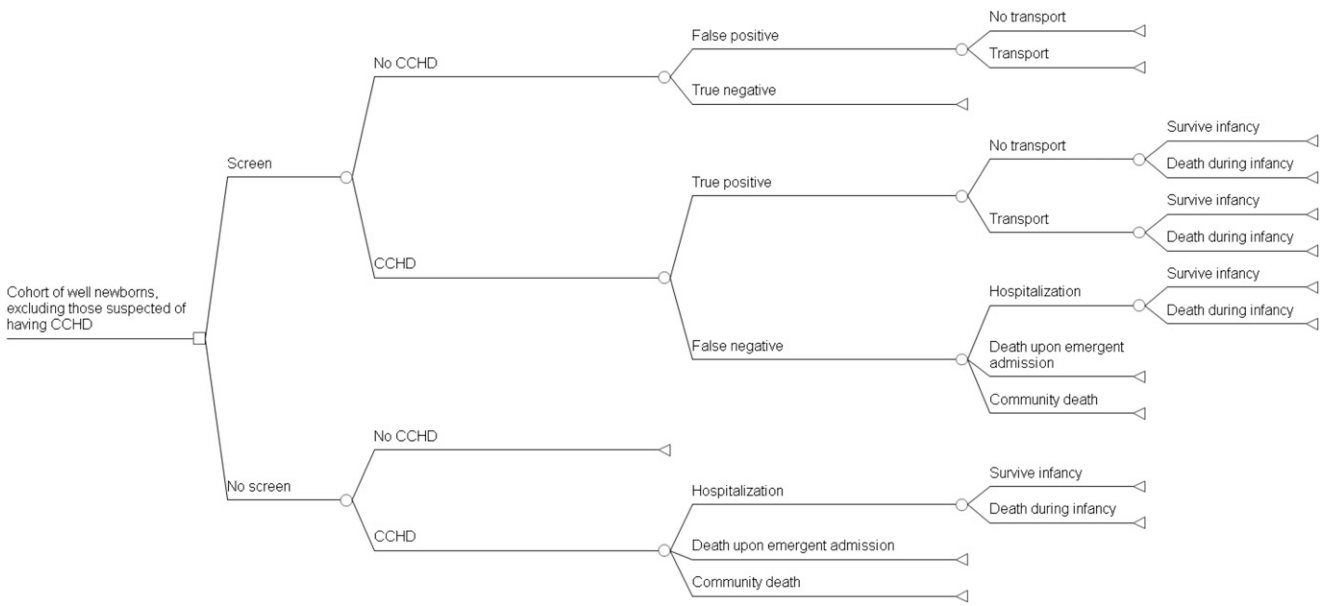

FIGURE 1
Cohort state transition model of routine screening for CCHD in the United States.

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TABLE 1 Model Inputs for Routine Newborn Screening for CCHD in the United States

Parameter	Base Case	Source	SA[a]/Alternate 1-way SA
Costs[b]			
Cost per newborn screened for CCHD through pulse oximetry	$13.50	Peterson et al[11]	±50%/$7.74[c]
Cost of echocardiography (positive result; CCHD diagnosis)	$236	MarketScan,[d] CPT code: 93303+93320+93325	$83, $1084
Cost of echocardiography (negative result; no CCHD diagnosis)	$206	MarketScan,[d] CPT code: 93306	$65, $976
Cost of ambulance transport for offsite echocardiography or treatment	$439	MarketScan,[d] CPT code: 99466	$16, $1582
Cost of daily hospital treatment of infants with CCHD	$4294	Healthcare Cost Utilization Project Kids' Inpatient Database[e]	±50%
Hospitalized days during infancy			
Screening-detected CCHD: survive infancy	37.5	Peterson et al[6]	±50%
Screening-detected CCHD: death during infancy	18.8	Assumption: 50% of days for infants who survive	±50%
Late-detected[f] CCHD: survive infancy[g]	44.3	Peterson et al[6]	±50%
Late-detected CCHD: death during infancy	22.1	Assumption: 50% of days for infants who survive	±50%
Late-detected CCHD: death upon emergent hospital readmission	3.0	Peterson et al[6]	
Transition probabilities			
Late-detected CCHD	0.2290	Peterson et al[6]	±50%
Newborn transported to another hospital for echocardiography or treatment	0.4290		±50%
Death during infancy if CCHD is screening detected[h]	0.0618		±50%
Death if CCHD is late detected:			
Nonhospital death after birth hospital discharge	0.0085		±50%
Death upon emergent hospital readmission after birth discharge	0.0097		±50%
Other death during infancy	0.0618		±50%/0
Pulse oximetry test performance:			
Sensitivity	0.7750	Thangaratinam (2012)[5]	0.60, 1.00[i]
False-positive rate	0.0005		0, 0.002[i]
Health outcomes			
Life-years saved (discounted 3%)	30.28	US National Center on Health Statistics (2007)[9]	

SA, sensitivity analysis.

[a] The probabilistic SA used triangular distributions for all inputs.

[b] All costs presented as 2011 US dollars.[9]

[c] Assumed hospitals exclusively used reusable sensors for well newborns.

[d] MarketScan 2009 Commercial Database query: private insurance, fee for service (capitated plans excluded), inpatient services for patients' age <1 y. Model inputs are mean payments for Current Procedural Terminology codes after eliminating high and low outliers (top and bottom 1%). Sensitivity analysis used minimum and maximum values.

[e] 2009 Agency for Healthcare Research and Quality Healthcare Cost Utilization Project Kids' Inpatient Database database query: mean hospital cost per day among infants with CCHD (by *International Classification of Diseases, Ninth Revision, Clinical Modification* code: aortic interruption/atresia/hypoplasia: 747.11, 747.22); coarctation/hypoplasia of the aortic arch: 747.10; d-transposition of the great arteries: 745.10; double-outlet right ventricle: 745.11; Ebstein anomaly: 746.2; hypoplastic left heart syndrome: 746.7; pulmonary atresia: 746.01; single ventricle: 745.3; teratology of Fallot: 745.2; total anomalous pulmonary venous connection: 747.41; single ventricle: tricuspid atresia: 746.1; truncus arteriosus: 745.0) as the principal diagnosis (includes newborn costs).

[f] Late detected = no CCHD diagnosis before birth hospital discharge (refers to no screening scenario and infants with false-negative results in screening scenario).

[g] Twenty percent more days than infants with screening-detected CCHD, estimate inferred from the source study.

[h] Mortality estimate based death among infants with late detected CCHD who died after a postbirth hospital admission in the source study.

[i] Sensitivity analyses values are maximum and minimum values from screening studies performed ≥24 h.

year of life.[2] A 2009 article endorsed by the American Heart Association and American Academy of Pediatrics identified a subset of CCHD conditions that present with hypoxemia among newborns as amenable to detection through screening with pulse oximetry at birth hospitals.[2] On the basis of available estimates from recent studies, clinical case criteria for this analysis included 12 screening-detectable CCHD conditions: aortic interruption atresia/hypoplasia, coarctation hypoplasia of the aortic arch, dexto-transposition of the great arteries, double-outlet right ventricle, Ebstein anomaly, hypoplastic left heart syndrome, pulmonary atresia (intact septum), single ventricle, tetralogy of Fallot, total anomalous pulmonary venous connection, tricuspid atresia, and truncus arteriosus. Although screening might also detect critical forms of aortic and pulmonary stenosis, we did not include those conditions because administrative diagnostic codes (*International Classification of Diseases, Ninth Revision, Clinical Modification*) from which we derived clinical information do not distinguish critical forms of those conditions. The 7 conditions identified as primary targets for CCHD screening in the United States are dexto-transposition of the great arteries, hypoplastic left heart syndrome, pulmonary atresia, tetralogy of Fallot, total anomalous pulmonary venous connection, tricuspid atresia, and truncus arteriosus, which mostly or always present with hypoxemia in the newborn period.[12]

Screening Cohort

Our model assessed a scenario in which all newborns unsuspected of having

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CCHD were screened at US birth hospitals. Nonhospital births were excluded, as were newborns diagnosed through existing pre- or postnatal procedures (referred to here as timely diagnosed) because we assumed they would not be subject to screening. We estimated the prevalence of newborns with late-detected CCHD in the current US hospital birth cohort (Table 2). We estimated an annual screening cohort of 3 952 138 newborns, of whom 1534 had CCHD not diagnosed through existing procedures.

Screening Cost

We estimated hospitals' screening cost was $13.50 per newborn based on a recent study in New Jersey, where a legislative mandate for CCHD screening offered an opportunity to collect cost information from a random sample of 7 hospitals.[11] This cost was based on a time and motion study and the US national average hourly wage for registered nurses plus a fringe benefit of 33.2%. Based on a national estimate that 6.7% of newborns are admitted to special/intensive care nurseries per year[13] the estimated screening time per newborn reported in that study, regardless of nursery care facility (eg, well-newborn or special/intensive care), was just over nine minutes. The associated labor and equipment costs per newborn screened were $6.68 and $6.82 (including amortization and maintenance of pulse oximeters and the cost of sensors), respectively, yielding a total estimate of $13.50 per newborn. Only 1 hospital among 7 in the New Jersey evaluation used fully reusable sensors to screen well newborns; therefore, the equipment cost estimate in our base case model primarily reflects the cost of fully or partially disposable screening sensors, which are more expensive than reusable sensors.

Screening Performance and Diagnostic Follow-up

Given the US recommendation to screen newborns after 24 hours of birth,[1] we used screening sensitivity (77.5%) and false-positive rate (0.05%) data from recent meta-analysis for our model based on the results of 7 screening studies (n = 132 361 newborns) conducted ≥24 hours of birth (Table 1).[7] CCHD detected among those newborns closely approximated the clinical conditions considered in this analysis, with the exception that some cases of aortic and pulmonary stenosis were detected in the screening performance studies but not included in our analysis due to available data.

We assumed that all newborns who screen positive for CCHD undergo a confirmatory echocardiography examination and that a proportion of those newborns require transportation to another facility for examination and/or follow-up treatment. The assumption that all newborns with questionable screening results undergo echocardiography may be conservative. It is recommended that newborns with low pulse oximetry readings undergo a full physical examination to rule out other causes of hypoxemia before undergoing an echocardiography;[12] we did not include the costs or outcomes of such testing in our model. A recent analysis of the Florida Birth Defects Registry reported that 43% (n = 1547/3603) of newborns with CCHD were transferred during their birth hospitalization.[6] We used this estimate to represent the number of newborns requiring transport to another facility after possible CCHD detection through screening.

Infants with true positive screening results were assigned the cost of an echocardiography with a positive result (eg, a CCHD diagnosis). Infants with false positive screening results were assigned the cost of an echocardiography with a negative result (i.e., no CCHD diagnosis). Infants with false

TABLE 2 Estimated US Screening Cohort

Parameter	Prevalence per 100 000	Annual Hospital-based Birth Cohort	Estimate Details	Source
US Live births, in-hospital		3 957 304	98.9% of 4 000 279 live births	US Vital Statistics Reports (2011; based on 2010 data for total live births),[4] US National Center on Health Statistics (2011; based on 2009 data for proportion of hospital-based births)[7]
Condition prevalence				
CCHD screening targets[a]	169.3	6700	Based on a population study[b]	Peterson et al[6]
Timely detected CCHD[c]	130.5	5165		
Late-detected CCHD	38.8	1534		
Screening cohort	99 939.3	3 952 138	Excludes newborns with timely detected CCHD	Calculation

[a] Aortic interruption/atresia/hypoplasia, coarctation/hypoplasia of the aortic arch, dexto-transposition of the great arteries, double-outlet right ventricle, Ebstein anomaly, hypoplastic left heart syndrome, pulmonary atresia (intact septum), single ventricle, tetralogy of Fallot, total anomalous pulmonary venous connection, tricuspid atresia, and truncus arteriosus.
[b] Refers to late CCHD detection of 825 of 3603 (22.9%) infants live-born from 1997 to 2008, matched to hospital discharge records and with 1 of the CCHD conditions assessed in this analysis among a Florida hospital-based, live-birth cohort of 2 128 236 for that period.[25]
[c] Timely detection defined in source study as CCHD diagnosis before birth hospital discharge.

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TABLE 3 Base Case Results for CCHD Screening in the United States

Result	Total		Incremental Cost-effectiveness Ratio
	Per Newborn	US Annual Screening Cohort[a]	
Screening performance			—
True positives (additional cases identified at birth hospitals)	0.000301	1189	—
False-positives	0.000500	1975	—
False-negatives	0.000087	345	—
Screening health benefits			—
Lives saved	0.000005	20	—
Life-years gained	0.000155	614	—
Screening cost			—
Average costs per newborn:			—
No screening	$70.32		—
Confirmatory echocardiography (% of total cost)	$ 0.09 (<1%)		
Hospitalizations during infancy (% total cost)	$ 70.23 (99%)		—
Screening	$76.59		—
Screening (% of total cost)	$13.50 (18%)		—
Confirmatory echocardiography (% total cost)	$ 0.19 (<1%)		—
Transportation to echocardiography or treatment (% of total cost)	$ 0.15 (<1%)		—
Hospitalizations during infancy (% total cost)	$62.72 (82%)		—
Total additional cost of screening compared with existing practice	$6.28	$24 802 782	—
Screening cost-effectiveness			
Per case identified	—	—	$20 862
Per life-year gained	—	—	$40 385

[a] Estimated annual cohort of hospital-born newborns unsuspected of having CCHD: 3 952 138 (see Table 2 for details).

negative screening results, excluding those that died in the community, were assigned the cost of a positive echocardiography (assumed to occur upon hospital re-admission). Infants with CCHD in the no screening scenario discharged without a diagnosis and subsequently re-admitted were also assigned the cost of a positive echocardiography. We used Current Procedural Terminology codes and a national private health insurance claims data set, the MarketScan 2009 Commercial Claims and Encounters Research Database,[14] to estimate the costs of inpatient infant echocardiography (including physician interpretation) and emergency ground transport by ambulance to another facility (Table 1). We assigned an aggregate hospital cost per day ($4294) to infants ultimately diagnosed with CCHD based on information from the online database of the Agency for Healthcare Research and Quality Health Care Utilization Project 2009 Kids' Inpatient Database (www.hcupnet.ahrq.gov).[15] This estimated cost represents the mean hospital cost per day for infant hospitalizations with a principal diagnosis for CCHD conditions considered in this analysis. We assumed infants who did not receive a CCHD diagnosis at the birth hospital would be readmitted to a facility capable of treating CCHD and would not require transfer to another hospital.

Hospitalizations and Mortality

We used available estimates from the published literature to make inferences about the likely experiences of infants detected through routine CCHD screening (Table 1). On the basis of the Florida Birth Defects Registry study, infants with late-detected CCHD (defined as diagnosis after birth hospital discharge) spent an average of 18% more days in inpatient care compared with infants with timely detected CCHD during the first year of life (44.3 vs 37.5 days). This estimate was adjusted for sociodemographic (eg, race/ethnicity) and clinical factors (eg, CCHD type). We assumed that infants that died during the first year of life would experience half the number of hospitalized days surviving infants did. As noted earlier, an analysis of the Florida Birth Defects Registry reported 1.8% of deaths among infants with late-detected CCHD occurred either outside a hospital following birth hospital discharge or upon emergent hospital readmission after birth hospital discharge.[6] We assumed CCHD detection through screening would eliminate such deaths but not affect other deaths among infants with CCHD.

Sensitivity Analyses

A dearth of previous research on this topic limited our options for sensitivity analysis of the model's base case assumptions. For this reason, we varied base case estimates by 50% in both directions for most model inputs. In addition, we examined 2 alternate scenarios. In one, we assumed hospitals exclusively used reusable screening sensors for well newborns at a cost of $7.74 per newborn (inclusive of labor and equipment), based on the recent New Jersey study of hospital

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TABLE 4 One-way Sensitivity Analyses

Parameter	Model Input	Incremental Cost of Screening per Newborn	Incremental Cost per Life-Year Gained From Screening
Costs			
Screening	High: $20.25	+$13.03	$83 821
	Low: $6.75	–$0.47	–$3052[a]
	Alternate: $7.74	+$0.52	$3319
Echocardiography (positive result [ie,CCHD diagnosis]/negative result)	High: $1084/$976	+$6.66	$42 874
	Low: $83/$65	+$6.20	$39 928
Transport for echocardiography	High: $1852	+$6.67	$42 909
	Low: $16	+$6.13	$39 448
Daily cost of hospital treatment	High: $6442	+$2.55	$16 436
	Low: $2147	+$10.00	$64 333
Hospitalized days during infancy			
Infants with screening detected CCHD: survive infancy	High: 56.3	+$2.55	$16 436
	Low: 18.8	+$10.00	$64 33
Infants with screening detected CCHD: death during infancy	High: 28.1	+$7.02	$45 202
	Low: 9.4	+$5.53	$35 567
Infants with late-detected[b] CCHD: survive infancy	High: 66.4	–$20.92	–$134 614[a]
	Low: 22.1	+$33.47	$215 383
Infants with late-detected CCHD: death during infancy	High:33.2	+$5.41	$34 803
	Low: 11.1	+$7.14	$45 966
Transition probabilities			
Late detected CCHD	High: 0.3435	+$2.56	$11 004
	Low: 0.1145	+$9.99	$108 528
Transport for echocardiogram or treatment	High: 0.6435	+$6.35	$40 870
	Low: 0.2145	+$6.20	$39 899
Mortality among infants with late-detected CCHD			
Nonhospital death after birth hospital discharge	High: 0.1272	+$6.51	$33 972
	Low: 0.0042	+$6.04	$50 701
Death upon emergent hospital admission	High: 0.0145	+$6.53	$33 156
	Low: 0.0048	+$6.02	$52 870
Other death during infancy (also the mortality rate among infants with screening-detected CCHD in the model)	High: 0.0937	+$6.39	$42 550
	Low: 0.0309	+$6.16	$38 357
		+$7.77	$10 817
	Alternate: 0 for infants with screening-detected CCHD		
Pulse oximetry test performance: sensitivity	High: 1.00	+$4.12	$20 553
	Low: 0.60	+$7.95	$66 093
Pulse oximetry test performance: false-positive rate	High: 0.002	+$6.87	$44 195
	Low: 0	+$6.08	$39 115

[a] Cost-saving.
[b] Late detected is no CCHD diagnosis before birth hospital discharge (refers to no screening scenario and infants with false-negative results in screening scenario).

screening costs.[11] This value already fell within the range of our primary sensitivity analysis, although we included this separate test to directly investigate the potential cost impact of reusable screening sensors. In the second alternate analysis, we tested a scenario in which all deaths among infants with late-detected CCHD were avoided as a result of timely detection. Such a mortality improvement is not likely, but this scenario seemed worth testing given the data challenges that hinder robust estimates of avoidable mortality among infants with late-detected CCHD.

We first assessed model inputs in isolation through 1-way sensitivity analyses. We then used a probabilistic sensitivity analysis of 1000 simulations in which all model inputs were simultaneously varied within their specified range using triangular probability distributions. We examined probability estimates that screening would be cost-effective at monetary values per life-year that decision makers might consider; specifically, $50 000 and $100 000 per life-year gained.[16]

RESULTS

Base Case

In a hypothetical scenario of routine CCHD screening for US newborns unsuspected of having CCHD, we estimated

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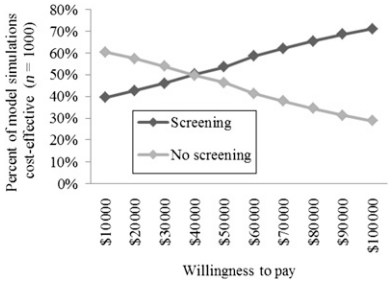

FIGURE 2
Probabilistic sensitivity analysis of cost per life-year gained.

1189 more newborns with CCHD would be identified at birth hospitals annually, 20 infant deaths would be averted, and 614 life-years would be gained (Table 3). We estimated 345 newborns with CCHD would still be discharged from birth hospitals annually without CCHD detection (because screening is not 100% sensitive to detect CCHD), and routine screening would yield 1975 false-positive results.

Without routine screening, the total estimated inpatient cost for CCHD during all of infancy averaged over the entire cohort was $70.32 per infant (Table 3). With screening, the total estimated average cost for inpatient care, plus screening and associated costs, was $76.59 per infant; hence, an incremental cost of $6.28 per newborn screened. This additional cost consists of screening and confirmatory testing, slightly offset by anticipated savings in inpatient costs during infancy. The estimated cost of false-positive screening results (confirmatory echocardiography and transportation when necessary) constituted a modest 3% ($0.20 per infant screened) of the estimated incremental screening cost per newborn (data not shown).

We estimated an incremental cost of $20 862 per additional newborn with CCHD detected at birth hospitals and $40 385 per life-year gained (Table 3). Taking into account only the additional cost of screening (without respect to any reduction in hospital treatment costs during infancy as a result of timely detection) the estimated cost per additional newborn with CCHD detected at the birth hospital was $45 724 (data not shown).

Sensitivity Analyses

We tested the influence of each model input in isolation through a series of 1-way sensitivity analyses (Table 4). On the basis of the primary sensitivity analysis range of ± 50%, we specified that for each model input (Table 1), the parameters that had the greatest relative influence on the results were as follows: the number of hospitalized days for infants with late-detected CCHD surviving infancy (range for the incremental cost per life-year gained: –$134 614 [cost-saving] to $215 383), the proportion of late detected CCHD among infants with CCHD (range: $11 004 to $108 528), and the hospital cost to screen each newborn (range: –$3052 [cost-saving] to $83 821). The parameters that had the least relative influence on the model results were the cost of echocardiography, cost and probability of transport for echocardiography and/or treatment, the mortality rate among infants with screening-detected CCHD, and the false-positive rate.

The alternate 1-way sensitivity analyses indicated reusable sensors and greater mortality improvements could have a substantial impact on the model results. If all hospitals used fully reusable sensors to screen well newborns, we estimated screening would incur just an additional $0.52 per newborn and $3319 per life-year gained (Table 4). If all deaths among infants with late-detected CCHD were avoided by virtue of screening detection, our model estimated 94 lives would be saved annually (data not shown), at an incremental cost per life-year gained of $10 817 (Table 4).

The probabilistic sensitivity analysis indicated a 33% chance the incremental cost of screening for CCHD compared with existing clinical practice would be cost-saving; that is, the net cost would be negative. The analysis indicated a 52% chance the incremental cost of screening would be <$50 000 per life-year gained and a 73% chance the incremental cost of screening would be <$100 000 per life-year gained (Fig 2).

DISCUSSION

We estimated routine screening of US newborns would identify an additional 1189 infants with CCHD at birth hospitals that would otherwise be discharged without a diagnosis. We estimated screening would save 20 infant lives annually at a cost of $40 385 per life-year gained under base case assumptions. Sensitivity analyses suggested screening is likely to be cost-effective under a range of plausible circumstances. Notably, screening was estimated to incur an additional cost of approximately just $0.50 per newborn if all hospitals used reusable sensors to screen well-newborns, which is a conceivable scenario. The average private insurance reimbursement for inpatient infant echocardiography in our analysis was approximately $200, which is low relative to hospital charges. That cost had little influence on the total estimated cost of screening due to the small number of infants referred for echocardiography. A sensitivity analysis tested the echocardiography cost at approximately $1000 for each infant. That analysis indicated the total cost per newborn screened would increase by less than $0.40 per newborn compared to the base case analysis (from $6.28 to $6.66) and the cost-effectiveness ratio per life year gained would rise only modestly (from $40 385 to $42 874).

A recently published UK study assessed the cost-effectiveness of adding CCHD

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screening through pulse oximetry to standard newborn clinical examinations.[17] UK researchers estimated an additional 30 cases of clinically significant CCHD would be detected through screening per 100 000 live births, at an incremental cost per case detected of ~£24 000 in 2009 currency, equivalent to $37 400 (stats.oecd.org; £1 = $1.52 during 2009). This is somewhat lower than our finding of an additional $45 724 (2011 value) cost per CCHD case detected before accounting for reduced hospital costs attributable to timely diagnoses. However, the UK study used a different definition of CCHD than we used here, our study was based on a different clinical setting, and UK health care costs are generally lower than US costs.

A strength of the present analysis is its explicit calculation of an incremental cost per life-year gained. No previous cost studies have provided such estimates.[2,17,18] Another strength was that we initiated original analyses to generate empirical estimates of hospital costs and outcomes using representative data from individual US states. The estimates of screening costs were derived from an analysis of observed screening practices in a representative sample of birthing hospitals in New Jersey.[11] The estimates of costs attributable to preventable hospitalized days and preventable deaths were derived from an analysis of the statewide, population-based Florida Birth Defects Registry and that state's hospitalization data.[6,19–21] Estimates of screening performance were taken from a recent systematic review and meta-analysis.[7]

Our study had a number of limitations. Hospitals in other states might implement CCHD screening differently than New Jersey does and do so at a different average cost. However, given the widespread use of disposable screening sensors in most NJ hospitals, screening costs may be lower in other states if reusable sensors are widely adopted. Recent CCHD screening time estimates have been as little as 3.5 minutes per newborn.[19] However, our screening time estimate of nine minutes per newborn was based on a random sample of screenings observed by researchers and is consistent with a similar recent observational study that estimated 10 minutes per newborn.[20] The assumption in the New Jersey study that the cost of nursing time for CCHD screening is approximated by the value of average hourly compensation, although standard in economic evaluations, may be questioned by some observers. If nurses are able to fit this activity in their daily work schedule, as was the case in the New Jersey hospital sample, hospital personnel budgets may not increase if routine screening is undertaken. However, this study did not account for start-up costs related to a new screening program, such as nurse training.

Florida has the fourth highest number of annual live births in the United States,[10] although experiences with CCHD among infants in that state may not be nationally representative. The Florida study was based on data from the state's birth defects registry, which identifies infants with CCHD based on *International Classification of Diseases, Ninth Revision, Clinical Modification* codes from primarily hospital discharge data but does not include clinically verified diagnoses.[21–24] The Florida Birth Defects Registry is reported to miss up to 15% of birth defects, depending on the defect.[24]

We used an overall estimate of 1.8% avoidable mortality among infants with late-detected CCHD based on an analysis of Florida infants,[6] which is equivalent to 28 avoidable deaths among the 1534 infants we estimated have late-detected CCHD in the current US birth cohort. This overall estimate, which does not take into account the fact that mortality among such infants is likely to vary substantially by CCHD type, may be conservative. As previously cited, a California study estimated a minimum of 36 deaths due to missed CCHD in the current birth cohort.[3] A study in Wisconsin from 2002 through 2006 assessed nonhospital and emergency department deaths within 2 weeks of birth among infants with all types of heart disease and reported a higher death rate, the equivalent of 103 deaths in the current US birth cohort.[25] However, that study did not report the total number of infants in the cohort with CCHD as required for our model.

Future analyses should go beyond our cost approach to include differences in noninpatient health care costs during and beyond infancy. Comparative data on health care resource utilization among children with CCHD who received timely diagnoses during their newborn period could facilitate a future cost-effectiveness analysis of CCHD screening with a longer time horizon. Such data could also provide additional estimates to refine the sensitivity analysis we presented in this preliminary economic evaluation of routine newborn CCHD screening. A future detailed analysis of mortality among infants with late-detected CCHD could also provide information to further refine model assumptions regarding deaths potentially avoidable through CCHD screening. Our analysis assumed full life expectancy for infants with CCHD who do not die due to late detection of their condition, although life expectancy varies substantially by CCHD type. An additional model extension could include the costs and health benefits of detecting non-CCHD conditions through CCHD screening. A prospective screening study from Sweden noted 45% of newborns with false-positive results from CCHD screening (ie, newborns with low pulse oximetry

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readings who did not ultimately receive CCHD diagnoses) had another significant heart malformation, lung problem, or infection.[18] Detecting such conditions through CCHD screening may have added health benefits, which could conceivably lower the overall incremental cost estimates reported here. Incorporating the costs and benefits of detecting non-CCHD conditions in a future cost-effectiveness analysis would, however, require robust, data on the outcomes of such conditions in the absence of CCHD screening.

CONCLUSIONS

Clinical evidence indicates newborn CCHD screening is a lifesaving program. Based on inputs from recent studies, CCHD screening appears cost-effective using conventional thresholds and may be cost-saving under some circumstances. We anticipate data from US states that have recently approved or initiated routine CCHD screening will become available over the next few years to refine these projections.

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Cost-Effectiveness of Routine Screening for Critical Congenital Heart Disease in US Newborns

Cora Peterson, Scott D. Grosse, Matthew E. Oster, Richard S. Olney and Cynthia H. Cassell

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New Study Findings: How cost-effective is screening for critical congenital heart defects?

Screening for critical congenital heart defects using a pulse oximeter sensor on a newborn's foot

The journal *Pediatrics* has published the first study to look at the costs and health outcomes (cost-effectiveness) of critical congenital heart defects (CCHD) screening in the United States. In this type of analysis the initial cost of doing the screening is weighed against the future health effects and cost-savings (money saved) that could occur because the screening was done. **In this study, CDC researchers found that newborn screening for CCHD appears to be good value for the money (cost-effective).** You can read the article's abstract here .

Main Findings from this Study

- The cost of critical congenital heart defects (CCHD) screening compared to infants' future health benefits and healthcare costs was found to be favorable.
  - Screening was estimated to potentially identify 1,189 more newborns with CCHD at birth hospitals in the United States each year (before they are discharged).
  - Detection at birth hospitals through screening might prevent 20 infant deaths in the United States each year.
  - Newborn screening for CCHD might cost $13.50 per newborn based on cost estimates from New Jersey.
    - A net cost estimate of $6.30 per newborn takes into account the expected cost savings that occur when readmission to a hospital is avoided because the CCHD diagnosis is made at the birth hospital rather than after discharge, using CCHD hospital cost estimates from Florida.
    - If hospitals were to use reusable screening equipment, the net cost could be reduced to about 50¢ per newborn.
  - Combining estimates of numbers and hospitalization costs of late-detected CCHD and potentially avoidable deaths from Florida, plus screening cost estimates from New Jersey, it is projected that screening may cost approximately $40,000 per life-year saved, which is considered cost-effective.

Basics about Critical Congenital Heart Defects (CCHD)

What are critical congenital heart defects?
About 1 in 4 babies born with a heart defect has a critical congenital heart defect (CCHD, also known as critical congenital heart disease).[1] Babies with a CCHD need surgery or other procedures within the first year of life.

How can newborn screening help babies with a CCHD?
Some babies born with a CCHD appear healthy at first and can be sent home before their heart defect is detected. These babies are at risk of having serious complications within the first few days or weeks of life and often require emergency care. Newborn screening can identify some of these babies so they can receive care and treatment that can prevent disability and death early in life.

Newborn screening for CCHD involves a simple bedside test to determine the amount of oxygen in a baby's blood. Low levels of oxygen in the blood can be a sign of CCHD. CCHD screening has begun in some states, and laws requiring this screening have been proposed or passed in other states. You can see what is happening in your state here.

- Several states have implemented or are considering newborn CCHD screening. Future analyses of data from states that conduct routine screening will help to refine these estimates.

About this Study

Researchers compiled information from previous studies to model the cost-effectiveness of newborn screening for CCHD.

More Information

To learn more about congenital heart defects, please visit http://www.cdc.gov/ncbddd/heartdefects/.

To learn more about screening for critical congenital heart defects, please visit http://www.cdc.gov/ncbddd/pediatricgenetics/CCHDscreening.html.

Key Findings Reference

Peterson C, Grosse SD, Oster ME, Olney RS, Cassell CH. Cost-Effectiveness of Routine Screening for Critical Congenital Heart Disease in US Newborns. *Pediatrics*. 2013 [epub ahead of date]

Heart Defects: CDC Activities

Centers for Disease Control and Prevention (CDC) works to identify causes of congenital heart defects (CHDs) and ways to prevent them. We do this through:

1. **Surveillance or disease tracking**:
    a. **State programs**: CDC funds and coordinates the Metropolitan Atlanta Congenital Defects Program (MACDP). CDC also funds 14 population-based state tracking programs. Birth defects tracking systems are vital to help us find out where and when birth defects occur and whom they affect.
    b. **Adolescents and adults:** CDC recently funded 3 projects to track congenital heart defects among adolescents and adults in order to learn about their health issues and needs across the lifespan.

2. **Research**: CDC funds a large study of birth defects called the National Birth Defects Prevention Study . This study is working to identify risk factors for birth defects, including heart defects.
3. **Collaboration**:
    a. CDC is assessing states' needs for help with CCHD screening and reporting of screening results. CDC worked with New Jersey and Georgia to assess their ability to track CCHD screening. CDC is also helping states and hospitals to better understand how much hospitals spend for each baby screened.
    b. CDC promotes collaboration between birth defects tracking programs and newborn screening programs for CCHD screening activities. State birth defects programs collect data on CHDs and could help evaluate the effectiveness of screening by looking at false positives (babies who failed the CCHD screening but do not actually have a CCHD after further evaluation) and false negatives (babies who passed the screen suggesting there was no CCHD but actually did have a CCHD).
    c. CDC provides technical assistance to the Congenital Heart Public Health Consortium and to states receiving funding from the Health Resources and Services Administration (HRSA) for CCHD screening activities.

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Poster

Session Title: Poster Session III

Abstract 228: A Cost-effectiveness Analysis Of Universal Pulse Oximetry Screening To Detect Critical Congenital Heart Disease In U.s. Newborns

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Background and objective: In 2011, critical congenital heart disease (CCHD) was added to the Recommended Uniform Screening Panel for newborns. Most state legislatures have not yet mandated pulse oximetry screening to detect CCHD, and evidence that the screening is cost-effective might be influential in these decisions. This study aimed to estimate the cost-effectiveness of universal newborn pulse oximetry screening for CCHD in the U.S. from the hospital system perspective.

Methods: A model was developed to estimate the direct medical costs and health effects of screening all newborns. The health benefits were the number of timely (prior to birth hospital discharge) detected CCHD and life-years saved with the screening compared to existing practice. The analysis focused on ductal-dependent CCHD lesions amenable to pulse oximetry detection. The time horizon was the neonatal period. Costs were not discounted, though future life-years were discounted at 3%. Model inputs related to the epidemiology of CCHD, treatment outcomes, and efficacy of pulse oximetry screening to detect CCHD were derived from published literature.

Results: The cost of screening was an estimated $3.83 per newborn, with an incremental cost of $4,693 per life year gained as a result of the screening. Using current U.S. hospital-based births, it was estimated that 248 more cases of CCHD would be identified at birth hospitals and 110 infant deaths averted annually with universal screening.

Conclusion: Pulse oximetry screening is a life-saving program and is cost-effective by usual standards of health economic evaluation. The results of this analysis might contribute to policymakers' decisions on universal pulse oximetry screening and may inform other stakeholders, including health care systems and payers, about likely budget impacts. Further analyses of CCHD hospitalization and screening costs can improve these model estimates.

Author Disclosures: **C. Peterson:** None. **S.D. Grosse:** None. **C.H. Cassell:** None. **M.E. Oster:** None. **R.S. Olney:** None.

Key Words: Cost-effectiveness analysis • Congenital heart disease • Newborn screening

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Strategies for Implementing Screening for Critical Congenital Heart Disease

Alex R. Kemper, William T. Mahle, Gerard R. Martin, W. Carl Cooley, Praveen Kumar, W. Robert Morrow, Kellie Kelm, Gail D. Pearson, Jill Glidewell, Scott D. Grosse and R. Rodney Howell

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Strategies for Implementing Screening for Critical Congenital Heart Disease

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KEY WORDS

congenital heart defects, neonatal screening, oximetry

ABBREVIATIONS

HHS—US Department of Health and Human Services
SACHDNC—Secretary's Advisory Committee on Heritable Disorders in Newborns and Children
AAP—American Academy of Pediatrics
AHA—American Heart Association
HRSA—Health Resources and Services Administration
CCHD—critical congenital heart disease
ACCF—American College of Cardiology Foundation
FDA—US Food and Drug Administration

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention, the Health Resources and Services Administration, the National Institutes of Health, the Food and Drug Administration, or the US Department of Health and Human Services.

This report has been endorsed by the American Academy of Pediatrics, the American College of Cardiology Foundation, and the American Heart Association Council on Cardiovascular Disease in the Young.

(Continued on last page)

abstract

FREE

BACKGROUND: Although newborn screening for critical congenital heart disease (CCHD) was recommended by the US Health and Human Services Secretary's Advisory Committee on Heritable Disorders in Newborns and Children to promote early detection, it was deemed by the Secretary of the HHS as not ready for adoption pending an implementation plan from HHS agencies.

OBJECTIVE: To develop strategies for the implementation of safe, effective, and efficient screening.

METHODS: A work group was convened with members selected by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, the American Academy of Pediatrics, the American College of Cardiology Foundation, and the American Heart Association.

RESULTS: On the basis of published and unpublished data, the work group made recommendations for a standardized approach to screening and diagnostic follow-up. Key issues for future research and evaluation were identified.

CONCLUSIONS: The work-group members found sufficient evidence to begin screening for low blood oxygen saturation through the use of pulse-oximetry monitoring to detect CCHD in well-infant and intermediate care nurseries. Research is needed regarding screening in special populations (eg, at high altitude) and to evaluate service infrastructure and delivery strategies (eg, telemedicine) for nurseries without on-site echocardiography. Public health agencies will have an important role in quality assurance and surveillance. Central to the effectiveness of screening will be the development of a national technical assistance center to coordinate implementation and evaluation of newborn screening for CCHD. *Pediatrics* 2011;128:e000

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Newborn screening has led to dramatic improvements in morbidity and mortality rates for a variety of conditions.[1] Historically, newborn screening has been based on analysis of dried blood spots and has operated as a partnership between health care providers, who obtain the samples and oversee medical follow-up, and state-based public health systems, which analyze the dried blood spots, assist health care providers and families in follow-up, and monitor the effectiveness of the screening process through surveillance activities. The US Health and Human Services (HHS) Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) was authorized by the US Congress to provide guidance to the Secretary of the HHS about which conditions should be included in newborn screening and how systems should be developed to ensure appropriate screening and follow-up care.[2,3]

Before 2010, the only condition recommended for newborn screening that did not follow the dried-blood-spot paradigm was newborn hearing screening. Newborn hearing screening relies on in-hospital testing before discharge and subsequent outpatient audiology testing for those with abnormal results.[4] Unlike dried-blood-spot testing, individual hospitals and birthing centers had to invest in screening devices, maintain sufficient numbers of skilled staff to conduct the screening and interpret the results, and develop systems to track and communicate results of testing with public health departments, health care providers, and families. Because results of hearing screening originate in the hospitals and birthing centers, public health programs face significant challenges to ensuring follow-up to ensure the success of newborn hearing screening.[5,6]

In September 2010, the SACHDNC recommended that critical congenital cyanotic heart disease be added to the recommended uniform screening panel on the basis of findings from a comprehensive evidence review. The goal of this recommendation was to identify those newborns with structural heart defects usually associated with hypoxia in the newborn period that could have significant morbidity or mortality early in life with closing of the ductus arteriosus or other physiologic changes early in life. The SACHDNC considered 7 specific lesions as primary targets for screening on the basis of advice from a technical expert panel: hypoplastic left heart syndrome; pulmonary atresia; tetralogy of Fallot; total anomalous pulmonary venous return; transposition of the great arteries; tricuspid atresia; and truncus arteriosus. This subset of lesions excludes those not usually associated with hypoxia (eg, aortic valve stenosis).[7]

This recommendation built on a 2009 statement from the American Academy of Pediatrics (AAP) and the American Heart Association (AHA), which found compelling reasons for newborn screening but called for "studies in larger populations and across a broad range of newborn delivery systems" before pulse-oximetry screening should be recommended.[7] The SACHDNC was especially persuaded by a prospective screening study of nearly 40 000 newborns in Sweden[8] and a separate study of nearly 40 000 newborns in Germany.[9] Comparing the accuracy of pulse-oximetry monitoring for the 7 defects specified by the SACHDNC to that of these other studies was somewhat challenging because of differences in the lesions that were targeted for detection by the screening. For example, the study in Sweden considered all ductal-dependent lesions. The researchers' approach, for example, was to add critical aortic stenosis and coarctation of the aorta but exclude tetralogy of Fallot. With this case definition, the study from Sweden found the sensitivity of pulse-oximetry monitoring to be 62.1% and the specificity to be 99.8%; the false-positive rate was 0.17%. In contrast, the AAP/AHA statement used a broader definition, which included all lesions that would require surgery or catheter intervention in the first year of life.

The SACHDNC made the recommendation for screening with the understanding that specific activities would be undertaken, including having the Health Resources and Services Administration (HRSA) guide the development of screening standards and the infrastructure needed for implementation of a public health approach to point-of-service screening and developing education materials; having research conducted by the National Institutes of Health; and surveillance and tracking by the Centers for Disease Control and Prevention. However, the Secretary of the HHS did not endorse the recommendation from the SACHDNC to begin screening, in part because of questions about how to implement that screening. Some states (eg, Maryland, New Jersey) have legislation that promotes newborn screening for critical congenital heart disease (CCHD), which increases the urgency for a draft implementation plan.

The SACHDNC, in collaboration with the AAP, the American College of Cardiology Foundation (ACCF), and the AHA, convened a work group to outline implementation strategies for the SACHDNC, which are summarized here. It is important to recognize that many newborns with the targeted congenital heart defects do not develop clinically appreciable cyanosis until after nursery discharge, and some lesions (eg, hypoplastic left heart syndrome) may present with significant cardiovascular compromise without apparent cya-

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nosis. Therefore, the work group recommended renaming the target conditions "critical congenital heart disease" (CCHD) (omitting the word "cyanotic").

METHODS

A work group was convened for a 2-day meeting in January 2011. Work-group members (see Appendix) included primary care providers; specialists, including pediatric cardiologists and neonatologists; nurses; representatives from the AAP, the ACCF, the AHA, the American College of Medical Genetics, the March of Dimes, the Association of Maternal and Child Health Programs, the Association of Public Health Laboratories, and the SACHDNC; parent screening advocates; state public health officials; and representatives from the Centers for Disease Control and Prevention, the US Food and Drug Administration (FDA), the HRSA, and the National Institutes of Health. Included were people who have implemented pulse-oximetry monitoring for CCHD in newborn nurseries in Arkansas, California, Minnesota, New York, Washington, and Washington, DC. The work group was moderated by William T. Mahle, MD, a pediatric cardiologist who led the development of the 2009 AAP/AHA statement,[7] and R. Rodney Howell, MD, chair of the SACHDNC. The work group was supported by other invited experts, including those from the Centers for Disease Control and Prevention and the FDA, and 2 who had conducted large-scale studies of screening in Europe. The work-group meeting was open to the public.

The meeting focused on recommendations for pulse-oximetry monitoring for CCHD, including recommendations for the service infrastructure needs for follow-up, and strategies for filling in important knowledge gaps. A smaller writing group prepared a summary report of the meeting, which was then iteratively revised with the work group until agreement was obtained. The report was subsequently reviewed by the AAP, the ACCF, and the AHA, each of which endorsed this report.

RESULTS

Screening Population and Targets

The work group chose to focus initially on screening in the well-infant nursery because of the risk of missed cases of CCHD among healthy-appearing newborns. The work group recognized the importance of also considering screening within NICUs. However, developing a simple algorithm for the NICU setting is challenging because of the heterogeneity of underlying conditions (eg, prematurity, meconium-aspiration syndrome, sepsis). Unlike the well-infant nursery, many infants in the NICU undergo repeated medical evaluations, are monitored by pulse oximetry, and have longer lengths of stay. However, there was concern that screening only in well-infant nurseries would miss newborns with short stays in intermediate care nurseries. The work group endorsed screening infants in intermediate care nurseries or other units in which discharge is common in the first week by using the work-group protocol for screening in the well-infant nursery. The work group chose not to focus on out-of-hospital births, which raise challenging coordination-of-care issues, which will be addressed in the future.

One of the advantages of pulse-oximetry monitoring is the ability to detect other hypoxic cardiac- or non–cardiac-associated conditions (eg, persistent pulmonary hypertension), characterized by the SACHDNC as targets secondarily detected by the screening technology ("secondary targets"). Secondary targets are common to other newborn screening tests (eg, identification of hemoglobin H disease when screening for sickle cell anemia[10]). Although the primary goal of screening on the basis of the SACHDNC recommendation is identification of the 7 specific lesions associated with CCHD, tracking rates of identification of important secondary targets could lead to modifications of the screening protocol.

Screening Technology

The work group recommended that screening be performed with motion-tolerant pulse oximeters[11] that report functional oxygen saturation, have been validated in low-perfusion conditions, have been cleared by the FDA for use in newborns, and have a 2% root-mean-square accuracy. Commercially available pulse oximeters often are labeled by manufacturers according to generation of technology (eg, "next generation"). However, generation designation is not standardized and may not be related to validity or reliability. Furthermore, no standards have been developed regarding motion tolerance. A new guidance document on the safety and effectiveness of pulse oximeters is being developed by the FDA.[12] When the guidance document is finalized, any pulse oximeter used for screening should meet FDA recommendations. Having specific FDA-cleared labeling and conformance to the relevant standard[13] will be an important strategy for ensuring that appropriate devices are used for screening.

Pulse oximeters can be used with either disposable or reusable probes. Reusable probes can reduce the cost of screening, but they must be appropriately cleaned between uses to minimize the risk of infection. Some probes have been developed to be partially reusable, which reduces the need to clean between uses and are less expensive than fully disposable

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probes. Probes with close coupling to skin (ie, taped rather than clamped) provide better performance for oximetry monitoring in newborns. Pulse oximeters are validated only with the specific probes recommended by the manufacturer; therefore, to optimize valid screening, manufacturer-recommended pulse-oximeter–probe combinations should be used.

Screening Criteria

The work group recommended that screening not begin until 24 hours of life, or as late as possible if earlier discharge is planned, and be completed on the second day of life. Earlier screening can lead to false-positive results because of the transition from fetal to neonatal circulation and stabilization of systemic oxygen saturation levels, and later screening can miss an opportunity for intervention before closing of the ductus arteriosus. Screening was recommended in the right hand and 1 foot either in parallel or in direct sequence. The pulse-oximetry measure is complete once the waveform on the oximeter's plethysmograph is stable or there is another indication that the device is appropriately tracking the infant's pulse rate.

Selecting the threshold for a positive pulse-oximetry monitoring result is challenging, because it must trade-off the harm of missing CCHD against the harm of false-positive screen results. None of the studies reviewed by the SACHDNC included receiver operator characteristic curves developed from primary data, which would allow a direct evaluation of this trade-off. However, on the basis of new data from the large population-based screening activities in Sweden[8] and England,[14] the work group developed a recommendation for screening that was based on what was shown to be effective in those studies.

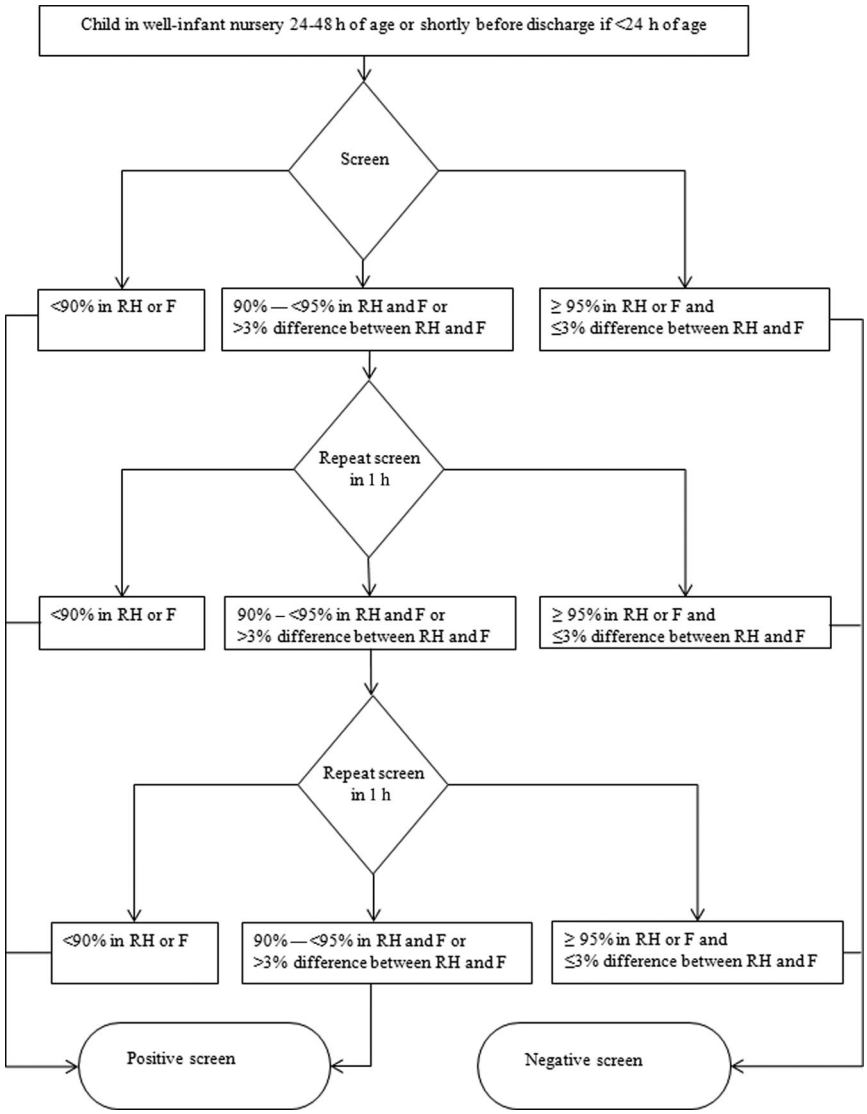

FIGURE 1
The proposed pulse-oximetry monitoring protocol based on results from the right hand (RH) and either foot (F).

The screening protocol is listed in Fig 1. A screen result would be considered positive if (1) any oxygen saturation measure is <90%, (2) oxygen saturation is <95% in both extremities on 3 measures, each separated by 1 hour, or (3) there is a >3% absolute difference in oxygen saturation between the right hand and foot on 3 measures, each separated by 1 hour. Any screening that is ≥95% in either extremity with ≤3% absolute difference in oxygen saturation between the upper and lower extremity would be considered a "pass" result, and screening would end.

Anecdotal reports have suggested that false-positive results are decreased if the infant is alert, possibly by reducing the likelihood of low oxygen saturations caused by hypoventilation in deep sleep. In addition, timing pulse-oximetry monitoring around the time of the newborn hearing screening improves efficiency, assuming that the hearing screening is conducted after 24 hours or immediately before dis-

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charge. The particular screening strategy should reflect the conditions within each particular nursery and the needs of infants, families, and the health care providers.

The work group noted that performing a typical physical examination alone for CCHD led to almost 10 times more false-positive results compared with using similar screening protocols in Sweden and the United Kingdom.[8,14] Repeated pulse-oximetry testing after an initial positive screen result if oxygen saturation is <95% in both extremities or there is a >3% absolute difference in oxygen saturation between the right hand and foot, as illustrated in the protocol, lowers the likelihood of a false-positive result compared with a single measurement. However, there is no need to repeat pulse-oximetry testing if the oxygen saturation is <90% in any screen.

The work group emphasized the importance of not having pulse-oximetry monitoring replace a complete history and physical examination, which can sometimes detect CCHD before the development of hypoxia. Pulse-oximetry monitoring, therefore, should be used to complement the physical examination. Although agreement was reached on the screening protocol, the work group was concerned that this screening protocol might lead to high rates of false-positive results in high-elevation communities, such as those in Denver, Colorado.[15–17] The criteria for a positive screen result may need to be modified for these areas. Regardless of the specific screening thresholds, comprehensive training will be central to implementing safe and effective screening.

Diagnostic Strategies

Any newborn with a positive screen result first requires a comprehensive evaluation for causes of hypoxemia. In the absence of other findings to explain hypoxemia, CCHD needs to be excluded on the basis of a diagnostic echocardiogram (which would involve an echocardiogram within the hospital or birthing center or transport to another institution) or through the use of telemedicine for remote evaluation. The work group also emphasized the need for high-quality echocardiograms with interpretation by a pediatric cardiologist because of the challenge of diagnosis in some cases (eg, total anomalous pulmonary venous return). The work group recommended against replacing a diagnostic echocardiogram with other evaluations (eg, chest radiograph, electrocardiogram, hyperoxia test), which can be inaccurate for diagnosing CCHD. The work group endorsed consulting a pediatric cardiologist, when feasible, before obtaining the echocardiogram.

Because of the importance of quickly establishing the diagnosis of CCHD, the work group recommended that hospitals and birthing centers establish a protocol to ensure timely evaluation, including echocardiograms and any necessary subsequent follow-up, before instituting a CCHD screening program. Future work will be needed to ensure the quality of in-center and telemedicine approaches to echocardiography. The work group also recognized the importance of training an adequate number of pediatric cardiologists to ensure that diagnostic services are available on-site, with short-distance transport, or through telemedicine. Similarly, pediatric cardiac surgery centers will have to be prepared to accept newborns with CCHD identified by pulse oximetry.

Connection to the Medical Home

The results of newborn CCHD screening should be communicated to newborns' primary care providers. During the first outpatient visit, primary care providers should ensure that all newborns were appropriately screened and received any necessary follow-up. The work group recognized the importance of developing health information exchange systems to allow primary care providers, in addition to cardiology subspecialists, to easily track this information. To facilitate this tracking, standards for electronic reporting of pulse-oximetry measurements will need to be developed. Standards for electronic reporting would also help facilitate the development of quality measures.

Primary care providers will also need to develop strategies for screening those newborns who missed screening. As with other newborn screening tests, primary care providers play a central role in ensuring long-term follow-up for those infants diagnosed with CCHD through newborn screening and coordinating their care with a pediatric cardiologist.[2]

Public Health, Quality Assurance, and Surveillance

Follow-up for a positive screen result should be managed by the hospital or birth center before discharge; therefore, the role of public health agencies in CCHD screening is different from that in the case of newborn dried-blood-spot screening or newborn hearing screening. However, public health agencies can play a central role in quality assurance and surveillance. There are several challenges to public health agencies' involvement with CCHD screening, including the inability to collect real-time screening data through health information exchange systems, absence of the direct presence of public health personnel in hospitals and birthing centers, and the financial and staffing pressures within public health departments.

State-level Title V Maternal and Child Health programs and birth-defect sur-

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veillance and prevention programs should play a role in surveillance and evaluation of CCHD screening. These programs already conduct public education and outreach; train providers; and support genetic services, newborn screening programs, and services for children with special health care needs. Although state birth-defect programs could assist with CCHD surveillance, there are differences across states in resources for such activities and the approaches to case ascertainment. As of February 2011, there were 40 birth-defect surveillance programs in the United States and 6 more in development. With adequate resources, some of these programs could potentially collect and track data on populations screened or not screened or those with false-negative screening results. Data could also be collected on whether a diagnosed CCHD was detected through prenatal ultrasound or newborn pulse-oximetry monitoring. Collecting data to understand the factors associated with false-positive pulse-oximetry monitoring results could also help refine the recommended screening activities. Although there is currently no capacity in birth-defect programs to undertake real-time follow-up of CCHD-positive screen results, including short-term follow-up, the infrastructure is in place in many states for birth-defect surveillance programs to play a critical role in conducting long-term surveillance and evaluation.

Health Care Costs

The main costs of a screening program for CCHD are related to staff time for screening, tracking results, and communicating with parents, the purchase and maintenance of screening equipment, consumables associated with screening (eg, probes, adhesive wraps, cleaning supplies), the costs associated with verifying a positive screen result, and the costs associated with treatment. The cost of conducting pulse-oximetry examination and follow-up is quite low in absolute terms; published estimates are $5 or less per infant[7,8] up to $10 per infant, depending on the protocol.[14] Although screening can sometimes be completed in <1 minute, other studies have estimated that the process takes 5 minutes of staff time, including communication with parents.[14] The cost estimate compares quite favorably with cost estimates for newborn hearing screening ($30 or more per infant with an average reimbursement by private health plans in 2004 of $84 if billed separately[17]). Moreover, the cost of pulse oximetry is significantly offset by avoided costs of care. The authors of the report from Sweden calculated that the savings in health care costs from the prevention of 1 case of complications of circulatory collapse resulting from an undiagnosed CCHD may exceed the cost of screening 2000 newborns.[8]

Another potentially important cost is related to delayed discharge because of the need to repeat screening or obtain diagnostic evaluation, which leads to extra hospital days that may not be reimbursed by insurance carriers. Echocardiography is typically reimbursed well. However, the cost of transport can be high and receive variable insurance reimbursement. Although telemedicine for remote echocardiography could be important for hospitals and birthing centers without ready access, it is unclear who would pay to develop and maintain the infrastructure.

At present, there is no clear way to bill for pulse-oximetry monitoring, because the currently available *Current Procedural Terminology* (CPT) codes for pulse oximetry are only appropriate when accompanied by a diagnostic code for a pulmonary disease associated with hypoxia.[19] The AAP, AHA, and ACCF should work with the American Medical Association, which develops CPT codes, to develop the appropriate CPT codes for pulse-oximetry monitoring and with public and private payers to ensure appropriate reimbursement. However, newborn hospital-based screening services such as hearing screening are commonly not reimbursed separately if conducted by regular hospital nursery staff, even with appropriate CPT codes available. Because the cost of conducting pulse-oximetry monitoring is quite low, the cost to hospitals and birthing centers should not be a major barrier. In Switzerland, for example, most birthing centers have adopted pulse-oximetry monitoring, and an estimated 85% of infants are screened despite no mandate for either screening or insurance reimbursement for screening.[20]

The work group recognized the concerns about limited health care resources and emphasized the need to weigh the costs of pulse oximetry against the potential benefits of early diagnosis of CCHD, including the costs saved by decreasing the morbidity associated with later diagnosis. Cost data should be compared with the screening-outcomes data, such as those collected by public health agencies, to inform policymakers and to develop new interventions to improve the efficiency of screening.

Health Care Provider and Family Education

Both health care providers and families must understand the rationale for and limitations of pulse-oximetry monitoring to detect CCHD, including the important understanding that a negative screening result does not exclude the possibility of CCHD or other congenital heart disease. Similarly, educa-

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tion is needed to minimize the harm that may be generated by false-positive screen results. Implementation of other newborn screening tests has been improved through the development of simple clinical decision-support tools for health care providers that explain the screening and what should be done in the event of a positive result (eg, the HRSA-funded ACTion sheets and simple fact sheets for families).[21] Similar materials need to be developed for pulse-oximetry monitoring and should be available in print and through electronic media in English, Spanish, and other local languages. Implementation toolkits used to help hospitals and birthing centers assess their degree of readiness for screening, to develop algorithms for screening, and to evaluate their ongoing activities are also important.

Coordination of Implementation Activities

The work group endorsed the development of a national clearinghouse and technical assistance center similar to the National Resource Center for Newborn Hearing Screening (www.infanthearing.org), the National Newborn Screening and Genetics Resource Center (http://genes-r-us.uthscsa.edu), and the Emergency Medical Services for Children National Resource Center (www.childrensnational.org/EMSC). These sites provide examples of ways to coordinate service delivery between health care providers and state public health agencies. Replicating this approach through partnership with state Title V Maternal and Child Health programs would allow implementation that takes into account specific local factors such as the availability of diagnostic services.

DISCUSSION

A significant body of evidence suggests that early detection of CCHD through pulse-oximetry monitoring is an effective strategy for reducing morbidity and mortality rates in young children. The work group identified strategies for hospitals and birthing centers to implement pulse-oximetry monitoring for CCHD and included the following specific recommendations.

- Screening should be conducted by using motion-tolerant pulse oximeters that report functional oxygen saturation and have been cleared by the FDA for use in newborns.
- Screening should be based on the recommended screening algorithm and be performed by qualified personnel (eg, nurses, allied health technicians) who have been educated in the use of the algorithm and trained in pulse-oximetry monitoring of newborns.
- The algorithm cutoffs may need to be adjusted in high-altitude nurseries.
- Any abnormal pattern of low blood oxygen saturation requires a complete clinical evaluation by a licensed, independent practitioner. In the absence of other findings to explain hypoxemia, CCHD needs to be excluded on the basis of a comprehensive echocardiogram interpreted by a pediatric cardiologist before discharge from the hospital. If an echocardiogram cannot be performed in the hospital or birthing center and diagnosis by telemedicine is not possible, strong consideration should be made for transfer to another medical center for diagnosis. Before implementing screening, protocols for arranging diagnostic follow-up should be established.
- Hospitals and birthing centers should establish partnerships with local and state public health agencies to develop strategies for quality assurance and monitor the impact of screening.
- Primary care providers should ensure that newborns in their practice were appropriately screened and should work to facilitate long-term follow-up for those diagnosed with CCHD.
- Standards should be developed for electronic reporting of pulse-oximetry monitoring and diagnostic outcomes.

CONCLUSIONS

The work group recognized the challenges of implementing a new screening program. To ensure that screening is implemented in a safe and effective manner, the work group strongly endorsed the development and funding of a national technical assistance center to disseminate best practices; to partner with public health agencies to monitor the impact of screening; to evaluate and make recommendations regarding workforce and related infrastructure needs; and to coordinate research to help answer the important unanswered questions regarding screening thresholds and optimal strategies for diagnosis and follow-up. The Secretary of the HHS has directed an interagency work group to develop a plan to address these critical gaps before recommending that CCHD be a part of the recommended uniform screening panel.

APPENDIX: WORK-GROUP MEMBERS

The following is a list of work-group members and the agencies or organizations they represented at the meeting (being listed as a work-group member does not imply that the members or the organization that they represent endorse all aspects of this report): Mona Barmash (Congenital Heart Information Network, Margate City, NJ), Robert H. Beekman, MD (Cincinnati Children's Hospital Medical Center,

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Strategies for Implementing Screening for Critical Congenital Heart Disease

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Newborn Screening for Critical Congenital Heart Disease: Potential Roles of Birth Defects Surveillance Programs — United States, 2010–2011

In September 2011, the Secretary of the U.S. Department of Health and Human Services (HHS) approved the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) 2010 recommendation that all newborns be screened for critical congenital heart disease (CCHD) using pulse oximetry, a noninvasive test of blood oxygenation, to prevent mortality and morbidity (*1*). CDC partnered with the National Birth Defects Prevention Network (NBDPN) to conduct a survey designed to assess state birth defect surveillance programs' potential roles, capabilities, and readiness to assist with newborn screening activities for CCHD. States were surveyed in November 2010, after the initial SACHDNC recommendation, and again in November 2011, after the Secretary's approval. From 2010 to 2011, the number of birth defects surveillance programs involved in CCHD screening increased from one to 10. Barriers exist, such as the lack of legislative authority, staffing, funding, and informatics infrastructure. Sixty-seven percent of programs take an average of more than 12 months to collect complete data on birth defect cases, including congenital heart defects. An assessment of state birth defects programs' existing data and capability to lead the evaluation of screening for CCHD is warranted.

Universal newborn screening is the practice of screening every newborn for certain serious genetic, endocrine, and metabolic conditions, as well as functional disorders that are not apparent at birth. Through early identification and treatment, newborn screening provides an opportunity for reduction in infant morbidity and mortality (*2,3*). SACHDNC provides national guidelines on newborn screening that are reviewed and endorsed by the HHS Secretary. The conditions for which screening is endorsed by SACHDNC, after a formal evidence review process, are known collectively as the Recommended Uniform Screening Panel (RUSP) (*3*). In 2012, a total of 31 conditions are included in RUSP. States use RUSP as guidance when establishing their state-specific screening panels.

The most recent addition to RUSP is CCHD (*1*). Congenital heart disease occurs in approximately eight in every 1,000 live births. Of these cases, approximately one quarter are considered to be CCHD, defined as requiring cardiac surgery or catheterization before age 1 year (*4*). Left undetected, infants with CCHD are at risk for the development of serious complications (e.g., end-organ damage, motor function impairments, and cognitive impairments) within the first few days or weeks of life. The seven CCHDs that are primary targets for screening are hypoplastic left heart syndrome, pulmonary atresia (with intact septum), transposition of the great arteries, truncus arteriosus, tricuspid atresia, tetralogy of Fallot, and total anomalous pulmonary venous return (*4*). In September 2010, SACHDNC recommended that screening for CCHD by pulse oximetry be included in RUSP. This recommendation was endorsed by the HHS Secretary in September 2011 (*1*). Screening for CCHD is a point-of-care test that will occur in hospitals before an infant's discharge from the nursery, with results entered into the hospital medical record. State birth defects surveillance programs often draw from hospital medical records; therefore, these programs could assist in tracking and evaluating screening outcomes. Most state surveillance programs already collect data to calculate CCHD prevalence; however, differences exist across states in resources

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and case ascertainment methodologies that might affect how state programs can provide assistance with the implementation and evaluation of CCHD screening and follow-up.

To assess the differences between state birth defect surveillance programs, in October 2010, after the SACHDNC recommendation to add screening for CCHD to RUSP, CDC collaborated with the National Birth Defects Prevention Network, a national network of state and population-based programs for birth defects surveillance and research, to create and distribute an electronic survey to birth defects surveillance program primary contacts (*6*) in all 50 states, the District of Columbia, and Puerto Rico. The purpose of the survey was to assess state birth defect surveillance programs' potential roles, capabilities, and readiness to assist with newborn screening activities for CCHD to strengthen CCHD screening and follow-up. In November 2011, following the HHS Secretary's approval of the addition of screening for CCHD to RUSP, the survey was revised and redistributed to state programs, requesting confirmation or revision of the responses received in 2010. Nonresponders were contacted via e-mail and telephone. The 2010 and 2011 surveys were distributed to the same person in each program, with no changes in personnel occurring in the 1-year interval between the surveys. Multiple-choice and open-ended questions were asked to assess state CCHD screening activities, ways in which state birth defects surveillance programs could lead the evaluation of CCHD newborn screening, the confirmation of CCHD cases, and barriers to involvement with CCHD newborn screening.

The 2010 and 2011 surveys were completed in all 50 states, the District of Columbia, and Puerto Rico, for a response rate of 100%. In both surveys, 43 states responded that they had a birth defects surveillance program. CCHD activities increased from one state in 2010 to 10 states in 2011 (Table). State birth defects surveillance programs reported ways in which they could lead the evaluation of CCHD screening. In 2011, 28 states reported the ability to evaluate mortality associated with CCHD, 16 could evaluate morbidities associated with CCHD, and 11 could evaluate interventions associated with CCHD. States were asked to identify programs that might get involved in screening for CCHD, other than birth defects surveillance programs. Ten states identified their state's newborn screening program, and four identified children's medical services/Title V programs. Other responses included genetic services programs, hearing screening programs, and private pediatric hospitals. State birth defects surveillance programs reported varying relationships with state newborn screening programs, with five programs reporting they have no relationship with the state newborn screening program. Eight of the 10 states that reported being involved in CCHD screening activities in 2011 reported insufficient funds, nine reported inadequate staffing, and five reported lack of legislation or regulatory authority as barriers to involvement in newborn screening for CCHD. One of the 10 states reported legislatively mandated screening activities; nine were still in the planning stages. Sixty-seven percent of programs reported that it took

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TABLE. Survey of state birth defects surveillance programs — United States, 2010 and 2011

Survey question	No. of state programs 2010	2011
Does your state have a birth defects surveillance program?		
Yes	43	43
No	8	8
If your state adopts newborn screening for CCHD, how could the birth defects surveillance program assist with the confirmed cases of CCHD?*		
Link children identified by screening to support services	24	24
Report on health-care utilization by affected children	12	11
Report on support services utilization by affected children	10	10
Report on enrollment of affected children into special education services	0	1
How could the birth defects surveillance program assist with evaluation of CCHD newborn screening?*		
Evaluate mortality associated with CCHD	33	28
Evaluate morbidities associated with CCHD	14	16
Evaluate interventions associated with CCHD	12	11
Compare outcomes of children with CCHD	8	14
Evaluate all true and false-positive screens†	NA	13
Evaluate false-negative screens†	NA	13
Assist with economic evaluation of screening†	NA	8
What are the likely barriers in your state to your program's involvement with newborn screening for CCHD?*		
Inadequate staffing	34	29
Insufficient funds	32	27
Lack of legislative/regulatory authority	19	19
Information technology/data linkage needs	19	19
What is the average time lag for collection of complete data (≥95%) for all major birth defects under surveillance in your state?		
0–6 mos	5	3
7–12 mos	9	6
13–24 mos	13	12
25–36 mos	9	8
≥37 mos	5	4
Unknown	2	4
Does your program have access to hospital-based point-of-care pulse oximetry screening records?		
Yes	10	11
No	30	24
Has your state been involved with pilot programs to conduct newborn screening for CCHD using pulse oximetry or another method?		
Yes	1	10
No	30	21
Unknown	12	3
Is your state engaged in pulse oximetry screening for CCHD?†		
Yes	NA	10
No	NA	21
Don't know	NA	3
If yes, is the screening*†		
Universal, statewide?	NA	4
Regional?	NA	1
Hospital-based?	NA	9
If yes, what components are included?†		
Screening only	NA	4
Screening and follow-up of positive screens	NA	5
What is the working relationship between your state's birth defects surveillance program and newborn screening program?*†		
Organizationally located together	NA	11
Contained within the same bureau/program	NA	15
Physically located in the same building	NA	14
Currently share same database/data system	NA	8
None/No working relationship	NA	5

Abbreviations: CCHD = critical congenital heart disease; NA = not applicable.
* Multiple responses allowed.
† Question added for 2011 survey.

≥12 months to complete birth defects surveillance case records. Sixty-eight percent of programs did not have access to hospital point-of-care screening records.

Reported by

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Editorial Note

State-level Title V maternal and child health programs and birth defects surveillance programs have potential roles in surveillance and evaluation of CCHD screening (*5*). These state programs routinely conduct public education, train health-care providers, and support newborn screening programs and services for children with special health-care needs. Many birth defects surveillance programs have the data and capabilities to lead the evaluation of newborn screening for CCHD. In addition to monitoring CCHD prevalence, state birth defects programs could incorporate data collection to evaluate false-positive and false-negative screens, because neonatal medical records are one of the key data sources for birth defects surveillance. Collecting data to reveal factors associated with false-positive and false-negative results also could help refine the nationally recommended screening algorithm (*5*) and screening activities.

The findings in this report are subject to at least two limitations. First, although 100% of states completed the survey, participants were not required to respond to every survey question; therefore, data are incomplete for some survey items. Second, only state birth defects surveillance programs were surveyed; no information on the capabilities of other state public health programs to participate in CCHD screening activities was sought.

State birth defects surveillance programs reported that they can lead evaluation of CCHD screening by evaluating sensitivity and specificity, reporting mortality and comorbidities, assisting with economic evaluation, and reporting service utilization by children with CCHDs. However, most state programs also report major barriers to their involvement in newborn screening for CCHD. Many state birth defects surveillance programs indicate that inadequate staffing and insufficient funds would hinder involvement with screening for CCHD. Given that 67% of programs reported that it took ≥12 months to complete birth defects surveillance case records, timeliness of data collection will need to be addressed before birth defects surveillance can truly maximize its potential.

States should evaluate infrastructure and resource needs before adoption of CCHD screening to ensure a successful screening program. Legislative mandates for universal newborn screening for CCHD began in June 2011, with New Jersey being the first state to implement legislatively mandated screening (*7*). Legislative activity increased in late 2011 and early 2012 (American Academy of Pediatrics, Division of State Government Affairs, unpublished data, 2012). Nineteen states reported that lack of legislative/public health authority required to obtain and collect CCHD screening data was a barrier to involvement with screening activities. Newborn screening for CCHD provides an opportunity for collaboration between state birth defects surveillance programs and state newborn screening programs.

What is already known on this topic?

Universal newborn screening is the practice of screening every newborn for certain serious but inapparent conditions so that early intervention can reduce morbidity and save lives. Birth defects surveillance programs collect data that are useful for research, program planning, and program evaluation.

What is added by this report?

Many birth defects surveillance programs have the data and capabilities to lead the evaluation of newborn screening for critical congenital heart disease (CCHD). From 2010 to 2011, the number of birth defects surveillance programs involved in CCHD screening increased from one to 10. During that period, 13 of 43 birth defects surveillance programs reported the capability to evaluate all true and false-positive screening results. Thirteen of 43 programs also reported the capability to evaluate all false-negative screening results.

What are the implications for public health practice?

Newborn screening for CCHD provides a unique opportunity for synergy among state public health programs. States should evaluate infrastructure and resource needs before adoption of screening for CCHD to ensure a successful screening program.

Acknowledgments

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Critical Congenital Heart Disease Screening with Pulse Oximetry in the Neonatal Intensive Care Unit

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ABSTRACT

A case study of an infant with interrupted aortic arch who was discharged from the newborn nursery is presented for root cause analysis and implementation of a modified pulse oximetry screening program at the parent institution where it was described. A rationale for modification of the American Academy of Pediatrics policy statement supporting universal pulse oximetry screening for congenital heart disease in the newborn is made.

Key Words: Pulse oximetry, congenital heart disease, neonate, screening

INTRODUCTION

Pulse oximetry has been shown to aid in the detection of critical congenital heart disease (CCHD) in newborn infants.[1-7] The Secretary of Health and Human Services (HHS) recently suggested addition of screening for CCHD to the recommended uniform screening panel currently in practice on discharge of a newborn infant. The American Academy of Pediatrics has also issued a policy statement strongly supporting the Secretary's recommendation.[8] This policy statement is targeted toward healthy newborn infants in the well-baby nursery. Currently, there are no national guidelines for the neonatal intensive care unit (NICU) population. However, screening protocols in the uniform screening panel such as hearing screen, blood spot test for metabolic, endocrine disorders and hemoglobinopathy have to be performed on all infant population including the NICU. We present a brief case report highlighting the importance of oximetry screening in the NICU. In the absence of standard established protocol for preterm and term infants discharged from the NICU, we suggest a modification to the algorithm recommended by the AAP,[9] for use in the

NICU. This algorithm is currently being practiced in our NICU.

CASE

A 38 week gestation infant was delivered by a repeat cesarean section. The neonate had respiratory distress in the delivery room requiring intubation. On admission to the NICU, normal blood pressures in all four extremities (55/39 mmHg in the right upper limb, 58/44 mmHg in the right lower limb, 47/37 mmHg in the left upper limb and 56/26 mmHg in the left lower limb) were documented. Femoral pulses were normal. A pulse oximeter probe placed on the right upper limb was 95-98% with 21-25% oxygen requirement. This infant's first chest X-ray demonstrated bilateral hazy lung fields and is shown in Figure 1. Within 24 h, the baby was extubated and a subsequent chest X-ray showed marked improvement (Figure 2). She was discharged home in room air with pulse oximeter reading in 98-100% in the right upper limb.

Two weeks after discharge, she came to the pediatrician's office for a routine visit and was noted to have absent femoral pulses. An echocardiogram demonstrated interrupted aortic arch with an aberrant left subclavian artery arising from the patent ductus arteriosus – PDA (Figure 3). The right common carotid artery, right subclavian and left common carotid artery came off the proximal part of the aortic arch prior to interruption (Figure 3). The infant underwent corrective surgery and was discharged home at four weeks of life.

Given the fact that the left upper extremity and the lower half of the body were supplied by the pulmonary artery through the ductus, it is likely that SpO_2 obtained from the left upper limb or any lower limb would have demonstrated a lower SpO_2 compared to the right hand. During her stay in the NICU, all SpO_2 readings were obtained from the right hand.

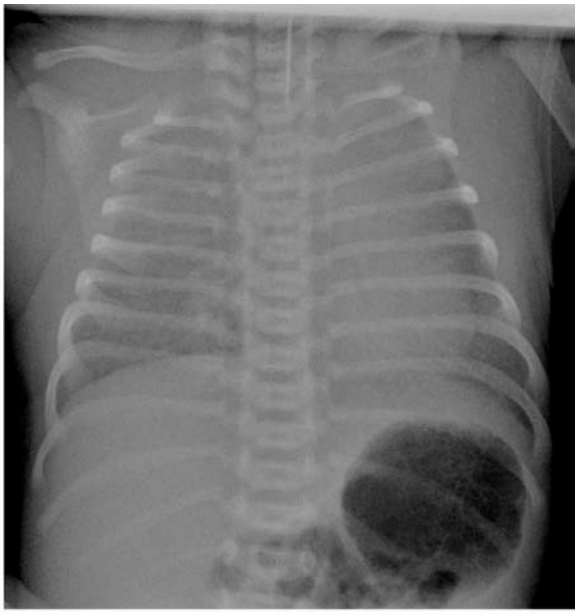


Figure 1: Chest x-ray at one hour of life showing bilateral hazy lung fields.

Figure 2: Repeat chest X-ray at 24 h of age, showing clearing of the lung fields.

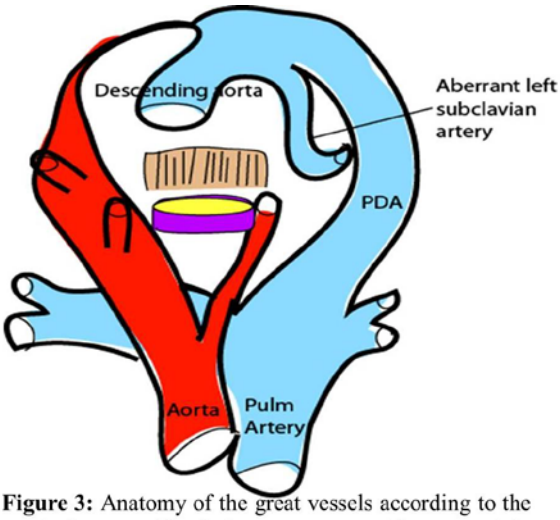


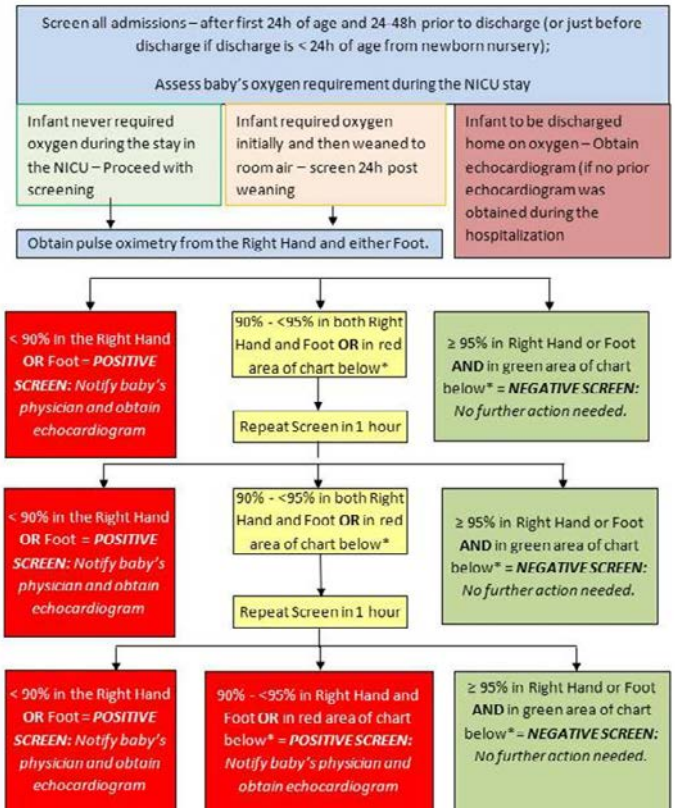
Figure 3: Anatomy of the great vessels according to the surgical notes. The left common carotid artery, right common carotid artery and right subclavian artery were branches of ascending aorta and the right aortic arch prior to interruption. The aberrant left subclavian artery was a branch of descending aorta at the junction of a large ductus arteriosus.

The detection of co-arctation of the aorta by pulse oximetry screening is only 53% (30-75% – 95% confidence interval)[10] but the precise detection rate for interrupted aortic arch is not known. The accuracy of this screening is variable with high specificity but low sensitivity.[6] Currently most units do not offer CCHD screenings for all infants admitted to the NICU. There always exists a potential for a positive screen, such as in a patient described above, provided all NICU patients are screened for CCHD. We have developed a modified algorithm, for all patients admitted to the NICU. Hospitals located at high altitude have to come up with protocols to compensate for low SpO_2 readings secondary to reduced barometric pressure.

Critical congenital heart disease (CCHD) is defined as CHD requiring surgery or catheter intervention in the first year of life and accounts for approximately one quarter of all children with CHD.[10] Timely recognition of CCHD by pulse oximetry could improve outcomes. In the US, many congenital surgery referral centers have reported prenatal detection rates > 50% for functional single ventricle lesions, although the detection rate is generally < 30% for CCHD with two-ventricle circulation and/or abnormal outflow view (such as total anomalous pulmonary venous return, transposition of great vessels and aortic arch abnormalities).[11-15] In a study from UK, Brown et al reported that recognition of CHD was antenatal in 20%, postnatal ward (before discharge) in 55% and after discharge to home in 25%.[16] Cardiovascular compromise and end organ dysfunction were least likely when recognition was antenatal and most common when presentation followed discharge to home.

The establishment of a cutoff threshold for an abnormal SpO_2 must be associated with high sensitivity and specificity. Setting a high SpO_2 cutoff value closer to the normal level will decrease the number of false-negative screening results at the cost of increasing the number of false-positive results. Conversely, a lower SpO_2 threshold will lower sensitivity and raise specificity.[10] The screening protocol as recommended by the AAP working group considers a positive screening result as (1) any oxygen saturation measure < 90%, (2) oxygen saturation < 95% in both extremities on three measures, each separated by one hour, or (3) an absolute > 3% difference in oxygen saturation between the right hand and foot on three measures, each separated by one hour. Any screening that is ≥ 95% in either extremity with ≤ 3% absolute difference in oxygen saturation between the upper and lower extremity would be considered a "pass" result and screening would end.[9]

In general, the mean difference between the oxygen saturation in the upper and lower extremities is < 1% after the first 24h of life; however, some newborns with CCHD, such as aortic arch abnormalities may have more



Algorithm for pulse oximetry screening for critical congenital heart disease (CCHD):

1. Newborn nursery: Pulse Oximetry screening should take place between 24 and 48 hours of life. If the baby is scheduled for discharge prior to 24 hours of life, perform screening just before discharge.

2. Neonatal Intensive Care Unit: Assess baby's oxygen requirement during the stay in the NICU:

A. If the neonate never required oxygen during the NICU stay, proceed with screening.
B. If the neonate required oxygen but has been weaned to room air, obtain screening at least 24h after weaning to room air.
C. If the neonate is being discharged home on oxygen, obtain an echocardiogram (if no prior echocardiogram was obtained during this hospitalization.)

3. Place pulse oximeter probe on right hand and wait until there is a good waveform. Record pulse oximeter value.

4. Remove pulse oximeter probe and place on either foot. Wait until there is a good waveform and record pulse oximeter.

5. Follow the above protocol using pulse oximeter values from both the right hand and the foot. Match the pulse oximeter reading from the foot with the pulse oximeter reading in the right hand using the table below.

6. A difference of >3% in pre-ductal and post-ductal pulse oximetry readings is a positive screen and requires an echocardiogram.

RIGHT HAND						FOOT						
100	100	99	98	97	96	95	94	93	92	91	90	<90
99	100	99	98	97	96	95	94	93	92	91	90	<90
98	100	99	98	97	96	95	94	93	92	91	90	<90
97	100	99	98	97	96	95	94	93	92	91	90	<90
96	100	99	98	97	96	95	94	93	92	91	90	<90
95	100	99	98	97	96	95	94	93	92	91	90	<90

Figure 4: Suggested algorithm for pulse oximeter screening of infants in the neonatal intensive care unit shown as flow chart above and with table version below. The table provides an easy to read combination of pre-ductal and post-ductal oxygen saturations that are acceptable (in green) and not acceptable (in red) to assist in rapid interpretation of results. The flow chart has additional information with regard to equivocal findings (yellow boxes).

profound difference in saturation as the ductus arteriosus supplies part of the systemic flow (Figure 3). Adding a difference of ≥ 3% between right hand and foot oxygen saturation enhanced the sensitivity of screening using a cutoff of < 95%[3] from 89.4% to 92.4%. The work group recommended that screening be performed with motion-tolerant pulse oximeters that report functional oxygen saturation, have been validated in low-perfusion conditions, have been cleared by FDA for use in newborns, and have a 2% root-mean-square accuracy.[9]

The modified algorithm presented in Figure 4 suggests that neonates requiring oxygen supplementation during their NICU stay be weaned to room air for at least 24 h prior to screening. Infants who are being discharged on home oxygen need to undergo an echocardiogram (if one was not obtained during their neonatal course).

CONCLUSION

We used a root cause analysis to modify the AAP guidelines for pulse oximetry screening in order to improve its specificity and sensitivity for aortic arch abnormality in our NICU. These recommendations are empirical, not evidence based and need critical evaluation by prospective studies. Collaborative studies among neonatal intensive care units conducting routine pulse oximetry should analyze pooled data and report detection, false positive rates, false negative rates, and cost-effectiveness of these screening measures for CCHD.

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FACTS

Precious Information

Pulse Oximetry Screening for Critical Congenital Heart Disease

OVERVIEW

Congenital heart defects are malformations of the heart or major blood vessels that occur before birth.[1] In many cases, however, hospital staff may not identify these defects and outwardly healthy infants may be admitted to nurseries and discharged from hospitals before signs of disease are detected.

Occurring in 8 out of 1,000 live births,[2] congenital heart defects account for 27% of infant deaths that are caused by birth defects.[3] A quarter of infants who have congenital heart defects will be diagnosed with critical congenital heart disease (CCHD), a life threatening condition that requires surgery or catheter intervention within the first year of life.[4] Failure to detect CCHD and late detection of CCHD may lead to serious morbidity or death.[5,6]

Fortunately, an emerging body of evidence suggests that measuring blood oxygen saturation can lead to early diagnosis and detection of CCHD.[7] Once detected, many heart defects can be surgically repaired. It is estimated that 85% of neonates who undergo surgery for CCHD will reach adulthood.[8]

RECOMMENDEDED UNIFORM SCREENING PANEL FOR NEWBORNS

Newborn screening is a well-established state-based public health program that involves testing all infants for metabolic, hormonal, genetic, and developmental disorders. Each year, more than 98% of newborns are screened across the United States for these disorders.[9,10]

In 2002, the Health Resources and Services Administration (HRSA) commissioned the American College of Medical Genetics to develop a list of conditions that all states could consider including in their screening programs.[11] This list is called the Recommended Uniform Screening Panel[12] and it currently advises all states to mandate testing for 31 core disorders and 26 secondary disorders. Creation of the Recommended Panel has led to greater uniformity among states in their adoption of screening programs.[10] New conditions for screening are frequently nominated for inclusion in the Panel.

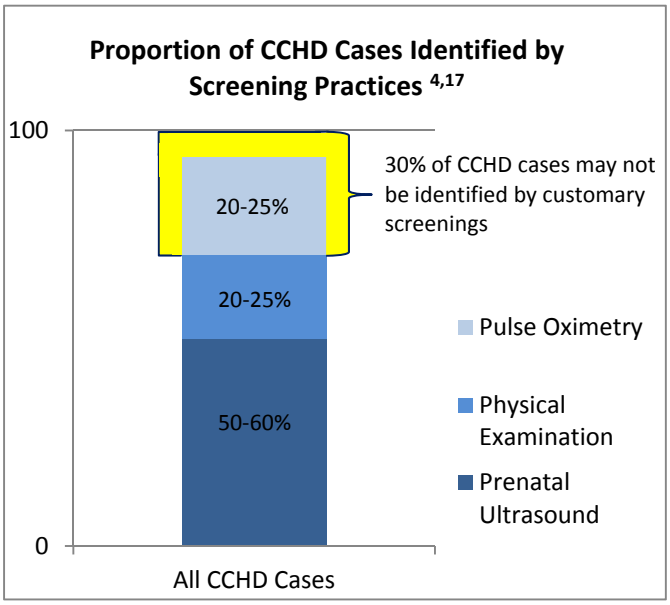
Recently, the U.S. Secretary of Health and Human Services endorsed the addition of CCDH screening to the Recommended Uniform Screening Panel for newborns.[13] The Secretary's Committee on Heritable Disorders in Newborns and Children recommends that hospitals use a specific type of test called pulse oximetry to screen infants for CCHD.[14]

CUSTOMARY SCREENING PRACTICE

Several tools are regularly used to identify infants who have heart defects.

- Prenatal ultrasounds performed 18-20 weeks into a pregnancy can reveal anatomical abnoramalities.[15] Routine prenatal ultrasounds, however, detect less than 50% of CCHD,[4] and rates of detection depend on differing levels of access to prenatal ultrasound and degree of practitioner training.[4]
- After birth, infants are physically examined by primary care providers both before hospital discharge and in routine follow-up visits. Physical exam results may lead clinicians to perform additional tests, including chest radiographs, echocardiograms, and pulse oximetry.[4]

Although prenatal ultrasounds and postnatal physical exams successfully detect many heart defects, they are not sufficient to diagnose all cases of CCHD.[4] New research suggests that when all infants are screened using pulse oximetry in conjunction with the routine practices, CCHD can be detected over in over 90% of newborns.[16]



PULSE OXIMETRY SCREENING

Pulse oximetry screening is a low-cost, non-invasive and painless bedside diagnostic test that can be completed by a technician in as little as 45 seconds.[4] Pulse oximetry testing is conducted to estimate the percentage of hemoglobin in the blood that is saturated with oxygen. When the screening identifies newborns with low blood oxygen concentration, additional testing can be completed to detect heart defects or other life-threatening conditions that could have gone undetected.

Many studies show that pulse oximetry screening for CCHD has a less than one percent chance of giving false positive results.[18] False positive screening results for CCHD can still offer information to doctors: roughly 25% of infants identified as having low blood oxygen without CCHD may be diagnosed with other conditions that require medical intervention. [19]

The American Heart Association (AHA), the American Academy of Pediatrics (AAP), and the American College of Cardiology Foundation (ACCF) recently outlined recommendations for a standardized pulse oximetry screening approach and diagnostic follow-up.[7] According to these recommendations, screening should be performed on asymptomatic newborns after 24 hours of life in order to avoid false-positive results.[7]

When pulse oximetry screening identifies newborns with low blood oxygen levels, echocardiography can be used to definitively diagnose heart defects.[4] The AHA/AAP/ACCF recommendations emphasize that echocardiograms should be interpreted by pediatric cardiologists.[7] Studies have shown that underserved and rural areas can use telemedicine to access pediatric cardiologists for CCHD diagnosis.[20,21]

Pulse oximeters are available in most neonatal units, and hospital staff are well trained in how to perform pulse oximetry screening.[18] A recent cost-effectiveness analysis estimated that universal newborn pulse oximetry screening would cost just under $4 per infant.[22] Although there are monetary costs associated with false positive results from pulse oximetry screening, these costs may be partially or fully offset by early diagnosis of infants with CCHD before they become ill and/or incur irreversible damage. Research suggests that the cost savings associated with early detection of a single case of CCHD could exceed the costs associated with screening 2,000 infants.[16] Many clinicians and experts agree that the benefits of detecting CCHD far outweigh the costs incurred by the screening itself.

Although there is not a clear way to bill insurers for pulse oximetry screening at this time, many other routine newborn tests, including hearing screenings, are frequently included in the bundle of services that hospitals provide to infants prior to discharge.[7]

STATE POLICY APPROACHES TO CCHD SCREENING

States across the nation are beginning to work to implement the Secretary's recommendation to screen all newborns for CCHD.

State policies have a substantial effect on newborn screening rates. Research shows that screening rates are significantly higher in states that have passed test-specific legislation than in states without these laws.[27] While some individual providers or hospital systems may initiate voluntary pulse oximetry screening, legislative action is the only way to ensure equitable and uniform CCHD screening for all newborns

THE AHA ADVOCATES

The AHA is committed to advancing public policies that will allow children and adults with heart defects to live longer and fuller lives. These policies include:

- State adoption of mandatory CCHD screening using pulse oximetry for all newborns;
- The collection of screening data to be used for surveillance, evaluation and continuous quality improvement of CCHD screening;[7]
- The development, dissemination, and validation of screening standards for CCHD;
- The continued development of FDA's guidance document regarding the safety and effectiveness of pulse oximeters.[29]

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SCID

Newborn Screening Advisory Committee
December 9, 2013

SCID Estimates for Arizona

Population[1]	Incidence	2011 Births	Expected Cases (**AZ Program**)[5] Cases/year	Years to 1st case	$15.51 SCID Revenue/Year	Cost to 1st Case[6]
General (not including below)	1/100,000	**46,962**	**0.47**	**2.13**	**$728,381**	$1,414,380
Hispanic[2]	1/25,000	**32,398**	**1.30**	**0.77**	**$502,493**	$353,595
AIAN (non-Athabascan)[3]	1/100,000	**2,334**	**0.02**	**42.84**	**$36,200**	$1,414,380
AIAN Athabascan (on-reservation)	1/2,000	1,294	0.65	1.55	$20,070	N/A
Off reservation births[4]	63%	**2,202**	**1.10**	**0.91**	**$34,160**	$28,288
Total:		**83,896**	**2.89**	**0.35**	**$1,301,234**	**$410,576**

1. Population categories based on mother's reported race/ethnicity.
2. Hispanic incidence is a rough estimate based on early California pilot study data.
3. AIAN (non-Athabascan) incidence is a very conservative estimate, but more likely closer to Hispanic than General.
4. Off reservation birth percentage was estimated from births at non-IHS facilities, then applied to Athabascans.
5. Calculations assume all on-reservation Athabascan births sent out of state.
6. Cost based on average annual cost over five years: $1,186,615

Newborn Screening for Severe Combined Immunodeficiency Disorder

Secretary's Advisory Committee on Heritable Disorders in Newborns and Children

REPORT

Executive Summary

In January 2010, the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) recommended to the Secretary of the Department of Health and Human Services the addition of Severe Combined Immune Deficiency (SCID) to the Recommended Uniform Screening Panel.[1] The Secretary accepted the recommendation in May 2010 and requested that SACHDNC submit a report in May 2011 on the status of newborn screening for SCID.[2] This report summarizes the current status of screening newborns for SCID in state-based newborn screening programs and proposes next steps for implementation.

Newborn screening to identify and treat infants with SCID and to educate and support families, public health providers, and health care providers has been successfully piloted in the State and Territory newborn screening programs of California, Louisiana, Massachusetts, New York, Puerto Rico, and Wisconsin, and in the Navajo Nation. These pilot studies currently cover approximately 25 percent of births in the United States. To date, 961,925 newborns have been screened and 60 infants, or approximately 1 in 16,032, have been identified with some form of immune deficiency. Fourteen infants with SCID (~1 in 68,000) have been diagnosed and received treatment. No missed cases of SCID have come to the attention of the newborn screening programs conducting the pilots.

The combined State and Federal efforts to address SACHDNC recommendations represent a model of collaboration across HHS agencies, as well as among State public health newborn screening programs.

- Highly accurate molecular methods have been developed and validated.
- Model protocols for screening have been employed, including high-throughput, automated testing in States with a large number of births and screening offsite for States with a small number of births.
- An international database to assess laboratory performance and participation in a national quality assurance program enabled real-time quality improvement.
- Emerging findings from the pilots are advancing understanding of SCID and triggering new research efforts.
- The sharing of expertise and lessons learned facilitated the timely resolution of positive screens and refinement of the screening effort.

The tools and knowledge generated through the pilot studies will be available for ongoing collaborations as other states consider implementing newborn screening for immune deficiency. As screening for SCID continues and expands, collaboration between the Federal agencies and States will increase our understanding of immune deficiencies and improve our ability to identify and treat affected infants.

Introduction

In September 2007, Severe Combined Immune Deficiency (SCID) was nominated to the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) for addition to the Recommended Uniform Screening Panel (RUSP). An evidence review was undertaken and the evidence report was discussed by SACHDNC in February 2009. At that time, SACHDNC voted not to add SCID to the RUSP, noting specific gaps in evidence that should be addressed before SCID could be added to the RUSP: (1) prospective identification of at least one confirmed case of SCID through a population-based newborn screening program, (2) demonstrated willingness and capacity of additional states to implement newborn screening for SCID, (3) reproducibility of the screening test and continuance of a false positive rate of less than 0.1 percent, and (4) creation of a laboratory proficiency testing program through the Centers for Disease Control and Prevention's (CDC) National Quality Assurance Program. In January 2010, the nomination of SCID to the RUSP was again brought to SACHDNC. At that time, SACHDNC reviewed the activities undertaken to address the evidence gaps and voted to recommend to the Secretary of the Department of Health and Human Services (HHS) the addition of SCID to the RUSP and related T cell deficiencies to the list of secondary targets,[1] with the understanding that the following activities would take place in a timely manner:

1. The National Institutes of Health (NIH) shall fund surveillance activities to determine health outcomes of affected newborns with any T cell deficiency receiving treatment as a result of prospective newborn screening;

2. The Health Resources and Services Administration (HRSA) shall fund the development of appropriate education and training materials for families and public health and health care professionals relevant to the screening and treatment of SCID and related T cell deficiencies;

3. CDC shall develop and distribute to performing laboratories suitable dried blood spot specimens for quality control and quality assurance purposes.

In May 2010, the Secretary adopted the recommendation to add SCID as a core condition to the RUSP, and related T cell deficiencies to the list of secondary targets and requested that SACHDNC submit a report in May 2011 on the status of States' implementation of this recommendation, including surveillance activities conducted through the Newborn Screening Translational Research Network (NBSTRN).[2] This report summarizes the current status of screening newborns for Severe Combined Immunodeficiency (SCID) in State-based newborn screening programs, as requested by the Secretary in May 2010.

Background

Immunodeficiency disorders, including SCID, are characterized by the lack of a functioning immune system. Babies born with SCID appear healthy but are extremely vulnerable to infection. Exposure to common infections and live vaccines is life threatening. SCID leads to death in infancy unless treatment, usually stem cell transplantation, is provided.[3-4] Variations or "misspellings" in the DNA sequence of more than 13 different genes can cause SCID or a form of combined immunodeficiency. In most cases, the misspelling occurs in a newborn with no family history of SCID. Since SCID is not apparent at birth and early recognition is essential for lifesaving treatment, SCID has been recognized as a candidate for newborn bloodspot screening for many years.[5] However, no laboratory test for detecting SCID on newborn bloodspots was available until the current testing platform for screening for SCID was developed and validated for population-based screening by NIH in 2005.[6] This screening test detects SCID through the absence of a by-product normally generated during the development of the T cell, an important part of a functioning immune system. Since patients with SCID have few or no T cells, the absence of this by-product, T cell receptor excision circles (TRECs), identifies SCID regardless of the underlying genetic defect or DNA variation. The TREC test uses molecular methods to count the TRECs present in DNA isolated from dried blood spots. In 2005, the TREC test was brought to the attention of SACHDNC at its inaugural meeting, and SACHDNC monitored its development and testing.

SCID Newborn Screening Pilot Studies

In 2007, scientists in Wisconsin (State Laboratory of Hygiene and Medical College of Wisconsin) and the New England Newborn Screening Program of the University of Massachusetts Medical School both developed high throughput TREC assays to screen births in Wisconsin and Massachusetts on a trial basis.[7-8] In 2008, a partnership among the Wisconsin State Laboratory of Hygiene, Children's Hospital of Wisconsin and the Jeffrey Modell Foundation led to the first pilot study screening all births in a State. Federal funding from CDC was then made available to continue the pilot study in Wisconsin and to initiate a second statewide pilot in Massachusetts. These two CDC-funded pilots are scheduled to conclude in October 2011. A third pilot study at the University of California at San Francisco began in 2009 and is screening up to 2000 births at two Arizona hospitals on the Navajo reservation (the Navajo Nation has a high incidence of SCID).

The pilot studies in Wisconsin and Massachusetts led to screening and follow-up algorithms, created educational materials for families and health care providers, hosted multiple State training programs in use of the assay, and partnered with CDC in the development of proficiency materials that are now available to all State newborn screening programs.[9-10] Investigators from these three pilots presented their findings to SACHDNC in January 2010 and, at the time, reported they had successfully screened more than 200,000 newborns. Although no cases of classic SCID (total failure of the immune system) were found, they did identify infants with immunodeficiency disorders (SCID variant, partial failure of the immune system) that required medical intervention, documented the feasibility of screening for SCID, provided valuable information to SACHDNC, and paved the way for larger efforts.[11-12]

Expansion of SCID Newborn Screening Pilot Studies

To increase the likelihood of detecting classic SCID cases, NIH increased the screening sample size through a larger pilot project initiated in 2010 with Health Research, Inc. (HRI), a not-for-profit corporation affiliated with the New York State Department of Health. The NIH-funded project enabled HRI and collaborators to provide evidence for the feasibility of screening technologies and to expand SCID newborn screening pilot studies to four additional States and Territories: New York, California, Louisiana, and Puerto Rico. The NIH-funded research priorities for this project were to:

- Assess screening technologies for SCID,
- Establish immediate confirmatory tests and procedures for presumed positive results,
- Ensure capacity and resources for tracking positive cases and arrange for appropriate follow-up care and referral in a timely manner, and
- Verify administrative structures necessary for a prospective pilot testing of SCID, including ability to obtain approval for human subject research.

The NIH initiative enabled screening to begin in two States with a large number of births, New York (236,656) and California (510,000). In addition, ongoing screening efforts in Wisconsin expanded to include Louisiana and ongoing efforts in Massachusetts expanded to include Puerto Rico. The efforts in New York and California were also supported with funds from the Jeffrey Modell Foundation (New York and California) and from PerkinElmer, Inc. (California). Piloting SCID screening in States with a large number of births provided evidence that TREC screening is compatible with a high-throughput, automated environment. Sending samples for screening from Louisiana to Wisconsin and from Puerto Rico to Massachusetts established feasibility for a regional approach to SCID screening, while the ongoing screening in Wisconsin and Massachusetts provided information about screening over several years.

Development, Validation, and Quality Assessment of SCID Newborn Screening Technologies

Investigators in New York, California, Wisconsin, and Massachusetts each developed high-capacity assays based on the principles of the NIH-developed research assay.[6] These assays, called laboratory developed tests (LDTs), were developed and validated independently by each laboratory. While the Food and Drug Administration (FDA) currently does not regulate this class of *in vitro* diagnostics, each laboratory is regulated by the Centers for Medicare & Medicaid Services through the Clinical Laboratory Improvement Amendments (CLIA) Act.[13-14] To support the quality assurance measures required by CLIA, CDC provided dried blood spot reference materials for within-laboratory quality control and between-laboratory proficiency testing. As of April 2011, results obtained from 11 newborn screening laboratories, including all pilot labs (California, New York, Massachusetts, and Wisconsin), showed excellent analytic validity (how well the test predicts the presence or absence of TREC). The tests showed 100 percent sensitivity (how often the test results are positive when TRECs are present) and more than 99 percent specificity (how often the test results are negative when TRECs are not present) in discriminating abnormal from normal TREC content in the reference materials.

To collect, aggregate, and analyze de-identified screening data generated during the pilot, NIH provided a subcontract to the HRSA/Maternal and Child Health Bureau (MCHB)-funded

Laboratory Performance Program to develop a SCID data portal as an expansion of a HRSA/MCHB-funded Region 4 Regional Genetic and Newborn Screening Service Collaborative effort.[15] The subcontract was administered through the NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development's NBSTRN, which was established to provide infrastructure resources for research in newborn screening. Access to the SCID data portal is widely available to any State newborn screening program, clinician, or researcher around the world interested in learning about or contributing to the understanding of the performance of SCID newborn screening assays. The aggregation of laboratory performance data in real-time during a pilot represents a useful model of translating a novel genomic technology to a high-throughput public health setting while using the latest in language standardization and electronic information exchange.[16-17]

Interim Pilot Study Results

Through March 2011, SCID newborn screening has been piloted in six States and one Territory (Wisconsin, Massachusetts, New York, California, Louisiana, and Puerto Rico) and the Navajo Nation, covering approximately 25 percent of total births in the United States during this time period and totaling 126 months of continuous screening (Table 1 and Figure 1). In all, 961,925 newborns have been screened, 364 newborns had a positive screen requiring additional testing and resulting in 60 cases of diagnosed immune deficiency (Tables 1 and 2). Fourteen cases of classic SCID, six cases of SCID variant, and 40 cases of Non SCID have been identified, diagnosed, and treated (Table 1, Figure 2). All infants with immunodeficiency disorders identified through the pilot studies have received treatment and are being followed by appropriate health care teams. Almost 80% (11/14) of the SCID patients received bone marrow transplants and are currently between 1 month and 10 months post-transplant (Figure 3). The remaining 20% (3/14) are receiving enzyme replacement, a treatment option for one type of SCID, Adenosine Deaminase Deficiency (ADA). Additional information regarding health outcomes is being collected and will be reported at a later date.

Although the pilots are still in progress, there are emerging findings that are important to note.

- A zero TREC value consistently means that the infant is at significant risk for SCID or a profound T cell lymphopenia. Future investigations of this valuable biomarker will accelerate research in immunology.
- The incidence of SCID and T cell deficiencies appears to be higher than previously reported (Table 3). Past studies reported the incidence of SCID as 1 in 100,000, and the newborn screening pilots are finding a range of incidences from a high of 1 in 34,159 (New York) to a low of 1 in 161,707 (Massachusetts). Past estimates of Non SCID have been difficult since this category comprises a number of distinct disorders that average around 1 in 20,000 (Table 3, Figure 4). The pilots are finding a range of incidences from a high of 1 in 9,705 (Puerto Rico) to a low of 1 in 121,854 (Wisconsin).
- The number of boys versus girls diagnosed with SCID in the pilots is consistent with past studies (Table 5). Past studies found the majority of SCID cases were male (79%)[3] and New York and California found that six of the nine SCID cases (67%) are male.
- The number and type of SCID at a molecular level appears to be different than previously reported (Table 5). Past reporting of the molecular type of SCID found that 48% of cases

are X-linked (IL2RG mutation), making this the most common cause of SCID.[3] The pilots in New York and California completed the molecular studies for eight of the nine SCID cases and found 66% (7/8) are consistent with autosomal recessive inheritance (Table 5). X-linked SCID was found in one case or 11% of the total.

- The subpopulation variability of SCID and T cell deficiency patients appears to be different than previously reported (Tables 4 and 5). Past reporting of the race or ethnicity of SCID patients followed long-term found that the majority (81%) are Caucasian, 9% African American and 6% Hispanic.[3] The pilots in New York and California found that six of the nine (65%) SCID cases are Hispanic, 2 (22%) are African American, and 1 (11%) is Asian (Table 5).

The emerging findings raise important questions. Analysis of future data will help answer these questions. Although the New York, California, Louisiana, and Puerto Rico NIH-funded pilots end in June 2011, and the CDC-funded pilots in Massachusetts and Wisconsin end in October 2011, efforts to analyze the pilot findings will continue.

Efforts in Nonpilot States

State adoption of SACHDNC's recommendation is voluntary, and the rules and regulations governing the addition of a new screening test vary by State. Nonetheless, consideration of SCID newborn screening by States not involved in the pilots has been extensive. All State newborn screening programs were invited to participate in monthly calls in which the principal investigators from the pilot States discussed their experiences, reviewed data portal entries and answered questions. Currently one-third of States participate in these monthly calls. In October 2010, CDC, the Association of Public Health Laboratories, and the HRSA-funded National Newborn Screening and Genetics Resource Center hosted a meeting devoted to SCID newborn screening.[18] The meeting was attended by 192 laboratory technicians, follow-up professionals and immunologists from 48 States and three countries. In addition, laboratory scientists from 28 U.S. newborn screening programs attended a supplementary laboratory workshop.

To ascertain interest in SCID testing among non-participating States, the Immune Deficiency Foundation (IDF) and NBSTRN conducted a nationwide survey and found that all State programs have actively considered implementing SCID newborn screening (Figure 5).[19] One state (Pennsylvania) is screening a portion of births, and two states are conducting small pilots (Texas and Arizona). Ten States (Colorado, Delaware, Florida, Iowa, Illinois, Michigan, Minnesota, North Carolina, New Jersey and Rhode Island) and the District of Columbia have presented SCID screening to their State advisory boards and received approval to begin screening as soon as logistically possible. Once these States are actively screening, more than 50 percent of babies born in U.S. States and Territories will be screened for SCID.

Twenty-eight State newborn screening programs are in various stages of assessment of analytical platforms, cost analysis, development of infrastructure for referral and treatment services, and recruitment of necessary personnel (Figure 5). Four States work with a regional partner who performs the screening test and are dependent on the regional partner to begin screening. There have been no instances of State advisory boards choosing not to implement SCID screening to date. Sixteen States participate in a monthly conference call to share experiences and expertise.

A small number of States report they prefer or require an FDA cleared or approved kit to begin screening. IDF and NBSTRN will continue to monitor State implementation until all newborns in the United States are screened at birth for SCID.

Education Materials Relevant to Screening and Treatment of SCID and Related T Cell Deficiencies

To support families and to encourage the adoption of SCID newborn screening, IDF launched several efforts, including a Web page for parents, a SCID newborn screening toolkit for use by families to educate policymakers, and a brochure to warn providers about the dangers of administering the live rotavirus vaccine to infants with SCID.[20] The six pilot State newborn screening programs also created and distributed educational materials for the parents of newborns with a positive screen and/or a confirmed diagnosis.[21-24] To support primary care providers and facilitate timely diagnosis and treatment, HRSA/MCHB funded the development of SCID clinical decision support materials, or ACT sheets,[25] through its National Coordinating Center for the Regional Genetic and Newborn Screening Service Collaboratives. As SCID newborn screening adoption increases, a directory of clinical specialists in pediatric immunodeficiencies and related T cell deficiencies will be developed for use by newborn screening programs, families, and health care professionals.

Lessons Learned and Next Steps

Seventeen months after SACHDNC recommended screening all newborns in the United States for SCID and related T cell deficiencies, one-fourth of births are being screened through pilot programs funded by multiple Federal and State agencies and private foundations. Most States have begun active consideration of SCID newborn screening, and several more States are planning to begin screening in the near future. In January 2011, IDF reported to SACHDNC several issues that may be delaying the implementation of SCID screening, including lack of cost benefit information, budgetary concerns (cost estimates for technology infrastructure estimated at $500,000–$1 million), prior commitment to implement other screening tests mandated by State legislation, lack of the widespread availability of experts in immunodeficiency within a State for diagnosis and treatment, and lack of an FDA-approved or -cleared assay.

NIH and CDC will continue to support the adoption of SCID newborn screening through ongoing efforts including technical assistance, publication of pilot project results, screening and follow-up protocols, creation of a long-term follow-up dataset to determine impact of screening on health outcomes, and creation of an expert work group to refine screening, diagnosis and treatment protocols and guidelines. CDC recently announced an opportunity to fund up to two newborn screening programs that had not yet implemented SCID screening before January 2011.[26] The NIH-funded Primary Immune Deficiency Treatment Consortium is working to identify factors, including early identification through newborn screening, that influence health outcomes in patients with immune deficiencies.[27]

In conclusion, the recommendation by SACHDNC to begin screening for SCID has almost certainly saved lives. In addition, the screening program has improved scientific understanding of immune deficiencies, including the molecular etiology and racial and ethnic distributions of molecular subtypes; expanded clinical knowledge of the care and treatment of SCID; and

emphasized the relevance of early diagnosis and intervention. The recommendation has also been a triggering event for the majority of State newborn screening programs to implement or start the process to implement newborn screening for SCID. Screening for SCID represents the largest expansion of newborn screening since the advent of tandem mass spectroscopy a decade ago and the RUSP five years ago. SCID screening is a DNA-based molecular test and State newborn screening programs will develop expertise in DNA-based technologies and/or create networks to share existing regional expertise to implement screening for SCID or DNA-based screening for other disorders. Both approaches to SCID screening establish valuable infrastructure, health information exchange and expertise within the State Newborn Screening Programs, and will be leveraged for future expansions of the RUSP.

The activities recommended by SACHDNC fostered collaboration among HHS agencies and enabled each agency to focus on their areas of expertise while sharing tools and infrastructure resources with stakeholders in public health and clinical health care teams. Highlights from this teamwork are

- Quality control and improvement materials to ensure accurate tests distributed by CDC to the pilot states;
- Clinical decision support tools supported by HRSA (ACT sheets) to guide infants' health care providers; and
- Expanded pilots and databases enabling the diagnosis, treatment, and long-term follow-up of SCID cases contracted by NIH.

This report on State implementation efforts affirms SACHDNC's system of evidence-based review of conditions nominated for addition to the RUSP and subsequent recommendations to begin newborn screening for nominated disorders and lays an effective foundation for future efforts to improve the health of newborns.[28-29]

Table 1. Summary of Pilots

State	Start of Screening	Number of Months Screening	Annual Births or Number Studied	Number of Infants Screened as of April 30, 2011	SCID[a]	SCID Variant[b]	Non SCID[c]
WI	1/1/2008	40	69,232	243,707	4	0	7
MA	2/1/2009	27	77,022	161,707	1	0	14
Navajo Nation	2/1/2009	27	2,000	1,297	0	0	0
NY	9/30/2010	7	236,656	136,635	4	0	12
CA	8/1/2010	9	510,000	358,000	5	6	3
PR	8/1/2010	9	45,620	29,115	0*	0	3
LA	10/1/2010	7	65,268	31,464	0	0	1
	Total	126	1,005,798	961,925	14	6	40

*One infant with suspected SCID expired before diagnosis confirmed.

a. SCID: Deleterious mutation in the DNA of one of the following genes, resulting in total failure of normal function of the protein encoded by that gene, whether IL2RG, JAK3, IL-7Ra, RAG-1, RAG-2, ADA, CD45, Artemis/DCLRE1C, CD3δ, CD3ε, CD3ζ, DNA PKc, or DNA Ligase IV. These proteins are crucial to the normal development of lymphocytes; therefore, any defect in one of these genes will result in a significant problem with immune function and associated susceptibility to infection. AKT2 defects, which cause severe lymphopenia and granulocytopenia, may have low TRECs but also poor amplification of peripheral blood DNA due to low numbers of nucleated blood cells. Patients with SCID have fewer than 300 autologous T cells per mL of blood, and their proliferative responses to the mitogen PHA are less than 10 percent of normal control responses. Some SCID patients do not have defects in any of the above genes, suggesting that additional disease genes for SCID remain to be discovered.

b. SCID variant: Variation in the DNA of one of the following genes resulting in impairment of functioning of the protein encoded by that gene. Also known as “leaky SCID”; Combined Immunodeficiency (CID); or Omenn syndrome, a particular clinical entity with skin rash, eosinophilia, and T cells that represent expansion of a restricted thymic output. CID and Omenn syndrome may be due to hypomorphic variations in the above SCID genes or may be caused by defects in genes such as PNP, AK2, Cernunnos, Coronin-1A, RMRP, or WHN/FOXN1. In addition, there are SCID variant patients s for whom defects in known genes are not found.

c. Non-SCID: Other defects either related directly to a component of the immune system with an associated malfunction or related to the loss of a section of DNA (e.g., DiGeorge syndrome, Jacobsen syndrome) or, in some cases, abnormal gain of DNA (e.g., Down syndrome/trisomy 21). Multisystem syndromes may be associated with variable severity of defects in immune function along with other serious health problems, including heart defects and developmental delay. The non-SCID category is a mixed group and includes individuals with a variety of genetic defects as well as infants who have poorly developed immune systems due to premature birth. Lymphopenia of prematurity, idiopathic T cell lymphopenia, DiGeorge syndrome/del(22)(q11.2), CHARGE syndrome, Jacobsen syndrome/del(11)(q24.1-11qter), Down syndrome/trisomy21, thymectomy, and RAC2 deficiency may be associated with low or undetectable TRECs in some cases. There are additional defects of cellular immunity, including CD25 and ataxia telangiectasia, in which TRECs may or may not be abnormal. There are insufficient data at this time to predict whether these conditions may be detected by TREC newborn screening. In addition, there are many non-SCID immunodeficient patients for whom a genetic cause is not found.

Note: In many T cell immunodeficiencies, the best treatment may be either hematopoietic stem cell transplantation or thymus transplantation because these infants are susceptible to life-threatening infections, as are the classic SCID and SCID variant babies. The confirmatory tests used to follow up babies with abnormal newborn screen results, along with additional specialized immune testing, can help the pediatric immunologist to make decisions regarding the severity of immune dysfunction and the need for transplantation for these infants. These infants would not be picked up without newborn screening, and they are often in just as much need of significant treatment as the more well recognized SCID babies. In addition, some babies require supportive care with intravenous immunoglobulin (IV IgG) and antibiotics, even when a transplant is not needed.

Table 2. Number of Negative and Positive Screens by State

Screening Result	State							Total Screened
	WI	MA	Navajo Nation	New York	California	Puerto Rico	Louisiana	
Negative[a]	243,657	161,679	1,296	136,412	357,954	29,107	31,456	961,561
Positive[b]	50	28	1	223	46	8	8	364
Total Screened	243,707	161,707	1,297	136,635	358,000	29,115	31,464	961,925

a Negative: TREC copy number above cut-off point. No further analysis needed.
b Positive: TREC copy number below cut-off point. Case referred for confirmatory diagnostic studies.

Table 3. Incidence of SCID, SCID Variant and Non SCID by State

Diagnosis	Incidence	State					
		WI	MA	NY	CA	Puerto Rico	Louisiana
SCID		1 in 60,927	1 in 161,707	1 in 34,159	1 in 76,500	NA	NA
SCID Variant		NA	NA	NA	1 in 76,500	NA	NA
Non SCID		1 in 121,854	1 in 11,551	1 in 11,386	1 in 76,500	1 in 9,705	1 in 31,464

Table 4. California Incidence in the First Six Months of Screening

Diagnostic Category	Race or Ethnicity	Incidence Rate	95% Confidence Intervals	
			Lower	Upper
SCID	All	1 in 33,000	1 in 20,000	1 in 65,000
SCID	Hispanic Only	1 in 22,000	1 in 9,000	1 in 40,000
All Related T-cell Lymphocyte Deficiencies	All	1 in 22,000	1 in 13, 300	1 in 35,000

Table 5. Clinical Characteristics of Nine SCID Cases in New York and California Pilots

Characteristic		Number of SCID Cases (%)
Sex	Male	6 (67%)
	Female	3 (33%)
Molecular Type of SCID*	Autosomal Recessive (IL-7Ra)	2 (22%)
	Autosomal Recessive (RAG-1)	2 (22%)
	Autosomal Recessive (ADA)	2 (22%)
	X-Linked (IL2RG)	1 (11%)
Race or ethnicity	Hispanic	6 (67%)
	African American	2 (22%)
	Asian	1 (11%)

*Molecular typing on one case is pending.

Figure 1.Timeline of SCID Newborn Screening Pilots

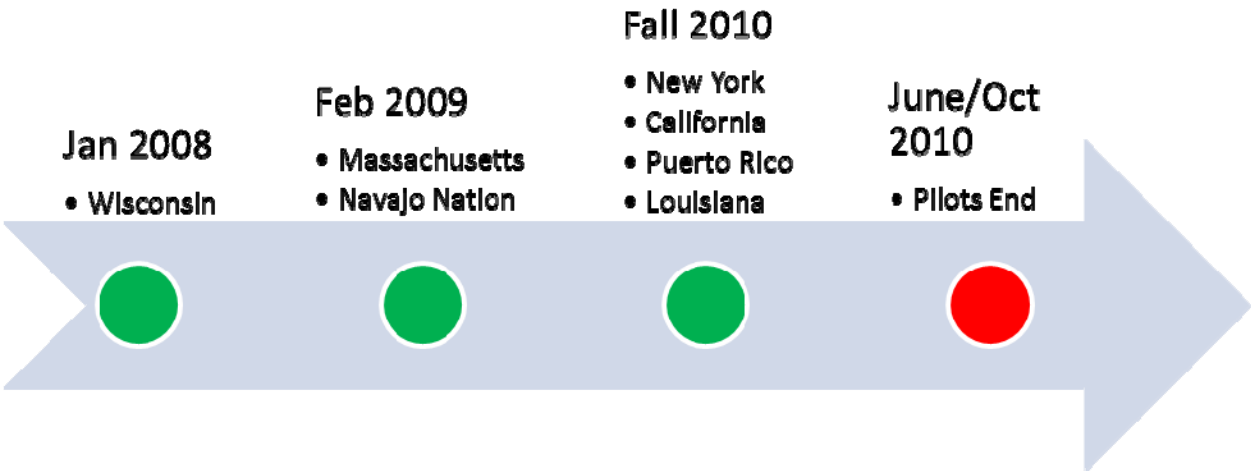


Figure 2: Cumulative Number of Newborns Screened and SCID Cases Diagnosed

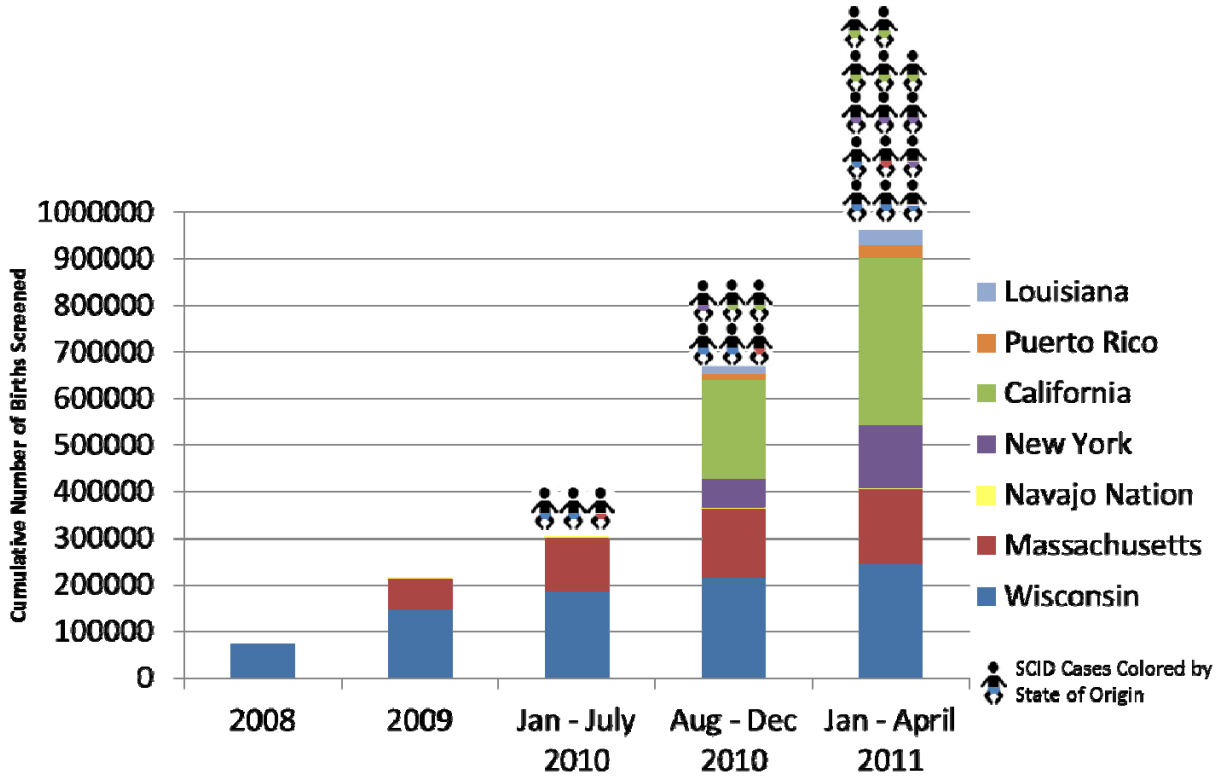


Figure 3: Type of Treatment for SCID Cases (N=14) in All Pilots

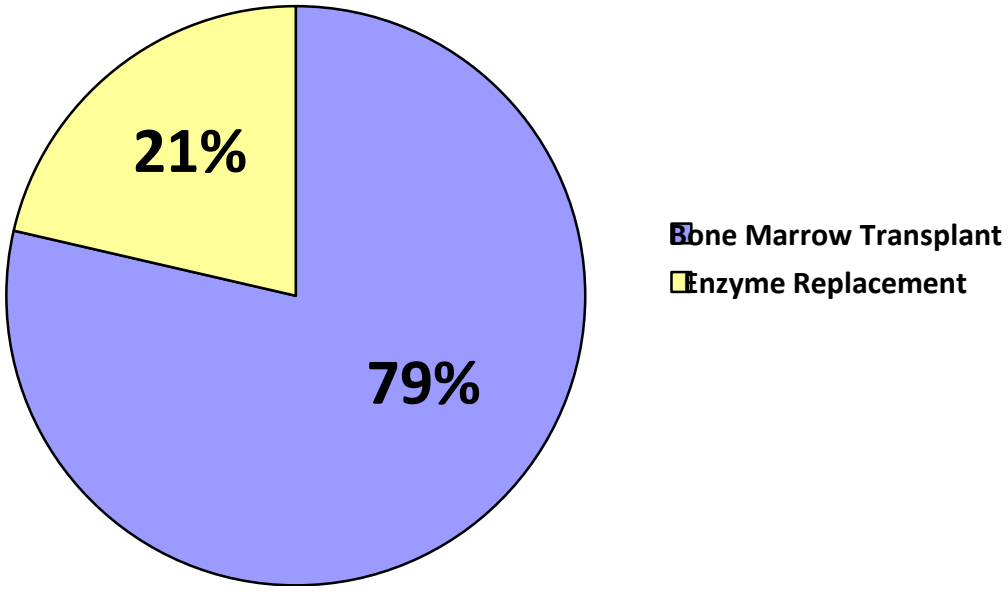


Figure 4: Diagnosis for Non SCID Cases for All Pilots (N=40)

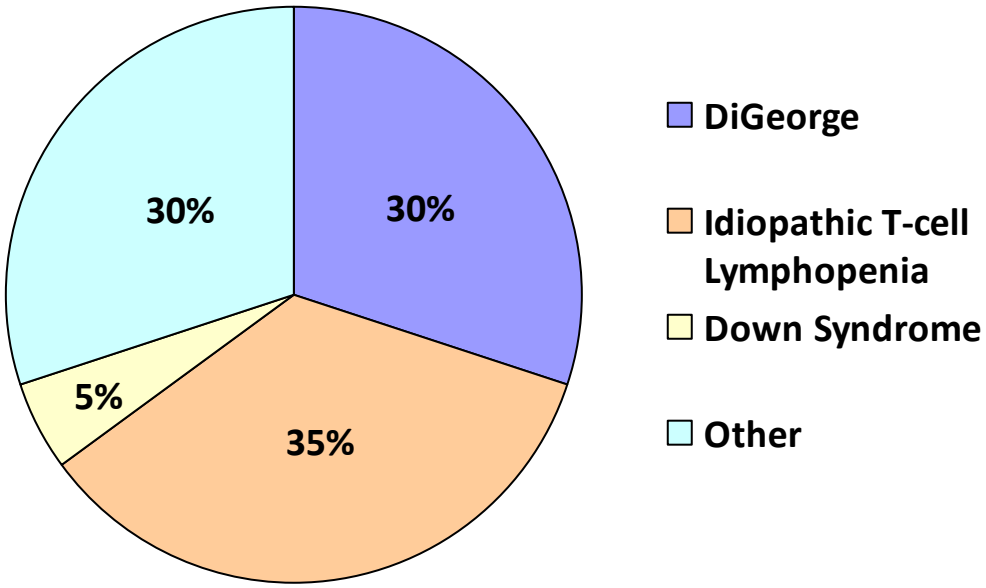
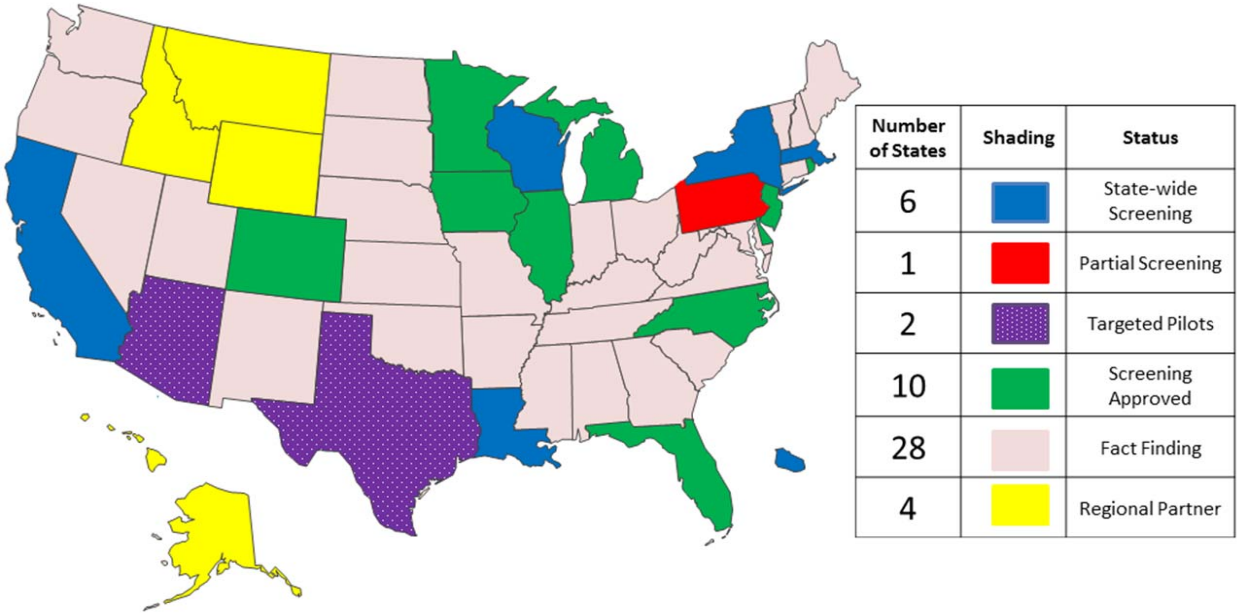


Figure 5. Map of Newborn Screening for SCID Implementation Status



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Rotavirus vaccine induced diarrhea in a child with severe combined immune deficiency

To the Editor:

Rotavirus is the most common cause of acute gastroenteritis in young children worldwide, and accounts for more than 2.5 million deaths annually.[1] Two live oral vaccines for rotavirus are currently licensed: RotaTeq (CSL Limited, Parkville, Victoria, Australia), a pentavalent bovine-human reassortant vaccine, and Rotarix (GlaxoSmithKline [GSK] Australia Pty Ltd, Boronia, Victoria, Australia), a human monovalent vaccine. Both vaccines became available on the Australian National Immunization Program in July 2007 with RotaTeq given on the National Immunization Program schedule at 2, 4, and 6 months of age. Live vaccines such as measles mumps rubella (MMR) are generally contraindicated in immunosuppressed populations because of potential morbidity and mortality.[2] This has not been applied to rotavirus vaccines, in which risk of vaccine-associated disease is felt to be less than the risk from being exposed to natural infection.[2] Current guidelines support the administration of rotavirus vaccine to children infected with HIV, the largest immunosuppressed population studied to date.[3] The side effect profile is likely to involve gastrointestinal symptoms (vomiting and diarrhea).

A 9-month-old girl born to nonconsanguinous parents presented to the hospital with a history of faltering growth and chronic diarrhea. She was fully immunized according to the National Immunization Program schedule, including oral RotaTeq at 2, 4, and 6 months of age. She had mild diarrhea after the first dose of RotaTeq and remained well until 4 months of age (weight, 6 kg, 50th percentile), at which time she developed persistent vomiting and diarrhea with poor weight gain, worsening at 6 months.

At 9 months of age, her weight was 5.8 kg (<3rd percentile), and assessment of her faltering growth and chronic diarrhea revealed rotavirus in her stool, lymphopenia (lymphocyte count, 2.08×10^9/L; range, 4.0-10.0 $\times 10^9$/L) and undetectable IgG, IgA, and IgM. Lymphocyte subsets confirmed absent T cells with absent lymphocyte function and normal levels of B and natural killer cells.

A diagnosis of severe combined immune deficiency (SCID) was made (genotype unspecified; IL7RA [interleukin 7 receptor alpha], ADA [adenosine deaminase], and PNP [purine nucleoside phosphorylase]-negative).

Serial stool samples (n = 14) were collected from admission (at age 9 months) to assess for the presence of rotavirus. RNA was extracted from each sample and subjected to a VP6 [viral protein 6]-specific RT-PCR assay.[4] Each PCR product was sequenced to characterize the origin of the VP6 gene. All VP6 genes exhibited 100% identity to the RotaTeq vaccine VP6. Successful cord blood transplantation was performed at 11 months of age from a matched unrelated donor. Vaccine rotavirus was cleared post-transplant and last detected at 13.5 months of age, thus excreted for at least 7.5 months.

Severe combined immunodeficiency is the most severe type of primary immune deficiency, occurring in 1 in 50,000 to 100,000 live births. It often presents within the first year of life with severe infections and faltering growth. Without stem cell transplantation, SCID is fatal. There are no previous reported cases of prolonged rotavirus shedding after vaccine administration in a patient with SCID. In this case, 3 doses of RotaTeq were administered before this diagnosis was made. It is likely that rotavirus vaccine excretion persisted from dose 1, with exacerbation of symptoms after doses 2 and 3. Studies of RotaTeq have shown that viral shedding occurred in 9% of 360 recipients after dose 1, 0% after dose 2, and 0.3% after dose 3, usually between days 1 and 15 after the dose.[5]

This is the first reported case of persistent rotavirus vaccine excretion and chronic diarrhea in a severely immunocompromised patient. Because the diagnosis of a primary immune deficiency, such as SCID, is often made in the first year of life, it is important to consider this diagnosis when treating children with prolonged diarrhea and faltering growth, especially as we enter the universal rotavirus vaccination era.

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Role of omalizumab and steroids in Churg-Strauss syndrome

To the Editor:

The first case report on a patient who developed Churg-Strauss syndrome (CSS) after therapy with omalizumab, the anti-IgE recombinant humanized mAb, was described by Winchester et al[1] in 2006. Later, several similar cases were reported in the medical literature; the authors suggested a possible role for anti-IgE treatment in the emergence of CSS and recommended careful monitoring of emerging symptoms of this vasculitis in patients treated with omalizumab.[2-4]

In contrast, Giavina Bianchi et al[5] presented the case of a patient with CSS with uncontrolled asthma that improved with omalizumab treatment without increase of CSS clinical severity. The authors hypothesized that steroid tapering during omalizumab therapy could have caused CSS clinical appearance.

Here we describe the case of a 42-year-old Caucasian man with a 5 year history of asthma. One year after asthma onset, blood hypereosinophilia became evident (1600/μL), and the patient

Neonatal screening for severe combined immune deficiency

Jennifer M. Puck

Purpose of review

Severe combined immunodeficiency has been identified as a high-priority disease for inclusion in population-based newborn screening programs. In this review, the justification, advances to date and remaining challenges for universal severe combined immunodeficiency screening are outlined.

Recent findings

Severe combined immunodeficiency is treatable by hematopoietic stem cell transplantation, with best outcome if recognized and treated early in life. Universal screening of newborns could make possible prompt diagnosis and lifesaving treatment for all affected infants. One screening test using the dried blood spots already collected from all newborns involves quantitation of T cell receptor excision circles, and other test methods have been proposed and are being evaluated. Development of screening programs will require integration of screening, contacting infants with abnormal screen results for definitive testing, prompt treatment of affected infants, and outcome tracking.

Summary

Newborn screening for severe combined immunodeficiency is advancing toward pilot trials.

Keywords

bone marrow transplantation, early diagnosis, hematopoietic stem cell transplantation, live vaccine, newborn screening, primary immunodeficiency

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Abbreviations

HSCT hematopoietic stem cell transplantation
SCID severe combined immunodeficiency
TREC T cell receptor gene excision circle

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Introduction

Infants affected with severe combined immunodeficiency (SCID) die of the infectious complications of this disease unless a functional immune system can be provided, usually by hematopoietic stem cell transplantation (HSCT). Presymptomatic diagnosis, before onset of infections, affords the best opportunity for successful treatment. Most cases have no family history, however, and therefore diagnosis in the first weeks of life would require the institution of universal newborn screening. Efforts by immunologists, public health officials and patient advocates to develop appropriate screening tests and to plan pilot trials of SCID newborn screening are underway.

Scope, earlier work, and context

Patients with primary immunodeficiencies are often not diagnosed promptly because the infectious manifestations of these rare disorders are not initially distinguishable from routine infections in otherwise healthy individuals. For other classes of diseases not readily diagnosed clinically, population-wide screening has been instituted. Such screening could be advantageous for primary immunodeficiencies, with SCID as the initial disease category under consideration.

Natural course and incidence of severe combined immunodeficiency

SCID encompasses over 12 known and additional as-yet unknown single gene disorders that share the clinical phenotype of profound impairment of both cellular and humoral immune function [1,2]. Infants with SCID are healthy at birth and have no signs of their underlying disorder that can be picked up on routine newborn physical examination. They are, however, destined to die of infections in their first years of life unless they can be provided with a functional immune system [1,2]. HSCT and enzyme replacement (PEG-ADA to treat adenosine deaminase deficient SCID) have made these previously fatal diseases treatable [2–6,7•–9•,10]. Gene therapy is also a promising treatment despite occurrences of leukemia related to retroviral insertional mutagenesis in one early trial of X-linked SCID gene therapy [11,12•]. Molecular diagnosis of mutations in SCID disease genes has made possible carrier and prenatal diagnosis in some families, after diagnosis in at least one proband who had developed recurrent, serious infections. Although most SCID is sporadic, in families known to be at risk for SCID affected infants have been identified by prenatal mutation diagnosis or postnatal evaluation.

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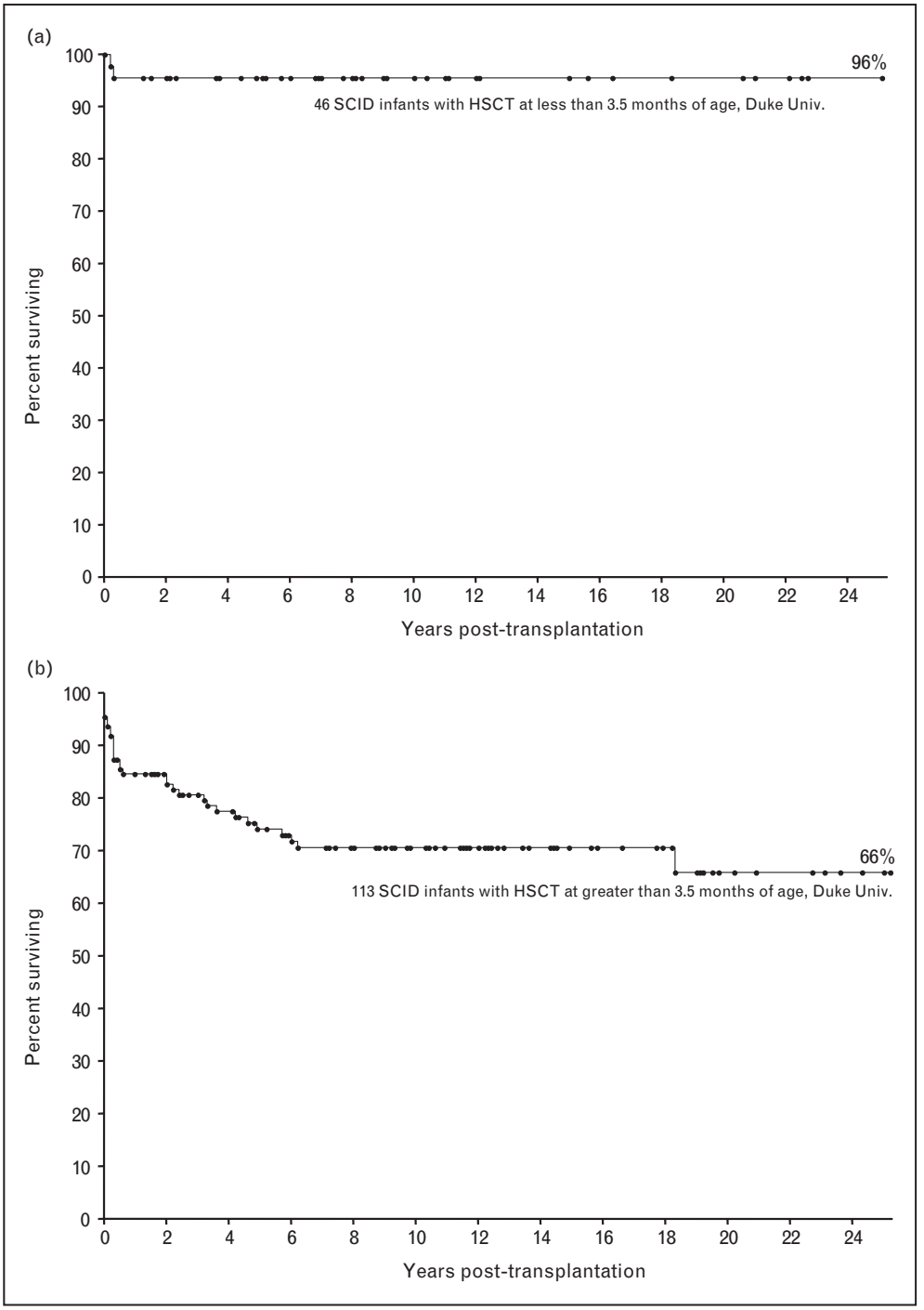
Such infants have in many instances received HSCT before they are 3.5-months old. In this presymptomatic setting, HSCT treatment produces strikingly higher survival rates, lower morbidity and lower treatment costs than HSCT after the onset of chronic diarrhea, infections and failure to thrive [13]. Figure 1 shows the difference in survival, in the largest single-institution series of HSCT for SCID at Duke University, between infants diagnosed and treated prior to 3.5 months of age (a) versus those treated later (b). Unfortunately most infants with SCID are not identified in the preinfectious period, and some die of infections without the correct diagnosis having

Figure 1 Kaplan–Meier plot of severe combined immunodeficiency patients transplanted at Duke University Medical Center



(a) Forty-six infants diagnosed and treated in the first 3.5 months of life. (b) One hundred and thirteen infants treated after age 3.5 months. Kindly provided by Rebecca Buckley. Reproduced with permission [15].

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been made. For this reason, the true incidence of SCID is unknown. A minimal estimate of 1 in 100 000 births affected with SCID is based on cases referred to Dr Puck's laboratory for mutation determination [14], but most experts believe that there are at least two-fold more, resulting in about 100 new cases of SCID per year in the US [15].

Newborn screening

Routine screening of all newborns for genetic disease began with testing for phenylketonuria using the Guthrie procedure on infant blood spotted onto filter paper and air-dried. Currently all states in the US collect dried blood spots for mandatory screening of all newborns for a variety of conditions. Criteria for including diseases in screening panels first suggested by Wilson and Jungner in 1968 [16] were as follows:

(1) The condition being screened for should be an important health problem.
(2) The natural history of the condition should be well understood.
(3) There should be a detectable early stage.
(4) Treatment at an early stage should be of more benefit than at a later stage.
(5) A suitable test should be devised for the early stage.
(6) The test should be acceptable.
(7) Intervals for repeating the test should be determined.
(8) Adequate health service provision should be made for the extra clinical workload resulting from screening.
(9) The risks, both physical and psychological, should be less than the benefits.
(10) The costs should be balanced against the benefits.

Clearly, from the early days of screening there were value judgments required in the selection of diseases for screening, but priority has always been given to conditions for which there is effective treatment; for which the best outcomes are achieved with treatment instituted soon after birth; and which are not readily recognized in the nursery except by means of a special test. The number of conditions currently screened for varies between countries and between states within the US, but is increasing to encompass multiple assays for metabolic disorders, hypothyroidism, hemoglobinopathies, and other genetic diseases such as cystic fibrosis [17]. In 2005, an extensive report, assembled by Watson *et al.* of the American College of Medical Genetics, established the goal of working toward evidence-based, uniform standards for newborn screening tests. This report was endorsed by the Advisory Committee to the Secretary for Health and Human Services, and several states have since moved to increase the number of conditions screened for. It is anticipated that tests for further conditions to be added to newborn screening panels in the future will be subjected to review using evidence-based criteria. In this report, SCID was noted to meet many criteria for inclusion in newborn screening panels, but at the time no SCID screening assay had been sufficiently validated for a complete rating to be possible [18].

Severe combined immunodeficiency screening conceptualization

A universal newborn screening program for SCID could in theory result in early diagnosis of all cases, allowing for optimal treatment to achieve the best possible outcomes. At a conference in 2001 entitled 'Applying Public Health Strategies to Primary Immunodeficiency Diseases' Buckley reported that because the majority of SCID infants have low numbers of circulating lymphocytes, a complete blood count and manual differential count could alert healthcare providers to suspect the diagnosis [2,13,19]. Because some infants have maternal lymphocytes, and some, especially those with *IL2RG*, *JAK3* and *IL7R* gene defects have substantial numbers of B lymphocytes, however, overlap between healthy infants with the lowest lymphocyte counts and SCID infants with the highest lymphocyte counts makes absolute lymphocyte counts alone problematic as a test.

A further workshop seeking public health partnerships to advance SCID newborn screening was held at the CDC in November 2006. By this time Chan and Puck [14] had introduced T cell receptor excision circle (TREC) copy number as an analyte that could distinguish T cell lymphopenic SCID infants from healthy controls and could be performed using the dried blood spots already collected routinely from newborns. In early 2007 [20], the Wisconsin newborn screening program announced its intention to pilot SCID newborn screening on a large scale.

In May 2007, a SCID Newborn Screening Working Group was convened in San Francisco with the goal of fostering teamwork among experts in newborn screening, trial design, immunologic diagnosis and SCID transplantation so that integrated approaches to SCID screening could be efficiently pursued [15]. Emphasizing that developing a successful newborn screening program requires integrated efforts in many disciplines, the participants reviewed recent additions to newborn screening panels and how they have been brought on line with pilot trials in one or more states [21••]. Successful genetic screening programs, including any program planned for SCID, must include 12 fundamental elements [15]:

(1) universality; all babies should be included (some states require parental permission);

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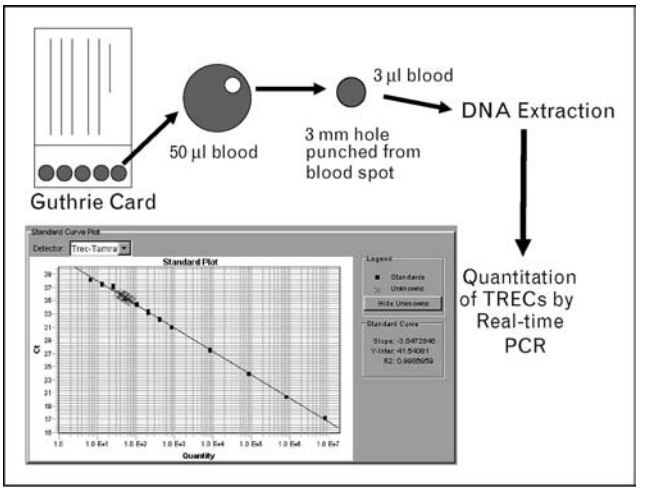
(2) prescreening education of parents, primary care providers;
(3) specimen quality control; every nursery, every day (obtain, transport to central lab);
(4) laboratory screening tests, cutoffs, standards, analysis, quality control;
(5) data integrity (HIPAA compliance);
(6) timely notification and follow-up;
(7) appropriate definitive diagnostic work-up;
(8) appropriate referral for treatment; immediate and long-term care of affected infants;
(9) education, reassurance for families with false positive tests;
(10) continuous monitoring of all phases of program, including outcomes;
(11) cost-effectiveness assessments to justify continuation, suggest improvements;
(12) acquisition of new knowledge about the conditions identified by screening.

Severe combined immunodeficiency screening test methodologies

There is not yet an assay that has been proven appropriate as a single-step screening test for SCID. Desirable features of an assay include using the dried blood spots already collected by state laboratories in addition to high sensitivity and specificity, low unit cost and scalability for high throughput. These features have been modeled in a hypothetical cost–benefit analysis by McGhee *et al.* [22]. The main barrier to implementation of currently proposed tests is the rate of false positive or indeterminate test results. Because of the rarity of SCID, the positive predictive value of a screening test needs to be very high to be accepted by the newborn screening community and pediatricians. Screening analytes are based on the inability of all SCID patients to make normal numbers of T cells, regardless of genotype, but must take into account the possibility of maternally engrafted T cells and the fact that T^-B^+ SCID patients may have high numbers of B cells.

Quantitation of TRECs has been the most extensively tested method to date. These DNA circles are byproducts of T cell receptor gene rearrangement in developing thymocytes joined together by the same recombinases that produce the mature T cell receptor gene from V, D and J gene segments. A particularly frequent intermediate TREC in humans can be assayed from peripheral blood DNA by quantitative PCR [23,24]. Puck and Chan showed that SCID patients, whose gene defects result in low output of mature T cells, have low or undetectable TRECs, as opposed to healthy newborns, who have high numbers of TRECs. Both blood of newly diagnosed SCID infants spotted onto standard filters and, more importantly, actual SCID infant Guthrie cards recovered from state laboratories have shown extremely low to undetectable TRECs (Fig. 2) [14,15]. Around 1.4% of anonymous, outdated Guthrie cards, however, have had indeterminate results due to poor DNA recovery, measured by low copy number of genomic actin in the same DNA sample used to enumerate TRECs. Repeat DNA isolation from the same sample may decrease the rate of indeterminate samples, and fresh samples appear to yield superior DNA with lower rates of indeterminate results. In Wisconsin, a commitment has been made to pilot SCID screening on a large scale within the next year using the TREC test as a first-line test [20].

Figure 2 The T cell excision circle (TREC) assay on dried blood spots



The Guthrie card, or standard filter card used to collect heel-stick blood, is obtained routinely from every newborn. At the screening laboratory a 3 mm punch, corresponding to about 3 µl of whole blood, is submitted for DNA extraction. Quantitative PCR is performed, and the number of TRECs is determined by comparison with standard serial dilutions of a plasmid containing the TREC sequence. Genomic DNA copy number can also be measured, such as with actin-specific primers to indicate DNA quality and approximate number of nucleated blood cells.

In Maryland and 11 other states in the US, a second blood spot filter card is requested from all infants during the first month of life. In these states, an indeterminate TREC test could be followed up automatically with a TREC assay on the second specimen, with a substantial reduction, to 0.1% or less, of persistently abnormal or indeterminate readings. In locales that do not get a routine second dried blood spot, the screening laboratory could ask for a repeat sample if the first one has proven inadequate.

Other assays for SCID newborn screening include immunoassays for IL-7 and T-cell specific proteins, as being evaluated by McGhee [25] and Ken Pass, respectively [15]. These protein-based assays might become first-line or second-line screening tests; or they could be used in

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combination with the TREC assay in a two-tier system. High IL-7 levels are associated with T-lymphocytopenic states, and 11 of 13 SCID patients in one study had greater than 15 pg/ml of IL-7 in serum or extracts from dried blood spots, while samples from controls generally had low or undetectable IL-7 [25]. It is not yet known, however, whether an association of high peripheral blood IL-7 levels with SCID can be developed into a robust newborn screening tool for SCID using dried blood spots. CD3 either alone or in combination with CD45 or other T-cell proteins could be assayed by sensitive, high-throughput Luminex bead capture technology or equivalent methods [15]. It is important to note that these assays are currently in the preliminary stages of exploration. Also, it is not clear whether the samples that are indeterminate with a TREC assay would have clear results with protein-based assays; it is possible that samples of poor quality for one assay would fail for all.

Another new approach is to detect mutations, either previously defined or as yet unreported, in known SCID genes by using resequencing microarray chips [26]. This technology is being investigated by Puck and Lebet in collaboration with Mansfield and Warrington at Affymetrix, Inc [15]. Still at a preliminary stage, this approach may have a substantial false negative rate; however, it would immediately yield a specific gene diagnosis if positive.

Severe combined immunodeficiency screening program development

Although SCID has unique features, the recent addition in public health programs of an expanded range of metabolic disorders and cystic fibrosis to newborn screening panels can provide a roadmap for the development of pilot trials and eventual widespread adoption of newborn screening for SCID. Addressing the elements listed in Table 2 will require new interactions between the pediatric immunology community and experts in newborn screening and public health. Major efforts to prepare health providers and prospective parents will be as important as test development. Additional aspects of planning for screening were addressed at the San Francisco meeting [15] as summarized below.

Recalling infants with abnormal or indeterminate screening test results

Available data with the TREC test indicate that dried blood spots without detectable TRECs will mostly represent poor quality or quantity of DNA extracted. These samples will have low genomic DNA and the result could be classified as indeterminate. There was consensus among the pediatric immunologists that while indeterminate test results will be problematic, any infant who truly lacks TRECs, has absent CD3, or has any test result that signifies a lack of T cells, should be brought to medical attention. Profound T cell lymphocytopenia for any reason is believed to confer a risk of life-threatening infections. Infants who do not have SCID, but have indeterminate or 'false positive' tests may have serious primary immunodeficiencies other than SCID, such as DiGeorge syndrome.

From the public health perspective, however, recalling babies may have negative consequences. A large number of 'false alarms' is costly and causes parental anxiety that may lead to increased utilization of health services [27•,28].

Confirmatory testing

State screening programs will need networks of immunology specialists available to be contacted in addition to the primary care provider for infants with screening results that need follow-up. The newborn screening labs and public health departments will need to work with immunologists to plan for the number of infants anticipated to require follow-up. Standardized evaluations will need to be designed. Ideally, a nationally coordinated workup would be used for all screen-positive infants with results deposited in a central databank to help monitor the performance of the screening process as well as provide population-based data on immune parameters.

The definitive diagnosis and treatment for SCID will likewise require recruitment of clinical specialists who have not traditionally been involved with newborn screening. For infants confirmed to have SCID, another immune deficiency or equivocal results on the confirmatory test panel, additional evaluation and treatment or follow-up would be indicated.

Treatment

Early treatment, generally by allogeneic HSCT, is recognized to be optimal for SCID. Given that most patients lack an HLA matched related donor, however, no single best approach to HSCT is currently agreed upon. The launching of newborn screening is eagerly anticipated by the pediatric immunology and transplant community in part as an impetus to establish multicenter collaborations to determine the best treatments for very young infants with SCID.

Long-term outcomes measurements

Newborn screening programs will require ongoing assessments not only of survival, but also long-term outcomes in order to justify continuation of screening or suggest improvements in the entire sequence from screening to treatment and beyond. Few studies of quality of life of HSCT survivors with SCID are available, but one new study from Italy found that the majority of such patients have a good clinical outcome [29].

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Conclusion

Primary immunodeficiencies are frustrating to patients, families and clinicians alike because the diagnosis is rarely suspected before the occurrence of severe infections or even tragic loss of life. Early recognition by presymptomatic screening would afford the ideal opportunity for effective treatment. SCID will be a prototype for immunodeficiency screening in the near future, and carefully planned and conducted pilot trials will form the basis to push for universal newborn screening for SCID. If suitable tests can be developed, additional primary immunodeficiencies should also be candidates for screening.

Acknowledgements

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Hematopoietic Stem Cell Transplantation for Severe Combined Immune Deficiency or What the Children have Taught Us

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KEYWORDS

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- Hematopoietic stem cell transplantation • Unrelated • In utero
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More than 40 years ago, the first successful allogeneic hematopoietic stem cell transplantation (HSCT) was reported by Robert A. Good, MD and his colleagues[1] for a child with severe combined immunodeficiency (SCID). In the succeeding years, HSCT for SCID patients have represented only a small portion of the total number of allogeneic HSCT performed. Nevertheless, the clinical and biologic importance of the patients transplanted for SCID has continued. SCID patients were the first to be successfully transplanted with nonsibling related bone marrow, unrelated bone marrow, T-cell depleted HSCT, and genetically corrected (gene transfer) autologous HSC.[2–5] In addition, many of the biologic insights that are now widely applied to allogeneic HSCT were first identified in the transplantation of SCID patients. Therefore, this article reviews the clinical and biologic lessons that have been learned from HSCT for SCID patients, and how the information has impacted the general field of allogeneic HSCT.

PRELUDES

In 1956 it was established that rodents receiving total body irradiation (TBI) could be rescued from the lethality of bone marrow failure by the infusion of histocompatible bone marrow.[6] In those studies the importance of histocompatibility for the successful rescue of the animals from lethal TBI by the prevention of graft-versus-host disease (GVHD) was identified. In the decade between the biologic reality that the transplantation of bone marrow could rescue irradiated animals and the first successful human allogeneic HSCT, clinical investigators attempted to apply the biologic principles to the treatment of patients. A sentinel event was the irradiation accident that occurred in Yugoslavia in 1959 where 6 patients, who were heavily irradiated, were subsequently treated by the infusion of either fetal liver and spleen cells or unrelated bone marrow cells.[7] No sustained donor hematopoietic engraftment was seen in any patients, although slight increases in donor-type erythrocytes were transiently seen in some patients. The patient with the highest dose of irradiation died whereas the other patients had autologous hematopoietic recovery. Other early attempts included the use of high-dose irradiation/chemotherapy and pooled allogeneic bone marrow for the treatment of related and unrelated patients with acute leukemia. Patients with aplastic anemia were infused with bone marrow from identical twins with some patients having hematopoietic improvement, but it was unclear whether their improvement in hematopoiesis was due to the HSCT or the spontaneous recovery of their underlying aplastic anemia. Many allogeneic recipients developed acute GVHD that had similarities to GVHD seen in rodents following histoincompatible transplants. Thus, clinicians were aware that histocompatibility might improve the likelihood of successful HSCT. During the 1960s, the development of serologic reagents to detect human leukocyte antigen (HLA)-A and HLA-B permitted physicians to determine the class I histocompatibility of potential donors and recipients. The development of the mixed lymphocyte culture (MLC) permitted the determination of class II histocompatibility because no antiserum to HLA-DR existed.

CLINICAL ADVANCES

Allogeneic-Related HSCT

The first successful allogeneic HSCT was a member of a kindred in which 11 male infants had died due to severe recurrent infections during the first year of life.[1] At admission, the child had draining skin pustules, no detectable lymph nodes, and lymphopenia. At that time, no phenotypic assays existed for the enumeration of T lymphocytes, but the diagnosis was confirmed by the absence of cutaneous delayed

hypersensitivity as well as functional assays showing that the patient's lymphocytes did not respond to stimulation with either phytohemagglutinin (PHA) or allogeneic cells. HLA-A and -B typing indicated that the patient and a sister were HLA-B identical but differed at one HLA-A antigen; however, the sister did not respond in MLC to stimulation with the patient's cells. The patient was transplanted with a mixture of peripheral blood leukocytes and bone marrow. The cells were given intraperitoneally. A total dose of 3.5×10^8 peripheral blood leukocytes and 1×10^9 nucleated bone marrow cells were given. A week after transplantation, the patient developed an erthymatous rash, which on skin biopsy had histopathological features characteristic of GVHD. Stimulation of the patient's peripheral blood lymphocytes showed the development of large lymphoblasts with a female karyotype, indicating that the circulatory lymphocytes were now responsive to stimulation by PHA and were of donor origin. The patient was challenged with dinitrofluorobenzene and responded to skin testing, demonstrating the development of normal delayed hypersensitivity.

The patient was blood group A and the donor blood group O. The patient's anti-B titers rose, but he developed a Coomb positive hemolytic anemia. Eight weeks after HSCT the patient's platelet and granulocyte counts began to drop, and a bone marrow aspirate showed hypocellularity with both male and female cells. The patient's bone marrow progressed to complete aplasia with all cells being of donor origin.

Three months after the first transplant the patient was transplanted for the second time with 1×10^9 bone marrow cells: 20% into the right ileac marrow space and 80% intraperitoneally. The bone marrow was treated in vitro with a horse antihuman lymphoblast globulin for 2 hours before infusion. By 2 weeks there was an increase in the platelet count, and the white blood cell count began to increase. All bone marrow cells had a female karyotype.[8] The patient is now more than 40 years old, with normal immune and hematopoietic function of donor origin.

The lessons

The authors of the initial report were not able to appreciate the significance of all their clinical and laboratory observations. The patient received peripheral blood T lymphocytes as well as bone marrow cells, and it is likely that the early onset of acute GVHD was due to the large number of donor T lymphocytes given, especially considering that the donor and patient were an HLA-A mismatch. In the second transplant to reduce the probability of GVHD, they tried to reduce the number of T lymphocytes infused by (1) taking smaller bone marrow aspiration to reduce peripheral blood contamination and (2) treating the bone marrow with antiserum to remove T lymphocytes.[9] The patient did not develop any acute GVHD after the second transplant.

Subsequent animal experiments demonstrated that the efficiency of the intraperitoneal injection of HSC was approximately one-tenth that of intravenous injection. The present clinical use of the intravenous route for HSC infusion is based on the canine experiments performed by Thomas and his colleagues. The success of the initial transplants in the SCID patient was, therefore, due to the relatively large number of cells given, the small size of the patient, and the use of a HLA-B identical and MLC nonreactive donor.

The patient developed immune-mediated bone marrow aplasia, which was also seen in some other SCID patients during the 1970s. It is of interest that, although hemolytic anemia has been seen following ABO-incompatible or histoincompatible HSCT in SCID patients in more recent years, rarely has bone marrow aplasia occurred. The reason for this clinical change is unclear. The development of bone marrow aplasia, however, clearly demonstrated that immune cell-mediated events including GVHD can produce severe aplastic anemia, indicating that immunosuppression might have

a role in the treatment of aplastic anemia, which was subsequently demonstrated in both animal studies and clinical trials using antithymocyte globulin and other immunosuppressive agents.[10]

The patient, in addition to being the first patient to have an immune deficiency corrected by HSCT, also represented the first successful treatment of bone marrow failure by allogeneic HSCT. No evidence of donor hematopoietic engraftment occurred following the initial transplant. It is now clear that in SCID patients, no clinically significant donor HSC engraftment occurs without some myelosuppressive therapy. However, once the immune-mediated destruction of the recipient hematopoiesis had occurred and adequate "space" had been developed, it was possible even with the intraperitoneal infusion of donor bone marrow to establish donor-derived hematopoiesis without any chemotherapy. The patient demonstrated what it took another decade to formally prove, that is, that engraftment of donor HSC requires the elimination or reduction of the number of recipient HSC to permit the engraftment of donor hematopoietic cells.[11] The present use of reduced intensity regimens that rely on the engraftment of the donor immune system to eliminate both normal and abnormal (neoplastic) recipient hematopoiesis is a direct descendant of the biologic events that occurred in the first SCID patient.[12]

Related Nonsibling Donors

Because most SCID patients did not have an MLC-nonreactive sibling donor, clinicians began to explore other relatives to see if any potential donors were MLC nonreactive. In a limited number of cases, MLC-nonreactive donors were identified that were successfully used to treat cases of SCID.[2,13] When related donors, who were MLC reactive, were used, patients usually died of acute GVHD, suggesting that MLC nonreactivity (HLA-DR locus identity with modern techniques) was a prerequisite for the successful HSCT of SCID without fatal GVHD. This approach to identifying appropriate donors was subsequently applied to other diseases as well.[14]

The lessons

Differences at single class I alleles do not significantly decrease the overall likelihood of event-free survival, whereas class II differences are almost uniformly associated with poor outcome. Thus, the results from the early transplants for SCID were the basis for focusing on identifying donors who were MLC nonreactive or Class II identical.

Unrelated Donors

Because the majority of SCID patients did not have an MLC-nonreactive related donor, the possibility that an MLC-nonreactive unrelated donor might exist who could be a successful donor was explored. Despite the fact that formal programs to identify unrelated MLC nonreactive donors did not exist, a SCID patient, who had a prevalent haplotype, received 7 transplants from an unrelated individual who was MLC nonreactive.[3] The donor and recipient were HLA-B identical but disparate at one HLA-A antigen. The patient was homozygous for HLA-A1 while the donor was heterozygous (HLA-A1, HLA-A2). At 5 months of age the patient received 10×10^6 bone marrow cells/kg by the intravenous route. The bone marrow had been shipped from Denmark to the United States. Ten days later the patient developed a macular rash consistent with GVHD, and PHA-responsive lymphocytes were detected. Three weeks later the patient received a second infusion of 10×10^6 cells. The patient developed detectable lymph nodes and increasingly severe acute GVHD. At 2 months the circulating donor lymphocytes disappeared, and the patient received a third transplant of

17×10^6 cells by the intravenous route. Again the patient developed PHA-responsive donor lymphocytes that persisted for 4 months. A fourth transplant at 13 months of age was performed with 10×10^6 bone marrow cells given intravenously. Again there was an increase in PHA-responsive lymphocytes of donor origin, but by 6 months after HSCT the PHA-responsive donor lymphocytes were no longer detected. Therefore, because of the possibility of hybrid resistance, the patient received 2 doses of cyclophosphamide (25 mg/kg) before HSCT, which consisted of 130×10^6 cells/kg of fresh bone marrow cells. The patient developed PHA-responsive donor lymphocytes and had in vitro responses to both mitogens and antigens. Donor T lymphocytes but no B lymphocytes were present in the patient's circulation. Three months following the fifth transplant, when the patient was about to be discharged from the hospital, he developed severe aplastic anemia with all detectable residual bone marrow cells being of donor origin. Two months later, without preconditioning, the patient received frozen bone marrow cells from his fifth transplant that did not result in any hematopoietic engraftment. Therefore, 4 months later, after preparation with full doses of cyclosphosphamide (50 mg/kg $\times$ 4 days), the patient received 1×10^8 bone marrow cells/kg intravenously. At 2 weeks he developed donor hematopoiesis and acute GVHD. All T lymphocytes were of donor origin. B lymphocytes were detected for the first time, with spontaneous rises in his serum immunoglobulin levels. After discharge, all lymphoid and hematopoietic elements were of donor origin by both karyotyping and cell surface antigen analysis.

The lessons

Previous attempts to use unrelated bone marrow to treat aplastic anemia had been unsuccessful. This patient demonstrated that significant pretransplant immunosuppression may be necessary, even in patients with SCID, to achieve successful donor hematopoietic engraftment. The successful treatment of this patient and other SCID patients with unrelated HSCT were a major impetus for the establishment both of the National Donor Marrow Program and the international cooperation that is now available for obtaining unrelated bone marrow, mobilized peripheral blood cells, and cord blood.

Fetal Liver Cells

Based on studies from neonatally thymectomized mice, it was determined that histoincompatible HSCT could be done if the HSC inoculum was devoid of T lymphocytes capable of causing acute GVHD.[15] Clinical investigators, therefore, attempted to identify sources of human HSC that did not contain T lymphocytes. Their attention initially focused on the potential use of fetal liver, which before 14 to 16 weeks of gestational age is a major source of hematopoiesis in the human fetus. Because no T lymphocytes are found in the circulation after 12 weeks of gestation, it was hypothesized that fetal liver obtained from electively aborted fetuses of less than 12 weeks of gestation would not contain significant numbers of T lymphocytes. Therefore, fetal liver cells could be an HSC source devoid of T lymphocytes. HLA typing was not possible before the transplantation of the fetal liver cells. Therefore, questions existed as to whether clinical benefit would be derived from the engraftment of the histoincompatible HSC.[16] Initially, transplants with fetal liver were unsuccessful, possibly due to the use of cryopreserved fetal liver cells in most cases. The first successful immune reconstitution reported using fetal liver cells was achieved in a patient with SCID due to adenosine deaminase (ADA) deficiency.[17] The patient received 25×10^8 fetal liver cells intraperitoneally when the patient was 5 months old. IgM-bearing cells were detected 19 days after transplantation, and an increase in T lymphocytes was seen by 40 days.

PHA-responsive cells were present by day 74. The patient developed in vitro proliferative responses to mitogens, specific antigens (candida), and allogeneic lymphocytes. Immunization with φX174 resulted in a low primary IgM response with little IgG production after a repeat immunization. The patient developed appropriate isohemagglutinin antibodies. The patient was taken off replacement immunoglobulin and did well until 1 year of age when he developed nephrotic syndrome, from which he died.

Subsequent SCID patients without ADA deficiency were also transplanted with fetal liver cells. One patient had the correction of his T-lymphocyte immune deficiency after the transplantation of 8.4×8^7 fetal liver cells intraperitoneally at 13 months of age. He developed GVHD, which lasted for 6 weeks, and had the presence of normal numbers of PHA-responsive T lymphocytes by 12 weeks after transplantation. The patient developed a cutaneous response to candida antigen. Serum IgM levels rose to normal levels by 1 year, but he had no detectable IgG, requiring the continued administration of replacement immunoglobulin.[18] However, subsequent series with larger numbers of patients confirmed the potential of fetal liver cells ± fetal thymus to correct T-lymphocyte and sometimes B-lymphocyte immunodeficiencies, but also demonstrated that durable engraftment was less than 30% with a low probably of achieving long-term immune reconstitution.

The lessons

The recipients of fetal liver cells demonstrated that fetal liver cells devoid of T lymphocytes were capable of supporting thymopoiesis without the development of GVHD. The first patient, who developed circulating B lymphocytes, had ADA deficiency. It is now known that cross-feeding can correct ADA deficiency. The investigators could not determine the origin of the circulating B lymphocytes, but they were most likely of recipient origin, while the donor-derived T lymphocytes were the source of ADA. Successful treatment of the ADA-deficient form of SCID with either exogenous enzyme therapy or HSCT results initially in increases in the number of B lymphocytes of recipient origin. Decreased primary and secondary response to φX174 stimulation suggests that there was a lack of normal T- and B-lymphocyte cooperation.

None of the initial recipients of fetal liver cells received any pretransplant chemotherapy.[19,20] Therefore, it is unlikely that HSC engraftment occurred. The cells that gave rise to T lymphocytes of donor origin may thus have been derived from committed lymphoid progenitors (CLP) that were able to migrate to the recipient thymus, induce its differentiation, and differentiate into circulating T lymphocytes of donor origin.[21] The follow-up of the fetal liver recipients should provide important biologic information about the longevity and the breadth of T-lymphocyte immunity derived from CLP.

T-Lymphocyte Depleted HSCT

In 1975 it was first demonstrated in mice that T-lymphocyte depletion of histoincompatible HSC permitted both the hematological and immunologic reconstitution of irradiated mice without GVHD.[22] Attempts were therefore undertaken in humans to eliminate T lymphocytes from histoincompatible bone marrow using a variety of techniques, both physical and biological. The selective separation of T lymphocytes from HSC by albumin density gradients as well as the suicide of donor T lymphocytes after stimulation by recipient antigens were attempted. None of these approaches led to the correction of the immune deficiency of any SCID patients. Most patients had no signs of the engraftment of any donor cells.

The approach to T-lymphocyte depletion that was first shown to be clinically successful was the physical removal of T lymphocytes based on their agglutination

with soybean agglutinin (SBA) followed by the physical rosetting of the residual T lymphocytes by sheep red blood cells (E), which had initially been used to immunophenotypically detect T lymphocytes. The combination of SBA agglutination followed by E rosette formation permitted the physical removal of the majority of T lymphocytes from human bone marrow, which could then be used for HSCT. Following preclinical studies in monkeys, patients were treated with HLA haploidentical disparate bone marrow depleted of T lymphocytes.[4,23]

Of the first 6 SCID patients treated with T-lymphocyte depleted MLC-reactive paternal marrow, 5 had durable immune reconstitution, whereas GVHD was limited or nondetectable. None of the patients had chemotherapy before their engraftment. One patient had graft rejection and was successfully retransplanted after pretransplant chemotherapy.

The lessons

The clinical experience confirms the experiments in mice that T-lymphocyte depletion before HSCT could permit the engraftment of histoincompatible HSC without the development of clinically significant or fatal acute GVHD. However, pretransplant immunosuppression is required in some cases to achieve donor immune reconstitution due to the presence of either engrafted maternal T lymphocytes or hybrid resistance. The use of T-lymphocyte depleted HSCT is now in general use for both related and unrelated HSCT.[24]

In Utero HSC Transplantation

A variety of genetic diseases (β- and α-thalassemia, adrenoleukodystrophy, Hurler disease, and so forth) can be cured or stabilized by the postnatal engraftment of normal allogeneic HSC. Some genetic diseases, however, have significant morbidity at the time of birth, suggesting that the engraftment of normal HSC before birth might provide clinical benefit to the patients. Fetuses with hemoglobinopathies have been transplanted in utero with HSC from either fetal liver or T-lymphocyte depleted parental bone marrow without any evidence of sustained hematopoietic engraftment.[25] However, the transplants were performed in fetuses of more than 16 weeks of gestation, by which time the fetuses had T lymphocytes capable of responding to allogeneic cells.[26]

In contrast, 2 SCID patients have been reported who were successfully transplanted with T-lymphocyte depleted parental histoincompatible bone marrow cells.[27,28] In both cases, the genetic basis for the patients' disease was defects in the common γ-chain. The first patient received a total of 18.6×10^6 cells intraperitoneally in 3 injections starting at 16 weeks of gestation. The second patient received 18×10^6 nucleated cells in 2 intraperitoneal injections beginning at 21 weeks of gestation. The clinical outcomes of both patients were similar. Both had PHA-responsive T lymphocytes of donor origin while their B lymphocytes continued to be of recipient origin. In the first case, immunizations were successful with the production of specific antibodies, whereas no information is available about antibody production in the second case. Thus, these patients with the X-linked form of SCID, who have defective natural killer (NK) cells, were able to be successfully engrafted with haploidentical T-cell depleted HSC without the development of any detectable GVHD.

The lessons

In contrast to the SCID patients, the patients with hemoglobinapathies, who have normal immune systems, were not able to be successfully transplanted with haploidentical T-lymphocyte depleted HSC even as early as 16 to 20 weeks of

gestation. It is not clear as to whether the immune reconstitution that occurred in the SCID patients was due to HSC engraftment or whether the T lymphocytes are derived from CLP in the HSC inoculum. Nevertheless, the persistence of the donor lymphoid cells was achieved in the SCID patients. Sustained donor lymphoid or hematopoietic engraftment was not achieved in patients with nonimmune genetic diseases, although one patient may have died of in utero GVHD.[29] Both successfully treated SCID patients had X-linked SCID and, therefore, an absence of functional NK cells and the ability to exhibit hybrid resistance. It would be interesting to know if patients with other forms of SCID, who had normal NK function after birth, could be successfully engrafted in utero.

Genetically Corrected HSC

The identification of the molecular basis of most forms of SCID (common γ-chain deficiency, ADA deficiency, interleukin [IL]-7 receptor deficiency, and so forth) made SCID patients logical candidates for the use of genetically corrected autologous HSC. Murine studies had demonstrated that retroviral vectors could transduce pluripotent hematopoietic stem cells as well as committed lymphoid progenitors. Thus, clinical investigators thought that transplantation of genetically corrected autologous HSC could provide all of the benefits associated with the transplantation of allogeneic HSC without the risks of acute or chronic GVHD.

The first gene to be cloned that was associated with SCID was ADA. Researchers in preclinical studies demonstrated that retroviral vectors containing the human ADA gene could transduce both murine HSC and human mature T lymphocytes.[30] The transduction of mature T lymphocytes normalized their intracellular metabolism, demonstrating that the transduced ADA gene produced adequate levels of functioning enzyme. The first human gene transfer trial was in patients with ADA-deficient SCID, who received their own T lymphocytes that had been transduced in vitro.[31] The patients had had adequate numbers of T lymphocytes for the transduction because they were on enzyme replacement therapy. The patients received multiple infusions of the transduced T lymphocytes. The persistence of the transduced cells could be detected for at least 7 years. It was difficult, however, to determine whether any clinical efficacy was associated with the transduced cells because the patients continued on their exogenous enzyme replacement therapy. However, no toxic effects were assessed with the infusion of the transduced T lymphocytes.

Additional patients were then transplanted with a mixture of transduced bone marrow plus transduced peripheral blood. Different retroviral vectors were used for the 2 transductions so that it would be possible to determine the source of any circulating T lymphocytes.[5] Posttransplant analysis of myeloid cells revealed that all transduced cells contain the vector used to transduce bone marrow cells, whereas all the T lymphocytes early after transplantation were derived from the infused mature T lymphocytes. Over the course of the first year the proportion of T lymphocytes derived from the transduced T lymphocytes decreased, whereas the proportion derived from the transduced bone marrow increased, so that by 1 year all the transduced T lymphocytes contained the bone marrow vector. After the patients had their ADA replacement enzyme therapy discontinued, the frequency of their transduced T lymphocytes was 5% and of the bone marrow precursors 25%. Thus, the patients were able to have significant immune reconstitution following the transplantation of the gene corrected cells with the production of specific antibody and the generation of responses to mitogen stimulation. However, the majority of their immune function was due to nontransduced cells, demonstrating the effect of cross-correction between the transduced and the nontransduced cells.

With the identification of defects in the common γ-chain as the basis for the X-link form of SCID, preclinical research was undertaken to evaluate gene transfer. Using a retroviral vector, French investigators transplanted patients with autologous bone marrow transduced with a retroviral vector containing the human common γ-chain gene. In the majority of patients there was the rapid development of T lymphocytes containing the transduced gene as well as the ability to develop antigen-specific T-lymphocyte proliferation and the production of specific antibodies, so that patients could be removed from immunoglobulin therapy.[32] In comparison with the results with the ADA gene transfer, all of the circulating T lymphocytes contained the transduced gene. Unfortunately, 5 patients have developed acute T-lymphocyte leukemia due to the activation of the *LMO2* gene by the inserted gene.[33] The development of leukemia has resulted in gene transfer trials for X-linked SCID being put on hold.

Because of the limited number of transduced T lymphocytes seen in the patients with ADA deficiency, Italian investigators explored the possibility of pretransplant myeloablative therapy to reduce the number of recipient HSC at the time of transplantation. Patients with ADA deficiency transplanted after reduced doses of busulfan have improved immune reconstitution compared with those with no pretransplant chemotherapy, with a larger percentage of both the myeloid cells and T lymphocytes containing the transduced gene.[34] No cases of leukemia have been seen in the patients receiving gene transfer for ADA deficiency.

The lessons

The major difference between the ADA deficiency and X-linked SCID is that a selective advantage exists in vivo for the transduced T lymphocytes in patients with X-linked SCID, whereas no significant selective advantage for the transduced T lymphocytes exists in patients with ADA deficiency due to the cross-correction of nontransduced T lymphocytes by enzyme replacement or enzyme produced by the transduced cells. Therefore, to increase the frequency of the engraftment of the transduced HSC it was necessary to administer pretransplant myelosuppressive therapy with anti-HSC activity. The use of pretransplant myelosuppressive therapy has the associated risks of neutropenia and thrombocytopenia as well as the possibility of the later development of leukemia. Nevertheless, the use of pretransplant myelosuppressive therapy has resulted in an increased frequency of engraftment of the transduced HSC as well as an increase in the frequency of transduced T lymphocytes. The use of pretransplant myelosuppressive therapy is therefore being entertained for gene transfer trials in which the transduced cells will not have a significant selective advantage, including the hemoglobinopathies.

BIOLOGIC INSIGHTS

HSC Niche

Most patients transplanted for SCID with allogeneic HSC, who did not receive pretransplant myelosuppressive therapy, did not have any evidence of sustained donor hematopoiesis as measured by the presence of donor-specific erythroid antigens or donor-specific HLA antigens on myeloid cells. However, when recipient hematopoiesis is eliminated by either severe GVHD or the administration of pretransplant chemotherapy, donor hematopoiesis was readily achieved after HSCT. Although rare donor-derived CD34+ and myeloid cells have been identified in the marrow of SCID patients after transplantation without pretransplant chemotherapy, the exact biologic nature of the cells is not clear. The absence of the sustained production of mature donor erythroid or myeloid elements indicates that clinically significant donor HSC engraftment cannot occur without the creation of “space.” The development of

bone marrow aplasia due to GVHD after their successful first transplant indicated that donor HSC engraftment had not occurred in the SCID patient.[8]

The complete correction of patients with Wiskott-Aldrich syndrome occurred only after they had received pretransplant myeloablative therapy in addition to immunosuppressive therapy. The first patient transplanted for Wiskott-Aldrich syndrome had improvement only of his lymphoid function with no correction of his platelet abnormalities after having received only immunosuppressive therapy.[35] Thus, the infusion of allogeneic HSC without HSC-targeted myelosuppression to create marrow space has not resulted in donor HSC engraftment.

Induction of Thymopoiesis

Patients with most forms of SCID are characterized by a thymus that maintains the normal architecture seen in fetuses of less than 12 weeks of gestational age. The fetal thymus is characterized by primarily epithelial elements, small blood vessels, no lymphoid elements and, rarely, Hassel corpuscles. The persistence of the fetal architecture indicates that the migration of prethymic lymphoid cells to the thymus is necessary for the induction of thymic differentiation. In a limited number of cases, patients who have been successfully transplanted have had thymus biopsies done, or have been analyzed at autopsy and have shown the development of normal thymic architecture, including normal lymphoid elements, indicating the inductive influence of the lymphoid precursors.

The fetal thymus first contains lymphoid cells at 12 weeks of gestation, which is 4 to 6 weeks after the development of hematopoiesis in the fetal liver. The transplantation of T-lymphocyte depleted HSC in SCID patients is reproductively characterized by the development of circulating immunophenotypic T lymphocytes 3 months after transplantation,[36] suggesting that it takes the CLP and other HSC-derived cells 3 months to develop into prethymic cells, which can then migrate to the thymus, induce thymic differentiation, and generate mature T lymphocytes. These results in SCID patients indicate that any mature T lymphocytes seen in the peripheral blood of HSCT recipients earlier than 3 months after HSCT are due to the homeostatic expansion of the mature T lymphocytes present in the HSC inoculum rather than thymopoiesis.

Duration of the Immune Correction in SCID Patients

An area of ongoing controversy is the duration of the correction of the immune deficiency of patients with SCID following HSCT. Although some SCID patients have functional B lymphocytes, all forms of SCID are characterized by the absence of functional antigen-specific T lymphocytes. Antigen-specific T-lymphocyte function after successful HSCT is due to donor-derived T lymphocytes. When unmodified HSC is used for transplantation, the initial donor-derived T lymphocytes are derived from the mature lymphocytes contained in the HSC inoculum. Starting 3 months after transplantation there is an increasing contribution from thymopoiesis. It is possible to quantitate recipient thymopoiesis by T-cell receptor excision circles (TREC) analysis as well as the immunophenotypic characteristics of naïve recent thymic emigrant (CD4+, CD45RA+) cells. Patients successfully transplanted with T-lymphocyte depleted HSC have the development of T lymphocytes between 3 and 6 months after HSCT. Recipient thymopoiesis peaks 1 year after transplantation.[37] Differences may then occur between patients who have received pretransplant myelosuppression and those who did not receive chemotherapy. Patients who did not receive pre-HSCT chemotherapy and who do not have detectable HSC engraftment have a slow decrease in their thymopoiesis, with a resultant decrease in TREC-positive T lymphocytes and PHA stimulation, as might be expected if the number of CLP capable of

entering the thymus decreased due to their lack of self-renewal. Patients who receive chemotherapy and have HSC engraftment have the ongoing production of new CLP capable of supporting recipient thymopoiesis, and the ongoing production of new T lymphocytes. It will be interesting to compare these 2 groups for the persistence of antigen-specific T-lymphocyte responses to infectious antigens, particularly herpes papilloma virus (HPV), because there has been an increased incidence of HPV infections in the long-term recipients who did not receive pretransplant chemotherapy.[38]

Maternal T-Lymphocyte Chimerism

Many SCID patients, especially those with X-linked SCID, are born with circulating T lymphocytes of maternal origin. Rarely do patients have clinical acute GVHD. Some defects in maternal T-lymphocyte function have been identified, including the inability to respond to allogeneic cells.[39] Nevertheless, the presence of maternal T lymphocytes without the presence of acute GVHD raises questions as to the mechanism of the tolerance that had been generated.

Mechanism of Tolerance

The successful HSCT of SCID patients with histoincompatible HSC, either haploidentical parents or incompatible fetal liver, demonstrated that successful HSC engraftment can occur without fatal GVHD. Studies of the successful recipients have revealed several mechanisms of tolerance, including clonal deletion and the presence of IL-10 producing regulatory T lymphocytes.[40,41]

HLA Restriction of Antigen-specific T-Lymphocyte Function

When the first successful fetal liver transplants were performed, Zinkernagel predicted that the recipients of the histoincompatible HSC would fail to achieve the functional reconstitution of T-lymphocyte immunity and would continue to have opportunistic infections because the histoincompatibility between the fetal liver cells and the recipient thymic epithelial cells would result in a lack of development of HLA-restricted antigen-specific T-lymphocyte function.[16] Surprisingly, the patients successfully transplanted with fetal liver cells did develop antigen-specific T-lymphocyte immunity and did not develop clinical opportunistic infections.[42] Subsequent murine experiments demonstrated that histoincompatible HSC could develop into antigen-specific T lymphocytes, restricting the recipient epithelial cell histocompatibility antigens.

The studies of the emergence of antigen restriction after haploidentical T-lymphocyte depleted transplantation for SCID gave additional insights into the development of major histocompatibility complex antigen restriction of human T-lymphocyte function.[43] The evaluation of antigen-specific T-lymphocyte clones during the first 2 years after HSCT demonstrated that the T-lymphocyte clones were restricted by the recipient HLA antigens. However, with time the antigen specificity broadened, and some T-lymphocyte clones restricted by the disparate parental haplotype were identified, suggesting that the T lymphocytes could also be restricted by the HLA alleles of the disparate donor haplotype. The patient who had received pretransplant myeloablative therapy had myeloid cells of donor origin, suggesting that donor antigen-presenting cells were present in the recipient thymus and controlled the development of T-lymphocyte histocompatibility restriction.

SUMMARY

In addition to being curative therapy, HSCT for SCID patients has provided major insights into the immunobiology of allogeneic HSCT, as well as leading the clinical

breakthroughs that have resulted in expanding the pool of potential donors for HSCT for non-SCID diseases.

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Expert Commentary: Practical Issues in Newborn Screening for Severe Combined Immune Deficiency (SCID)

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Kate Sullivan: We asked experts in the field to comment on some of the more pressing questions in the burgeoning field of newborn screening for severe combined immune deficiency (SCID). Their valuable perspectives are provided to guide the establishment of policies as additional states consider and implement newborn screening for SCID. Jennifer Puck has been a strong advocate for newborn screening and originated the concept of T cell receptor excision circle (TREC) screening using dried blood spots; the TREC assay has been performed on all newborns in California since August 2010, and Dr. Puck is the immunology consultant for the California Genetic Disease Lab; she has instituted a centralized follow-up model, with the screening program obtaining and sending follow-up tests throughout the state to a single immunology lab. Dr. Puck and her Southern California colleague, Dr. Joseph Church, interpret all flow cytometric results from a designated laboratory with a standardized analytic panel. Dr. Jack Routes was responsible for implementing the first state newborn screening program for SCID, which started in Wisconsin in January 2008. Wisconsin is a leader in the field of newborn screening. Dr. Alexandra (Lisa) Filipovich has developed Cincinnati Children's Hospital into one of the preeminent transplant centers. Novel protocols to limit toxicity and improve outcomes are central to the innovations at Cincinnati Children's Hospital.

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Commentary

It is well accepted that SCID patients treated with hematopoietic cell transplantation early in life have the highest likelihood of long-term survival. This is largely due to a lower burden of acquired infections, which can limit the ultimate success of the transplant procedure, as well as the less clearly defined belief that very young infants are more accepting of allogeneic stem cells and do not have as severe graft versus host disease as those treated at an older age. The long-anticipated advent of early diagnosis of life-threatening T cell disorders, using TREC quantitation, has arrived in several parts of the USA.

The TREC test is an excellent biomarker for the number of naive T cells that have recently emigrated from the thymus. Infants with low or absent TRECs may have inadequate thymic production of autologous T cells or excessive losses of such cells from the peripheral blood, which is sampled to make dried blood spots for TREC

quantitation using real-time PCR. Importantly TRECs are non-replicating and become diluted during T cell division. As a result, allogeneic cells, such as maternal cells, as well as autologous cells that may have undergone oligoclonal peripheral expansion, such as in Omenn syndrome, do not confound the TREC test.

Historically, SCID patients could be transplanted only if they had an HLA-identical sibling donor, and this is still the optimal treatment. Use of haploidentical parental donors for T cell-depleted SCID transplants without preconditioning made every SCID infant a candidate for transplantation treatment. While this has been life saving in many cases, long-term follow-up from a number of centers has revealed incomplete immune reconstitution of B cell function in the majority of patients, and some patients experience a waning immune repertoire associated with poor/undetectable myeloid engraftment. Chronic complications such as graft versus host disease with wasting and disseminated warts 10 to 20 years post-transplant have also been described. Conditioning has been advocated by some as a strategy to improve the rate of full donor chimerism, but outcome data currently are limited. Furthermore, the growth of unrelated donor registries has now made it possible to find excellent HLA-matched donors for most SCID patients. However, there is currently no consensus as to the most effective and uniformly safe protocols for infants whose metabolic immaturity may leave them at risk for toxicity from chemotherapy or who have a type of SCID associated with radiosensitivity. Indeed, a single conditioning protocol may not be best for all genotypes. Therefore, immunologic and genetic evaluations after a positive TREC test are critically important.

SCID has been called a medical emergency. It is critical to have infants with severe T cell impairment evaluated on an urgent basis and managed by an immunologist familiar with SCID. Although definitive treatment may not be instituted for several weeks, immediate intervention is to maintain the infant under close observation in an isolated environment, to avoid live vaccines, to prevent the use of non-irradiated blood, and to give immunoglobulin and prophylactic antibiotics to prevent *Pneumocystis* and other infections. In cases where there is no known family history of SCID, a stepwise process is begun toward a definitive diagnosis and treatment. A fresh sample for flow cytometry should be analyzed to enumerate the numbers of T cells, B cells, and NK cells, and for examining the distribution of naive/memory (e.g., CD45RA/RO) T cells. If the flow cytometry is abnormal, this is followed by referral to a pediatric immunologist. Further testing to specifically define the underlying defect may take months, and if a suitable family donor is not identified, securing an unrelated donor also takes time. Nevertheless, rapid definition of the type of immune deficiency is essential

Table I Current practices for specific settings

Issue	Jennifer Puck	Jack Routes	Alexandra Filipovich
Low TRECs in a premature infant	If a replicate is low, the baby is referred for flow cytometry.	TRECs are repeated until >37 weeks corrected gestational age; if low at that point, referral is made to an immunologist.	Reassessment when the baby reaches term.
The ideal time interval between a positive TREC result and a formal immunologic assessment	Under 2 weeks, less if TRECs are undetectable; a baby with low TRECs should not receive live vaccines.	Within 2 weeks. (The mean time from any abnormal TREC assay to flow cytometric evaluations in Wisconsin is about 7 days; if the TREC is zero; the mean time is 2 days.) If the TREC is zero, the family is cautioned to avoid sick contacts and isolate the baby.	2 weeks. The family should be cautioned to isolate and protect the baby
The ideal time between the definitive diagnosis of SCID and transplantation	2 weeks to 4 months. The workup is overseen by a designated Immunology Referral Center, which coordinates referral to a transplant center.	Once the diagnosis is established, a referral is made to a transplant center. The timing is dictated by donor availability.	3–6 months
If the gene defect is not known, is the transplant protocol modified to accommodate potential DNA repair defects?	Radiation sensitivity testing is available for all California SCID infants. DNA damaging conditioning regimens are particularly dangerous in patients with radiation-sensitive SCID.	Reduced intensity conditioning is preferred. Infants without a molecular diagnosis are tested for radiation sensitivity, although if clinically indicated, transplantation is not delayed based on the pending results.	Reduced intensity conditioning is preferred.

although the specific gene mutation is not required in most cases to begin a transplant protocol.

Not every infant with a positive SCID screen will require transplantation, however. Every population-based newborn screening test for a condition previously understood only from the perspective of clinical cases has revealed unexpected findings among individuals with abnormal screening results. The TREC assay has detected infants who have T lymphopenia but do not have classical SCID as defined by the Primary Immune Disease Treatment Consortium as <300 T cells/μL and <10% of normal PHA proliferative responses. Such T lymphocytopenic infants may have (1) leaky mutations in recognized SCID genes; (2) severe phenotypes associated with gene defects that generally cause less profound T cell deficiency, such as CHH, DOCK8, NEMO; or (3) variants of SCID with undetermined genetic cause. Since genotyping is slow, laborious, and expensive, and many rare disease genes are not sequenced in clinical labs, it is challenging to arrive at a molecular diagnosis for these infants. There are also infants with secondary T lymphocytopenia and with syndromes such as DiGeorge or CHARGE that can be associated with low T cells. Identification in the early weeks of life before any infectious complications have occurred provides important protection for the patient from the harm of infection but removes a critical element of the phenotype when it comes to establishing the need for transplantation therapy. The infant may thrive in good health, often with immunoglobulin and antibiotic treatments that potentially obscure the natural trajectory of the condition. In these uncharted waters, it is incumbent on the immunodeficiency experts caring for the infant to pursue lymphocyte functional studies while carefully following clinical exam and lab values over time. Transplantation outcomes in SCID are generally good, but fatalities occur, and transplantation should not be performed without demonstration of serious defects of lymphocyte function.

In Table I, the current practices for specific settings are detailed. This field is rapidly evolving, and as highlighted above, there are situations where the intervention strategy may not be well defined. These guidelines represent a forum for ongoing discussions and refinement.

Newborn Screening for Severe Combined Immunodeficiency Disorder

Secretary's Advisory Committee on Heritable Disorders in Newborns and Children

REPORT

Executive Summary

In January 2010, the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) recommended to the Secretary of the Department of Health and Human Services the addition of Severe Combined Immune Deficiency (SCID) to the Recommended Uniform Screening Panel.[1] The Secretary accepted the recommendation in May 2010 and requested that SACHDNC submit a report in May 2011 on the status of newborn screening for SCID.[2] This report summarizes the current status of screening newborns for SCID in state-based newborn screening programs and proposes next steps for implementation.

Newborn screening to identify and treat infants with SCID and to educate and support families, public health providers, and health care providers has been successfully piloted in the State and Territory newborn screening programs of California, Louisiana, Massachusetts, New York, Puerto Rico, and Wisconsin, and in the Navajo Nation. These pilot studies currently cover approximately 25 percent of births in the United States. To date, 961,925 newborns have been screened and 60 infants, or approximately 1 in 16,032, have been identified with some form of immune deficiency. Fourteen infants with SCID (~1 in 68,000) have been diagnosed and received treatment. No missed cases of SCID have come to the attention of the newborn screening programs conducting the pilots.

The combined State and Federal efforts to address SACHDNC recommendations represent a model of collaboration across HHS agencies, as well as among State public health newborn screening programs.

- Highly accurate molecular methods have been developed and validated.
- Model protocols for screening have been employed, including high-throughput, automated testing in States with a large number of births and screening offsite for States with a small number of births.
- An international database to assess laboratory performance and participation in a national quality assurance program enabled real-time quality improvement.
- Emerging findings from the pilots are advancing understanding of SCID and triggering new research efforts.
- The sharing of expertise and lessons learned facilitated the timely resolution of positive screens and refinement of the screening effort.

The tools and knowledge generated through the pilot studies will be available for ongoing collaborations as other states consider implementing newborn screening for immune deficiency. As screening for SCID continues and expands, collaboration between the Federal agencies and States will increase our understanding of immune deficiencies and improve our ability to identify and treat affected infants.

Introduction

In September 2007, Severe Combined Immune Deficiency (SCID) was nominated to the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) for addition to the Recommended Uniform Screening Panel (RUSP). An evidence review was undertaken and the evidence report was discussed by SACHDNC in February 2009. At that time, SACHDNC voted not to add SCID to the RUSP, noting specific gaps in evidence that should be addressed before SCID could be added to the RUSP: (1) prospective identification of at least one confirmed case of SCID through a population-based newborn screening program, (2) demonstrated willingness and capacity of additional states to implement newborn screening for SCID, (3) reproducibility of the screening test and continuance of a false positive rate of less than 0.1 percent, and (4) creation of a laboratory proficiency testing program through the Centers for Disease Control and Prevention's (CDC) National Quality Assurance Program. In January 2010, the nomination of SCID to the RUSP was again brought to SACHDNC. At that time, SACHDNC reviewed the activities undertaken to address the evidence gaps and voted to recommend to the Secretary of the Department of Health and Human Services (HHS) the addition of SCID to the RUSP and related T cell deficiencies to the list of secondary targets,[1] with the understanding that the following activities would take place in a timely manner:

1. The National Institutes of Health (NIH) shall fund surveillance activities to determine health outcomes of affected newborns with any T cell deficiency receiving treatment as a result of prospective newborn screening;

2. The Health Resources and Services Administration (HRSA) shall fund the development of appropriate education and training materials for families and public health and health care professionals relevant to the screening and treatment of SCID and related T cell deficiencies;

3. CDC shall develop and distribute to performing laboratories suitable dried blood spot specimens for quality control and quality assurance purposes.

In May 2010, the Secretary adopted the recommendation to add SCID as a core condition to the RUSP, and related T cell deficiencies to the list of secondary targets and requested that SACHDNC submit a report in May 2011 on the status of States' implementation of this recommendation, including surveillance activities conducted through the Newborn Screening Translational Research Network (NBSTRN).[2] This report summarizes the current status of screening newborns for Severe Combined Immunodeficiency (SCID) in State-based newborn screening programs, as requested by the Secretary in May 2010.

Background

Immunodeficiency disorders, including SCID, are characterized by the lack of a functioning immune system. Babies born with SCID appear healthy but are extremely vulnerable to infection. Exposure to common infections and live vaccines is life threatening. SCID leads to death in infancy unless treatment, usually stem cell transplantation, is provided.[3-4] Variations or "misspellings" in the DNA sequence of more than 13 different genes can cause SCID or a form of combined immunodeficiency. In most cases, the misspelling occurs in a newborn with no family history of SCID. Since SCID is not apparent at birth and early recognition is essential for lifesaving treatment, SCID has been recognized as a candidate for newborn bloodspot screening for many years.[5] However, no laboratory test for detecting SCID on newborn bloodspots was available until the current testing platform for screening for SCID was developed and validated for population-based screening by NIH in 2005.[6] This screening test detects SCID through the absence of a by-product normally generated during the development of the T cell, an important part of a functioning immune system. Since patients with SCID have few or no T cells, the absence of this by-product, T cell receptor excision circles (TRECs), identifies SCID regardless of the underlying genetic defect or DNA variation. The TREC test uses molecular methods to count the TRECs present in DNA isolated from dried blood spots. In 2005, the TREC test was brought to the attention of SACHDNC at its inaugural meeting, and SACHDNC monitored its development and testing.

SCID Newborn Screening Pilot Studies

In 2007, scientists in Wisconsin (State Laboratory of Hygiene and Medical College of Wisconsin) and the New England Newborn Screening Program of the University of Massachusetts Medical School both developed high throughput TREC assays to screen births in Wisconsin and Massachusetts on a trial basis.[7-8] In 2008, a partnership among the Wisconsin State Laboratory of Hygiene, Children's Hospital of Wisconsin and the Jeffrey Modell Foundation led to the first pilot study screening all births in a State. Federal funding from CDC was then made available to continue the pilot study in Wisconsin and to initiate a second statewide pilot in Massachusetts. These two CDC-funded pilots are scheduled to conclude in October 2011. A third pilot study at the University of California at San Francisco began in 2009 and is screening up to 2000 births at two Arizona hospitals on the Navajo reservation (the Navajo Nation has a high incidence of SCID).

The pilot studies in Wisconsin and Massachusetts led to screening and follow-up algorithms, created educational materials for families and health care providers, hosted multiple State training programs in use of the assay, and partnered with CDC in the development of proficiency materials that are now available to all State newborn screening programs.[9-10] Investigators from these three pilots presented their findings to SACHDNC in January 2010 and, at the time, reported they had successfully screened more than 200,000 newborns. Although no cases of classic SCID (total failure of the immune system) were found, they did identify infants with immunodeficiency disorders (SCID variant, partial failure of the immune system) that required medical intervention, documented the feasibility of screening for SCID, provided valuable information to SACHDNC, and paved the way for larger efforts.[11-12]

Expansion of SCID Newborn Screening Pilot Studies

To increase the likelihood of detecting classic SCID cases, NIH increased the screening sample size through a larger pilot project initiated in 2010 with Health Research, Inc. (HRI), a not-for-profit corporation affiliated with the New York State Department of Health. The NIH-funded project enabled HRI and collaborators to provide evidence for the feasibility of screening technologies and to expand SCID newborn screening pilot studies to four additional States and Territories: New York, California, Louisiana, and Puerto Rico. The NIH-funded research priorities for this project were to:

- Assess screening technologies for SCID,
- Establish immediate confirmatory tests and procedures for presumed positive results,
- Ensure capacity and resources for tracking positive cases and arrange for appropriate follow-up care and referral in a timely manner, and
- Verify administrative structures necessary for a prospective pilot testing of SCID, including ability to obtain approval for human subject research.

The NIH initiative enabled screening to begin in two States with a large number of births, New York (236,656) and California (510,000). In addition, ongoing screening efforts in Wisconsin expanded to include Louisiana and ongoing efforts in Massachusetts expanded to include Puerto Rico. The efforts in New York and California were also supported with funds from the Jeffrey Modell Foundation (New York and California) and from PerkinElmer, Inc. (California). Piloting SCID screening in States with a large number of births provided evidence that TREC screening is compatible with a high-throughput, automated environment. Sending samples for screening from Louisiana to Wisconsin and from Puerto Rico to Massachusetts established feasibility for a regional approach to SCID screening, while the ongoing screening in Wisconsin and Massachusetts provided information about screening over several years.

Development, Validation, and Quality Assessment of SCID Newborn Screening Technologies

Investigators in New York, California, Wisconsin, and Massachusetts each developed high-capacity assays based on the principles of the NIH-developed research assay.[6] These assays, called laboratory developed tests (LDTs), were developed and validated independently by each laboratory. While the Food and Drug Administration (FDA) currently does not regulate this class of *in vitro* diagnostics, each laboratory is regulated by the Centers for Medicare & Medicaid Services through the Clinical Laboratory Improvement Amendments (CLIA) Act.[13-14] To support the quality assurance measures required by CLIA, CDC provided dried blood spot reference materials for within-laboratory quality control and between-laboratory proficiency testing. As of April 2011, results obtained from 11 newborn screening laboratories, including all pilot labs (California, New York, Massachusetts, and Wisconsin), showed excellent analytic validity (how well the test predicts the presence or absence of TREC). The tests showed 100 percent sensitivity (how often the test results are positive when TRECs are present) and more than 99 percent specificity (how often the test results are negative when TRECs are not present) in discriminating abnormal from normal TREC content in the reference materials.

To collect, aggregate, and analyze de-identified screening data generated during the pilot, NIH provided a subcontract to the HRSA/Maternal and Child Health Bureau (MCHB)-funded

Laboratory Performance Program to develop a SCID data portal as an expansion of a HRSA/MCHB-funded Region 4 Regional Genetic and Newborn Screening Service Collaborative effort.[15] The subcontract was administered through the NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development's NBSTRN, which was established to provide infrastructure resources for research in newborn screening. Access to the SCID data portal is widely available to any State newborn screening program, clinician, or researcher around the world interested in learning about or contributing to the understanding of the performance of SCID newborn screening assays. The aggregation of laboratory performance data in real-time during a pilot represents a useful model of translating a novel genomic technology to a high-throughput public health setting while using the latest in language standardization and electronic information exchange.[16-17]

Interim Pilot Study Results

Through March 2011, SCID newborn screening has been piloted in six States and one Territory (Wisconsin, Massachusetts, New York, California, Louisiana, and Puerto Rico) and the Navajo Nation, covering approximately 25 percent of total births in the United States during this time period and totaling 126 months of continuous screening (Table 1 and Figure 1). In all, 961,925 newborns have been screened, 364 newborns had a positive screen requiring additional testing and resulting in 60 cases of diagnosed immune deficiency (Tables 1 and 2). Fourteen cases of classic SCID, six cases of SCID variant, and 40 cases of Non SCID have been identified, diagnosed, and treated (Table 1, Figure 2). All infants with immunodeficiency disorders identified through the pilot studies have received treatment and are being followed by appropriate health care teams. Almost 80% (11/14) of the SCID patients received bone marrow transplants and are currently between 1 month and 10 months post-transplant (Figure 3). The remaining 20% (3/14) are receiving enzyme replacement, a treatment option for one type of SCID, Adenosine Deaminase Deficiency (ADA). Additional information regarding health outcomes is being collected and will be reported at a later date.

Although the pilots are still in progress, there are emerging findings that are important to note.

- A zero TREC value consistently means that the infant is at significant risk for SCID or a profound T cell lymphopenia. Future investigations of this valuable biomarker will accelerate research in immunology.
- The incidence of SCID and T cell deficiencies appears to be higher than previously reported (Table 3). Past studies reported the incidence of SCID as 1 in 100,000, and the newborn screening pilots are finding a range of incidences from a high of 1 in 34,159 (New York) to a low of 1 in 161,707 (Massachusetts). Past estimates of Non SCID have been difficult since this category comprises a number of distinct disorders that average around 1 in 20,000 (Table 3, Figure 4). The pilots are finding a range of incidences from a high of 1 in 9,705 (Puerto Rico) to a low of 1 in 121,854 (Wisconsin).
- The number of boys versus girls diagnosed with SCID in the pilots is consistent with past studies (Table 5). Past studies found the majority of SCID cases were male (79%)[3] and New York and California found that six of the nine SCID cases (67%) are male.
- The number and type of SCID at a molecular level appears to be different than previously reported (Table 5). Past reporting of the molecular type of SCID found that 48% of cases

are X-linked (IL2RG mutation), making this the most common cause of SCID.[3] The pilots in New York and California completed the molecular studies for eight of the nine SCID cases and found 66% (7/8) are consistent with autosomal recessive inheritance (Table 5). X-linked SCID was found in one case or 11% of the total.

- The subpopulation variability of SCID and T cell deficiency patients appears to be different than previously reported (Tables 4 and 5). Past reporting of the race or ethnicity of SCID patients followed long-term found that the majority (81%) are Caucasian, 9% African American and 6% Hispanic.[3] The pilots in New York and California found that six of the nine (65%) SCID cases are Hispanic, 2 (22%) are African American, and 1 (11%) is Asian (Table 5).

The emerging findings raise important questions. Analysis of future data will help answer these questions. Although the New York, California, Louisiana, and Puerto Rico NIH-funded pilots end in June 2011, and the CDC-funded pilots in Massachusetts and Wisconsin end in October 2011, efforts to analyze the pilot findings will continue.

Efforts in Nonpilot States

State adoption of SACHDNC's recommendation is voluntary, and the rules and regulations governing the addition of a new screening test vary by State. Nonetheless, consideration of SCID newborn screening by States not involved in the pilots has been extensive. All State newborn screening programs were invited to participate in monthly calls in which the principal investigators from the pilot States discussed their experiences, reviewed data portal entries and answered questions. Currently one-third of States participate in these monthly calls. In October 2010, CDC, the Association of Public Health Laboratories, and the HRSA-funded National Newborn Screening and Genetics Resource Center hosted a meeting devoted to SCID newborn screening.[18] The meeting was attended by 192 laboratory technicians, follow-up professionals and immunologists from 48 States and three countries. In addition, laboratory scientists from 28 U.S. newborn screening programs attended a supplementary laboratory workshop.

To ascertain interest in SCID testing among non-participating States, the Immune Deficiency Foundation (IDF) and NBSTRN conducted a nationwide survey and found that all State programs have actively considered implementing SCID newborn screening (Figure 5).[19] One state (Pennsylvania) is screening a portion of births, and two states are conducting small pilots (Texas and Arizona). Ten States (Colorado, Delaware, Florida, Iowa, Illinois, Michigan, Minnesota, North Carolina, New Jersey and Rhode Island) and the District of Columbia have presented SCID screening to their State advisory boards and received approval to begin screening as soon as logistically possible. Once these States are actively screening, more than 50 percent of babies born in U.S. States and Territories will be screened for SCID.

Twenty-eight State newborn screening programs are in various stages of assessment of analytical platforms, cost analysis, development of infrastructure for referral and treatment services, and recruitment of necessary personnel (Figure 5). Four States work with a regional partner who performs the screening test and are dependent on the regional partner to begin screening. There have been no instances of State advisory boards choosing not to implement SCID screening to date. Sixteen States participate in a monthly conference call to share experiences and expertise.

A small number of States report they prefer or require an FDA cleared or approved kit to begin screening. IDF and NBSTRN will continue to monitor State implementation until all newborns in the United States are screened at birth for SCID.

Education Materials Relevant to Screening and Treatment of SCID and Related T Cell Deficiencies

To support families and to encourage the adoption of SCID newborn screening, IDF launched several efforts, including a Web page for parents, a SCID newborn screening toolkit for use by families to educate policymakers, and a brochure to warn providers about the dangers of administering the live rotavirus vaccine to infants with SCID.[20] The six pilot State newborn screening programs also created and distributed educational materials for the parents of newborns with a positive screen and/or a confirmed diagnosis.[21-24] To support primary care providers and facilitate timely diagnosis and treatment, HRSA/MCHB funded the development of SCID clinical decision support materials, or ACT sheets,[25] through its National Coordinating Center for the Regional Genetic and Newborn Screening Service Collaboratives. As SCID newborn screening adoption increases, a directory of clinical specialists in pediatric immunodeficiencies and related T cell deficiencies will be developed for use by newborn screening programs, families, and health care professionals.

Lessons Learned and Next Steps

Seventeen months after SACHDNC recommended screening all newborns in the United States for SCID and related T cell deficiencies, one-fourth of births are being screened through pilot programs funded by multiple Federal and State agencies and private foundations. Most States have begun active consideration of SCID newborn screening, and several more States are planning to begin screening in the near future. In January 2011, IDF reported to SACHDNC several issues that may be delaying the implementation of SCID screening, including lack of cost benefit information, budgetary concerns (cost estimates for technology infrastructure estimated at $500,000–$1 million), prior commitment to implement other screening tests mandated by State legislation, lack of the widespread availability of experts in immunodeficiency within a State for diagnosis and treatment, and lack of an FDA-approved or -cleared assay.

NIH and CDC will continue to support the adoption of SCID newborn screening through ongoing efforts including technical assistance, publication of pilot project results, screening and follow-up protocols, creation of a long-term follow-up dataset to determine impact of screening on health outcomes, and creation of an expert work group to refine screening, diagnosis and treatment protocols and guidelines. CDC recently announced an opportunity to fund up to two newborn screening programs that had not yet implemented SCID screening before January 2011.[26] The NIH-funded Primary Immune Deficiency Treatment Consortium is working to identify factors, including early identification through newborn screening, that influence health outcomes in patients with immune deficiencies.[27]

In conclusion, the recommendation by SACHDNC to begin screening for SCID has almost certainly saved lives. In addition, the screening program has improved scientific understanding of immune deficiencies, including the molecular etiology and racial and ethnic distributions of molecular subtypes; expanded clinical knowledge of the care and treatment of SCID; and

emphasized the relevance of early diagnosis and intervention. The recommendation has also been a triggering event for the majority of State newborn screening programs to implement or start the process to implement newborn screening for SCID. Screening for SCID represents the largest expansion of newborn screening since the advent of tandem mass spectroscopy a decade ago and the RUSP five years ago. SCID screening is a DNA-based molecular test and State newborn screening programs will develop expertise in DNA-based technologies and/or create networks to share existing regional expertise to implement screening for SCID or DNA-based screening for other disorders. Both approaches to SCID screening establish valuable infrastructure, health information exchange and expertise within the State Newborn Screening Programs, and will be leveraged for future expansions of the RUSP.

The activities recommended by SACHDNC fostered collaboration among HHS agencies and enabled each agency to focus on their areas of expertise while sharing tools and infrastructure resources with stakeholders in public health and clinical health care teams. Highlights from this teamwork are

- Quality control and improvement materials to ensure accurate tests distributed by CDC to the pilot states;
- Clinical decision support tools supported by HRSA (ACT sheets) to guide infants' health care providers; and
- Expanded pilots and databases enabling the diagnosis, treatment, and long-term follow-up of SCID cases contracted by NIH.

This report on State implementation efforts affirms SACHDNC's system of evidence-based review of conditions nominated for addition to the RUSP and subsequent recommendations to begin newborn screening for nominated disorders and lays an effective foundation for future efforts to improve the health of newborns.[28-29]

Table 1. Summary of Pilots

State	Start of Screening	Number of Months Screening	Annual Births or Number Studied	Number of Infants Screened as of April 30, 2011	SCID[a]	SCID Variant[b]	Non SCID[c]
WI	1/1/2008	40	69,232	243,707	4	0	7
MA	2/1/2009	27	77,022	161,707	1	0	14
Navajo Nation	2/1/2009	27	2,000	1,297	0	0	0
NY	9/30/2010	7	236,656	136,635	4	0	12
CA	8/1/2010	9	510,000	358,000	5	6	3
PR	8/1/2010	9	45,620	29,115	0*	0	3
LA	10/1/2010	7	65,268	31,464	0	0	1
	Total	126	1,005,798	961,925	14	6	40

*One infant with suspected SCID expired before diagnosis confirmed.

a. SCID: Deleterious mutation in the DNA of one of the following genes, resulting in total failure of normal function of the protein encoded by that gene, whether IL2RG, JAK3, IL-7Ra, RAG-1, RAG-2, ADA, CD45, Artemis/DCLRE1C, CD3δ, CD3ε, CD3ζ, DNA PKc, or DNA Ligase IV. These proteins are crucial to the normal development of lymphocytes; therefore, any defect in one of these genes will result in a significant problem with immune function and associated susceptibility to infection. AKT2 defects, which cause severe lymphopenia and granulocytopenia, may have low TRECs but also poor amplification of peripheral blood DNA due to low numbers of nucleated blood cells. Patients with SCID have fewer than 300 autologous T cells per mL of blood, and their proliferative responses to the mitogen PHA are less than 10 percent of normal control responses. Some SCID patients do not have defects in any of the above genes, suggesting that additional disease genes for SCID remain to be discovered.

b. SCID variant: Variation in the DNA of one of the following genes resulting in impairment of functioning of the protein encoded by that gene. Also known as “leaky SCID”; Combined Immunodeficiency (CID); or Omenn syndrome, a particular clinical entity with skin rash, eosinophilia, and T cells that represent expansion of a restricted thymic output. CID and Omenn syndrome may be due to hypomorphic variations in the above SCID genes or may be caused by defects in genes such as PNP, AK2, Cernunnos, Coronin-1A, RMRP, or WHN/FOXN1. In addition, there are SCID variant patients s for whom defects in known genes are not found.

c. Non-SCID: Other defects either related directly to a component of the immune system with an associated malfunction or related to the loss of a section of DNA (e.g., DiGeorge syndrome, Jacobsen syndrome) or, in some cases, abnormal gain of DNA (e.g., Down syndrome/trisomy 21). Multisystem syndromes may be associated with variable severity of defects in immune function along with other serious health problems, including heart defects and developmental delay. The non-SCID category is a mixed group and includes individuals with a variety of genetic defects as well as infants who have poorly developed immune systems due to premature birth. Lymphopenia of prematurity, idiopathic T cell lymphopenia, DiGeorge syndrome/del(22)(q11.2), CHARGE syndrome, Jacobsen syndrome/del(11)(q24.1-11qter), Down syndrome/trisomy21, thymectomy, and RAC2 deficiency may be associated with low or undetectable TRECs in some cases. There are additional defects of cellular immunity, including CD25 and ataxia telangiectasia, in which TRECs may or may not be abnormal. There are insufficient data at this time to predict whether these conditions may be detected by TREC newborn screening. In addition, there are many non-SCID immunodeficient patients for whom a genetic cause is not found.

Note: In many T cell immunodeficiencies, the best treatment may be either hematopoietic stem cell transplantation or thymus transplantation because these infants are susceptible to life-threatening infections, as are the classic SCID and SCID variant babies. The confirmatory tests used to follow up babies with abnormal newborn screen results, along with additional specialized immune testing, can help the pediatric immunologist to make decisions regarding the severity of immune dysfunction and the need for transplantation for these infants. These infants would not be picked up without newborn screening, and they are often in just as much need of significant treatment as the more well recognized SCID babies. In addition, some babies require supportive care with intravenous immunoglobulin (IV IgG) and antibiotics, even when a transplant is not needed.

Table 2. Number of Negative and Positive Screens by State

Screening Result	State							Total Screened
	WI	MA	Navajo Nation	New York	California	Puerto Rico	Louisiana	
Negative[a]	243,657	161,679	1,296	136,412	357,954	29,107	31,456	961,561
Positive[b]	50	28	1	223	46	8	8	364
Total Screened	243,707	161,707	1,297	136,635	358,000	29,115	31,464	961,925

a Negative: TREC copy number above cut-off point. No further analysis needed.
b Positive: TREC copy number below cut-off point. Case referred for confirmatory diagnostic studies.

Table 3. Incidence of SCID, SCID Variant and Non SCID by State

Diagnosis	Incidence	State					
		WI	MA	NY	CA	Puerto Rico	Louisiana
SCID		1 in 60,927	1 in 161,707	1 in 34,159	1 in 76,500	NA	NA
SCID Variant		NA	NA	NA	1 in 76,500	NA	NA
Non SCID		1 in 121,854	1 in 11,551	1 in 11,386	1 in 76,500	1 in 9,705	1 in 31,464

Table 4. California Incidence in the First Six Months of Screening

Diagnostic Category	Race or Ethnicity	Incidence Rate	95% Confidence Intervals	
			Lower	Upper
SCID	All	1 in 33,000	1 in 20,000	1 in 65,000
SCID	Hispanic Only	1 in 22,000	1 in 9,000	1 in 40,000
All Related T-cell Lymphocyte Deficiencies	All	1 in 22,000	1 in 13, 300	1 in 35,000

Table 5. Clinical Characteristics of Nine SCID Cases in New York and California Pilots

Characteristic		Number of SCID Cases (%)
Sex	Male	6 (67%)
	Female	3 (33%)
Molecular Type of SCID*	Autosomal Recessive (IL-7Ra)	2 (22%)
	Autosomal Recessive (RAG-1)	2 (22%)
	Autosomal Recessive (ADA)	2 (22%)
	X-Linked (IL2RG)	1 (11%)
Race or ethnicity	Hispanic	6 (67%)
	African American	2 (22%)
	Asian	1 (11%)

*Molecular typing on one case is pending.

Figure 1.Timeline of SCID Newborn Screening Pilots

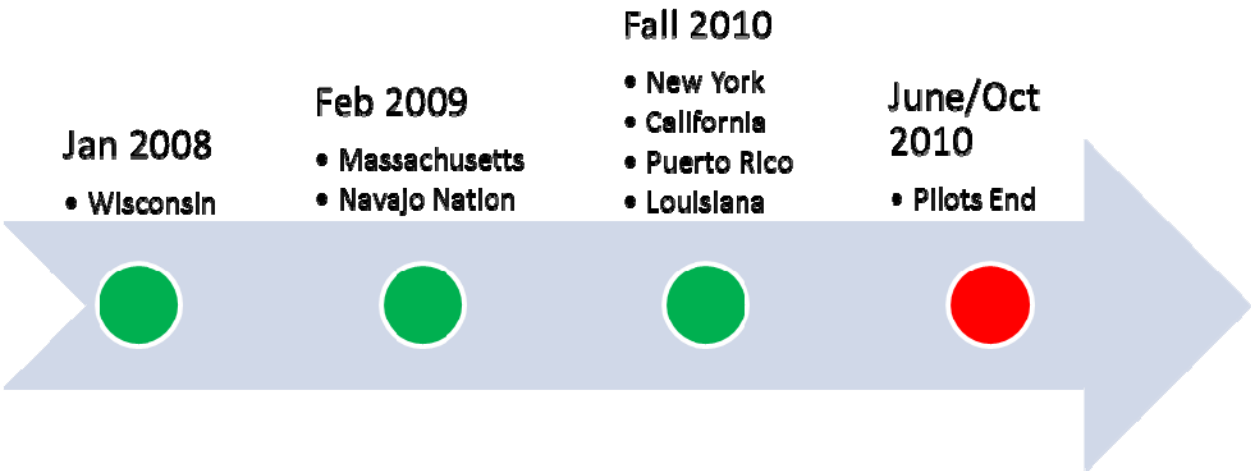


Figure 2: Cumulative Number of Newborns Screened and SCID Cases Diagnosed

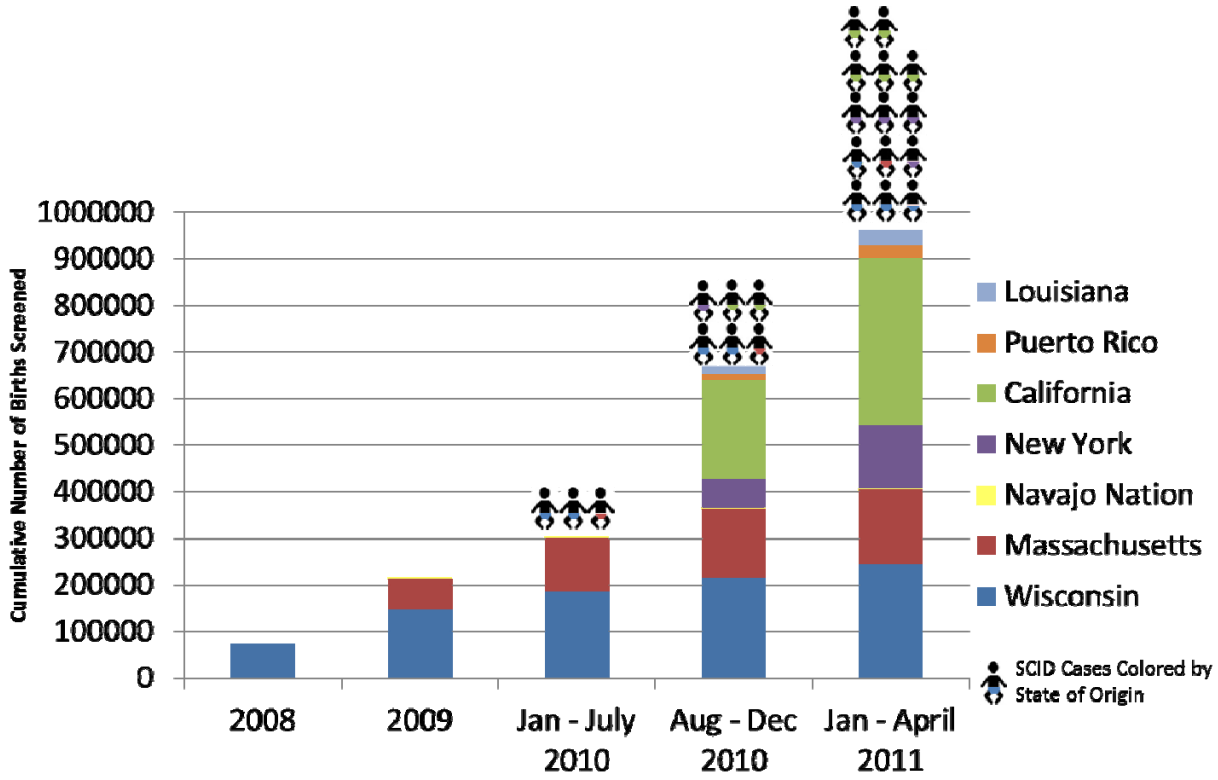


Figure 3: Type of Treatment for SCID Cases (N=14) in All Pilots

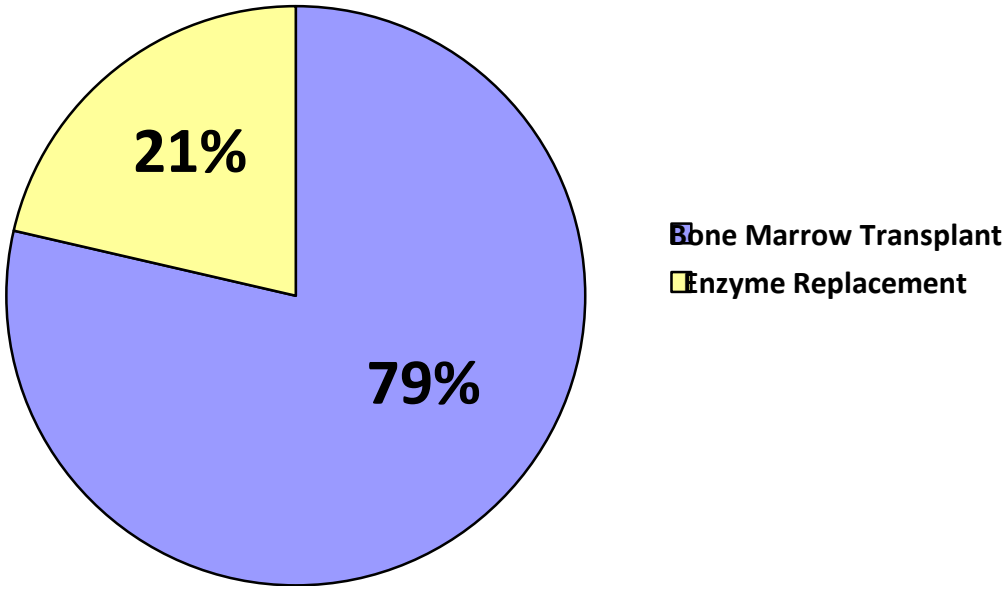


Figure 4: Diagnosis for Non SCID Cases for All Pilots (N=40)

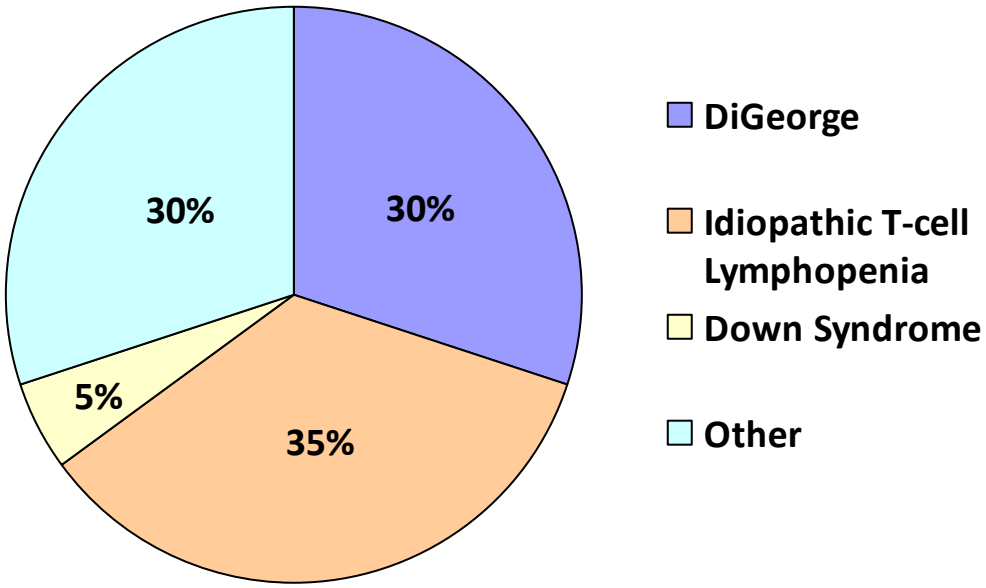
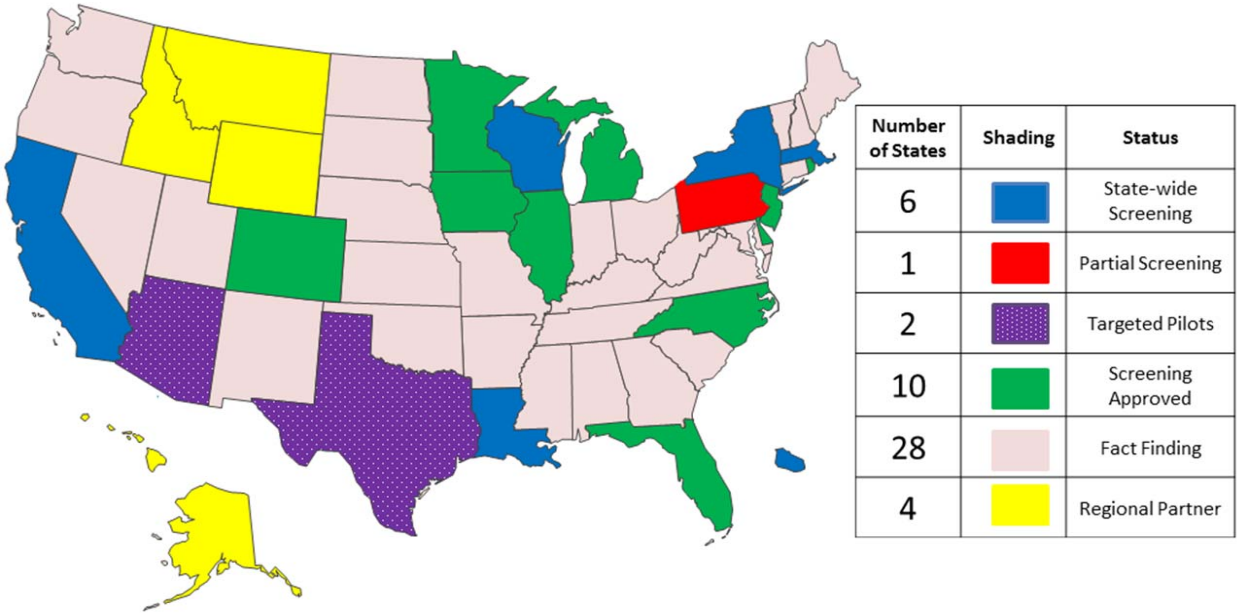


Figure 5. Map of Newborn Screening for SCID Implementation Status



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Guide to the Newborn Screening Cost-Benefit Model for Adding Severe Combined Immunodeficiency (SCID)

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Introduction

Severe combined immunodeficiency (SCID) is a deadly immune system disorder and is a candidate for adding to the mandatory newborn screening panel. One of the SBOH criteria for prospective conditions is evaluating the benefits and the costs of adding screening. Newborn screening staff researched the primary literature, reports from states already screening for SCID and consulted with expert immunologists while preparing the following cost-benefit analysis. The accompanying spreadsheet is the medical model for comparing the status quo, or a "No Screening Model" (upper section) with the SCID "Newborn Screening Model" (lower section). The model predicts a benefit-cost ratio of 4.93, meaning that for every dollar of costs to screen newborns for SCID, there will be almost $5 worth of benefits.

Model Parameters

This narrative describes the estimates for the parameters in the models. First, we chose numbers for the base case: if we had several estimates from the published data, we either used an average or the middle value. Following the base case is a sensitivity analysis that varies the parameters to give what we judge to be very conservative and moderately liberal estimates of the benefit-cost ratio. Note: the spreadsheet calculates the percentages and estimates, which have in some instances been rounded for simplicity. Subsequent calculations are unaffected by this rounding, so sometimes the numbers appear to not match perfectly.

- ***Birthrate.*** This analysis is for a hypothetical birth cohort of **90,000 babies** (cells B10 and B37) which is the average number of babies expected to be screened per year in Washington State between 2013 and 2018. This number is based on estimates published in the *November 2011 Components of April 1 Population Change* by the Washington State Office of Financial Management, Forecasting Division (OFM 2011).
- ***Prevalence.*** The prevalence used was **1 SCID case per 49,827 births** (cells D10 and D28) which is the prevalence found among 1,345,341 babies tested for SCID by four newborn screening programs (Baker 2011, Caggana 2011, Comeau 2011, Lorey 2012). This predicts 1.81 babies born with SCID in Washington each year.
- ***Percent of babies with SCID with a positive family history of SCID.*** These babies will be treated early in the "No Screening Model" because of a positive family history of SCID (mostly an older affected sibling). The estimate for this parameter (**20.3%** - cell G5) was the middle value of three reported in the literature (Chan 2011, also Hague 1994 and Myers 2002). These babies are assumed to derive the same benefits of early treatment that babies screened at birth would enjoy (better survival rate and lower treatment costs).
- ***Sensitivity.*** The sensitivity, or the ability of the screen to correctly identify babies with SCID, is estimated at **93.8%** (cell G25). This is a conservative estimate as there have been no known cases of SCID missed by newborn screening programs (zero false negatives). The estimate used is the mid-point of the 95% binomial confidence interval calculated from 27 reported cases (Baker 2011, Caggana 2011, Comeau 2011, Lorey

2012) with no false negatives (27 screening successes for the 27 cases). This sensitivity value predicts 1.69 true positives identified early and 0.11 false negatives (missed cases of SCID) per year.

- ***Specificity.*** The specificity, or the ability of the screen to correctly identify babies who do not have SCID, is estimated at **99.983%** (cell G47). The value used is the average of specificities from Wisconsin and Massachusetts (Baker 2011 and Comeau 2011). The specificity from New York was not used because the program changed cutoffs twice post implementation to reduce the number of false positives. Data from California did not include false positives; therefore no specificity calculation was possible. This specificity value predicts 15.2 false positives per year: these are babies who need diagnostic testing called flow cytometry, and sometimes clinical follow-up for other forms of immune deficiency (they do not have SCID).
- ***Mortality of cases identified early.*** The numbers used for mortality (**8.6%** - cells J3 and J23) is data compiled from Duke University and the two transplant centers in the UK regarding survival rates of babies with SCID. This estimate is the percent survival of 81 babies with SCID who received early transplants prior to 28 days of age (Myers 2002) or had an older sibling diagnosed with SCID (Brown 2011). This percentage is used in both models and predicts 0.03 deaths in the "No Screening Model" and 0.15 deaths in the "Screening Model" among the babies treated early. Recent publications from Duke University reported a 6.1% mortality rate for 48 babies with treatment prior to 3.5 months of life (Buckley 2012 and Buckley 2010).
- ***Mortality of cases identified late.*** The numbers used for mortality (**37.5%** - cells J13 and J32) is data compiled from Duke University and the two transplant centers in the UK regarding survival rates of babies with SCID. This estimate is the percent survival of 144 babies with SCID who received transplants after 28 days of age (Myers 2002) or were probands, meaning the first in their family diagnosed with SCID (Brown 2011). This percentage is used in both models and predicts 0.54 deaths in the "No Screening Model" and 0.04 deaths in the "Screening Model" among the babies who were treated later. Recent data from Duke University show a mortality rate for 118 babies treated after 3.5 months of life of 31.4% (Buckley 2010).
- ***Monetary value of a life.*** The value of one life saved is estimated at **$ 7.7 million** (cell Q35). This is the average of estimates used by three Federal Agencies in 2010 (Appelbaum 2011): Environmental Protection Agency ($9.1 million), Food and Drug Administration ($7.9 million) and the Transportation Department ($6.1 million).
- ***Difference in treatment costs: early v. late treatment.*** The cost difference between early v. late treatment is estimated at **$ 350,000/baby** (cell H18 subtract cell H8). This data comes from Dr. Rebecca Buckley's data on cost of treatments of the two cohorts (Buckley 2012).

The next step is to evaluate the differences between the models to quantify the benefits of screening. This is done by combining the mortality estimates and assigning a dollar value to deaths avoided and the difference in treatment costs.

- ***Deaths averted.*** The total number of deaths for each model are compared; there are 0.57 deaths (cell Q2) predicted in the "No Screening Model" and 0.19 deaths (cell Q22) in the "Newborn Screening Model." The "No Screening Model" has three times the mortality rate of the "Newborn Screening Model." The difference between the two models is **0.38 deaths averted** (cell Q34). This means that approximately one baby every three years will not die because of early treatment afforded by newborn screening.
- ***Value of lives saved.*** The value of lives saved by newborn screening is the number of deaths averted multiplied by the monetary value of a life. The model estimates yearly benefits of **$ 2.9 million** (cell Q36) for saving lives of babies with SCID.

- ***Shift in treatment costs.*** The early and late treatment costs for each model are calculated and combined to determine the costs of treatment in each model (**No Screening = $ 685,000**, cell Q6; **NBS = $ 220,000**, cell Q26). The annual treatment costs saved by screening (**$ 465,000**, cell Q37) are the difference between these totals.
- ***Total benefits.*** The total benefits (**$ 3.4 million**, cell Q38) are the sum of the value of lives saved and the treatment cost saved by screening.

Costs are estimated next.

- ***Cost of screening.*** The estimated costs of TREC analysis are **$ 7.10 per baby** (cell B40).
- ***Costs of clinical care and diagnostic testing for false positives.*** Only the false positive babies are counted for diagnostic testing costs because the babies with SCID will have clinical evaluation and diagnostic flow cytometry testing regardless. Based on discussion during the advisory committee meeting, we looked carefully into potential costs for babies that have abnormal TREC screening but do not have SCID. We consulted with Dr. Skoda-Smith and the team of immunologists for treatment and cost estimates, which included additional diagnostic testing, clinic visits and prophylactic antibiotics. The false positives fall into three categories with the following estimated costs (data not included on spreadsheet):
    - Transient: 0.77 babies/year costing $3,370/baby (1 year follow-up).
    - Idiopathic: 2.42 babies/year costing $8,570/baby (5 year follow-up).
    - Other: 3.45 babies/year costing $8,570/baby (5 year follow-up).

  Please note: Ideally, we would also include the benefits to the babies of early identification for these infants. However, we lack sufficient data to adequately estimate their value. The benefits include: not administering live virus vaccinations (the live virus can cause dangerous infections in babies with impaired immune systems), avoiding resource-intensive diagnostic odysseys, and preventing infections that could range from chronic to severe, even life threatening.

- ***Total costs for SCID newborn screening.*** The birthrate multiplied by cost per baby is **$ 639,000** (cell Q41).
- ***Total costs for clinical care and diagnostic testing of false positives.*** The total cost per year for the false positive cases outlined above is **$52,900** (cell H42)
- ***Total costs of Newborn Screening Model.*** The annual costs of NBS for SCID are estimated to be **$ 692,000** (cellQ43).

Finally, the ratio of benefits to cost is calculated. Any ratio greater than 1 signifies that the benefits outweigh the costs.

- ***Benefit/Cost Ratio.*** $ 3.2 million of benefits divided by $ 692,000 of costs yields a benefit/cost ratio of **4.93** (cell Q47).

After completing the base case benefit-cost ratio, we performed a sensitivity analysis to evaluate how the benefit-cost ratio changes when estimates for the parameters are varied.

- ***Sensitivity Analysis.*** Table 1 contains three estimates for each parameter, the best guess estimate used in the base case followed by conservative and liberal estimates. Only one parameter was changed at a time to generate unique benefit/cost ratios for each of the scenarios. The only exception is that the parameters for

mortality of early versus late identification were varied together to achieve a larger difference between the conservative and liberal estimates.

Table 1

Parameter	Base Case	Conservative Estimate	Liberal Estimate	B/C Ratio Swing
Prevalence	~1:49,000	~1:71,000	~1:37,000	3.45 to 6.68
% early ID – family history of SCID	20.3%	28.9%	17.9%	4.35 to 5.09
Sensitivity	93.8%	86.7%	100%	4.51 to 5.35
Specificity	99.983%	99.886%	99.986	3.44 to 5.00
Mortality – early ID	8.6%	10.0%	4.8%	3.04 to 8.89
Mortality – late ID	37.5%	26.0%	60.4%	
Monetary value of a life	$ 7.7 million	$ 6.1 million	$ 9.1 million	4.05 to 5.71
Δ in treatment costs: early v. late tx	$ 350,000	$ 0	$ 475,000	4.26 to 5.17

- ***Break Even Points.*** Table 2 contains the break-even point for each parameter. This is what the estimate would need to be, holding all other parameters constant, to reduce the favorable benefit/cost ratio to 1 (meaning it is no longer beneficial).

Table 2

Parameter	Base Case	Break-Even Point
Prevalence	~1:49,000	1:245,000
% early ID – family history of SCID	20.3%	78.9%
Sensitivity	93.8%	35.1%
Specificity	99.983%	99.112%
Mortality – early ID	8.6%	35.2%
Mortality – late ID	37.5%	10.9%
Monetary value of a life	$ 7.7 million	$ 600,000
Δ in treatment costs: early v. late tx	$ 350,000	- $ 1,700,000 (early tx would need to cost more than late tx)
Cost of NBS (per baby)	$ 7.10	$37.40

Conclusion

Early identification of babies with SCID is critical to their health. The mortality rate is greatly reduced with early treatment and medical costs are dramatically lower compared to babies treated after becoming symptomatic (the last baby born with SCID in California prior to starting screening generated more than $4 million in medical bills) (Puck 2012). This analysis used data from the first four newborn screening programs to begin testing for SCID to predict the medical outcomes for a hypothetical birth cohort of Washington babies. We used data from the primary literature and expert opinion to quantify the costs and benefits of treatment for babies with early and late treatment. The benefit-cost ratio was 4.93, meaning that for every dollar of costs to provide SCID screening, there

will be $4.93 worth of benefits. The sensitivity analysis showed that the model is robust because the benefit-cost ratio did not change much when more conservative or liberal estimates for parameters were made in the model.

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WA State Cost-Benefit Analysis for adding NBS for SCID

	A	B	C	D	E	F	G	H	I	J	K	L	N	O	P	Q
1																
2	**No Screening Model**			*rate*			*rate*			*rate*	death			No Screening	deaths	0.57
3										*0.086*	**0.03**				surviving	1.23
4								early ID - family hx							early tx costs	$ 36,581.94
5							*0.203*	**0.37**							late tx costs	$ 648,186.33
6											surviving				total tx costs	$ 684,768.27
7								early tx cost/baby		*0.914*	**0.33**					
8								$ 100,000.00								
9		Birthrate		Prevalence	# SCID											
10		**90,000**		*0.0000201*	**1.81**											
11			1 in:	49,827												
12											death					
13										*0.375*	**0.54**					
14								late ID - clinical sx								
15							*0.797*	**1.44**								
16											surviving					
17								late tx cost/baby		*0.625*	**0.90**					
18								$ 450,000.00								
19																
21																
22	**Newborn Screening Model**			*rate*			*rate*			*rate*	death			Screening	deaths	0.19
23										*0.086*	**0.15**				surviving	1.62
24							Sensitivity	early ID - true (+)							early tx costs	$ 169,370.52
25							*0.938*	**1.69**							late tx costs	$ 50,637.76
26											surviving				total tx costs	$ 220,008.27
27				Prevalence	# SCID			early tx cost/baby		*0.914*	**1.55**					
28				*0.0000201*	**1.81**			$ 100,000.00								
29			1 in:	49,827												
30																
31											death					
32								late ID - false (-)		*0.375*	**0.04**					
33							*0.062*	**0.11**						SHIFT		
34														Benefits	deaths averted	0.38
35								late tx cost/baby			surviving				value of a life	$ 7,700,000.00
36		Birthrate						$ 450,000.00		*0.625*	**0.07**				value of lives saved	$ 2,947,812.03
37		**90,000**													less tx costs	$ 464,760.00
38															TOTAL benefits	$ 3,412,572.03
39		cost per baby						false (+)								
40		$ 7.10					*0.00017*	15.2								
41					unaffected									Costs	costs of screening	$ 639,000.00
42				*0.9999799*	**89998.19**			cost of dx test							costs: false(+) dx	$ 52,881.66
43								$ 250.00							TOTAL costs	$ 691,881.66
44																
45																
46							Specificity	true (-)								
47							*0.99983*	89983.0							Benefit/Cost ratio	4.93

DRAFT - 5/23/2012