Arizona Department of Health Services

Meeting Notice

Newborn Screening Advisory Committee
Meeting Notice and Agenda
Wednesday, September 24, 2014

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 September 24, 2014 from 3:00 p.m. until 5:00 p.m., at the Arizona Department of Health Services, 150 North 18th Avenue, Fourth Floor ALS Training Room.

The agenda for the meeting is as follows:

I. Call to Order, Welcome and Introductions (Director Will Humble)
II. NBS Transit Time Project Update
III. Proposed Panel Additions – Discussion
   a. Severe Combined Immune Deficiencies (SCID)
   b. Krabbe Disease
IV. 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.
V. Committee Recommendations Vote
VI. NBS Rulemaking Update
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 15th day of September, 2014.

ARIZONA DEPARTMENT OF HEALTH SERVICES

Ward B. Jacox
Acting Chief, Office of Newborn Screening

Senate Engrossed House Bill

State of Arizona
House of Representatives
Fifty-first Legislature
Second Regular Session
2014

CHAPTER 171

HOUSE BILL 2491

AN ACT

AMENDING SECTION 36-694, ARIZONA REVISED STATUTES; RELATING TO CHILD HEALTH.

(TEXT OF BILL BEGINS ON NEXT PAGE)

Be it enacted by the Legislature of the State of Arizona:

Section 1. Section 36-694, Arizona Revised Statutes, is amended to read:

36-694. Report of blood tests; newborn screening program; committee; fee; definitions

A. When a birth or stillbirth is reported, the attending physician or other person required to make a report of the birth shall state on the certificate whether a blood test for syphilis was made on a specimen of blood taken from the woman who bore the child or from the umbilical cord at delivery, as required by section 36-693, and the approximate date when the specimen was taken.

B. When a birth is reported the attending physician or person who is required to make a report on the birth shall order or cause to be ordered tests for certain congenital disorders, INCLUDING HEARING DISORDERS. The results of tests for these disorders must be reported to the department of health services. The department of health services shall specify in rule the disorders, the process for collecting and submitting specimens and the reporting requirements for test results.

C. When a hearing test is performed on a newborn, the initial hearing test results and any subsequent hearing test results must be reported to the department of health services as prescribed by department rules.

D. The director of the department of health services shall establish a newborn screening program within the department to ensure that the testing for congenital disorders and the reporting of hearing test results required by this section are conducted in an effective and efficient manner. The newborn screening program shall include an education program for the general public, the medical community, parents and professional groups. The director shall designate the state laboratory as the only testing facility for the program, EXCEPT THAT THE DIRECTOR MAY DESIGNATE OTHER LABORATORY TESTING FACILITIES FOR CONDITIONS OR TESTS ADDED TO THE NEWBORN SCREENING PROGRAM ON OR AFTER THE EFFECTIVE DATE OF THIS AMENDMENT TO THIS SECTION. IF THE DIRECTOR DESIGNATES ANOTHER LABORATORY TESTING FACILITY FOR ANY CONDITION OR TEST, THE DIRECTOR SHALL REQUIRE THE FACILITY TO FOLLOW ALL OF THE PRIVACY AND SAMPLE DESTRUCTION TIMEFRAMES THAT ARE REQUIRED OF THE STATE LABORATORY.

E. The newborn screening program shall establish and maintain a central database of newborns and infants who are tested for hearing loss and congenital disorders that includes information required in rule. Test results are confidential subject to the disclosure provisions of sections 12-2801 and 12-2802.

F. If tests conducted pursuant to this section indicate that a newborn or infant may have a hearing loss or a congenital disorder, the screening program shall provide follow-up services to encourage the child's family to access evaluation services, specialty care and early intervention services.

G. The director shall establish a committee to provide recommendations and advice to the department on at least an annual basis regarding tests that

the committee believes should be included in the newborn screening program. Any recommendation by the committee that a test be added to the newborn screening program shall be accompanied by a cost-benefit analysis.

H. The committee shall include the following members who are appointed by the director and who serve without compensation or reimbursement of expenses at the pleasure of the director:

1. Seven physicians who are licensed pursuant to title 32, chapter 13 or 17 and who represent the medical specialties of endocrinology, pediatrics, neonatology, family practice, otology and obstetrics.

2. A neonatal nurse practitioner who is licensed and certified pursuant to title 32, chapter 15.

3. An audiologist who is licensed pursuant to chapter 17, article 4 of this title.

4. A representative of an agency that provides services under part C of the individuals with disabilities education act.

5. At least one parent of a child with a hearing loss or a congenital disorder.

6. A representative from the insurance industry familiar with health care reimbursement issues.

7. The director of the Arizona health care cost containment system administration or the director's designee.

8. A representative of the hospital or health care industry.

I. The director may establish by rule a fee that the department may collect for operation of the newborn screening program, including contracting for the testing pursuant to this section. The fee for the first specimen and hearing test shall not exceed thirty dollars.

J. For the purposes of this section:

1. "Infant" means a child who is twenty-nine days of age to two years of age.

2. "Newborn" means a child who is not more than twenty-eight days of age.

Sec. 2. Department of health services; newborn screening program; rulemaking; exemption

A. On or before July 1, 2015, the department of health services shall adopt rules regarding the newborn screening program that require the physician or person who is required to make a report on the birth to order or cause to be ordered critical congenital heart defect screening using pulse oximetry on each newborn delivered before discharging the newborn and to report the results of the critical congenital heart defect screening to the department of health services as specified in rule.

B. The department of health services may adopt rules regarding adding severe combined immunodeficiency testing and krabbe disease testing to the newborn screening program established pursuant to section 36-694, Arizona Revised Statutes, as amended by this act. The department shall perform and

consider a cost benefit analysis and seek stakeholder input, including input from health care providers, in the development of these rules.

C. For the purposes of implementing this act, the department of health services is exempt from the rulemaking requirements of title 41, chapter 6, Arizona Revised Statutes, through July 1, 2015, except that the department shall provide public notice and an opportunity for public comment on proposed rules at least thirty days before a rule is adopted or amended.

Sec. 3. Department of health services; vaccine financing and availability advisory committee; report

A. The department of health services shall establish a vaccine financing and availability advisory committee to study the financing and availability of vaccines for newborns, children and adolescents.

B. The director of the department of health services shall serve as chairperson of the committee and shall appoint the following members:

1. Two members who are representatives of different health care insurers that are licensed pursuant to title 20, Arizona Revised Statutes, and that offer products in the commercial market that include coverage for newborn, childhood and adolescent vaccines.

2. Three health professionals who are licensed pursuant to title 32, Arizona Revised Statutes, whose current practice includes administering newborn or childhood and adolescent vaccines as follows:

(a) A physician who is licensed pursuant to title 32, chapter 13 or 17, Arizona Revised Statutes and who specializes in pediatrics.

(b) A physician who is licensed pursuant to title 32, chapter 13 or 17, Arizona Revised Statutes and who specializes in family medicine.

(c) A nurse practitioner who is licensed and certified pursuant to title 32, chapter 15, Arizona Revised Statutes.

3. Two directors of local health departments one of whom shall be from a county having a population of at least three million persons.

4. One member who is a representative of an Arizona nonprofit statewide coalition whose mission is to foster a comprehensive, sustained community program for the immunization of residents of this state against vaccine-preventable diseases.

5. One member who is a representative of a vaccine manufacturer or a national association of vaccine manufacturers and who has experience in vaccine policy.

6. One member who is a representative of a statewide association of pharmacists.

7. One member who is a representative of an Arizona company that is not a health care insurer or a self-insured employer and that offers its employees a health insurance product in the commercial market that includes coverage for newborn, childhood and adolescent vaccines.

C. The directors of the Arizona health care cost containment system administration and the department of insurance, or their designees, shall serve as nonvoting members of the committee.

D. Committee members are not eligible to receive compensation or reimbursement of expenses.

E. The committee shall develop recommendations regarding the following and submit a written report of its findings on or before December 15, 2014, to the governor, the president of the senate and the speaker of the house of representatives and shall provide a copy of this report to the secretary of state:

1. The existing system of the financing, storage, distribution and availability of newborn, childhood and adolescent vaccine products and the potential impacts on the health care system, taxpayers and the community at large.

2. The costs associated with, and the adequacy of reimbursement levels for newborn, childhood and adolescent vaccines administered by private and public providers in all counties in this state.

3. The vaccine financing, storage, distribution and reimbursement models utilized in other states.

F. To the extent possible, the committee shall include and consider any estimated costs or cost savings to state and local governments associated with the committee's recommendations.

G. The committee may:

1. Request information, data and reports from any state agency, political subdivision or other persons or businesses involved in the public or private financing or administration of newborn, childhood or adolescent vaccines.

2. Hold hearings and take testimony from affected persons, including members of the public.

H. The committee shall maintain documents in a manner that preserves the confidentiality of confidential business information that may be disclosed to the committee during the course of its business.

I. This section is repealed from and after December 31, 2015.

APPROVED BY THE GOVERNOR APRIL 23, 2014.

FILED IN THE OFFICE OF THE SECRETARY OF STATE APRIL 24, 2014.

Transit Time Project Report

Newborn Screening Advisory Committee
September 24, 2014

NEWS RELEASE
Arizona Department of Health Services

HEALTH AND WELLNESS FOR ALL ARIZONANS

FOR IMMEDIATE RELEASE – September 18, 2014
Contact: Laura Oxley, ADHS Public Information: (602) 542-1094

Arizona Recognized for Outstanding Leadership in Newborn Screening Process

The March of Dimes today announced a new award, the Newborn Screening Quality Award, and gave it to the Arizona Department of Health Services for outstanding changes in the newborn screening process. The March of Dimes cited the Department's ability to turn around such a critical program in months and creating a transparent system that other states can copy as the reasons for the new award.

"Our staff and hospitals across the state embraced the issue knowing that the sooner we could test the newborn blood spots for life-changing or -ending disease, the better it would be for the babies," said Will Humble, director of the Arizona Department of Health Services. "This intense group effort to make sure the babies' tests quickly made it to lab shows what can happen when you identify a situation, set goals and work together to overcome obstacles."

Blood spots are taken from babies within the first few hours of birth and sent to the Arizona Public Health Laboratory for evaluation. At the lab, 28 tests check for diseases that can alert physicians to digestive or developmental issues; quick intervention for babies with those diseases will make a significant difference in their lives.

In December 2013, 67 percent of the samples were making it to the state laboratory within three days; others were taking more than five. By July 2014, 98 percent were checked into the lab within three days and none took five days. The department's transit time task force worked with hospitals to identify issues including the courier service, when the state lab was open and clear processes in hospitals to make sure everyone from the delivery room to the mailroom knew the importance of the tests. The monthly reports are available online for anyone to see.

The March of Dimes established the new awards in honor of Dr. Robert Guthrie, known as "the father of newborn screening" for developing the first mass screening test for babies 51 years ago. The awards recognize leadership in establishing culture of safety as a way to avoid those deadly delays in states' newborn screening process.

For more information on the March of Dimes, please contact Elizabeth Lynch, (914) 997-4286. Locally, contact Terri Spitz, (602) 321-7989.

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Transit Time Website: http://www.azdhs.gov/lab/aznewborn/transit-time-project/

Arizona newborn-screening process improves

Michelle Ye Hee Lee, The Republic | azcentral.com *10 p.m. MST July 22, 2014*

(Photo: Charlie Leight/Republic)

Nearly all Arizona babies are now being screened for potentially life-threatening diseases in record time, dramatically reversing a trend that ranked the state among the worst in the U.S. in testing delays just seven months ago.

The Arizona Department of Health Services and hospitals across the state have made an aggressive effort to improve the time it takes blood-screening samples from newborn babies to arrive at the state lab in downtown Phoenix.

Hospitals use a simple heel prick to draw blood samples from every newborn infant within 24 to 48 hours of birth. Each sample must be submitted within 24 hours, or the next working day after the sample is collected. State health officials consider it acceptable for lab samples to take up to four days to deliver.

RELATED: Arizona hospitals reducing newborn blood-sample delay (/story/news/politics/2014/05/26/arizona-hospitals-reducing-newborn-blood-sample-delays/9615921/)

RELATED: Arizona adds heart defects to newborn screening panel (/story/news/arizona/2014/04/28/arizona-newborn-screening-heart-defects-added/8359681/)

Timely processing of blood samples is crucial for newborn screening. The effectiveness of the test relies on how quickly the sample is tested. The diseases tested for are rare, but can be severe — even deadly — if not diagnosed and treated quickly.

Last November, an investigative report by the *Milwaukee Journal Sentinel* found hospitals nationwide were sending samples late — in some cases, up to 14 days. A few Arizona hospitals were among the nation's worst for delays in 2012.

The Arizona Republic subsequently reported that in 2012, at least one-third of blood samples collected at 17 of 42 Arizona hospitals took five days or longer to arrive at the state lab.

In December, state Health Director Will Humble set a six-month goal of having 95 percent of samples to the state lab within three days. Under his direction, the ADHS Office of Newborn Screening launched the Transit Time Project.

Today, 99 percent of Arizona hospitals are sending blood samples to the state lab within three days, and 100 percent are sending within four days, exceeding Humble's goal.

"It shouldn't take a baby dying or a big news story for there to be change made," said Jill Levy-Fisch, president of Save Babies Through Screening Foundation, a national non-profit that advocates for newborn screening. "It's something that should be a matter of course. All that being said, I think Arizona is doing a great job to address its deficiencies — and there were many."

The delays in blood-sample deliveries gained national attention after being reported, and a number of contributing factors were found in hospitals nationally and in Arizona. Among them:

• Hospitals that infrequently delivered babies were "batching" samples to save money by delivering several samples at a time to the lab. But hospitals were doing so needlessly. They already were paying the state for a courier service.

• There was a disconnect among hospital staffers. Nurses were pricking babies' heels, but other staff members were responsible for mailing samples. That meant a turnover in staff or someone taking a sick day could throw off the process.

• The state lab was closed on Saturdays, and the FedEx delivery service ran only on weekdays. That posed a problem, especially for samples that arrived on a Friday before a three-day holiday weekend.

• There was not enough education and communication between the state and hospitals about program standards.

ADHS and hospitals in the state addressed those issues over the past six months.

The state and the Arizona Hospital and Healthcare Association have held educational sessions for hospitals. Recordings of the sessions are available online.

Additional training sessions were held because of hospital demand, said Debbie Johnston, senior vice president of policy development at the health-care association. Training covered everything from gathering specimens to the availability of the courier service, Johnston said.

The health-care association will continue to work with ADHS so that if there are delays again, training sessions and education efforts can be restarted, Johnston said.

Meanwhile, a new state website also compares hospitals' blood-sample delivery times, driving competition and awareness. The online updates will continue.

The state lab now processes newborn blood samples on Saturdays, and a new, local courier service also picks up samples on Saturdays. The new courier was a major component in improving sample-delivery times, said Celia Nabor, Transit Time Project manager.

"We knew that the end goal was to be able to save the babies' lives," Nabor said.

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MORE STORIES

Krabbe

Newborn Screening Advisory Committee
September 24, 2014

Krabbe Estimates for Arizona (~$15/screen)

		AZ FY2016				
		Projected	Expected Cases		$15.12	
Population	Incidence	1st screens	Cases/year	Years to 1st case	Krabbe Revenue/Year[1]	Cost to 1st Case[2]
General	1/100,000	**86,113**	**0.86**	**1.16**	**$1,302,419**	$1,512,454
Total:						
1. Revenue assumes cost per newborn billed to first screen.						
2. Cost based on average annual cost over five years:		$1,302,419				

New York Screening (August 7, 2006 to July 21, 2014)

~2 million infants screened
- 771 samples with < 20% daily mean of GALC activity
  - 605 samples sent for DNA
  - 348 referred for diagnostic testing
    - 37 Moderate risk (Followed over time, but no LTFU data yet)
    - 14 high risk
      - 5 Transplants (2 patients died, 1 refused)

KEY POINTS

- NY relies on experts to review and modify the screening algorithm results and their program has been characterized as an "expert solution". Relative to other NBS disorders, the full screening algorithm (to diagnosis) is very complex and results in estimated risk categories to determine suitability for treatment. However, it remains unclear how well the algorithm reliably predicts early onset infantile Krabbe. False positive patients are subject to a lengthy and invasive diagnostic process.
- The only cost effectiveness study found was a summary from New Jersey (provided by Hunter's Hope Foundation), but it included all lysosomal storage disorders (not just Krabbe):

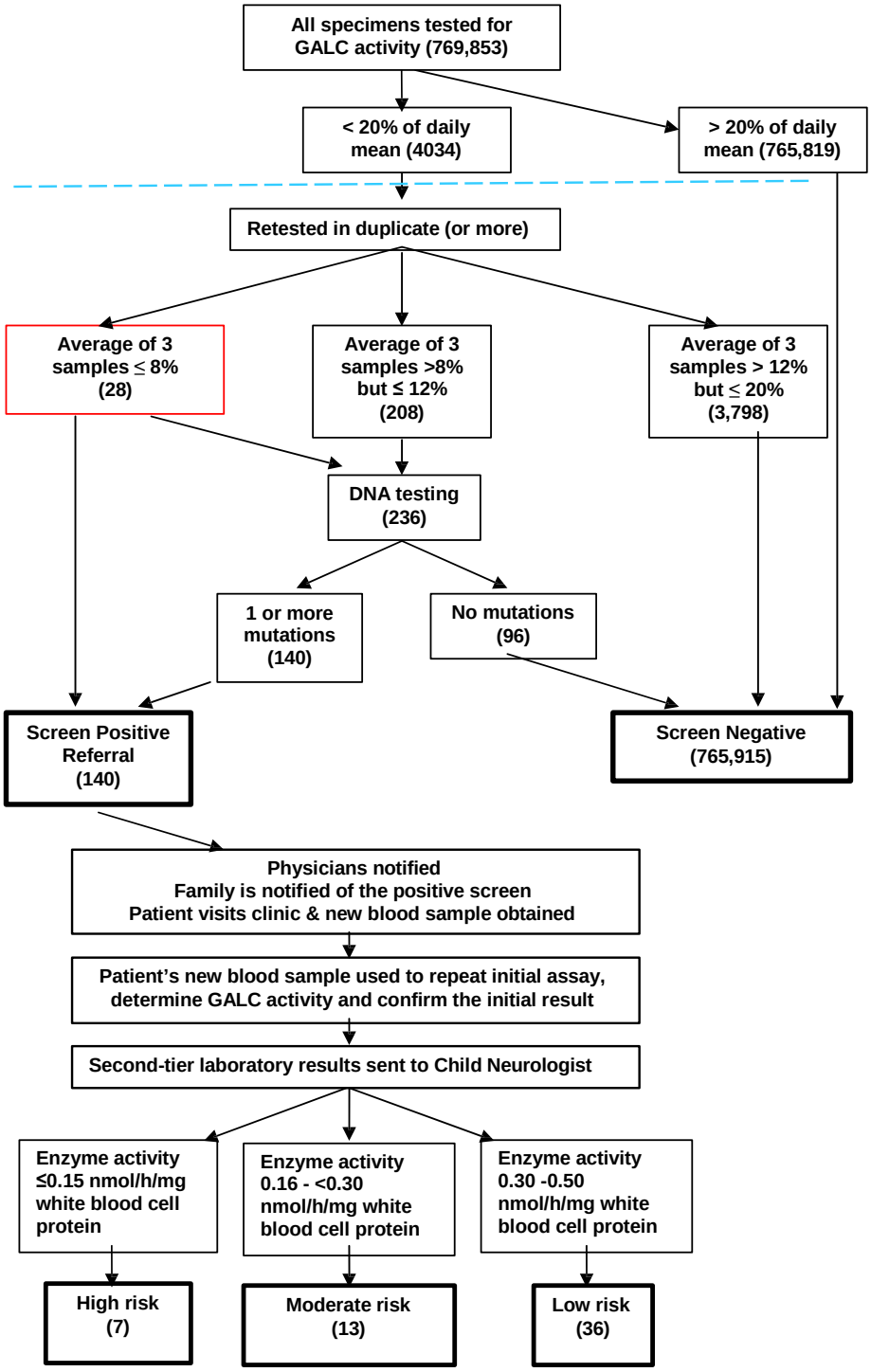
Economics of Newborn Screening in New Jersey
NJ – 2010 live births – 110,434
# of Births financed by Medicaid = ~ 35% (www.statehealthfacts.org)
1:5000 diagnosed with LSD = 21 potential cases (7 potential Medicaid cases)
$700,000 annually for medical expenses to care for a child with LSD
$700,000 x 21 = $14,700,000 (annual care for children born in NJ w/ LSD)
$14,700,000 X 2 = $29,400,000 – (care for LSD children with expected lifespan of 2 years)

Potential of 7 children born annually with LSD under NJ Medicaid
$4,900,000 for 1 year of medical care for children on Medicaid (7 children x $700,000 annual cost for med expense)
$9,800,000 for 2 years of medical care for children on Medicaid
Transplant expense ranges from $300,000 - $700,000 (a one time expense)
$500,000 x 7 = $3,500,000

65 % Economic benefit for the state to screen at birth and administer treatment than to care for undiagnosed Medicaid cases
$9,800,000 care for 2 years vs $3,500,000 for treatment
Because of the rareness of these diseases, diagnosis is made too late for treatment to be an option. Newborn Screening is the only way for medical professionals to detect these diseases in time for treatment to be a viable option.

Krabbe Screening (NY - 2009)

Figure 2 - New York State pilot screening program cutoffs, testing algorithm and number of newborns screened (in parentheses) at each stage as of June 2009



Newborn Screening for Krabbe Disease

Krabbe disease is caused by the complete deficiency of the enzyme galactocerebrosidase. It is considered both a lysosomal storage disorder and a leukodystrophy involving the central and peripheral nervous systems. Krabbe disease generally presents in the first six months of life, though it has been diagnosed in older children and adults. There are usually no obvious congenital anomalies present at birth. Early symptoms of the infantile form include feeding difficulties, gastroesophageal reflux, irritability and clasped thumbs. Late symptoms include hypertonicity followed by hypotonicity, flaccidity, deafness and blindness. In the infantile form, there is rapid mental deterioration, which usually leads to death before the age of two. Dietary treatment has not been effective at either reversing the symptoms or halting their progression. Currently, no enzyme replacement therapy is available. Hematopoetic stem cell transplantation from umbilical cord blood following myeloablative chemotherapy prior to the onset of symptoms has been shown to stabilize the disease, although gross motor skills may still be affected. Unfortunately, symptomatic infants receiving umbilical cord blood transplantation continue to show declining cognitive and physical functions.

Newborn screening for Krabbe disease provides the earliest window for population-based diagnosis and treatment. The screening is accomplished at the New York State Department of Health, in the Wadsworth Center, using specimens already collected for other newborn screening tests. There is no change in the way the specimens are currently collected and shipped. Wadsworth Center expects to refer approximately 50 infants each year for further Krabbe disease testing - 0.02% screen-positives from the annually screened population of about 250,000 infants. The screening protocol is designed to minimize screen positive results while preventing an infant with Krabbe from being missed. The items below briefly outline the screening and follow-up process:

Stage One: Wadsworth Center, Newborn Screening Program

Mass Spectrometry
A 3 millimeter "punch" is taken from the bloodspot card and transferred to the Krabbe testing laboratory. Mass spectrometry is used to test the sample for galactocerebrosidase (GALC) activity. An infant with GALC activity greater than 12% of the daily mean is considered to be screen-negative and her/his primary care physician is notified by written report per the normal NBS protocol. DNA analysis is initiated for any sample with confirmed enzyme activity less than 12% of the daily mean.

DNA Analysis
The specimen is tested for three polymorphisms and five common mutations using a rapid assay. If one or more mutations are found and confirmed, the infant is considered

General Information

- Welcome
- History
- Information on Disorders:
- Links
- NYS Genetic Services
- NYMAC

New Information and Updates

- UPS 2012 Days of Operation
- UPS Contact Notification
- Changes to cut-off values for the new neonatal 17OHP kit for congenital adrenal hyperplasia screening (10/26 - PDF)
- Screening for Severe Combined Immunodeficiency Disorder(SCID) began on September 29, 2010 (10/10 - PDF)
- Change to the NY Newborn Screening Program's algorithm for congenital hypothyroidism (5/10 - PDF)
- Funds received for Electronic HIE for Newborn Screening (12/09 - PDF)
- Evaluation protocol for acylcarnitines change (11/09 - PDF)

- All Updates

Archived Information and Updates

Health Provider Information

- Annual Reports
  - A Guide for Health Professionals
  - Obtaining Results (SRV, VRS)

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to be screen-positive and a physician is notified immediately. If no mutations are found, sequence analysis is performed. If sequence analysis demonstrates any mutation, the infant is considered to be screen-positive and a physician is notified immediately. If no mutations and only polymorphisms are observed after sequence analysis, the infant is considered to be screen-negative and her/his primary care physician is notified by written report of the findings by the normal NBS protocol.

Stage Two: Child Neurologist, Inherited Metabolic Disease Physician

Notification
The Newborn Screening Program staff reports screen-positive results to the Child Neurologist and the Inherited Metabolic Disease Specialist at the Treatment Center nearest the infant's home. The Inherited Metabolic Disease Specialist notifies the family of the positive screen for Krabbe disease. The infant is then given an appointment for evaluation at the Inherited Metabolic Disease Treatment Center as soon as possible.

Evaluation
The infant is seen by the Inherited Metabolic Disease Specialist and the Child Neurologist. The family is counseled about Krabbe disease and the infant is examined for early signs. Blood is collected using a kit provided by Wadsworth Center. Five milliliters of blood is drawn and sent to the second tier laboratory. In addition, two bloodspot cards are collected; one card is sent to the American Red Cross for Human Leukocyte Antigen (HLA) typing and one card is returned to Wadsworth Center for identity testing and confirmation of the previous result.

- Blood Specimen Collection Video (Start Healthy – Stay Healthy)
- On-Line Ordering
  - Blood Collection Forms
  - Newborn Screening Brochures and Educational Material
  - Specimen Collection DVD
- Watch Blood Specimen Collection Video
- Management Guidelines:
- Public Health Law
- Regulations
- Annual Reports
- Obtaining Results
- Hospital Designee Form (PDF) fill out, print and mail...

Contact Us

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Stage Three: Second Tier Laboratory

The second tier laboratory tests the specimen for galactocerebrosidase activity. The results are reported back to the ordering physician and Wadsworth Center.

Stage Four: Child Neurologist

If the second tier laboratory finds enzyme activity, the infant is at low risk for Krabbe disease and resumes routine care.

If the second tier laboratory finds borderline enzyme activity, the infant is at moderate risk for Krabbe disease and is closely monitored by the Child Neurologist.

If the second tier laboratory finds no enzyme activity, the infant is at high risk for Krabbe disease. The Child Neurologist and Inherited Metabolic Disease Specialist coordinate an immediate inpatient neurodiagnostic evaluation to determine whether signs of infantile Krabbe disease are present. This evaluation includes a detailed neurologic exam, lumbar puncture, MRI, nerve conduction studies, visual evoked response and brain stem auditory evoked response. If the neurodiagnostic evaluation is not consistent with infantile Krabbe disease, the infant is closely monitored by the Child Neurologist. If the neurodiagnostic evaluation is consistent with infantile Krabbe disease, the infant is referred for consideration of an umbilical cord blood transplant.

The transplant center with the most experience with neonatal Krabbe disease is Duke University Medical Center in Durham, North Carolina. The transplant physicians at Duke will accept patients with Krabbe from New York who may be in need of an umbilical cord blood transplant. There are also several centers in New York with experience transplanting young infants, although none have transplanted a newborn with Krabbe disease. These centers may be options if a family in need of a transplant chooses not to go to Duke.

Buffalo Spree
Press Pass: Common Core and New Urbanism

Focus On Education
Regents chancellor defends Common Core

Focus On Education
Ken-Ton names new superintendent

WBFO News **11:15** AM THU JULY 28, 2011

Jim Kelly and Hunter's Hope families push for universal newborn screening

(/sites/wbfo/files/styles/x_large/public/201110/3515940-274646286.jpg)
Zoey, 6, received a cord blood transplant.
WBFO News photo by Sharon Osorio

By Sharon Osorio

Listen 5:05

Java, NY – Many of us know former Buffalo Bill Jim Kelly as a Hall of Fame quarterback. But he's also making great strides through Hunter's Hope, the organization named in honor of his deceased son, Hunter, who died from a disorder called Krabbe Disease.

This past week, Hunter's Hope hosted a symposium for researchers, physicians, and families of children with diseases like Krabbe's.

WBFO's Sharon Osorio brings us the story of one Hunter's Hope family that's been through it all.

Zoey Moore, from Iowa, jumps into the pool at Beaver Hollow Conference Center in Java, while the annual Hunter's Hope Family & Medical Symposium takes place there. To look at Zoey, you'd never know she was born with a disease that could have landed

her paralyzed. The six-year-old was born with Krabbe Disease, the same disorder that afflicted Hunter Kelly, the son of NFL Hall-of-Famer Jim Kelly.

While the state of Iowa does not test for Krabbe Disease with the heel prick given to all babies at birth, Zoey's parents knew to test her for Krabbe Disease because her big sister, Raegan, also had the disorder. Raegan was diagnosed late, and died at 19 months old. But Zoey's Krabbe Disease was found right away, and she was able to receive an umbilical cord transplant that saved the quality and length of her life.

"The only reason Zoey was ever tested was because of our first little girl passing away," says Zoey's mother, Amber Moore. "Without that, we would have just watched another child die. But thankfully because of Raegan, and although you hate to say it's a life for a life, but in reality that's what it was for us. We had to give up one to have another -- to give Zoey the chance that Raegan never had."

Zoey's mother, Amber, says no parent should have to go through that ordeal when the test for Krabbe Disease could be offered at birth. But each state offers different tests in the heel prick to newborn babies.

Hunter's Hope, founded by former Buffalo Bill Jim Kelly and his wife, Jill, is one of the driving forces urging universal newborn screening, which means all states would offer the same, full spectrum of tests from that heel prick -- including a test for disorders like Krabbe.

Jim Kelly travels around the country, speaking to governors, lawmakers, and -- as he puts it -- anyone who'll listen to him, about implementing universal newborn screening. And as a Hall of Fame football player, many people do listen to him -- much more than they would if he were an average concerned parent.

"They do just as much as we do, but we're the ones who get noticed, and it is sad," says Kelly. "I remember going to Pennsylvania, and the March of Dimes was a little bummed out that, they said, they'd been trying to get into the governor's office for over a year, and it took a quarterback coming in and being able to say a few words to the governor, and have legislation changed within a year. But if that's what it takes, I'm going to do it. Unfortunately you wish they (officials) would get it, and some do and some don't."

Children who genetically inherit Krabbe Disease lack a specific enzyme, which leads to the production of toxins in the brain. Hunter Kelly died at eight- and-a-half years old, which was considered a long life for a child with this disorder.

But now, an umbilical cord transplant like Zoey's, performed before the child shows symptoms of Krabbe Disease, is showing remarkable results.

"We went in for 10 days of intense chemo, went through an umbilical cord blood transplant, so they just take the cord blood from a healthy baby that's full of stem cells and they put them into Zoey, and those cells start doing the job that replacing the enzyme that she's missing," Moore recalls. "So it's rough. You don't want to put your child through that if you don't have to, but we watched the alternative, and we just knew this time there was hope that we never had with our first little girl."

Zoey will soon start first grade and she's cognitively normal. Mom says Zoey does sometimes get off balance a bit, and she's small for her age, but otherwise, this medical marvel is just a kid.

"I see life," says Moore. "I see everything that a normal child gets to experience. I get to see her when she's happy, see her when she's mad, when she's screaming at me. I mean, I get to see a normal kid, as compared to our first little girl who when she died at 19 months old, was blind and deaf and paralyzed, and no true function whatsoever . That's two totally different worlds from one blood test." "When you have families walking up to you parents, and they are holding their child in their arm and they're thanking you for the life of their children, then you understand why you do it," says Kelly. "We see it right in front of us. We see families walking up to us, holding their

kids, that said if it wasn't for Hunter's Hope, change in legislation in Pennsylvania, New York, Arizona when you get the letters, and so many things, you know we're making a difference. And that's what it's about."

And the work toward more progress continues.

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Parents Seen as Critical Stakeholders in Expanding Newborn Screening

June 21, 2012

Parents must be considered when states decide to expand genetic screening programs for newborns, according to a new study that looked at mandatory testing panels and political pressure by advocacy groups.

Nearly all infants in the United States undergo a heel prick within days of birth for a simple blood test to detect rare genetic disorders. For decades, state-based mandatory newborn screening programs have focused on disorders such as phenylketonuria (PKU) or hypothyroidism in which a prompt diagnosis and treatment could prevent disability or even death.

In recent years, advocacy groups have been pushing to expand newborn screening to include lysosomal storage diseases (LSDs), a group of rare metabolic disorders, despite the lack of consensus on which children should be treated or the effectiveness of available therapies. With the high degree of uncertainty around LSDs, many medical ethicists as well as some genetic health professionals and public health officials are questioning the clinical value and the morality of screening mandates.

In an article published by *The Journal of Pediatrics*, researchers from the University of Chicago Medicine argue that parents should be critical stakeholders in the expansion of newborn screening. Despite federal recommendations against the addition of these conditions, LSDs have been tacked on to the screening panels in several states and strong lobby efforts are under way across the nation with little or no consideration for parental consent or even notification.

"A problem with incorporating LSD screening into state screening programs is the 'all-or-nothing' constraint," said co-author Lainie Friedman Ross, MD, PhD, professor of pediatrics, medicine and surgery, and assistant director of the MacLean Center for Clinical Medical Ethics at the University of Chicago. "Parents cannot say that they want their child to be tested for some conditions and not others. There is simply not enough available information on many LSDs to justify overriding the ethical standard of parental informed consent."

The push for more widespread screening for once little-known diseases is largely the result of impassioned campaigns led by parents of children affected by these conditions. Among the most notable advocates is former Buffalo Bills quarterback Jim Kelly, whose son died of complications from Krabbe disease, a rare genetic disorder of the nervous system. In 2006, Kelly successfully lobbied the New York State Department of Health for the inclusion of Krabbe disease in its mandatory newborn screening program. Since then Missouri and New Mexico have passed legislation to screen for a broader array of LSDs.

Similarly, in Illinois, seven LSDs have been mandated to the newborn screening program due to the efforts of the Evanosky Foundation, formed by parents of three children diagnosed with metachromatic leukodystrophy (MLD).

Ross says that while such stories are heartbreaking, this trend is worrisome because arguments from parent advocacy groups tend to be based on anecdotal experience rather than scientific, peer-reviewed evidence -- and they represent only one side of the coin.

"There are many parents whose voices are not being heard: parents who have experienced the distress of a false positive or who have children identified with conditions that may not present until adulthood, if ever," Ross said. "There are also parent advocacy groups around the country worried that their children's blood spots are being used for research without their permission, even without their awareness."

Another concern for ethicists is the funding advocacy groups often receive from pharmaceutical companies that have a vested interest in the promotion of treatments for the disorders the group represents. Studies have confirmed that many of these groups fail to disclose conflicts of

interest on their websites, promotional brochures and lobbying activities.

Ross and co-author Darrel Waggoner, MD, associate professor of human genetics and pediatrics and medical director of human genetics at the University of Chicago Medicine, join a chorus of experts calling for expansion of newborn screenings to be initially conducted within research protocols, including oversight from a human-subject protection committee known as an institutional review board (IRB).

"By placing such conditions under an IRB protocol, it acknowledges that there is much still to be learned," Waggoner said. "It acknowledges that we need parents to be co-adventurers. It also means that additional reviews will be necessary before these conditions become entrenched in mandatory newborn screening programs."

Watchers of New York's adoption of Krabbe disease screening are closely tracking the outcomes. In the state's first four years of testing for LSD, hundreds of children were called back for further testing. Of those, 29 tested positive for Krabbe and only four were diagnosed with the infant-onset form of the disease. Another 25 children were classified as moderate to high risk for developing a later onset form of the disease, but none has developed any symptoms. New York does not follow the psychological impact on parents of these "patients in waiting."

"What we've learned from New York's Krabbe screening program is how incompletely we understand the natural history of the disease and that late onset of symptoms is likely to be more common than previously diagnosed clinically," Ross said.

LSD screening pilots in Taiwan and Italy, both of which employed research protocols including parental consent and IRB review, have provided key insights. One of the most fundamental findings, say the researchers, is that when given an option, more than 98 percent of parents elected to move forward with testing.

The observation helps strengthen the case for a proposed two-tiered screening program in Illinois. The first tier could include mandatory screening for conditions with established therapies and consensus on when treatment is necessary. A second tier, designated to less understood diseases, could be offered under a research protocol with active parental consent. This model was adopted by the Massachusetts Department of Public Health with the expansion of its newborn screening program in the 1990s.

Waggoner and Ross acknowledge that large-scale screening initiatives are needed to uncover the many unknowns regarding LSDs, yet they strongly oppose policies that allow research studies to operate under the guise of public health programs.

"The development of enzyme replacement and other innovative therapies for many LSDs is exciting and motivate the pursuit of IRB-approved research on populations that may benefit from early identification and treatment," Ross said. "But infants are vulnerable and need their guardians to determine whether participation is in their best interest. Let's give voice to all parents by requiring their permission for the enrollment of their children in experimental newborn screening protocols."

The article, "Parents: Critical Stakeholders in Expanding Newborn Screening," has been published by *The Journal of Pediatrics*, DOI 10.1016/j.jpeds.2012.04.035.

Waggoner and Ross serve in a pro bono capacity on the Illinois Department of Public Health's Genetic and Metabolic Diseases Advisory Committee. The views expressed are their own and do not represent the Illinois Department of Public Health or the Advisory Committee.

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Screening Newborns For Disease Can Leave Families In Limbo

by NELL GREENFIELDBOYCE

December 23, 2013 3:46 AM ET

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Morning Edition

8 min 58 sec

Ben Shutts/Courtesy of the Wojtesta family

For Matthew and Brianne Wc' 'sta, it all started about a week 'ter the birth of their daughter Vera. Matthew was picking up his son from kindergarten when he got a phone call.

It was their pediatrician, with some shocking news. Vera had been flagged by New York's newborn screening program as possibly having a potentially deadly disease, and would need to go see a neurologist the next day.

Like every state, New York requires that newborns get a small heel prick so that a few drops of blood can be sent to a lab for testing. The idea is to catch health problems that could cause death or disability without early intervention.

But in recent years, patient advocacy groups have been pushing states to adopt mandatory newborn screening for more and more diseases, including ones that have no easy diagnosis or treatment.

One of those is Krabbe disease, a rare and devastating neurological disorder.

In 2006, New York became the first state to screen for Krabbe, and until recently it was the only state to do so. Screening for this disease is expanding, even though some experts say the treatment available doesn't seem to help affected children as much as was initially hoped — and testing can put some families in a kind of fearful limbo.

The New York Experience

The state began screening newborns for Krabbe disease in August 2006. As of November 20, 2013:

- 1,955,754 newborns were screened.
- 319 were referred to doctors for additional testing.
- 30 babies were considered to have moderate risk.
- 14 babies were deemed to be at high risk. Of those, five were candidates for immediate treatment. Four of them got stem cell transplants, and two of those children died. One family declined treatment.

New York has screened nearly 2 million children for Krabbe. About 300 have been picked out as needing follow-up tests and evaluation to see if they really have the disease. One of those was Vera Wojtesta.

After getting that disturbing news, Matthew Wojtesta went to the family's home in Rochester, where his wife was still recuperating from childbirth. Brianne remembers that he sat on the bed and woke her up very gently, putting his hand on her knee and saying, "You know, honey, the doctor just called ... "

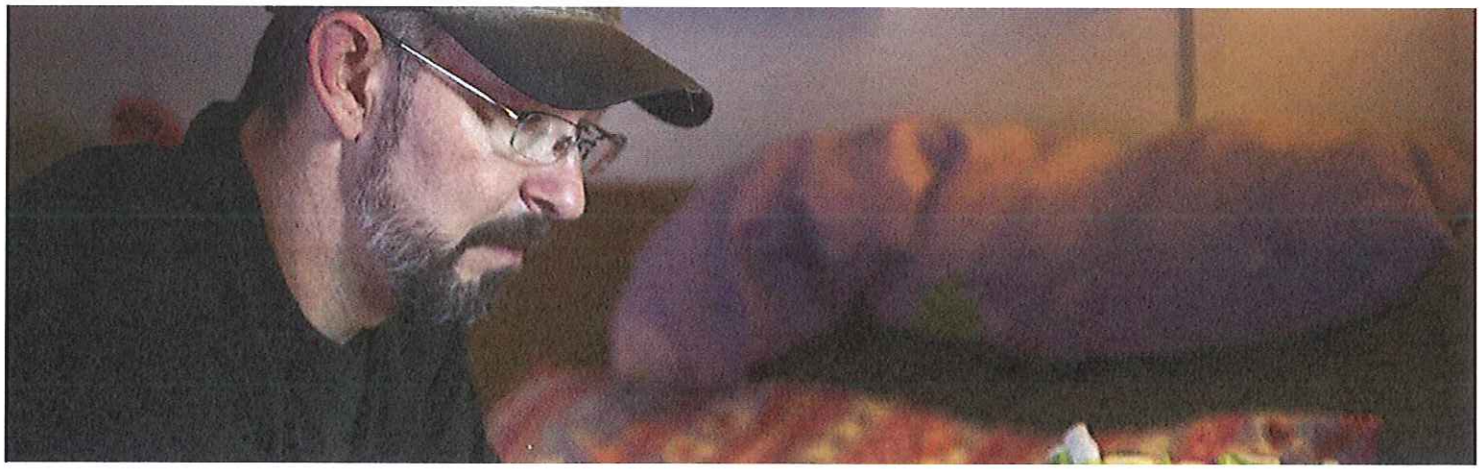
That night, after their older children were sleeping, they got on the Internet and read and read. It was terrifying to learn what Krabbe can do to a child.

Babies with Krabbe have an enzyme deficiency that damages a coating around nerves called myelin. At first, babies with the disease seem normal. But then everything starts to change — and without screening, families become desperate as they struggle to figure out what's wrong.

Angel Custer and Anthony Shaffer had that awful experience. They are "Grammy" and "Pappy" to Jaylah Donaire-Bechtel, Custer's 20-month-old granddaughter. She lives with them in Harrisburg, Pa.

When Jaylah was a few months old, she stopped drinking from her bottle because she couldn't suck on it. She was screaming in pain almost nonstop. "She stopped smiling, she stopped laughing," says Custer. "We lost all that."

By the time a doctor diagnosed Krabbe disease, it was too late for any treatment. Jaylah can't move her arms or legs. She can't sit up or talk. She can't even swallow her own spit — someone has to suction it out with a tube, many times an hour.



Mark Pynes /pennlive.com

Custer and Shaffer work staggered shifts so they can care for Jaylah around the clock. They try to help her experience everything she can. She eats through a tube, but they let her taste pickles and olives, and give her Dum Dum lollipops. Jaylah watches cartoons like Dora and SpongeBob, and Shaffer gives her elaborate manicures.

But like other children with Krabbe, Jaylah will eventually go deaf and blind and then die. "I always said you wouldn't put your dog through that. But we've got to watch our child go through that," says Custer.

> She stopped smiling, she stopped laughing. We lost all that.
>
> *- Angel Custer, grandmother*

That's why Custer has been urging lawmakers in her state to follow the lead of New York.

The New York screening program really only began because of Jim Kelly, a former Buffalo Bills quarterback who is in the Pro Football Hall of Fame. After his son, Hunter, was diagnosed with Krabbe, Kelly and his family started a foundation called Hunter's Hope.

In 2005, physicians published an article in the *New England Journal of Medicine* on using umbilical cord blood transplants to treat newborns with Krabbe. Babies who survived this risky treatment did much better than babies who got no treatment. But the transplant had to be done before symptoms appeared. And babies were only being diagnosed that early if they had an older sibling who previously had developed Krabbe, revealing that the disease ran in the family.

With a viable treatment s[illegible]denly available, the Hunter's H[illegible]e Foundation convinced New York officials that every newborn in the state should be tested.

"I was frankly amazed when it went through. I really never thought they'd be able to do it," says Dr. Patricia Duffner, a neurologist who was working at the University at Buffalo School of Medicine when she diagnosed Hunter Kelly in 1997.

Don Heupel/AP

"I didn't realize how complicated it was going to be," says Duffner. "None of us realized how complicated it was going to be."

Because the disease is so rare, there was a lot that doctors didn't know. One thing was clear: There are different forms of Krabbe. The early infantile form hits babies, but late-onset forms of Krabbe can start in childhood, the teen years or even decades into adulthood.

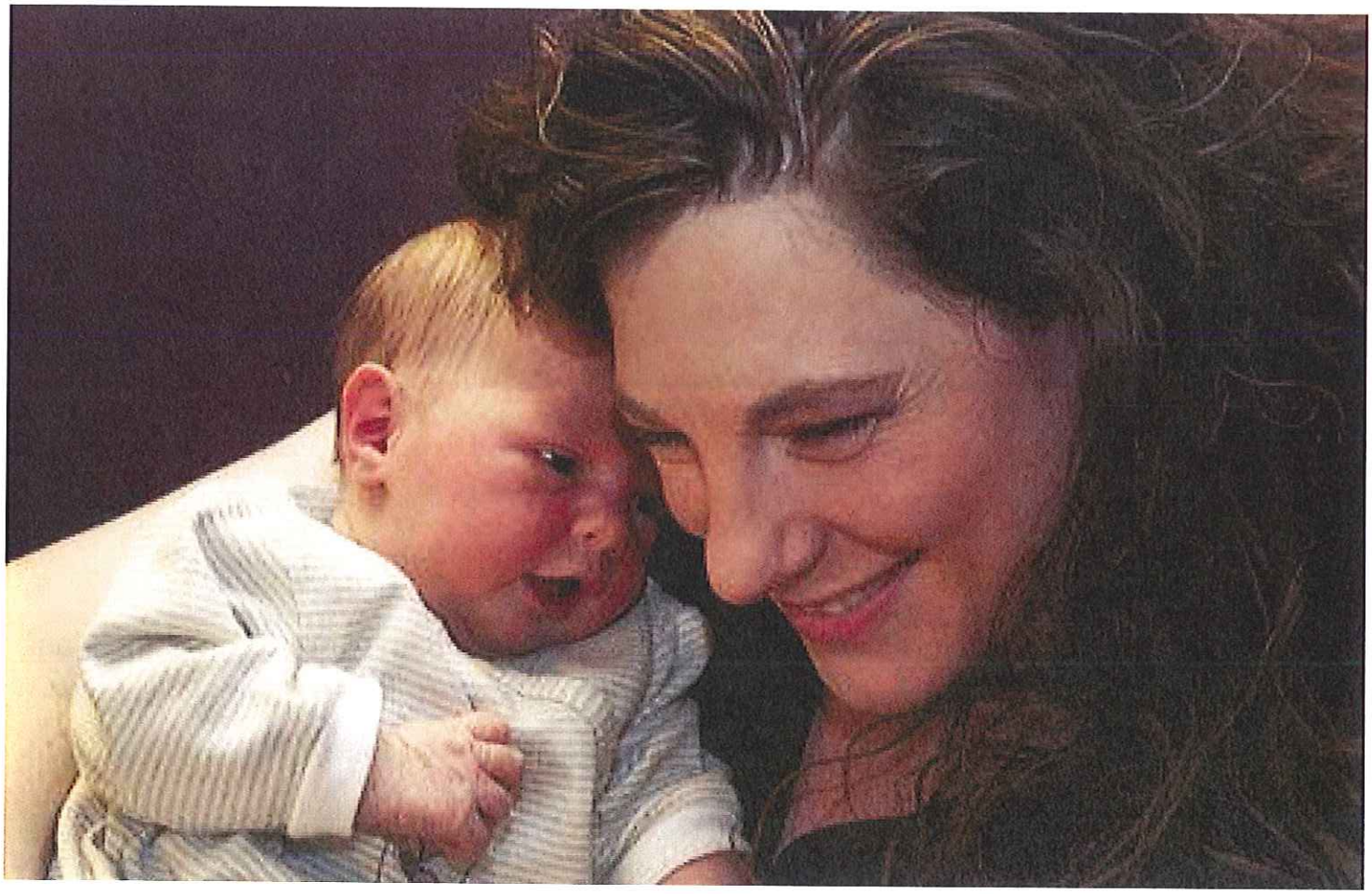
Duffner says a consortium of experts in New York had to quickly come up with an approach that would let them identify newborns with the severe, early form that requires urgent action.

"No one else had done it prior to New York state," says Michele Caggana, director of the state's newborn screening program. "And so there wasn't really demonstration, at least early on, that the screening test actually worked or that it could be done."

The state lab in Albany checks a baby's enzyme level, and if it's below a certain cutoff, the lab also examines part of the baby's DNA. Then these initial screening results are sent to a specialist who meets with the family and evaluates the infant.

Brianne and Matthew Wojtesta didn't sleep much as they waited for Vera's neurology appointment.

"I think the scariest part was that they are asymptomatic at the very beginning," says Brianne. Vera looked so healthy. But if Vera had Krabbe, they'd have to fly her to specialists at Duke University in North Carolina for an irreversible procedure that she might not survive.



Ben Shutts/Courtesy of the Wojtesta family

They went to the University of Rochester Medical Center, where a neurologist, Dr. Jennifer Kwon, had their lab results. She told them that what was seen in Vera's DNA probably meant she's just a carrier who did not actually have the disease.

> I think the scariest part is that they are asymptomatic at the very beginning.
>
> *- Brianne Wojtesta, parent*

"I didn't think it was going to be a difficult situation at all," says Kwon. But she couldn't be sure until she ran more tests.

The parents spent an anxious week waiting for the results. "We talked a lot, we cried, we read science," says Matthew.

To their great relief, the tests showed Vera does not have any form of Krabbe.

In this case, Kwon says, she could be reassuring. But for other families, she can't.

When doctors run DNA tests and see genetic mutations, it's not clear what they all mean. There is one mutation strongly associated with the early infantile form of Krabbe, but many other mutations are a mystery.

With ambiguous test results, sometimes Kwon has to tell parents that it's possible that their child may develop some form of Krabbe at some point. "But I can't tell you when, I can't tell you what it's going to look like. I can't tell you if there's any way to prevent it. And I can't tell you that we will be able to treat it if it develops," says Kwon. "So that's very difficult for families to hear."

She says they're often angry and scared. Now, as they watch their children grow up, they're haunted by the thought of this terrible disease. This has happened to dozens of families in New York. None of these kids has shown any symptoms, as far as anyone knows.

And when the screening program does find unmistakable signs of infant Krabbe, the treatment has turned out to be problematic as well. Five infants in New York have been candidates for cord blood transplants. One family refused. Four babies got treatment. Two of them died of complications. One child is severely neurologically impaired. And one child has had problems but has been able to start kindergarten.

> No one should be screening for disorders that are this difficult.
>
> *- Jennifer Kwon, neurologist*

All of this has left Kwon feeling like the benefits do not outweigh the potential harms.

"No one should be screening for disorders that are this difficult," Kwon says. She wants to help children and doesn't want Krabbe to exist, but she is not convinced that newborn screening is the way to make it go away.

She's not the only one who takes this view.

"My heart goes out to any parent who is going to have a child with this diagnosis. It is a devastating diagnosis. But just because parents are desperate doesn't mean that we should offer them things that actually aren't going to help," says Dr. Lainie Friedman Ross, a medical ethicist at the University of Chicago.

With so many unknowns, newborn screening for Krabbe has to be seen as research, Ross says. And, she points out, it's unethical to enroll people in a research experiment without their consent. If states want to try screening newborns for Krabbe, she says, they should first get parents' permission, instead of simply requiring the test by law.

"When we think of a public health mandate, we think about something for which early testing and screening is going to prevent morbidity and mortality," says Ross. "We don't think of creating individuals for whom we say we don't know if this is a health problem, we don't know when it will be a health problem."

> Just because these parents are desperate doesn't mean that we should offer them things that actually aren't going to help.
>
> *- Lainie Friedman Ross, ethicist*

It can be wrenching for pa nts who get false positives or certain results from newborn screening, says Stefan Timmermans, a sociologist at the University of California, Los Angeles, who has studied families' reactions to screening for rare disorders.

"You have completely changed the experience of having a baby. You have completely changed what it means to have a newborn," he says. "Rather than looking at your little bundle of joy and smiling, you are looking at a child as if he or she can die at any moment."

But some doctors do support Krabbe screening. Dr. Maria Escolar, a Krabbe specialist at Children's Hospital of Pittsburgh, says that even if the available treatment isn't perfect, "families develop relationships with their children, and no matter what degree of disability they have, they treasure each day that they are spending with their children."

And without screening, undiagnosed babies with Krabbe will suffer, she says. They won't get the right drugs to ease pain and other symptoms until doctors finally figure out that they have this uncommon disease.

"It is a terrible thing to see. And when you experience that, when you live that, that's when you realize how important newborn screening is," says Escolar.

The small group of families whose children have lived is the driving force behind an expansion of Krabbe screening.

> When you have a child who's going to face a terminal disease, do you want knowledge and options and choice, or do you want it to just happen to you?
>
> *- Christina Levasheff, parent*

Missouri started last year and has found a half-dozen ambiguous cases with test results that suggest a risk of some form of this disease.

New Jersey and Illinois will start screening next year, and New Mexico has decided to do it, too.

Christina Levasheff is trying t ɟet her home state, California, start screening. Levasheff and her husband lost their son Judson to Krabbe. He seemed perfectly healthy until he was about 2 1/2 years old. Then he began to have symptoms, and within five months he could no longer speak, move or see.

Levasheff, who lives in Orange County, says she first heard of newborn screening for Krabbe after Judson had passed away. Thinking back to the days before Krabbe struck her son, she asked herself: "Would I have wanted to know that he had this disease?"

She decided that the answer is yes. "When you have a child that's going to face a terminal disease," she says, "do you want knowledge and options and choice, or do you want it to just happen to you?"

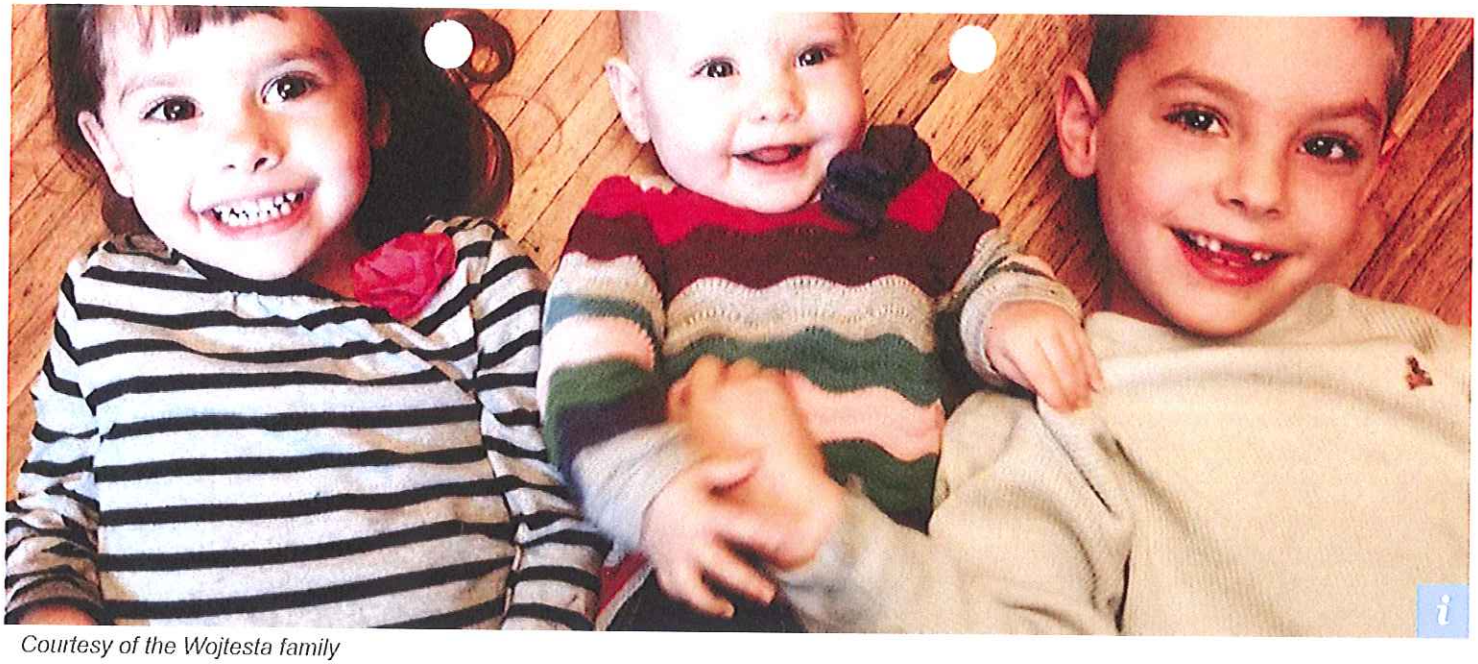
> What part of this disease do we not know, what part of the genetic composition do we not know, what about the late onset? Irrationally, I know, it still hangs over me. It's still scary.
>
> *- Brianne Wojtesta*

Levasheff says screening is needed because all efforts to find new treatments for Krabbe in the future are going to depend on knowing about this progressive disease before symptoms appear.

The Hunter's Hope Foundation ultimately wants screening to be done nationwide.

"Children are not being screened for Krabbe at birth and dying because of it. And they die a very slow and painful death," says Anna Grantham, who runs the foundation's newborn screening effort.

In 2009, an expert committee that advises the federal government looked at New York's results and did not recommend that all states adopt it. Grantham says she hopes the committee will revisit that decision, but that will take time. "We feel like there's not time to wait for that, because lives are being lost," says Grantham.



Courtesy of the Wojtesta family

Brianne and Matthew Wojtesta say they don't know if mandated screening is the right way to handle all of these difficult issues. They personally were glad for the testing, even though they also say it was traumatic.

Brianne says for her, the fear lingers, even though the good news they got about Vera was the best possible outcome.

"What part of this disease do we not know, what part of the genetic composition do we not know, what about the late onset?" she wonders. "Irrationally, I know, it still hangs over me. It's still scary."

The experience has changed her, and she says it will forever be a part of her relationship with her daughter.

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Case Discussion

The Ethics of Krabbe Newborn Screening

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The experience of newborn screening for Krabbe disease in New York State demonstrates the ethical problems that arise when screening programs are expanded in the absence of true understanding of the diseases involved. In its 5 years of testing and millions of dollars in costs, there have been very few benefits, and the testing has uncovered potential cases of late-onset disease that raise difficult ethical questions in their own right. For these reasons, we argue that Krabbe screening should only be continued as a research project that includes the informed consent of parents to the testing.

Introduction

In 2006, New York State instituted the first newborn screening for Krabbe disease, though not at the behest of public health officials. The American College of Medical Genetics had just recommended a radical expansion of newborn screening programs in the USA but they explicitly refused to endorse screening for Krabbe (ACMG, 2006: 6S). Instead, the push for Krabbe screening was spearheaded by Hall-of-Fame quarterback Jim Kelly and his wife, Jill, whose son died from the disease, and who were able to convince Governor George Pataki to issue an executive order mandating the test. However, the New York State experience shows the problems with efforts to expand screening programs in the absence of true understanding of the diseases involved. In its 5 years of testing and millions of dollars in costs, there have been very few benefits, and the testing has uncovered potential cases of late-onset disease that raise difficult ethical questions in themselves. For these reasons, we argue that Krabbe screening should only be continued as a research project that includes the informed consent of parents to the testing.

Background

Krabbe disease is an inherited, autosomal recessive, neurodegenerative disease caused by a deficiency in a lysosomal enzyme, galactocerebrosidase (GALC). At birth, children appear normal, but they soon develop irritability, spasticity, feeding difficulties, blindness and deafness. Soon their development slows and then stops. Eventually, the children cease to have any voluntary motion, and they die in childhood, often early (Duffner *et al.*, 2009a: 246). The disease is rare and occurs in about 1 in 100,000 births (Wenger, 2011). Until recently, there was no treatment, but hematopoietic stem cell transplantation (HSCT) using umbilical cord blood seems to result in significantly better outcomes for the recipients, but only if the transplant is done pre-symptomatically (Escolar *et al.*, 2005). The treatment is still experimental, and not all eligible patients have undergone the therapy. And it is far from benign: it involves chemotherapy to ablate the bone marrow of the patient, followed by HSCT, all on an infant less than 2 months old. HSCT carries an estimated 10 per cent risk of death and higher risk of morbidity (Duffner *et al.*, 2009a: 246). However, it seems to replace the missing enzyme, and the children that survive the procedure grow and develop, though in many cases, with significant disabilities; the exact long-term prospects are still unclear (Escolar *et al.*, 2005; Duffner *et al.*, 2009b).

Because HSCT is only effective if done pre-symptomatically, newborn screening is the only systematic way to find infants who could benefit from it. On that basis, advocates argued for its inclusion in the newborn screening panel. They claimed that it fit the model of other newborn screening programs, like that of

doi:10.1093/phe/phs033
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phenylkentonuria (PKU), an inborn error of metabolism which causes severe cognitive disabilities unless the child is placed on a special diet before symptoms begin to appear in the first few months of life. Krabbe advocates believed that the screening and subsequent confirmatory enzyme assay would be sufficient to identify those infants with severe GALC deficiency, who would be appropriate candidates for HSCT.

Despite this comparison, testing for Krabbe disease does not meet the traditional criteria for medical screening, as outlined in the classic report by J.M.G. Wilson and G. Jungner (see Ross, 2012):

(1) The condition sought should be an important health problem.
(2) There should be an accepted treatment for patients with recognized disease.
(3) Facilities for diagnosis and treatment should be available.
(4) There should be a recognizable latent or early symptomatic stage.
(5) There should be a suitable test or examination.
(6) The test should be acceptable to the population.
(7) The natural history of the condition, including development from latent to declared disease should be adequately understood.
(8) There should be an agreed policy on whom to treat as patients.
(9) The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
(10) Case-finding should be a continuing process and not a 'once and for all' project (Wilson and Jungner, 1968: 26, 27).

If anything, we should expect a mandatory newborn screening program—which uses the power of the state to require all newborns to be tested—to meet all these criteria quite clearly.[1] But Krabbe testing does not do so. While the disease is serious, it affects a very small number of children, so New York State, with a birth rate of about 250,000 a year, expected to see only two cases a year, so it may meet criteria (1), but not clearly. The question then becomes whether the resources needed to detect these two cases might be better spent on other public health programs, and so Krabbe testing does not clearly meet criteria (9).

In addition, while the treatment is only effective if provided pre-symptomatically (4), that treatment is not well established (2). Indeed, in this respect, it is quite unlike PKU where the benefits of treatment for the child are so great that if parents are unable or refuse to provide the PKU diet, a strong case can be made for medical neglect. But parents who refuse the treatment for Krabbe are not clearly acting against the best interest of their child. These parents are faced with subjecting their 2-month-old infant to an unproven process that may itself damage, if not kill, their child with the end result that the child will be severely disabled. Against that option is the high probability—though, given our lack of knowledge about the disease, not the certainty—that their child will develop a disease that is certain to kill her in early childhood. We may disagree with a decision to forego treatment, but it is not so out-of-bounds that it would constitute medical neglect.

Finally, Krabbe testing fails to meet the Wilson–Jungner criteria because, although a test is available and relatively easy to administer (3), (6), what the results mean is still unknown (7), (8). Indeed, from the beginning, experts knew there might be complications in interpreting the results. While the infantile form of Krabbe disease is the focus of newborn screening, there are also late-onset forms. In these forms, symptoms may begin at any time, from the age of 6 months to late adulthood, and the patient's condition has a variable rate of deterioration that may not be related to the age of onset. HSCT has been tried for these forms, but it has not been consistently successful (Kolodny *et al.*, 1991; Krivit *et al.*, 1998; Duffner *et al.*, 2009a). So currently, there are no established treatments for the late-onset forms of Krabbe disease, and no clear benefit in pre-symptomatic testing of this cohort. Unfortunately, the newborn screening test and confirmatory GALC enzyme activity by themselves do not distinguish between the early infantile and late-onset forms. Furthermore, the natural history of late-onset Krabbe disease is so poorly understood that no one knows if or when a child at risk for the late-onset form of the disease will actually develop it. It thus burdens the parents and the child with knowledge that in no way benefits the child. It thereby adds stress to lives of these families and creates a cadre of 'patients in waiting', stuck indefinitely in a no man's land between illness and normality (Timmermans and Buchbinder, 2010).

To deal with the uncertainty that pervades the findings in the testing, the ad hoc group formed to implement the program in New York, the Krabbe Consortium (a group that includes one of us), devised a procedure to make recommendations to assess the risk of developing the infantile form of the disease based on GALC enzyme activity, on GALC genotype and on a comprehensive

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medical evaluation of the infant[2] (Duffner *et al.*, 2009a: 248–50). Through this method, the Consortium has tried to pick out the infants who are most at risk for the infantile form of the disease and who might, therefore, benefit from HSCT. According to data collected and reviewed by the Consortium, in the first 5 years of testing, from August 2006 to August 2011, 1 million children have been screened for Krabbe disease. Of those, 228 had an initial positive test. Upon further testing, 114 of these were found to be normal. Of the remaining, 84 were considered 'low risk', meaning that their GALC enzyme activity was low, but apparently functional. The remaining 30 had low enzyme levels that were felt to put them at either moderate ($n = 19$) or high ($n = 11$) risk for the disease. None of those at moderate risk has shown any symptoms of Krabbe disease, but 13 of them have two GALC mutations. Whether these children in the moderate-risk category will develop a form of Krabbe disease later in life is unclear; certainly those with low GALC activity and two GALC mutations are at risk, both biochemically and genetically. Of the 11 infants found to be at high risk, all have two GALC mutations, and their particular mutations, enzyme activity, clinical evaluations and neurodiagnostic testing were reviewed to determine the likelihood that they would develop the infantile form of Krabbe disease. For seven of these 'high-risk' infants, the likelihood of onset in infancy was not thought high enough to recommend HSCT. None are known to have developed any symptoms of Krabbe disease at this time. The parents of the remaining four patients were encouraged to seek HSCT for their children. Of these four, the parents of one refused treatment and the child has developed Krabbe disease; the treatment of one was done after neurologic symptoms had developed, and the child has severe neurological problems; one had the treatment and is doing relatively well with motor delays; and one died of complications from the treatment.

In 5 years of Krabbe disease newborn screening and a cost of $3.5 million (Salveson, 2011: 98–102), the program has identified, at best, four cases for which the testing was designed. It has also created considerable frustration and anxiety for the families of some 20 other infants, who are told that their children *might* develop a devastating neurodegenerative illness, but that there is no good way to predict if, much less when, it would occur or how it might be avoided (DeLuca *et al.*, 2011; Salveson, 2011: 66–69, 75–82). For these families, the state has screened for a late-onset disease for which there is no pre-symptomatic treatment, subjected their children to a multitude of tests, created considerable anxiety and then told them that no one knows what the results mean and that there was nothing that could be done. Understandably, some parents became angry with the whole process (Salveson, 2011: 66, 67, 83–90).

Confronting the future

The Krabbe program cannot, then, be considered a success. At best, it has effectively treated one infant, but in the process it has created considerable anxiety at a substantial cost to the state. We can respond to this situation in one of three ways.

First, we could abandon Krabbe newborn screening altogether, arguing that the benefits for the very few children who might be helped are outweighed by the cost of the program and the unwarranted anxiety it creates. Part of the argument would be that the Krabbe screening program was badly conceived in the first place as it mandates universal screening when the disease is so poorly understood. And part of the argument is that the money could be spent on other programs—like increased pre-natal screenings—that would save more lives (Baily and Murray, 2008). For just these reasons, the US Advisory Committee on Heritable Disorders in Newborns and Children has recently confirmed the conclusion of the ACMG report not to recommend Krabbe testing (Kemper *et al.*, 2010).

Second, we could continue to screen for Krabbe disease on the theory that we should treat the few cases we find and follow other at-risk children over time to understand better the natural history of the late-onset forms. Obviously, the case for this strategy would be stronger if the treatment for Krabbe disease were less risky and its benefits more clear. Nevertheless, we might still justify the testing by arguing that the best way—and perhaps the only way—to understand early and late-onset Krabbe disease would be to follow the patients at risk to discover which of them develops the disease and how it progresses when they do.[3] Such knowledge is crucial for our ability to develop treatments, and it can only be found by identifying pre-symptomatic patients with newborn screening. But if a key goal of the newborn screening program is to conduct research, then the State of New York appears to be forcing every newborn to participate in a research study without the consent of her parents. Even if no newborn is enrolled in one of the follow-up studies without the consent of her parents, the state has already coerced families into becoming *potential* research subjects, whether they want to be or not.

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Finally, we could simply treat Krabbe testing as the long-term research project that it is. Under this plan, we would eliminate the *mandate* for Krabbe testing, so that we would no longer use the power of the state to force parents to test their children as the state does not have a compelling interest to do so. Instead, the test would be *recommended* to parents under a research protocol. In doing so, we would be able to achieve two goals: first, we could find and treat most cases of infantile Krabbe disease and thereby learn how to improve that treatment and second, we could gain important information about how late-onset forms develop in the hope that we can develop treatments for it in the future. As with any research program enrolling children, the state would need to obtain the consent of the parents after providing them with information about the disease, about the treatments for the infantile form and about the research program to follow all at-risk children. Then, at least, parents would know what to expect if their child tests positive, and they could decide if the program sounds too burdensome. This approach, in fact, seems to be favored by parents, who accept newborn screening for diseases that have no treatment because they want to prepare themselves, but who do not favor mandatory screening for late-onset diseases (Hasegawa *et al.*, 2011).

Nevertheless, this proposal has at least two problems. First, requiring consent implies that some parents will *not* consent to the testing, and that raises the possibility that a child with infantile Krabbe will be missed. Because the treatment is burdensome, parents can reasonably reject it, and if the parents would reject the treatment, then the screening is pointless. Gaining the consent of the parents, besides putting the research program on a better ethical footing, has an important side benefit: it would help to create an alliance between the researchers and parents by involving the parents in the process from the beginning, and it would thereby demonstrate respect for their role in their children's health. Such an alliance may prove crucial in helping parents make decisions if their children do develop Krabbe disease (Ross, 2010).[4] The limited experience of parental consent for newborn screening has shown that most parents will usually agree to testing if given the choice (Faden *et al.*, 1982; Botkin, 2009; Comeau and Levin, 2009), so we have reason to think that few, if any, children with disease will be missed.

The second problem is that requiring consent comes with a cost. Getting meaningful consent takes time and effort, and someone will have to pay for it. Past experience has had mixed results (Faden *et al.*, 1982; Laing and MacIntosh, 2004; Feuchtbaum *et al.*, 2007; Miller *et al.*, 2010; Ross, 2010: 304), so we cannot assume that the costs of the consent process will be negligible. In addition, as there will be some costs associated with setting up a mechanism by which only some of the newborn samples are tested for Krabbe, this proposal is likely to increase the costs of the program. These costs, of course, would be part of a research program, and we would have to decide if this research program is the best use of our limited research funds. So, even if this proposal is the best option for dealing with the ethical issues, it may still not win in a competition for research funding.

If such a research program is worthwhile, it should stand on its own merits, and it should not be conducted by hijacking the newborn screening mandate. By gaining the consent of the parents, the state can perform a valuable service by facilitating this research, but it should not coercively recruit patients into it. Thus, while requiring consent from the parents does not solve all of the ethical issues with Krabbe newborn screening, we think it presents the best available approach.

Conclusions

As newborn screening continues to expand and ethical and social conflicts arise (Kemper *et al.*, 2010; Timmermans and Buchbinder, 2010; DeLuca *et al.*, 2011), now is the time to think about how to strike the balance between the ethical concerns. We think that states should proceed cautiously, but that they should be willing to be creative in managing potential conflicts. We make the following recommendations: (i) Mandatory newborn screening should be reserved for diseases that require pre-symptomatic treatment, but only if that treatment is well established and known to have good results and (ii) voluntary screening for diseases can be considered for other diseases, where we have some reason to believe that we can develop better therapies by learning more about the course of the disease. Voluntary screenings, of course, will always require the informed consent of the parents. Such a cautious approach may not be what some newborn screening advocates desire, but it is the best way to minimize the ethical harm that these programs can cause.

Conflicts of interest

J.M.K. is a member of the Krabbe Consortium, an ad hoc group formed to help implement the Krabbe

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Newborn Screening program in New York State. R.H.D. has no conflicts to report.

Notes

1. The extent to which parents can opt out of newborn screening varies from state to state in the USA and from country to country, but even in those places where parents may opt out, they are often unaware that they may do so (Mandl et al., 2002: 272; Kim et al., 2003: e122; Clayton, 2005; Detmar et al., 2007; DeLuca et al., 2011: 58; Nicholls, 2012).
2. A nice flowchart of this process can be found in Kemper et al., 2010: 541.
3. One such study has already been funded by National Institutes of Health to evaluate the progression of brain changes using advanced imaging techniques to develop better prognostic tools (Escolar, 2011).
4. For that reason, some ethicists think that *all* newborn screening should require parental consent (Ross, 2010).

References

ACMG (American College of Medical Genetics). (2006). Newborn Screening: Toward a Uniform Screening Panel and System: Executive Summary. *Genetics in Medicine*, **8**, 1S–11S.

Baily, M. A. and Murray, T. H. (2008). Ethics, Evidence, and Cost in Newborn Screening. *Hastings Center Report*, **38**, 23–31.

Botkin, J. R. (2009). Research for Newborn Screening: Developing a National Framework. In Baily, M. A. and Murray, T. H. (eds), *Ethics and Newborn Genetic Screenings: New Technologies, New Challenges*. Baltimore: Johns Hopkins Press, pp. 212–236.

Clayton, E. W. (2005). Talking with Parents Before Newborn Screening. *Journal of Pediatrics*, **47**, S26–S29.

Comeau, A. M. and Levin, D. E. (2009). Population-based Research with a Public Health Service: Two Models for Compliance with the Common Rule in the Massachusetts Newborn Screening Program. In Baily, M. A. and Murray, T. H. (eds), *Ethics and Newborn Genetic Screenings: New Technologies, New Challenges*. Baltimore: Johns Hopkins Press, pp. 274–291.

DeLuca, J. M., Kearney, M. H., Norton, S. A. and Arnold, G. L. (2011). Parents' Experience of Expanded Newborn Screening Evaluations. *Pediatrics*, **128**, 53–61.

Detmar, S., Hosli, E., Dijkstra, N., Nijsingh, N., Rijnders, M. and Verweij, M. (2007). Information and Informed Consent for Neonatal Screenings: Opinions and Preferences of Parents. *Birth*, **34**, 238–244.

Duffner, P. K., Caggana, M., Orsini, J. J., Wenger, D. A., Patterson, M. C., Crosley, C. J., Kurtzberg, J., Arnold, G. L., Escolar, M. L., Adams, D. J., Andriola, M. R., Aron, A. M., Ciafaloni, E., Djukic, A., Erbe, R. W., Galvin-Parton, P., Helton, L. E., Kolodny, E. H., Kosofsky, B. E., Kronn, D. F., Kwon, J. M., Levy, P. A., Miller-Horn, J., Naidich, T. P., Pellegrino, J. E., Provenzale, J. M., Rothman, S. J. and Wasserstein, M. P. (2009a). Newborn Screening for Krabbe Disease: The New York State Model. *Pediatric Neurology*, **40**, 245–252.

Duffner, P. K., Caviness, V. S. Jr, Erbe, R. W., Patterson, M. C., Schultz, K. R., Wenger, D. A. and Whitley, C. (2009b). The Long-term Outcomes of Presymptomatic Infants Transplanted for Krabbe Disease: Report of the Workshop Held on July 11 and 12, 2008, Holiday Valley, New York. *Genetics in Medicine*, **11**, 450–454.

Escolar, M. L. (2011). *Diffusion Tensor Imaging (DTI) in Krabbe disease*. Studied registered at Clinical Trials.gov., available from: http://clinicaltrials.gov/ct2/show/NCT00787865?term=krabbe+disease&rank=1 [accessed 6 September 2012].

Escolar, M. L., Poe, M. D., Provenzale, J. M., Richards, K. C., Allison, J., Wood, S., Wenger, D. A., Pietryga, D., Wall, D., Champagne, M., Morse, R., Krivit, W. and Kurtzberg, J. (2005). Transplantation of Umbilical-cord Blood in Babies with Infantile Krabbe Disease. *New England Journal of Medicine*, **352**, 2069–2081.

Faden, R., Chwalow, J., Holtzman, N. A. and Horn, S. D. (1982). A Survey to Evaluate Parental Consent as Public Policy for Neonatal Screening. *American Journal of Public Health*, **72**, 1347–1352.

Feuchtbaum, L., Cunningham, G. and Sciortino, S. (2007). Questioning the Need for Informed Consent: A Case Study of California's Experience with a Pilot Newborn Screening Research Project. *Journal of Empirical Research on Human Research Ethics*, **2**, 3–14.

Hasegawa, L. E., Fergus, K. A., Ojeda, N. and Au, S. M. (2011). Parental Attitudes Toward Ethical and Social Issues Surrounding the Expansion of Newborn Screening Using New Technologies. *Public Health Genomics*, **14**, 298–306.

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Kemper, A. R., Knapp, A. A., Green, N. S., Comeau, A. M., Metterville, D. R. and Perrin, J. M. (2010). Weighing the Evidence for Newborn Screening for Early-infantile Krabbe Disease. *Genetics in Medicine*, **12**, 539–543.

Kim, S., Lloyd-Puryear, M. A. and Tonniges, T. F. (2003). Examination of the Communication Practices Between State Newborn Screening Programs and the Medical Home. *Pediatrics*, **111**, e120–e126.

Kolodny, E. H., Raghavan, S. and Krivit, W. (1991). Late-onset Krabbe Disease (Globoid Cell Leukodystrophy): Clinical and Biochemical Features of 15 Cases. *Developmental Neuroscience*, **13**, 232–239.

Krivit, W., Shapiro, E. G., Peters, C., Wagner, J. E., Cornu, G., Kurtzberg, J., Wenger, D. A., Kolodny, E. H., Vanier, M. T., Loes, D. J., Dusenbery, K. and Lockman, L. A. (1998). Hematopoietic Stem-cell Transplantation in Globoid-cell Leukodystrophy. *New England Journal of Medicine*, **338**, 1119–1126.

Laing, I. A. and MacIntosh, N. (2004). Practicalities of Consent. *Lancet*, **364**, 659.

Mandl, K. D., Feit, S., Larson, C. and Kohane, I. S. (2002). Newborn Screening Program Practices in the United States: Notification, Research, and Consent. *Pediatrics*, **109**, 269–273.

Miller, F. A., Hayeems, R. Z., Carroll, J. C., Wilson, B., Little, J., Allanson, J., Bytautas, J. P., Paynter, M., Christensen, R. and Chaktraborty, P. (2010). Consent for Newborn Screening: The Attitudes of Health Care Providers. *Public Health Genomics*, **13**, 181–190.

Nicholls, S. G. (2012). Proceduralisation, Choice and Parental Reflections on Decisions to Accept Newborn Bloodspot Screening. *Journal of Medical Ethics*, **38**, 299–303.

Ross, L. F. (2010). Mandatory Versus Voluntary Consent for Newborn Screening? *Kennedy Institute of Ethics Journal*, **20**, 299–328.

Ross, L. F. (2012). Newborn Screening for Lysosomal Storage Diseases: An Ethical and Policy Analysis. *Journal of Inherited Metabolic Disease*, **35**, 627–634.

Salveson, R. (2011). *Expansion of the New York State Newborn Screening Panel and Krabbe Disease: A Systematic Program Evaluation*. New York: Dissertation, Columbia University.

Timmermans, S. and Buchbinder, M. (2010). Patients-in-waiting: Living Between Sickness and Health in the Genomics Era. *Journal of Health and Social Behavior*, **51**, 408–423.

Wenger, D. A. (2011). Krabbe Disease. In Pagon, R. A., Bird, T. D., Dolan, C. R., Stephens, K. and Adam, M. P. (eds), *GeneReviews*. Seattle: University of Washington.

Wilson, J. M. G. and Jungner, G. (1968). *Principles and Practice of Screening for Disease*. Public Health Papers 34, Geneva: World Health Organization.

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Dev Disabil Res Rev. Author manuscript; available in PMC 2014 May 08.

Published in final edited form as:
Dev Disabil Res Rev. 2011 ; 17(1): 15–18. doi:10.1002/ddrr.133.

Dangerous and expensive screening and treatment for rare childhood diseases: the case of Krabbe disease

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Abstract

Public policy surrounding newborn screening is in flux. New technology allows more screening for more diseases at lower cost. Traditional criteria for target diseases have been criticized by leading health policymakers. The example of newborn screening for Krabbe disease highlights many of the dilemmas associated with population-based screening programs. Krabbe is difficult to diagnose, variable in its natural history, and does not always respond to treatment. The only available treatment is hematopoetic stem cell transplantation, which is expensive, risky, and of uncertain efficacy. This paper analyzes the debate about Krabbe as an example of the sorts of debates that will likely arise for many more diseases over the next decade. I conclude that pilot programs in pioneer states should be carefully evaluated before testing for Krabbe is universalized.

Keywords

newborn screening; lysosomal storage disease; Krabbe; cost-effectiveness; ethics

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There are many dilemmas associated with innovative, potentially dangerous, and expensive treatments for rare and debilitating childhood diseases. First, there is the risk-benefit ratio. New treatments inevitably have unknown risks. That is why we study them carefully. The uncertainty about relative risks and benefits creates tension between our natural and justifiable desire to save children and our justifiable fear that experimental experimental approaches to screening, diagnosis and treatment will do more harm than good. There is a haunting fictional portrayal of such an outcome in Camus' novel, *The Plague,* in which the physician-scientist, Dr. Castel, tries an experimental antiserum on a child. It merely prolongs the child's agonizing final hours, "For moments that seemed endless he stayed in a queer, contorted position, his body racked by convulsive tremors; it was as if his frail frame were bending before the fierce breath of the plague, breaking under the reiterated gusts of fever."[1]

A second sort of dilemma arises if an experimental therapy turns out to be only partially successful and, instead of providing a cure or a successful long-term treatment, is in the case of thyroid hormone for congenital hypothyroidism, it only slows the progression of the disease. In such cases, screening, diagnosis and treatment might savechildren's lives, only to leave them with severe lifelong impairments. This situation does not only arise in the context of rare diseases. It has been an ongoing concern in other areas of pediatrics, such as

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neonatal intensive care for babies born at the borderline of viability. Both of these two concerns ultimately become part of cost-benefit analysis. If screening, diagnosis and treatment programs are expensive and lead to unsatisfactory outcomes, they can be criticized as an inappropriate allocation of scarce societal resources. These concern raise issues of justice, efficiency, and the opportunity costs associated with expensive and marginally successful programs. Since we never have enough money, we should try to spend it where it will do the most good.

Newborn screening for Krabbe disease as a paradigm case

Newborn screening for Krabbe disease illustrates all of these dilemmas. The disease is rare but devastating, the screening program is costly, the natural history of the disease is not well understood, and the only available treatment – hematopeotic stem cell transplantation – is expensive and risky.

How does screening for Krabbe work?

Krabbe disease, also referred to as globoid cell leukodystrophy, causes a deficiency in galactocerebrosidase (GALC), the enzyme responsible for preventing a build up of galactolipids in the brain. Without the regulation of galactolipids, the growth of the myelin sheath around nerve cells is severely impaired. Krabbe disease usually presents in the first 6 months of life, with symptoms such as loss of muscle tone, spasticity, irritability, seizures, and loss of head control, hearing, and sight. A child in the later stages of Krabbe disease is immobilized and has reducing levels of responsiveness and brain activity. Most die before age 2. The younger the child is at the age of diagnosis, the faster the disease progresses.[2] The only potentially effective treatment for Krabbe disease is hematopoetic cell transplant. This has generally been done using umbilical cord blood. In 2005, Escolar et al reported the results of a study of the efficacy of umbilical cord blood transplantation for Krabbe disease. They compared outcomes for eleven infants who were transplanted before the onset of symptoms to outcomes for 14 infants who were transplanted after the development of symptoms. They reported that "Infants who underwent transplantation before the development of symptoms showed progressive central myelination and continued gains in developmental skills, and most had age-appropriate cognitive function and receptive language skills, but a few had mild-to-moderate delays in expressive language and mild-to-severe delays in gross motor function. Children who underwent transplantation after the onset of symptoms had minimal neurologic improvement."[3]

This description of the natural history of Krabbe disease and of the possibility of successful treatment would make it seem like an ideal target for a population-based newborn screening program. However, the story is a little more complicated. Screening programs are designed to identify the gene that is associated with Krabbe disease. But not all children who carry the gene actually develop the disease. Thus, the screening program and the confirmatory tests that follow allow the identification of a population that is "at risk" of developing Krabbe, rather than a population that is destined to develop the disease. Those children must then be followed carefully in order to determine when and whether they show early symptoms of the disease.

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Thus, screening and diagnosis of Krabbe disease is a complex and expensive undertaking. It requires three stages. First, newborn blood spots are analyzed using tandem mass spectrometry. Those that screen positive are sent for DNA testing to determine if they have a mutation in the GALC gene. Finally, those with positive blood spot results and positive DNA analysis are analyzed for galactocerebrosidase activity. Based on the level of galactocerebrosidase activity, they are then categorized as being at high, medium or low risk of actually developing the disease. Those with the lowest levels are at highest risk of becoming symptomatic, while those with higher levels of enzyme activity are at lower risk. The incidence of clinically symptomatic Krabbe is slightly lower than previously thought: 0.26 cases per 100,000 instead of 0.9 cases per 100,000.

Screening for Krabbe disease is complex and expensive. What is the experience in New York State

In 2006, the state of New York became the first state to initiate a newborn screening program for Krabbe. Since then, over a million children have been tested. In 2010, Kemper et al described New York's experience with the first 550,000. [4]

New York's program has increased our understanding of the complexity of Krabbe disease and, by implication, of other lysosomal storage diseases. As with many screening programs, there were some surprises. First, they found that population screening yielded different estimates of the prevalence of disease than prior estimates. Prior to the newborn screening programs, Krabbe disease was thought to affect 1:100,000 newborns in the U.S. In the newborn screening program in New York, however, the rate of positive tests was 5:100,000. Many of the children who screened positive, however, were asymptomatic.

Second, New York realized that not everyone with a positive test had symptoms of the disease. They implemented a program to follow such children clinically. They are tested every child every three months during the first year of life. Testing consisted of neurologic examation, MRI, lumbar puncture, audio and visual evoked response tests, and nerve conduction studies. These tests resulted in a composite risk score.

Children would be referred for transplantation if they had a combination of abnormal neurologic exam, abnormal MRI, increased cerebrospinal fluid protein or abnormalities on other tests. [5] All children in the New York program were to be followed, including those who received a transplant and those who did not. This database should allow evaluation of the efficacy of the screening program, including the program of periodic clinical evaluation of children who test positive but who remain asymptomatic.

Of the 25 babies in New York who have screened positive, only 2 have developed symptoms of Krabbe disease. This gives the screening test a positive predictive value of 8%. Both of the positive children who developed symptoms received a transplant. One died. The other child did not develop any further symptoms of Krabbe but was reported to be "developmentally delayed." Kemper et al concluded, "Diagnosing affected infants identified by newborn screen from a general population is particularly challenging. Children who have screened positive require repeated and sometimes invasive testing to confirm or rule out a

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diagnosis. No peer-reviewed published information is available regarding the completeness of this follow-up or the impact of follow-up on families." [6]

Part of the challenge in such a screening program is to decide how to interpret test results in order to determine with reasonable certainty which infants actually have the disease. The presence of children who screen positive but who remain asymptomatic has led to some difficult choices for doctors, parents and policy makers. The stakes are high. Those who have the disease may benefit from an early stem cell transplant. Such transplants, however, are risky.. The mortality rate after a hematopoetic stem cell transplant is 5–10% Another 10% of patients will develop severe graft-versus-host disease. The outcomes for any particular child may be altered by the histocompatibility factors of the donor bone marrow. In Krabbe, transplants need to be done early if they are to succeed, so the pressure to monitor and diagnose early neurologic symptoms is intense. Any child whose transplant is delayed will have a worse outcome than they might have had with an earlier transplant. But those who do not have the disease will be harmed by undergoing a transplant.

What do we know about cost-effectiveness?

There have been no published cost-effectiveness analyses of newborn screening for Krabbe. There are, however, many analyses of other newborn screening programs. They generally conclude that such screening programs are cost-effective.[7] Some of these analyses focus on screening for a specific disease. Others examine the overall cost-effectiveness of expanding the number of tests on the newborn screening panel. Examples of the former are studies by Haas et al.[8] and van der Hilst et al[9] of screening for medium-chain acyl-CoA dehydrogenase deficiency in Australia and the Netherlends. Examples of the latter include studies by Schulze et al[10] and by Feuchtbaum and Cunningham[11] on screening programs in Germany and in California that used tandem mass spectrometry (MS/MS). Both concluded that expanded screening panels were cost-effective. Schulze et al estimate that each test costs seven dollars, that 1:4100 infants test positive, and that most benefit from early diagnosis. Thus, "costs would be quickly offset by the reduction of expenses for hospitalization and medications…for a patient with an inborn error of metabolism not diagnosed and treated in a timely fashion." Interestingly, they don't include in their analysis the cost of false positive tests or the cost of treatment that doesn't cure the underlying disease. Their model is based on screening for disease for which there is a relatively cheap, safe, and effective treatment. Feuchtbaum and Cunningham, similarly, conclude, "We found that the benefits of MS/MS screening outweighed the costs and that the net benefits were significant and robust in various scenarios with various conservative underlying assumptions." Their analysis was a little more comprehensive than that of Shulze, and included scenarios that modeled differed levels of treatment effectiveness.

None of these cost-effectiveness studies examine situations comparable to the current situation with Krabbe disease. In that situation, the testing is more expensive than is testing for most other newborn diseases. In addition, the treatment is more expensive and less effective than treatment for many other diseases that are diagnosed by newborn screening.

The only analysis of the costs (but not the benefits!) of the New York experience is an unpublished doctoral thesis by Salveson that is available on the internet (http://

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academiccommons.columbia.edu/catalog/ac:132317). Salveson reports, "Over the time period from August 2006 through July 2010, the total cost of the program was estimated to cost an average of $3,002,607. This translates into an annual average cost of $750,652. For the fiscal year 2006–2007, New York State appropriated $11 million to the total newborn screening program, an increase of $2,000,000 from the previous year." This does not include the cost of the confirmatory follow-up testing that is not covered by the state. The average cost to families was $2700, some of which was covered by insurance. They estimated that the total cost of testing was $500,000 and $750,000 per case of disease diagnosed. That did not include the cost of the treatment that those who were diagnosed would need. Thus, Krabbe screening is more expensive than many other screening programs ($11M to screen from 29 diseases), but it is not different by orders of magnitude. It is simply at the high end of costliness. Most other diseases, however, either have simple and effective treatments or no treatment at all. If one combines the cost of screening for Krabbe with the cost of treatment and the uncertain outcomes after treatment, the cost-effectiveness analysis becomes more complex. At this point, there isn't enough data to actually calculate a dollar figure for cost-effectiveness.

This has led to debate. At a meeting reported by the newspaper, *Neurology Today*, two neurologists argued about the value of Krabbe screening. Jennifer Kwon, from University of Rochester, argued that the costs weren't worth it. Nigel Banford, from University of Washington, responded, "There is always a cost consideration, but there is a humanity component as well, If you can rescue a child with a stem cell transplant or other therapies, what a difference that would make to that particular baby and family."[12]

Debates about cost-effectiveness are mired in a set of irresolvable internal tensions that allow different conclusions to be drawn from the same data. The central question is this: what is the value of a life saved? From that question, one can spin off other derivative questions. How should the value of a life be adjusted for quality of life? Are there measures that we can all agree upon to assess the quality of life in a quantitative, objective, and standardized way? Without such measures, cost effectiveness studies must either exclude any considerations of the impairment in their assessments, or they must assign a dollar value to those impairments. Either approach is problematic, the former because it doesn't reflect the way most people think about the value of medical treatments, the latter because it is devalues the lives of people with disabilities.

More importantly, cost-effectiveness analysis are unlikely to be the determining factor in decisions about whether or not to implement programs to screen and treat for rare but devastating diseases. Because the diseases are rare, many of the individual children and families who suffer will be identifiable. It is difficult to deny treatment to identifiable children, no matter how expensive the treatment may be. In the end, cost-effectiveness analysis may indicate just how much we are willing to pay to save the life of a child with Krabbe disease, but they will not persuade anyone about the wisdom of screening or treatment decisions. Those decisions will be driven by emotional factors, political alliances, and moral commitments, rather than underlying costs.

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What do parents think?

If cost is not the driving factor, then decisions will likely be driven by the sentiments of citizens – that is, of voters – who participate in these programs. Thus, we might ask whether parents and pediatricians find the programs helpful or harmful,

Answers to these questions come from qualitative research Salverson interviewed parents whose children tested positive. She reports that most parents were glad to have gotten the information. One parent said, "… to know one way or the other was really important to us, and when I found out what it [Krabbe disease] was and how quickly it hit, that knowing part would be so vital because the amount of time that you would have is so short, and whatever plans you have to make in terms of care and how to deal with the disease would have to be made so quickly." Another parent said, "I think that's a good idea that they do screen for Krabbe because I would never believe my child could have Krabbe, it's beyond thinkable. I would think…they should screen for any of that kind of disease in every state, not only New York State, all throughout the states." Salverson concludes that "Parents were generally supportive of KD screening, and satisfied they knew important information about their child's health." (http://academiccommons.columbia.edu/catalog/ac:132317, p 77.)

Such sentiments by parents, along with the enthusiasm of many doctors and politicians, along with further advances in screening technology all suggest that, in the future, we will see more such screening and treatment programs, not less. This juggernaut of science and politics will create challenges for practicing pediatricians, who must become more knowledgeable about these new tests in order to guide parents through the complicated decisions surrounding newborn screening.

The Future of Newborn Screening. Broadly speaking, there are two ways of analyzing the appropriateness of newborn screening for any particular disease or condition. One view, that might be called the "classic view," is that screening should only be done for diseases that can be treated with proven treatments that are affordable and readily available to all children who are identified by the screening program. This approach evolved out of principles that were famously articulated by Wilson and Jungner in a report that they did for the World Health Organization in 1968.[13]

Recently, some leading scientists and policy makers have challenged the classic view and argue that screening is appropriate even for diseases for which there is no proven treatment available. In such cases, screening has many other purposes. It gives parents diagnostic and prognostic information about their child. It allows parents to make more informed reproductive decisions in the future. In some cases, it may allow research on new treatments for previously untreatable diseases.

Proponents of the classic view include a group of leading pediatric bioethicists who recently warned clinicians, parents and policy makers to "proceed with caution."[14] They warn of the dangers of expanded screening, including the problem of dealing with false-positive results, the lack of a service-delivery infrastructure to care for children who are diagnosed by screening programs, and the legal and ethical issues associated with mandating dozens of new tests. They note that "population screening of asymptomatic individuals is rarely an

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effective approach to uncommon diseases." They advocate more research on the efficacy of the testing programs. They note, "By pooling data on a regional or national basis, information could be acquired on program benefits, harms, and costs with a sufficient number of affected children to inform newborn screening policy decisions." They cite historical examples of situations in which expensive screening programs led to more harm than good., including early screening programs for PKU, sickle cell disease, and neuroblastoma.[15] Instead, these screening programs revealed how little we had understood about the natural history of this childhood cancer.

Opponents of the classic view argue for a new paradigm in evaluating new born screening. Duane Alexander, former head of the National Institute for Child Health and Development, argues that newborn screening programs should be expanded beyond situations that meet the Wilson-Jungner criteria in order to identify as many children with congenital diseases as possible. He acknowledges that, for many such children, there is no currently available treatment. However, he thinks that only through screening will we be able to identify such children and be able to develop new treatments for the. He proposes that we should screen for as many conditions as possible, "including genetic metabolic disorders (especially those associated with mental retardation or neurodegenerative diseases), immunodeficiency disorders, muscular dystrophies, cystic fibrosis, hemoglobinopathies, coagulopathies, and genetic deafness syndromes."[16] His hope is that such screening will become the basis of national registries and that those registries would enable research on innovative treatments for many diseases for which no treatment is currently available. In advocating for such an approach, he explicitly rejects the conventional wisdom that has guided such screening programs for the last forty years, the idea that screening programs should only focus on diseases for which effective treatments are currently available. Alexander calls this cautious approach an outmoded dogma that "dooms us to continued ignorance and unavailability of treatment because affected individuals are not identified until they exhibit symptoms, too late for effective preventive interventions to be tested or applied."

This tension between gung-ho, optimistic scientists and nay-saying, doom-and-gloom bioethicists is a constant feature of the cultural politics of medical innovation today. Scientists tend to see the potential benefits of innovation while ethicists see the potential risks.

For today, Alexander's arguments seem to have prevailed over those of the bioethicists. Most developed countries have expanded the panel of diseases for which routine newborn screening is now done beyond those that meet Wilson-Jungner criteria. [17,18,19] That, of course, does not mean that such programs will ultimately be beneficial or that the ethicists' warnings can be ignored. Only time, and data, will answer that question. For today, Krabbe disease screening, diagnosis and treatment is at the cutting edge of such debates. It is the most controversial newborn screening test in widespread use today. New York State has a program up and running. Illinois and Missouri are about to start newborn screening for Krabbe. Policy makers around the country will watch these vanguard states closely to determine whether the programs are effective, whether they can be implemented as a reasonable cost, and whether children actually benefit from early treatment.

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Acknowledgments

Grant Support: This work

References

1. Camus. The Plague. Modern Library; New York: p. 272
2. Nakamura K, Hattori K, Endo F. Newborn screening for lysosomal storage disorders. Am J Med Genet C Semin Med Genet. 2011; 157:63–71. [PubMed: 21312327]
3. Escloar ML, Poe MD, Provencale JM, et al. Transplantation of Umbilical-Cord Blood in Babies with Infantile Krabbe's Disease. N Engl J Med. 2005; 352:2069–81. [PubMed: 15901860]
4. Kemper AR, Knapp AA, Green NS, et al. Weighing the evidence for newborn screening for early infantile Krabbe disease. Gen Med. 2010; 12:539–43.
5. Duffner PK, Caggana M, Orsini JJ. Newborn sreening for Krabbe disease: the New York State model. Pediatr Neurol. 2009; 40:245–252. [PubMed: 19302934]
6. Kemper AR, Knapp AA, Green NS, et al. Weighing the evidence for newborn screening for early infantile Krabbe disease. Gen Med. 2010; 12:539–43.
7. Grosse SD, Rogowski WH, Ross LF, et al. Population screening for genetic disorders in the 21st century: evidence, economics, and ethics. Public Health Genomics. 2010; 13:106–15. [PubMed: 19556749]
8. Haas M, Chaplin M, Joy P, et al. Healthcare use and costs of medium-chain acyl-CoA dehydrogenase deficiency in Australia: screening versus no screening. J Pediatr. 2007; 151:121–6. [PubMed: 17643760]
9. van der Hilst CS, Derks TG, Reijngoud DJ, et al. Cost-effectiveness of neonatal screening for medium chain acyl-CoA dehydrogenase deficiency: the homogeneous population of The Netherlands. J Pediatr. 2007; 151(2):115–20. [PubMed: 17643759]
10. Schulze A, Lindner M, Kohlmuller D, et al. Expanded newborn screening for inborn errors of metabolism by electrospray ionization-tandem mass spectrometry: results, outcome, and implications. Pediatrics. 2003; 111:1399–1406. [PubMed: 12777559]
11. Feuchtbaum L, Cunningham G. Economic evaluation of tandem mass spectrometry screening in California. Pediatrics. 2006; 117:S280–6. [PubMed: 16735254]
12. Friedman R. Newborn Screening for Krabbe Disease - A Grand Experiment Changes Lives, But Cries for Oversight. Neurology Today. 2008; 8:4–5.
13. Wilson, JMG.; Jungner, G. Principles and practice of screening for disease. Geneva: WHO; 1968. Available from: http://www.who.int/bulletin/volumes/86/4/07-050112BP.pdf
14. Botkin JR, Clayton EW, Fost NC, et al. Newborn screening technology: Proceed with caution. Pediatrics. 2006; 117:1793–99. [PubMed: 16651338]
15. Woods WG, Gao RN, Shuster JJ, et al. Screening of infants and mortality due to neuroblastoma. N Engl J Med. 2002; 346:1041–6. [PubMed: 11932470]
16. Alexander D, van Dyck PC. A vision of the future of newborn screening. Pediatrics. 2006; 117:S350–4. [PubMed: 16735262]
17. Schulze A, Lindner M, Kohlmüller D, et al. Expanded newborn screening for inborn errors of metabolism by electrospray ionization-tandem mass spectrometry: results, outcome, and implications. Pediatrics. 2003; 111(6 Pt 1):1399–406. [PubMed: 12777559]
18. Therrell BL, Adams J. Newborn screening in North America. J Inherit Metab Dis. 2007; 30:447–65. [PubMed: 17643194]
19. Giugliani R. Inborn errors of metabolism in Latin America: challenges and opportunities. J Inherit Metab Dis. 2010; 33(Suppl 2):S315–2. [PubMed: 20454860]

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February 17, 2010

Ms. Jacque Waggoner
Chief Executive Officer
Hunter's Hope Foundation
PO Box 643
Orchard Park, NY 14127

Dear Ms. Waggoner:

The Secretary of Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) appreciates your nomination of Krabbe Disease for inclusion in the Committee's recommended uniform newborn screening panel for State newborn screening programs. Acknowledging the importance of the condition and the status of the test development and treatment, the Committee requested its external evidence review workgroup to formally review the evidence from both published and unpublished data regarding screening, diagnosis, and follow-up care for Krabbe. The attached report from the comprehensive evidence review was presented to the Committee and thoroughly discussed at its September 2009 meeting.

The Committee found Early Infantile Krabbe Disease (EIKD), the "the better defined end of the spectrum, would benefit from early diagnosis and intervention" thus indicating a benefit from screening. However, Committee members also found that "substantial harm is possible (either from testing and/or identification; from treatment/other interventions, or both)". The Committee determined that there are some specific gaps in the evidence that must be addressed in order to further consider adding Krabbe disease to the recommended uniform newborn screening panel. Therefore, the Committee voted to recommend not adding the condition. The wording of that motion is as follows: "*There is insufficient evidence for the Committee to make a recommendation to add the condition to the core panel, and there is insufficient evidence of potential net benefit to lead the Committee to want to make a strong recommendation regarding pilot studies*."

EVIDENCE REVIEW: Krabbe Disease

Prepared for:
MATERNAL AND CHILD HEALTH BUREAU

Revised Final Draft
Version: 12.21.2009

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This review was made possible by subcontract number SC-07-028 to Massachusetts General Hospital, Center for Child and Adolescent Health Policy under prime contract number HHSP23320045014XI to Altarum Institute, from the Maternal and Child Health Bureau (MCHB) (Title V, Social Security Act), Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services (DHHS).

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*****Appendices C, D and E available upon request.

i. Abbreviations used

ACHDNC	Advisory Committee on Heritable Disorders in Newborns and Children
BAEP	Brain-stem auditory evoked potential (also known as **BAER**, brain-stem auditory evoked response)
BMT	Bone marrow transplant
CBT	Cord blood transplant
CI	Confidence interval
CNS	Central nervous system
CSF	Cerebral spinal fluid
CT	Computed tomography
DBS	Dried blood spot
DNA	Deoxyribonucleic acid
EEG	Electroencephalogram
EIKD	Early infantile Krabbe disease
ERG	Evidence review group
FDA	Federal Drug Administration
GALC	Galactosylceramidase
GLD	Globoid Cell Leukodystrophy
GVHD	Graft versus host disease
HSCT	Hematopoietic stem cell transplant
KD	Krabbe disease
LIKD	Late infantile Krabbe disease
LOKD	Late onset Krabbe disease
LSD	Lysosomal storage disease
MeSH	National Library of Medicine medical subject heading
MRI	Magnetic Resonance Imaging
MS/MS	Tandem mass spectrometry
NCS	Nerve conduction studies
NCV	Nerve conduction velocity
VEP	Visual evoked potential

I. Introduction

Krabbe disease (OMIM #245200) is an inborn error of lipid metabolism associated with mutations in the galactosylceramidase (GALC) gene, which is located on the long arm of chromosome 14 (14q31). Krabbe disease is a lysosomal storage disease (LSD) inherited in a classic autosomal recessive manner. Mutations in the GALC gene can cause a deficiency of the hydrolytic enzyme galactocerebrosidase (Wenger et al. 2000), which is responsible for the degradation of certain galactolipids, including galactosylceramide (gal-cer), psychosine (galactosylsphingosine), and monogalactosyldiglyceride (MGD) (Wenger et al. 2000). The inability to degrade these galactolipids, which are found almost exclusively in the myelin sheath, causes abnormal accumulation of galactosylceramide and psychosine, resulting in the death of myelin-producing oligodendrocytes, myelin breakdown, and the presence of Krabbe disease's histologic hallmark: globoid cells (Suzuki 2003). Globoid cells are macrophages, often multi-nucleated, accumulating myelin fragments and undigested galactosylceramide, and are frequently found clustered around blood vessels and abundant in the region of active demyelination (Wenger et al. 2000, Suzuki 2003). Nearly all progressive damage occurs in the white matter of the peripheral and central nervous systems, leading to a rapidly fatal course for untreated infants. Krabbe disease is also referred to as globoid cell leukodystrophy (GLD) for its distinguishing attribute.

In 1916, Danish neurologist Knud Krabbe first described infantile Krabbe disease in two siblings with spasticity who died in infancy and were found to have "diffuse sclerosis" of the brain (Krabbe 1916). A broad range of ages at symptom onset have been documented since the original description of Krabbe disease, leading to four main clinical sub-types distinguished by age of symptom onset: early infantile, late infantile, juvenile and adult (Suzuki 2003, Escolar et al. 2005). Over 60 disease-causing mutations have been identified in the GALC gene (Wenger et al. 2001). Only homozygosity for one specific mutation (a 30-kb deletion that eliminates the entire coding region for one of the enzyme subunits and 15% of the coding region for the other subunit) has been found to be strongly predictive of infantile Krabbe disease (Wenger et al. 2000).

Across all types of Krabbe disease, the average incidence based on data collected prior to the implementation of newborn screening is approximately 1/100,000 in the United States and Europe (Wenger 2008, Wenger et al. 2001). Data from these studies suggest that most (85-90%) of those with Krabbe disease have the infantile form presenting with extreme irritability, spasticity, and developmental delay before age six months (Wenger et al. 2000, Wenger 2008).

Patients with early infantile Krabbe disease (EIKD) present with extreme irritability, spasticity, and developmental delay before six months of age. These children will enter a decerebrate state in early infancy with most dying before two years of age (Wenger et al. 2000). Hematopoietic stem cell transplant (HSCT), often through cord blood transplant (CBT) is the only currently available treatment. HSCT prior to the development of symptoms is believed to be important to maximize treatment outcomes

(Suzuki 2003, Escolar et al. 2005). Although family history leads to early detection of some infants, most infants with Krabbe disease are not detected until they develop clinical symptoms and irreversible neurologic damage (Escolar et al. 2005, Weinberg 2005). The potential value of presymptomatic HSCT has led to a search for methods for population-based newborn screening.

II. Case definition

In order to identify asymptomatic infants with Krabbe disease through newborn screening it is necessary to have a reliable approach to rapid diagnosis in children one month of age or younger. At this age, globoid cells, the pathologic hallmark of Krabbe disease, may not yet be present. Interpretation of genetic testing results is problematic because of the heterogeneity of mutations associated with Krabbe disease and the lack of clear genotype-phenotype correlations.

For this report, we based our case definition on the one used by the New York State screening program. This case definition was based on a consensus of expert opinion. The New York State screening program (Duffner et al. 2009) considers an individual with galactocerebrosidase activity < 0.5 nmol/h/mg protein in peripheral blood leukocytes to be potentially affected. Individuals are then further subdivided by galactocerebrosidase level into high risk (≤ 0.15 nmol/h/mg protein), moderate risk (0.16- < 0.30 nmol/h/mg protein), and low risk (0.3-0.5 nmol/h/mg protein). This risk stratification is used to determine the frequency of evaluation. To be referred for HSCT, children have to receive a certain score based on a combination of neurologic exam findings, magnetic resonance imaging (MRI), cerebral spinal fluid (CSF) protein levels, nerve conduction velocity (NCV), brainstem auditory evoked potentials (BAEP), and visual evoked potentials (VEP). Points are given for abnormal findings as follows: neurological exam (2 points), MRI (2), increased CSF protein (2), NCS (1), BAEP (1), VER (1) and genotyping results of homozygous 30-kb deletion (4). A total score of greater than or equal to 4 indicates the patient may be considered for transplant. Alternatively, individuals who are found to have the 30-kb deletion mutation in both alleles of the GALC gene are referred directly for HSCT. We expect that this case definition will evolve as more data are collected from the New York State screening program.

III. Rationale for review

The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) has directed the Evidence Review Group (ERG) to produce this report for the nominated condition of Krabbe disease. Krabbe disease has been nominated for the following reasons:

1. Without treatment, individuals with early or late infantile Krabbe disease have significant morbidity and die by six years of age (Wenger et al. 2001, Escolar et al. 2005).

2. HSCT before the onset of symptoms may decrease the morbidity and mortality associated with infantile Krabbe disease (Escolar et al. 2005).
3. Methods to screen infants for Krabbe disease have been developed. New York State began newborn screening for Krabbe disease in August 2006.

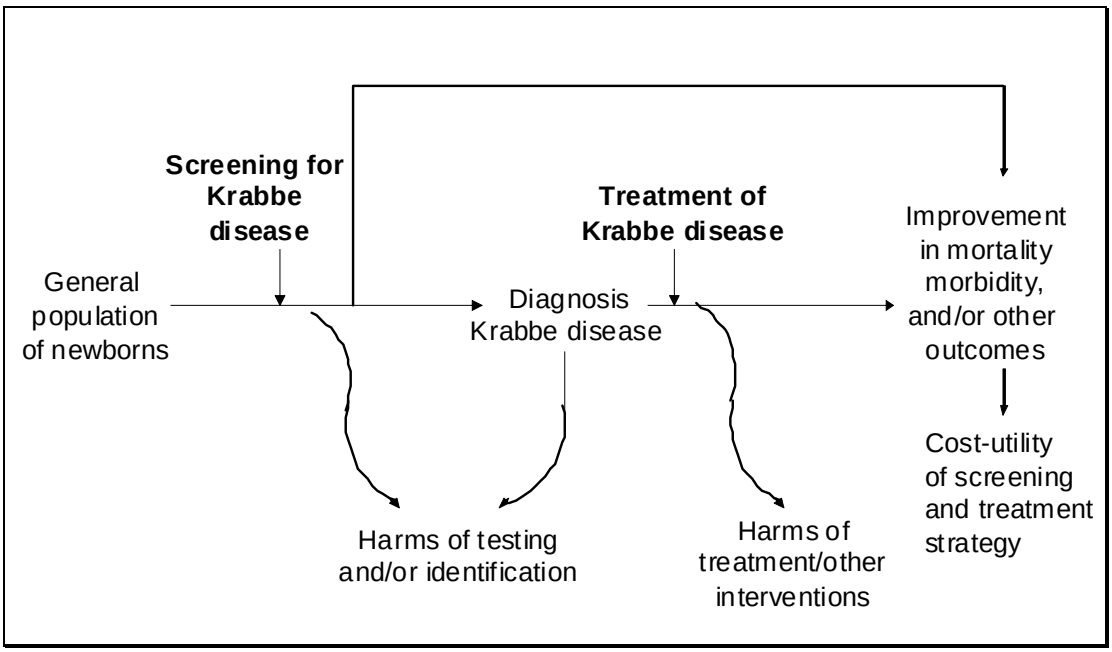
IV. Objectives

The objective of this review is to provide information to the ACHDNC to guide recommendations regarding screening newborns for Krabbe disease. Specifically, the ERG's goal was to summarize the evidence available from published studies, and the critical unpublished data available from key investigators and experts in the field.

V. Conceptual framework

The conceptual framework below (Figure 1) illustrates our approach to evaluating the evidence regarding the potential benefits and harms of newborn screening for infantile onset Krabbe disease. Our goals are (1) to assess the effectiveness of screening and (2) to assess the impact of treatment for those identified through newborn screening versus those identified later through clinical diagnosis.

Figure 1 - Conceptual framework



VI. Statement of main questions

We sought to answer the following questions, with a particular emphasis on the questions related to screening and the potential benefits of early treatment.

A. Natural History and Diagnosis:
   i. Is the condition well-defined?
   ii. What are the prevalence and incidence of the condition and its variations?
   iii. What is the natural history, including the spectrum of severity, of the condition and are there clinically important phenotypic or genotypic variations?

B. Screening Test:
   i. What methods exist to screen newborns for the condition? How accurate are those methods? Do they distinguish between infantile/juvenile and late onset? What are their sensitivity, specificity and analytic validity?
   ii. Do current screening tests effectively and efficiently identify cases of the condition that may benefit from early identification?
   iii. What are the potential harms or risks associated with screening?
   iv. What pilot testing has there been—population-based or other? Which populations have been screened? What have the results shown regarding the sensitivity and specificity of the screening test?

C. Diagnostic Test:
   i. What methods exist to diagnose individuals with positive screens?

D. Treatment:
   i. What treatment options and interventions exist for affected children? Is treatment for affected children standardized, widely available and/or FDA approved?
   ii. Does presymptomatic or early symptomatic intervention in newborns or infants with the condition improve health outcomes? What benefit does treatment, particularly presymptomatic, confer? What is the relationship between treatment outcomes and the timing of treatment intervention? In other words, does identification prior to clinical detection allow for better outcomes?
   iii. What are the potential harms or risks associated with treatment?

E. Economic Evaluation:
   i. What are the incremental costs associated with the screening test for newborn screening programs? What is the cost-effectiveness of newborn screening for the condition?
   ii. What are the costs associated with diagnosis, and the failure to diagnose in the presymptomatic period?
   iii. What is the availability of treatment and what are the costs associated with treatment?

VII. Literature review methods

For this report, we conducted a systematic evidence review. We searched MEDLINE for all relevant studies published over the 20 year period from January 1988 to November 2008. We completed searches combining the National Library of Medicine Medical Subject Heading (MeSH) “Leukodystrophy, Globoid Cell” and the keywords “Krabbe’s Disease” and “Krabbe disease” in an effort to capture all articles written about the disease over this time period. In order to capture articles that have not yet been assigned MeSH terms, we also searched the following keywords within the OVID In-Process and Other Non-Indexed Citations database: Leukodystrophy, Globoid Cell, Krabbe disease and Krabbe’s disease. The search was limited to human studies and

English language publications. This search strategy yielded 316 articles, and captured all references included on the nomination form submitted to the ACHDNC.

Two investigators (authors ARK and AAK) reviewed all abstracts to select articles for inclusion in the review. Articles were eliminated if they were: not human studies; did not focus on infantile onset Krabbe disease; did not address at least one key question; reviews or editorials that did not include new data; case reports or case-series of four or fewer subjects unless there were novel data not available in other larger studies (Appendix B). After abstract review, 72 articles were reviewed in full. After this process, 24 articles met all inclusion criteria and were included in this evidence review. The process was repeated in late March 2009 and again in July 2009 to capture articles published since the initial November 2008 search. The March 2009 search yielded six abstracts, from which three articles were included in this review. The July 2009 search yielded eight abstracts, of which two were included in this review.

The 29 selected manuscripts were divided in half for independent data abstraction by the two investigators. A 20% subset was selected for data abstraction by each investigator to validate the process. Each article was evaluated, using standardized tools, for the quality of the study design (NHS Center for Reviews and Dissemination March 2001, Accessed: October 17, 2008) and the quality of the evidence, as it relates to the category of evidence (Pandor et al. 2004, Pollitt et al. 1997). A given article received only one rating per reader for study design, but may have received multiple quality evaluations for the type of evidence. For example, a study that discusses prevalence and natural history would be evaluated for the quality of the evidence in each of those domains. There were no significant differences in the data extracted by the reviewers.

Table 1 - Study design for abstracted articles

Study Design	Number of Articles
Experimental intervention	0
Cohort study	1
Case-control study	4
Case series	15
Sample size ≤ 10	5
Sample size 11 to 50	7
Sample size ≥ 51	3
Economic Evaluation (from Drummond)	0
Cross-Sectional study	9
Total studies	29

To assure completeness and clarity of the report, a draft of the report was sent to an independent external review panel (see Appendix C for sample conflict of interest form). The report was revised based on their suggestions.

VIII. Methods for interviews with experts

The ERG and the ACHDNC recognize that in a rapidly developing field such as newborn screening for Krabbe disease there may be important but unpublished data. We identified experts, including researchers and Krabbe disease newborn screening advocates, to help us identify this information. These individuals were identified as authors of key papers included in the literature review, through discussions with content experts, and through recommendations from the ERG. These individuals are listed in Table 2.

Experts were sent a letter via e-mail (Appendix D for researchers, Appendix E for advocates) explaining the purpose of the review, a conflict of interest form (Appendix C) and an open-ended survey. Experts had one week to respond. The project coordinator sent a reminder e-mail to those who did not reply. In cases where clarifications were needed regarding the responses, individuals were either sent a follow-up e-mail or contacted via telephone by a member of the ERG (ARK, AAK, or JP). Information from survey responses is provided in this report when the experts and advocates provide information regarding the key questions that are not otherwise available from the selected articles.

Table 2 - List of experts contacted and degree of participation

Name		Title	Replied	Completed written survey	Telephone interview
Georgianne	Arnold, MD	Director of Inherited Metabolic Disorders Clinic, Department of Pediatrics and Genetics, Associate Professor, University of Rochester School of Medicine and Dentistry, Rochester, New York		✓	
Scott	Baker, MD, MS	Director, Fred Hutchinson Cancer Research Center Survivorship Program, Seattle Cancer Care Alliance, Seattle, WA, Professor of Pediatrics, University of Washington, Seattle, WA	✓ ^		
Susan	Berry, MD	Professor & Director, Division of Genetics & Metabolism, Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota	✓ ^		
Paula	Brazeal	President, United Leukodystrophy Foundation	✓ #		
Barbara	Burton, MD	Member of the Division of Genetics, Birth Defects and Metabolism at Children's Memorial Hospital in Chicago, Director of PKU Program and Professor of Pediatrics, Northwestern University's Feinberg School of Medicine, Chicago, Illinois		✓	
Michele	Caggana, ScD	Director, Newborn Screening Program, New York State Department of Health, New York		✓	✓
Victor	De Jesus, PhD	Newborn Screening and Molecular Biology Branch Centers for Disease Control and Prevention Atlanta, Georgia		✓	

Name		Title	Replied	Completed written survey	Telephone interview
Patricia	Duffner, MD	Clinical Director, Hunter James Kelly Research Institute, Professor of Neurology and Pediatrics, Children's Hospital, Buffalo, New York		✓	✓
Florian	Eichler, MD	Assistant Professor of Neurology, Harvard Medical School, Director of the Leukodystrophy Clinic at the Massachusetts General Hospital (MGH), Boston, Massachusetts		✓	
Maria	Escolar, MD	Director, Neurodevelopmental Function in Rare Disorders (NFRD), Carolina Institute for Developmental Disabilities, University of North Carolina, Chapel Hill, North Carolina	✓		✓
Bob & Sonja	Evanosky	Evanosky Foundation	✓#		
Michael	Gelb, PhD	Harry and Catherine Jaynne Boand Professor of Chemistry, Departments of Chemistry and Biochemistry, University of Washington, Seattle, Washington	✓^		
George	Hoganson, MD	Associate Professor of Pediatrics, Head, Division of Genetics, Director, Biochemical Genetics Laboratory University of Illinois at Chicago Medical School, Chicago, Illinois			
Rhona	Jack, PhD	Division Head, Clinical Chemistry, Associate director of biochemical genetics laboratory, Clinical Associate Professor of Laboratory Medicine, Children's Hospital and Regional Medical Center, Seattle, Washington	✓^		
David	Jinks, PhD	Newborn Screening Laboratory Director Division of Laboratories Illinois Dept. of Public Health, Chicago, Illinois	✓*		
Joan	Keutzer, PhD	Vice-President of Scientific Affairs Genzyme Corporation, Cambridge, Massachusetts	✓#		
Edwin	Kolodny, MD	Bernard A. and Charlotte Marden Professor of Neurology and Chairman, New York University, New York, New York	✓#		
Kim	Kubilus	Director of member services, National Tay-Sachs and Allied Diseases Association	✓^		
Joanne	Kurtzberg, MD	Director, Duke Pediatric Blood & Marrow Transplant Program, Chapel Hill, North Carolina		✓	✓
Jennifer	Kwon, MD	Pediatric Neurologist and Associate Professor of Neurology and Pediatrics, University of Rochester Medical Center, Rochester, New York		✓	
Joe	Orsini, PhD	New York Department of Health, Wadsworth Center, Albany, New York		✓	✓
Lawrence	Shapiro, MD	Director of Regional Medical Genetics Center, Professor of Pediatrics and Pathology, New York Medical College, Valhalla, New York	✓^		
Jakub	Tolar, MD	Assistant Professor of Pediatrics, Division of Hematology-Oncology and Blood and Marrow Transplantation, University of Minnesota, Minneapolis, MN		✓	✓
Jacque	Waggoner	CEO of Hunter's Hope Foundation		✓	

Name		Title	Replied	Completed written survey	Telephone interview
Melissa	Wasserstein, MD	Director of the Program for Inherited Metabolic Diseases (PIMD), Associate Professor of Genetics, Genomic Sciences and Pediatrics, Mount Sinai Medical Center, New York, New York			
Kenneth	Weinberg, MD	Anne T. and Robert M. Bass Professor in Pediatric Cancer and Blood Diseases, Division Chief, Division of Stem Cell Transplantation, Stanford Institute for Cancer/Stem Cell Biology and Medicine, Stanford School of Medicine, Stanford, CA			
David	Wenger, PhD	Director, Lysosomal Diseases Testing Laboratory, Neurology Department, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania	✓		✓

* Unable to contribute due to internal policy reasons
# Unable to contribute due to time constraints
^ Deferred to other experts

IX. Results: evidence findings to address the main questions

This section presents the evidence from the included articles organized by key question. Each subsection includes a summary of findings from the literature review, an assessment of the quality of the evidence from each included article, and additional information from the Krabbe disease experts.

A. **Natural history and diagnosis:**

Table 3 - Quality assessment of abstracted literature pertaining to condition

Type of evidence	Number of articles
Incidence (cases per 100,000), average within the U.S.	**4**
Data obtained from whole-population screening or comprehensive national surveys of clinically detected cases.	1
Ia. As in I but more limited in geographical coverage or methodology.	3
Extrapolated from class I data for non-U.S. populations.	0
Estimated from number of cases clinically diagnosed in U.S.	0
Genotype-Phenotype correlation	**8**
Data from retrospective screening studies in U.S. or similar population.	0
Data from systematic studies other than whole population screening.	2
Estimated from the known clinical features of the condition as described for individual cases or short series.	6
Other natural history of disease	**8**

Adapted from Pandor et al. 2004, Pollitt et al. 1997

We sought to answer the following questions on the natural history and diagnosis of Krabbe disease through a literature review and information provided by experts:

i. Is the condition well-defined?
ii. What are the prevalence and incidence of the condition and its variations?

iii. What is the natural history, including the spectrum of severity, of the condition and are there clinically important phenotypic or genotypic variations?

Literature review:
Estimates of the birth incidence of all types of Krabbe disease based on large population case ascertainments in Europe and Japan ranges from about 0.6 – 2 per 100,000 (Heim et al. 1997, Poorthuis et al. 1999). However, the rate has been reported to be higher in some populations (e.g., a specific Arab population) (Korn-Lubetzki, Nevo 2003).

Of the approximately 550,000 newborns screened as of June 30, 2008 (Duffner et al. 2009) in New York, four high-risk children have been identified (0.73 per 100,000), of whom two met criteria for infantile Krabbe disease (0.36 per 100,000) (Duffner et al. 2009). The other two children have not met the case definition criteria by 16 and 8 months of age and are developmentally normal. Six moderate-risk (1.09 per 100,000) and 15 low-risk newborns (2.72 per 100,000) have been identified, none of whom met their case definition criteria.

EIKD is associated with profound neurological impact leading to death. The neurologic effects can be seen as white matter changes on MRI and prolonged or absent BAEP and VEP. There is poor genotype-phenotype correlation (Tatsumi et al. 1995) other than homozygosity of the 30-kb deletion, which is strongly predictive of EIKD. Low levels of galactocerebrosidase activity (Duffner et al. 2009) do not entirely predict the age of symptom onset or severity of white matter changes. There are ongoing efforts being made to develop methods for determining the degree of neurologic involvement prior to symptom development. In EIKD patients, Husain et al. (2004) found that abnormal nerve conduction studies (NCS) were seen first, followed by BAEP, electroencephalogram (EEG) and eventually VEP abnormalities. Their findings illustrated peripheral nervous system involvement very early in EIKD disease process, even before central nervous system (CNS) involvement and onset of symptoms. Additionally, Aldosari et al. (2004) studied BAEP and VEP, and found abnormal BAEP is among the first indications of EIKD onset, and may precede clinical symptoms. Barone et al. 1996 used computed tomography (CT) scans and found high density areas as an early and specific finding in EIKD patients. They also found through imaging studies that EIKD patients displayed cerebellar atrophy, appearing during the first year of life.

Most recently, Escolar et al. (2009) performed diffusion tensor imaging (DTI) studies to identify early markers of Krabbe disease onset in the motor tracts of neonates with EIKD. DTI with quantitative tractography is a method for assessing myelination patterns of the motor tracts. Fractional anisotropy (FA) allows for a quantitative and reproducible analysis of the motor tract images (McGraw et al. 2005). Six neonates with Krabbe disease, diagnosed because of family history or through the New York State screening program, were first evaluated and imaged between one and three weeks of age. Five of the neonates had relatively normal neurological findings and one of the neonates exhibited mild neurological symptoms (clonus in one lower extremity). Compared to 45 unaffected neonates, the images from the neonates with Krabbe showed a more

immature pattern of myelination in the first month of life. All six neonates with EIKD underwent HSCT. Two of the neonates died from complications of the HSCT procedure. The four remaining infants were evaluated again at six, nine, 12 and 24 months of age. At the time of publication, they were all within the age-appropriate ranges for cognitive, receptive language and fine motor development; however, three of the four had gross motor delays at the last follow-up visit. The findings show that DTI can detect differences in corticospinal tracts of neonates with Krabbe disease presymptomatically. Additionally, among the affected children in follow-up, those with higher FA values performed better in standardized assessments.

The most comprehensive description of the natural history of Krabbe disease comes from a description of 334 families abstracted from the Hunter's Hope Krabbe Family Database (Duffner, Jalal & Carter 2009). This database began collecting data on children with Krabbe disease in 1997 through family self-report. Subjects who underwent HSCT were excluded. Information regarding age of symptom onset was available for 114 children in the database. Among them, 71% presented with symptoms at or before six months, 19% between seven and 12 months, 6% between 13 and 24 months, 3% between 25 and 36 months, and 1% at five years. The most common presenting symptom was crying or irritability. The average time to diagnosis was approximately five months (n=103). Eleven children were not diagnosed until after death or the diagnosis of an affected sibling. The average survival was associated with the age of onset of symptoms, ranging from 24 months for those with symptoms that developed at or before 6 months compared to 89 months for those with symptoms that developed between 7 and 12 months.

Expert information:
Experts responding to our survey corroborated the literature findings. They agreed that prior to the New York State pilot screening experience, the incidence of Krabbe disease was estimated to be 1 per 100,000 births in the United States and nearly all (90%) were expected to have infantile onset disease.

Dr. Caggana and Dr. Orsini provided updated data regarding the New York State Department of Health Krabbe disease screening program. New York State has screened 769,853 newborns as of June 30, 2009; seven high-risk children have been identified (0.91 per 100,000), of whom two met criteria for EIKD (0.26 per 100,000). Thirteen moderate-risk newborns have been identified (1.69 per 100,000), and 36 low-risk (4.68 per 100,000). None of the screen positive newborns who have not been diagnosed with Krabbe disease have been diagnosed with another lysosomal storage disease. These data demonstrate a lower incidence (0.26 per 100,000) than initially estimated (approximately 0.9 per 100,000) for EIKD.

New York State created consensus-based criteria to determine which infants should be referred for transplant, and created "risk" categories (high, moderate, low). Dr. Caggana and Dr. Orsini state the risk categories are based primarily on the enzyme activity level measured at the diagnostic testing laboratory of Dr. Wenger, in conjunction with their genotyping results. Because there is a wide normal GALC activity range, the New York

screening program assesses any polymorphisms and sequences variants by full gene DNA sequence analysis of the coding and promoter regions and the 5' and 3' intronic sequences along with GALC activity to predict risk level. Dr. Wenger shared that there may be many more mutations that have never been previously identified, the impact of which are unknown. In individuals identified without a family history of Krabbe disease, Dr. Wenger's lab makes predictions of disease onset based upon experience with previously diagnosed individuals having severe and mild mutations and combinations of mutations. Dr. Wenger reports that approximately 45% of patients diagnosed with Krabbe disease have at least one copy of the 30-kb deletion.

Dr. De Jesus agrees that neither enzyme level nor genotype reliably predicts disease course, and Dr. Burton stated that the type of Krabbe disease is usually determined by clinical presentation and especially the age of symptom onset. Experts agreed that unless the child is homozygous for the 30-kb deletion, it is usually unclear what the significance of a given genotype will be since much of the literature consists of single case reports. Expert consensus maintains that genotypes homozygous for the 30-kb deletion are associated with the early infantile phenotype. Dr. Duffner reported more than 75 mutations associated with Krabbe disease exist, with numbers too small at this time to predict clinical course of a child's genotype with certainty.

Dr. Escolar believes a very detailed clinical exam of the baby is the most predictive of developing Krabbe disease; however, exams are not easily reproducible. Dr. Escolar is working to develop better tools for clinicians using MRI and nerve conduction studies, in the hope of developing consistent and standardized ways to detect the disease before children become symptomatic. Dr. Escolar states that her work with MRI to date has shown that even at birth, the corticospinal tracts of children with Krabbe disease look much more affected than age-matched control newborns. She reports that in general, MRIs of newborns with Krabbe disease compared to MRIs of unaffected newborns revealed demyelination of the cortical spinal tracts in the affected newborns. Due to the uncertainty of timing of symptom onset, Dr. Kurtzberg reports that infants diagnosed in-utero (because of a sibling's diagnosis) have been delivered earlier than term to try to start the transplant process as quickly as possible. No evidence was provided on outcomes of babies delivered early.

B. **Screening test:**

Table 4 - Quality assessment of abstracted literature pertaining to screening test

Type of evidence	Number of articles
Overall sensitivity and specificity of screening	**3**
Data obtained from screening programs in U.S. population or similar.	1
Data from systematic studies other than from whole population screening.	0
Estimated from the known biochemistry of the condition.	2
False positive rate	**2**
Data obtained from screening programs in U.S. population or similar.	1
Data from systematic studies other than from whole population screening.	0
Estimated from the known biochemistry of the condition.	1
Repeat specimen rate	**1**
Data obtained from screening programs in U.S. population or similar.	1
Data from systematic studies other than whole population screening.	0
Estimated from the known biochemistry of the condition.	0
Second-tier testing	**1**
Data obtained from screening programs in US population or similar.	1
Data from systematic studies other than whole population screening.	0
Estimated from the known biochemistry of the condition.	0
Other screening test characteristics	**6**

Adapted from Pandor et al. 2004, Pollitt et al. 1997

We sought to answer the following questions on the screening test for Krabbe disease through a literature review and information provided by experts:

i. What methods exist to screen newborns for the condition? How accurate are those methods? Do they distinguish between infantile/juvenile and late onset? What are their sensitivity, specificity and analytic validity?
ii. Do current screening tests effectively and efficiently identify cases of the condition that may benefit from early identification?
iii. What are the potential harms or risks associated with screening?
iv. What pilot testing has there been—population-based or other? Which populations have been screened? What have the results shown regarding the sensitivity and specificity of the screening test?

Literature review:

Newborn screening for Krabbe disease, which is based on determining GALC enzyme activity in dried blood spots (DBS), is possible with tandem mass spectrometry to detect enzyme products (Li et al. 2004a, Li et al. 2004b, Zhang et al. 2008). The New York State screening program, which has screened more than 700,000 newborns, retests the same blood spot if GALC activity is < 20% of the daily mean activity and considers the

result positive if the level is ≤ 8% of the daily mean activity (Duffner et al. 2009). The rationale for these cutoff values was published recently in Orsini et al. (2009). Data have not been reported in the literature regarding the overall number of positive test results or the false positive rate. There is a published report describing the number of infants who have tested positive. We updated those data below with the most recent data provided by the New York screening program.

The New York State screening algorithm cutoff values were developed as a result of a study that measured the GALC activity of 139,000 anonymous newborn DBS in comparison to unaffected and affected controls by MS/MS methodology (Orsini et al. 2009). GALC activities were converted to a percent of the daily mean activity (%DMA) over a seven month testing period. The cutoffs of the New York screening method were established by considering the highest %DMA of the Krabbe positive specimens. Because cross-contamination was thought to contribute to elevated %DMA, the screening method includes retesting samples with GALC activity less than or equal to 20% to minimize false negative results. The authors report that conservative cutoff values were set to minimize false negative results. Krabbe positive samples were compared to known Krabbe carrier samples (from parents and unaffected siblings of Krabbe disease patients) and the ranges of %DMA were found to overlap between the two groups. For this reason, the screening method includes sequence analysis so that only those individuals with a GALC activity in the intermediate range with one or more known or novel mutations are considered a screen positive referral (Orsini et al. 2009) – i.e., those without any mutations are considered screen negative.

Figure 2 - New York State pilot screening program cutoffs, testing algorithm and number of newborns screened (in parentheses) at each stage as of June 2009

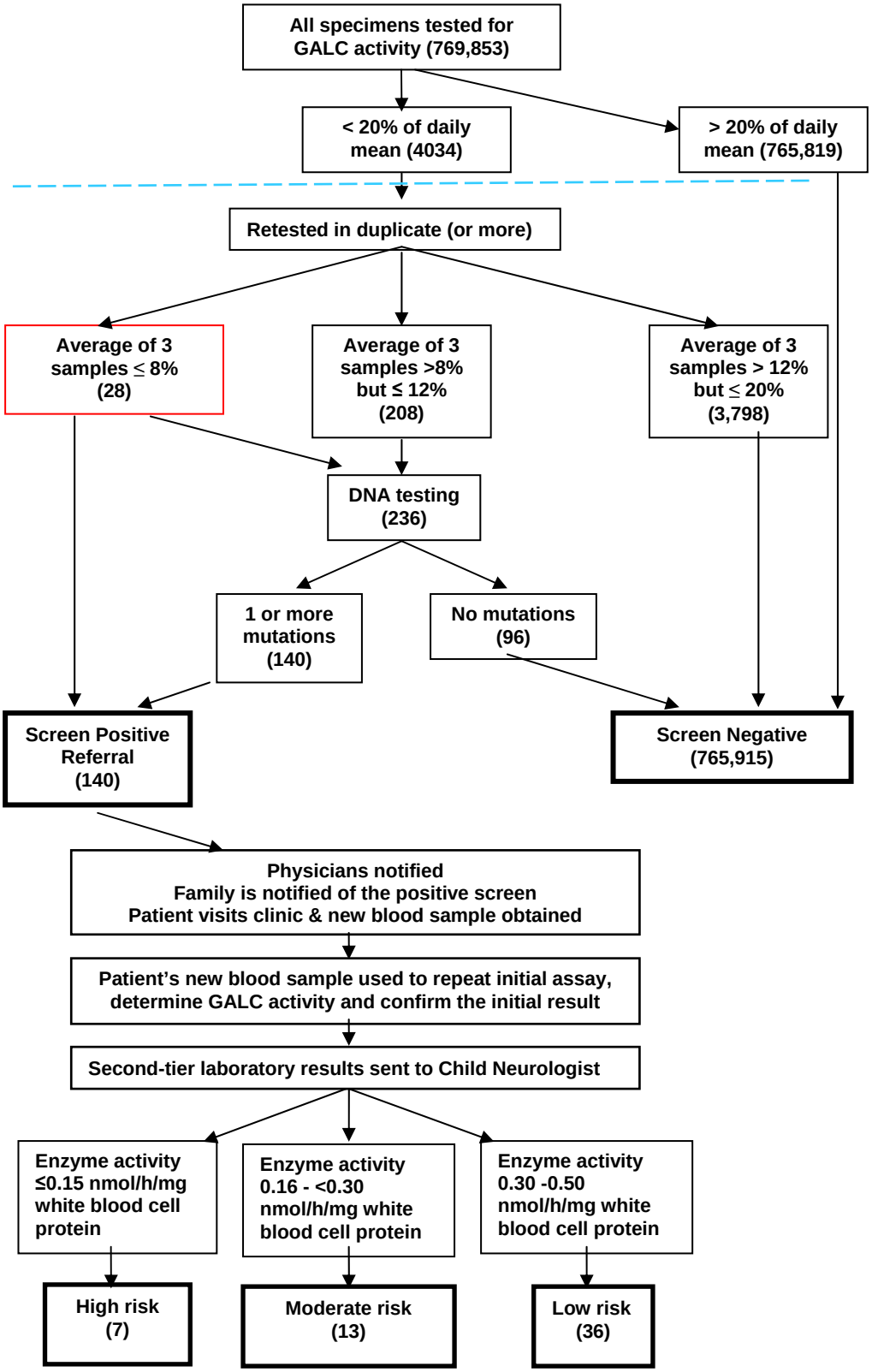


Figure adapted from the Management Guidelines: Krabbe disease published by the Wadsworth Center, New York State Department of Health (http://www.wadsworth.org/newborn/krabbe.htm), Duffner et al. 2009 and data from interviews with Dr. Caggana and Orsini

Expert information:

The most recent New York state pilot screening program information has been provided by Dr. Caggana and Dr. Orsini from the New York State Department of Health. They have tested 769,853 specimens for GALC activity as of June 2009. Those with less than 20% GALC activity are retested in duplicate using at least two new dried blood spot punches from the original sample. To that date, 4,034 specimens had been retested at this stage. Any specimen with less than 8% GALC activity is referred. All specimens with less than or equal to 12% GALC activity detected undergo DNA testing to determine genetic mutations. DNA results are usually available the afternoon after the low GALC activity is determined.

Full gene DNA sequence analysis is completed for all specimens with activities less than or equal to 12% GALC activity to determine the complete genotype. New York State does not refer the newborn for either diagnosis or treatment, if DNA testing indicates only polymorphisms, i.e., benign sequence variations known to not be associated with Krabbe disease. Any specimen with less than 8% GALC activity is considered a screen positive, even if no mutations are detected upon DNA testing. However, Dr. Caggana and Dr. Orsini believe that as more data become available, this protocol will likely be modified to refer any specimen with GALC activity less than or equal to 12% and 1 or 2 mutations identified, in order to minimize false positives. They report this second-tier test reduces their screen positive rate by approximately 40%. With GALC activity level in conjunction with DNA sequencing results, newborns are placed into either the high- or moderate-risk category. Both the newborn screening GALC activity and DNA results are made available to the newborn's physician when they are notified of the screen positive result; typically five days after the lab receives the initial sample. New York State and the Krabbe Consortium have no evidence of any missed cases, no evidence of screen positive newborns being diagnosed definitively with later onset Krabbe disease, and none of the screen positive newborns have been diagnosed with another leukodystrophy.

Table 5 - New York State pilot screening program August 2006 - June 2009*

Activities of pilot screening program	June 2009 data
Total newborns screened	769,853
Screen positive newborns (referred for and completed diagnostic evaluations)	140
High-risk newborns (enzyme activity ≤ 0.15 nmol/h/mg white blood cell protein)	7
Referred for HSCT (Genotype:1 newborn homozygous for 30-kb deletion, 1 newborn compound heterozygous for 30-kb deletion and novel mutation)	2/7
Moderate-risk newborns (enzyme activity 0.16 - <0.30 nmol/h/mg white blood cell protein)	13
Low-risk newborns (enzyme activity 0.30 - 0.50 nmol/h/mg white blood cell protein)	36

*Most recent data provided by Dr. Orsini and Dr. Caggana

Of the seven high-risk cases detected in New York (Table 6), two were considered EIKD and referred for HSCT because of their GALC genotypes and the early signs of neurologic disease. One of these patients was homozygous for the 30-kb deletion mutation, while the other patient was heterozygous for the 30-kb deletion and a novel mutation. Dr. Wenger reports that the five remaining children who screened high risk had genotypes considered to put them at a low risk for early onset of disease. Dr. Caggana and Dr. Orsini state that two of these children were lost to follow-up and three are being followed on a quarterly basis by a neurologist. One of these children is known to be asymptomatic and the other two are assumed to be asymptomatic as Dr. Caggana and Dr. Orsini have not heard otherwise. If the goal of screening is to detect those at moderate or high risk for Krabbe disease, the positive predictive value is 14.3%. If the goal is only to detect those at high risk, the positive predictive value is 5.0%.

Regarding the two high-risk screen positive infants who are not followed up clinically, Drs. Duffner, Caggana and Orsini shared that one is a child whose family returned to their country of origin and the other child's family refused follow-up.

Table 6 - Follow-up of the seven high-risk infants from New York State*

Infant	Birth month	Outcome
1	March 2007	Following up, assumed asymptomatic
2	March 2007	Confirmed EIKD, underwent HSCT
3	July 2007	No follow-up, returned to country of origin
4	August 2008	No follow-up, family refused
5	August 2008	Confirmed EIKD, underwent HSCT, died approximately 11 days posttransplant **
6	November 2008	Following up, asymptomatic
7	December 2008	Following up, assumed asymptomatic

*As described by Dr. Caggana and Orsini
** As described by Dr. Kurtzberg

Dr. Duffner currently follows patients who have screened in the low and moderate risk categories. She says that when these children are asymptomatic, families agree to BAEP, NCS, and other testing that does not require anesthesia. She reports that no one performs tests such as MRI that require anesthesia on low- and moderate-risk children unless there is a particular concern, since it is difficult for families of otherwise healthy appearing children to agree to participate in exams needing anesthesia.

Hunter's Hope Foundation has compiled a database with over 400 Krabbe-affected families sharing their personal experiences with their child's clinical course. When parents with an affected child were asked whether they think newborns should be screened for Krabbe disease and why, many stated their frustrations with initial wrong diagnoses or too late diagnosis, thereby missing the treatment window prior to their child's onset of severe symptoms. Parents state that learning of the diagnosis earlier, through newborn screening, would have decreased the lengthy search for a diagnosis, which families report was a painful experience. They believe that learning of the diagnosis through newborn screening would also provide the choice of a treatment option. One family that tested positive through the New York state pilot screening program contributed to the database. This newborn and mother were both found to be carriers through the newborn screening process.

Dr. Caggana and Dr. Orsini share that New York State uses full gene sequencing to distinguish affected newborns from carrier newborns. They explained the difficulty in cases where a novel mutation is detected, and it is difficult to determine whether it is a "disease-causing" mutation or a common polymorphism. They also test both parents (if possible) and examine their genotypes to determine mutations present only in the newborn. New York State has sequenced over 200 specimens with normal activity to acquire data on common polymorphisms, giving them more information than what is currently reported in the literature. DNA results from New York State show all newborns in the high, and all newborns but one in the moderate risk categories have two variants and multiple polymorphisms in the GALC gene. Some of the mutations found are known to be "disease-causing," while others are novel mutations. Predictions of phenotype,

which can be difficult, are based on the presence of a frameshift, type of amino acid change, and location in the gene.

Dr. Kwon adds that she cannot predict which, if any, of the moderate- and low-risk patients will become symptomatic. She suspects some of these patients are carriers, but the program will continue to follow them. Dr. Arnold agrees and adds that they cannot predict which, if any, of the asymptomatic infants will develop Krabbe disease in their lifetime, particularly among the moderate- and low-risk infants having two variants. She appreciates the dilemma created by the identification of novel variants. She notes that the number of infants having two variants (known or novel) is many times higher than the predicted incidence of Krabbe disease and thus late onset Krabbe disease (LOKD) is either underdiagnosed or these patients will not become symptomatic in their lifetime. She adds that because of this uncertainty, physicians are unable to provide prognostic information to parents of asymptomatic patients at the present time.

Dr. Duffner has created a registry to track the outcomes of each child who screens positive for Krabbe disease in New York State, in addition to an international Krabbe disease registry. Dr. Duffner reports that as of July 2009, of the 60 New York children who have screened low to high risk, 22 are followed by her registry. Participation in the Krabbe disease registry and outcome study varies between follow-up centers. Follow-up data is not consistently captured from all of the screen positive children, even among those in the low and moderate risk ranges that are being followed clinically. Dr. Duffner also described a proposed follow-up study of Krabbe disease screen positive children based on a model for studying quality of life in infants with medulloblastomas. This model uses telephone-based interviews with parents and has the potential to be independent of the child's clinical follow-up visits.

Dr. De Jesus stated the Centers for Disease Control and Prevention (CDC) has established a quality assurance program for LSD newborn screening, including Krabbe disease (De Jesus et al. 2009). This effort was created in response to New York's Krabbe disease newborn screening activities. Dr. De Jesus also informed us that the State of Illinois has mandated newborn screening for five LSDs, including Krabbe disease, for which the CDC provides reagents. Dr. Burton states the newborn screening program has not yet been initiated in Illinois, and Dr. De Jesus estimated that the pilot testing program in Illinois will commence in late 2010. In addition, Missouri has pending legislation to mandate newborn screening for five LSDs in its newborn screening panel.

C. **Diagnostic test**

We sought to answer the following question on a diagnostic test for Krabbe disease through a literature review and information provided by experts:

i. What methods exist to diagnose individuals with positive screens?

Literature review:

Diagnosis is based on GALC activity with either supportive genetic analysis (i.e., homozygous for 30-kb deletion) or clinical findings (Duffner et al. 2009). Approximately

nine laboratories in the country offer GALC enzyme testing (University of Washington, 2009). Close follow-up is necessary because of the variable phenotypic expression of Krabbe disease associated with low GALC activity. Clinical evaluation and follow-up schedule for children who are screen positive for Krabbe disease in New York State depend on the risk category of the positively screened child (Duffner et al. 2009). All risk categories maintain specific intervals of follow-up and children in all risk categories undergo a neurologic examination at each visit. If this examination is abnormal, all patients proceed to have neurodiagnostic studies completed which include MRI, CSF protein and cells, BAEP, VEP, and NCS (Duffner et al. 2009). Children in the high-risk category undergo these exams at the baseline visit and every three months; those in the moderate-risk category only annually or if other concerns arise; and those in the low-risk category only when the neurologic examination is abnormal (Duffner et al. 2009). All patients annually undergo neuro-psychologic testing.

Expert information:
Experts responding to our survey corroborated the literature findings.

Dr. Caggana and Dr. Orsini report that measurement of GALC activity in lymphocytes is most commonly used to diagnose patients. This diagnostic test cannot accurately phenotype Krabbe patients, thus if the activity is low, a combination of diagnostic tests described by Duffner et al. (2009) (in literature section above) is performed to phenotype the patients. They shared that one issue concerning the diagnosis is that there is a limited, but growing, body of reference data for newborns for the panel of tests used (NCS, BAEP, VEP, MRI).

Dr. Kwon shares that when there is referral to her metabolic center, they send a confirmatory enzyme level to Dr. David Wenger's lab as a part of the New York State pilot screening program. They also send blood for HLA typing at the same time to expedite tissue matching in the event that the child should need a rapid transplant. In addition, they repeat the heel stick on a fresh screening card. At times, they have had to use arterial puncture or scalp veins to obtain the blood. Samples are also obtained from the parents to confirm the DNA findings. Dr. Kwon adds that it is challenging to diagnose any young infant with only subtle neurologic abnormalities.

Dr. Wenger believes that his laboratory could manage nationwide confirmatory GALC testing for Krabbe disease screen positive samples, based on the volume he receives from New York State (approximately one sample per week). He says he is unsure of the potential number of samples to expect with a nationwide screening program; he is not sure if the burden on his laboratory would be too great if other state programs had higher false positive rates, thereby more samples, than New York. Dr. Wenger has spoken with Illinois concerning their potential screening program.

D. **Treatment:**

Table 7 - Quality assessment of abstracted literature pertaining to treatment

Type of evidence	Number of articles
Effectiveness of treatment	**5**
I. Well-designed RCTs.	0
II-1. Well-designed controlled trials with pseudo randomization or no randomization.	0
II-2. Well-designed cohort studies:	1
A. prospective with concurrent controls	0
B. prospective with historical control	1
C. retrospective with concurrent controls.	0
II-3. Well-designed case-control (retrospective) studies.	1
III. Large differences from comparisons between times and/or places with and without intervention	0
IV. Opinions of respected authorities based on clinical experience, descriptive studies and reports of expert committees.	2
Other treatment characteristics	1

Adapted from Pandor et al. 2004, Pollitt et al. 1997

We sought to answer the following questions on the treatment of Krabbe disease through a literature review and information provided by experts:

i. What treatment options and interventions exist for affected children? Is treatment for affected children standardized, widely available and/or FDA approved?
ii. Does presymptomatic or early symptomatic intervention in newborns or infants with the condition improve health outcomes? What benefit does treatment, particularly presymptomatic, confer? What is the relationship between treatment outcomes and the timing of treatment intervention? In other words, does identification prior to clinical detection allow for better outcomes?
iii. What are the potential harms or risks associated with treatment?

Literature review:

The only currently accepted treatment for Krabbe disease is HSCT, usually accomplished through CBT (Escolar et al. 2005, Siddiqi, Sanders & Massey 2006, Escolar et al. 2006, Gaipa et al. 2003, McGraw et al. 2005). As described, the New York screening program has referred two infants for HSCT. Both received CBT before 28 days of life. One of the infants died during transplantation (Duffner et al. 2009).

Enzyme replacement therapy (ERT) for EIKD has not yet been developed. Shire Human Genetic Therapies has announced a clinical trial for Krabbe disease ERT that is currently in the preclinical phase with a projected launch between 2012 and 2015.

Characteristics used for determining which children receive transplants

A retrospective case series (Escolar et al. 2006) was conducted to develop a staging system to predict outcome after CBT. This study included 26 patients with EIKD and 11 patients with late infantile Krabbe disease (LIKD), of whom 29 were treated (26 with CBT, three with matched related donor bone marrow). The authors created a four-stage system based on groupings of neurologic problems: stage 1 patients appeared to be developing normally but may have had inconclusive neurological findings, stage 2 patients had obvious neurological symptoms, stage 3 patients had signs of moderate to severe neurological involvement and stage 4 patients had advanced disease. Individuals in stages 1 and 2 had 100% survival through HSCT versus those in stages 3 (61.5% survival) and 4 (0% survival). The five stage 3 individuals who died lived 7.5–50 months posttransplant. Follow-up data are available for ten of the stage 3 individuals; 6/10 made no developmental gains over time.

Infants with an older sibling with EIKD may be tested and diagnosed prenatally or at birth based on this family history. Duffner et al. (2009) state that with EIKD there is much less clinical variability within families than in LOKD and that there is certain knowledge to assume that without transplant, an infant diagnosed with EIKD will experience neurological destruction and eventually death (Duffner et al. 2009).

Mortality and morbidity for those transplanted presymptomatically and postsymptomatically (see also: Table 8 & 9 and Expert information)

Data about the effectiveness of HSCT for Krabbe disease are available from outcomes of children who were treated after the development of symptoms compared to outcomes of asymptomatic newborns diagnosed prenatally or soon after birth. Because of the difficulty in establishing the diagnosis of EIKD in asymptomatic newborns and the genotype-phenotype variability, it is possible that the asymptomatic neonates may have had a different disease course than their affected siblings.

One case series (Escolar et al. 2005) identified 11 asymptomatic newborns and 14 symptomatic infants, all of whom underwent CBT. This report compared survival for these two groups and an untreated control group. The untreated control group was made up of 190 individuals from the Hunter's Hope registry. This report did not provide the ages of symptom onset for the control group.

Among the 11 asymptomatic children, six were diagnosed with Krabbe disease prenatally and five shortly after birth because of an affected sibling. This report did not provide the case definition used to diagnose Krabbe disease, the age of symptom onset for the affected sibling and did not provide the children's' genotypes and pre-transplant GALC levels for the asymptomatic newborns. All untreated affected siblings died between approximately 10 and 50 months of age. Nine of the 11 asymptomatic newborns had abnormal NCS before transplantation. Two of the 11 asymptomatic newborns had an abnormal EEG before transplantation. Seven of the 11 asymptomatic newborns had abnormal MRI findings before transplantation. Three of the eight

asymptomatic newborns tested had abnormal VEP before transplantation. Four of the eight asymptomatic newborns tested had abnormal BAEP before transplantation. The median age at CBT was 28 days for the asymptomatic neonates. The 14 symptomatic children were diagnosed between four and nine months of age. The median age at CBT was 236 days for the symptomatic children.

All 11 of the asymptomatic newborns survived for 36 months, the entire period for which data were available for this group at the time of writing. In contrast, only six of the 14 symptomatic infants survived for a median follow-up of 41 months. Death was due to progressive disease (n=4), graft-versus-host disease (GVHD) (n=1), procedural complication (n=1), and infection (n=2). The survival rate among these asymptomatic newborns was greater than both the control group of untreated children (P=0.001) and the symptomatic infants (P=0.01). The survival rate of the symptomatic infants was not statistically different from the control group (P=0.28),

A group of experts convened in July 2008 to address the long-tem outcomes of presymptomatic infants transplanted for EIKD (Duffner et al. 2009). Transplant centers from around the United States and Canada presented 25 cases of presymptomatic transplant for Krabbe disease. The mortality rate from transplant in this cohort was 15%. Of the children who survived, none have died of progressive Krabbe disease (with the oldest among them at 13 years of age) as compared to the average lifespan of children with untreated EIKD, which is 23 months (however children living beyond eight years has been reported). HSCT appears to attenuate the disease, but over time most children have developed slowly progressive spasticity, leading to eventual inability to walk without assistive devices, somatic growth failure, expressive language deficits and poor brain growth (Duffner et al. 2009).

Table 8 - Abstracted literature regarding early transplant morbidity

Study	Population	Patient Survival Outcomes
Escolar et al. 2005 & 2006* (USA)	Asymptomatic children: 2005:11 patients diagnosed prenatally or at birth because of an affected sibling 2006: 11 Stage 1 patients (appear to be developing normally but may have inconclusive neurological findings) Symptomatic children: 2005:14 patients diagnosed between 4 and 9 months of age 2006: 4 Stage 2 patients 13 Stage 3 patients 1 Stage 4 patient	2005: • Donor cell engraftment was 100% for both infants and newborns • Transplants prior to symptom onset maintained progressive central myelination, maintained normal vision and hearing and normal cognitive development except for areas influenced by gross motor development, some continued to gain gross motor skills compared to untreated controls • Transplants post symptom onset did not result in substantive neurologic improvement from transplant • GVHD developed in 8/11 newborns and 5/14 infants 2006: • All stage 1 and 2, and some stage 3 children achieved normal enzyme levels (1–7 nmol/hour/mL) posttransplant • Two children in stage 3 and the child in stage 4 failed to meet normal enzyme levels posttransplant • All eleven Stage 1 children continued to show an adequate rate of development in all of the domains except for gross motor development, the greatest variation among the group was in gross motor development, most of these children seem to gain skills normally for a period of time after transplant followed by no further development of skill • Stage 2 late infantile patients posttransplant continued to gain skills in all areas except gross motor, where there was no further development of skills • Stage 2 early infantile patients showed gains in most developmental domains except gross motor function • Stage 3 late infantile patients showed very minimal gains in most developmental areas and had no gains in motor function posttransplant • Stages 3 and 4 children had no developmental gains posttransplant •
Gaipa et al. 2003^ (Italy)	Symptom status not stated: 3 patients	• All 3 patients achieved 100% donor chimerism, required only one HSCT each • One patient's GALC activity was equal to that of donor's post-HSCT • No patients developed GVHD
McGraw et al. 2005*,^ (USA)	Asymptomatic children: 3 patients identified because of an affected sibling and very low or absent levels of GALC, received transplant in first month of life Symptomatic children: 4 patients received clinical diagnosis based on neurologic symptoms and signs of Krabbe disease and very low or absent levels of GALC, received transplant in first year of life	• Neurodevelopmental evaluations were performed and compared to age-matched controls, a standard score of 5 in each domain represented a score equal to or above the age-adjusted general population score • Early transplant group mean scores - expressive language, 3.33 (range, 3– 4), receptive language, 3.67 (range, 3–4), gross motor skills, 2.67 (range, 1–5), fine motor skills, 3.67 (range, 3–5), cognitive ability, 3.33 (range, 3– 4) • All patients in the late transplantation group had developmental scores of 1 in every category

Study	Population	Patient Survival Outcomes
Siddiqi et al. 2006*,^ (USA)	Early treatment: 3 patients with EIKD – transplant within first month of life	• At baseline, the average peroneal motor conduction velocity was comparable in the early and late treatment groups • One year after HSCT the average peroneal motor CV and F-wave latency improved in both groups though significantly more in the early group
	Late treatment: 3 patients with EIKD – transplant between four and six months	

Table 9 - Abstracted literature regarding symptoms at transplant and survival rates

Study	Population	Age at HSCT	Survival	Death
Escolar et al. 2005 & 2006* (USA)	Asymptomatic children: 2005:11 patients diagnosed prenatally or at birth because of an affected sibling 2006: 11 Stage 1 patients (appear to be developing normally but may have inconclusive neurological findings)	2005: 12-44 days 2006: Stated stage at transplant, but not age	2005: 100% survival at median of 36 months posttransplant (last data provided) 2006: 100% survival rate (follow-up between 24-108 months old)	2005: None 2006: None
	Symptomatic children: 2005:14 patients diagnosed between 4 and 9 months of age 2006: 4 Stage 2 patients 13 Stage 3 patients 1 Stage 4 patient	2005: 142–352 days 2006: Stated stage at transplant, but not age	2005: 6/14 at median of 41 months posttransplant (last data provided) 2006: Stage 2: 100% survival rate (follow-up between 24-108 months old) Stage 3: 61.5% survival rate;	2005: 8/14 patients died, due to: progressive disease (n=4), graft-versus-host disease (n=1), procedural complication (n=1), infection (n=2) 2006: Stage 3: 5/13 patients died, mean survival time was 21.4 months posttransplant (range 7.5-50 months) Stage 4: 1/1 patient died, a few weeks after the procedure
Gaipa et al. 2003^ (Italy)	Symptom status not stated: 3 patients	74, 79 and 109 months of age	100% survival at 68, 708, 384 days post-HSCT (last follow-up for each patient prior to publication), 100% donor chimerism, one patients' GALC activity was equal to that of donor's	None

Study	Population	Age at HSCT	Survival	Death
McGraw et al. 2005*,^ (USA)	Asymptomatic children: 3 patients	Prior to 1 month of age	100% survival at 24, 36 and 48 months after transplant (last follow-up for each patient prior to publication)	None
	Symptomatic children: 4 patients	During first year of life (mean 6.5 months; range 5-8 months)	3/4 patients are alive approximately two years posttransplant (last follow-up for each patient prior to publication)	One patient died at 34 months of age, and 28 months posttransplant of unexplained causes
Siddiqi et al. 2006*,^ (USA)	Asymptomatic children: 3 patients	Prior to 1 month of age	Average follow-up was 18 months (6 months to 3 years); did not state survival rates	Not stated
	Symptomatic children: 3 patients	During first year of life (average of 5 months; range 4-6 months)	Average follow-up was 18 months (6 months to 3 years); did not state survival rates	Not stated

*Potential patient overlap between Escolar et al. 2005, Escolar et al. 2006, McGraw et al. 2005 and Siddiqi et al. 2006
^Article included data on more subjects; however, patients with a different leukodystrophy than GLD, or later onset Krabbe disease were not included in table

Neurodevelopmental outcomes for those transplanted presymptomatically and postsymptomatically

Escolar et al. (2005) evaluated brain imaging and other neurologic studies to determine the differences in impact of treatment between the groups of asymptomatic and symptomatic children described above. All 11 of the asymptomatic newborns who underwent CBT had normal myelination changes by MRI. In contrast, disease progression was found by MRI among the symptomatic children (n=12 of 13 with available data). Among those asymptomatic neonates with VEP available before and after transplant (n=8), three were abnormal (considered abnormal if the P100 wave was missing) before HSCT but were normal by four months after transplant. Among symptomatic children with VEP available before and after transplant (n=12), eight were abnormal both before and after HSCT and four subjects developed abnormal VEP after CBT. CBT was associated with improvements in NCS among the asymptomatic neonates (7 out of 9 improved). However, two children in this group initially had improvement in NCS but worsened after one year. In the symptomatic group, thirteen had abnormal NCS (considered abnormal if they showed prolongation of the distal latency, low amplitude, no evoked response, or prolonged latency of the F wave) prior to treatment and seven had abnormal NCS after CBT. All symptomatic patients had abnormal EEGs (considered abnormal if focal or generalized slowing or if spikes or sharp waves were present) before and after CBT, and all survivors had clinical seizure activity. In contrast, eight of the 11 asymptomatic children had normal results both prior to CBT and 4 months to 6 years posttransplant. One asymptomatic child had a normal EEG prior to CBT but an abnormal result at six and a half months. However, subsequent EEGs were normal. Two of the asymptomatic children had abnormal EEGs prior to CBT (one newborn showed temporal sharp waves and the other showed sharp waves and asymmetric delta activity). Follow-up EEGs were not performed for either child.

Complete neurodevelopmental assessment was described for 10 of the 11 asymptomatic neonates and eight of the 14 symptomatic children who underwent CBT. One of the challenges of neurodevelopmental assessment is that motor delays can impact the assessment of cognitive function and language. Overall, all asymptomatic newborns developed cognitive skills at a normal rate, two were below average for adaptive behavior skills, one was below average for receptive language, two were below average for expressive language, four had mild-to-severe gross motor delay, two had subtle motor abnormalities, and two had severe delays in fine motor function. Over time, gross motor development could change. For example, two of six children with previously normal gross motor development developed leg spasticity and truncal weakness that interfered with standing or walking. In contrast to the asymptomatic newborns, the symptomatic children had poor neurodevelopment.

Expert information:
The consensus from experts is that HSCT is the only treatment option besides palliative care. Dr. Burton states that palliative care includes supportive care measures such as nutrition with gastric tube feedings if needed, sedation and/or pain medication. There is no standard protocol for transplantation.

Characteristics used for determining which children receive transplants

New York State follows a clinical and neurodiagnostic evaluation rating scale to determine which of the high-risk screen positive infants are candidates for HSCT (Duffner et al. 2009). Points are given for abnormal findings as follows: neurological exam (2 points), MRI (2), increased CSF protein (2), NCS (1), BAEP (1), VER (1) and genotyping results of homozygous 30-kb deletion (4). A total score of greater than or equal to 4 indicates the patient may be considered for transplant. Dr Kurtzberg reports she determines if a newborn with low GALC activity is a candidate for transplant by relying on family history, genotype and nine clinical parameters. These nine clinical parameters were the basis of the scoring system used by New York State (Duffner et al. 2009).

Mortality and morbidity for those transplanted presymptomatically and postsymptomatically

Dr. Escolar has managed the care of children with Krabbe disease for approximately ten years. She currently follows 17 patients post-HSCT, ranging from two to 12 years post-HSCT. Pre-transplant GALC values and genotype data for this cohort were unavailable. Regarding outcomes, onset of symptoms post-HSCT has varied among her patients, some before they were able to walk and others after. She has noted no further progress in development of their motor skills however, she has not observed regression. Of her 17 patients, two or three can ambulate completely independently (one can run, jump and has normal gross motor development); most of the others need walkers or other support for ambulation, and a few use wheelchairs. She has noted that peripheral neuropathy worsens over time.

Dr. Kurtzberg reported on her experience with children with Krabbe disease. She described the same cohort of newborns as Dr. Escolar who were transplanted for EIKD, not including the two children who screened positive in New York. Of the18 transplanted, she noted they all had a family history of Krabbe, at least one 30-kb deletion and in most of these children, six of the nine clinical parameters were abnormal upon examination. Of the18 newborns transplanted for EIKD in her cohort, one died from sepsis posttransplant. Referring to the same population as Dr. Escolar, she reports that a third of these individuals have had normal motor function through the first decade of life, another third are ambulatory but need devices to help them walk and the final third have severe spasticity and use wheelchairs. The oldest transplanted patient Dr. Kurtzberg follows is 13 years of age. This child was transplanted at three weeks old. She reports that this child is 95% normal. The child runs and plays normally but has some stiffness in one ankle that developed at nine years of age. Dr. Kurtzberg has also been involved in the transplants of the two children who were identified as high-risk through the New York State screening program. She reports that one of these children died approximately 11 days posttransplant.

Dr. Tolar reported on his experience in Minnesota. He shared that 17 children with symptomatic Krabbe disease have been transplanted in Minnesota since 1986. Nine are alive today, all of whom are quite delayed. He has experience with one child who was diagnosed with Krabbe very early in life due to a family history. This child had a transplant last April, at three and half months of age. He says that at the age of one year and three months, the child is able to sit, but not walk.

Dr. Burton reports that her team has performed HSCT on two EIKD patients not reported in the literature. Both infants were transplanted at under one month of age, and a second transplant was completed between two and three months of age on one patient due to failure to engraft. The patient who received two transplants is developmentally delayed, but is otherwise doing well at three years of age; this patient's older affected sibling died at 18 months of age. The other patient had symptoms at three weeks of age at the time of transplant and is ventilator dependent at five months of age and is doing poorly; the patient's affected sibling died at nine months of age.

Neurodevelopmental outcomes for those transplanted presymptomatically and postsymptomatically

Several experts reported on the neurodevelopmental outcomes of the children described above. Dr. Escolar reported that of the 17 post-HSCT patients she follows, the less involved patients have normal cognitive abilities. The more involved patients have difficultly with speed of processing. They are able to answer questions (for example, on an IQ test) but it takes them longer than control children. However, if these tests are adapted for their degree of motor impairment, the speed of processing appears more normal. Dr. Kurtzberg says of the same group of patients that they all have normal intelligence and all communicate well. Dr. Tolar reports on the one child he follows who was transplanted early at three and half months of age. He says that at

the age of one year and three months, the child can vocalize but lacks understandable words.

Dr. Eichler reported his experience that neurodevelopmental outcome is closely tied to the age of the child at HSCT. Furthermore, damage related to the EIKD continues until there is full engraftment and new glial cells develop. Dr. Eichler believes that the cortico-spinal tract is most sensitive to Krabbe disease, thus explaining the greater impact on motor function. He has not noted regression in neurodevelopment after HSCT, but at least ten years of follow-up would be helpful to ensure that this does not occur.

Experts concur about the lack of substantial data regarding the potential harms of HSCT. Dr. Duffner shared that the chemotherapy used to suppress the infant's immune system prior to HSCT is a potential harm of the treatment, including the potential damaging effects of chemotherapy on oligodendrites and myelin in the brain. She notes that late deterioration occurring in children who have had transplants could reflect a combination of chemotherapy toxicity, pre-existing disease and progressive Krabbe disease.

Treatment locations and Krabbe disease transplant registry

Duke University in North Carolina and the University of Minnesota in Minnesota are the main sites currently treating Krabbe disease with HSCT. Mt. Sinai Hospital in New York has begun to perform transplants in metabolic patients, and Dr. Kurtzberg states there are approximately eight centers total in the United States currently experienced in transplantation of infants with Krabbe disease. Dr. Duffner shares that there have been transplants performed for both EIKD and LOKD at sites besides Duke University and University of Minnesota, which include sites in: Chicago, Illinois, Columbus, Ohio, St. Louis, Missouri, Grand Rapids, Michigan in the United States and Canada (Montreal, Quebec and Vancouver, British Columbia). Additionally, Dr. Burton reports two centers in Illinois. Dr. Kurtzberg states that the protocol for transplant for Krabbe disease is the same as for other childhood diseases except that radiation is not used. She believes other centers familiar with this protocol can be trained to transplant for Krabbe disease.

The registry of the Pediatric Bone Marrow Transplantation Consortium (PBMTC) continues to compile data on patients transplanted for Krabbe disease. Dr. Duffner shared that a multidisciplinary workshop is planned for late summer 2009 with the goal of developing a standardized protocol to assess long-term outcomes.

E. **Economic evaluation**

Table 10 - Quality assessment of abstracted literature pertaining to economic evidence

Type of evidence	Number of articles
Economic	**0**
I. Evaluation of important alternative interventions comparing all clinically relevant outcomes against appropriate cost measurement and including a clinically sensible sensitivity analysis.	0
II. Evaluation of important alternative interventions comparing a limited number of outcomes against appropriate cost measurement, but including a clinically sensible sensitivity analysis.	0
III. Evaluation of important alternative interventions comparing all clinically relevant outcomes against inappropriate cost measurement, but including a clinically sensible sensitivity analysis.	0
IV. Evaluation without a clinically sensible sensitivity analysis	0
V. Expert opinion with no explicit critical appraisal, based on economic theory	0

Adapted from NHS Centre for Reviews and Dissemination Report 4, March 2001

We sought to answer the following questions on the economic evaluation of newborn screening for Krabbe disease through a literature review and information provided by experts:

i. What are the incremental costs associated with the screening test for newborn screening programs? What is the cost-effectiveness of newborn screening for the condition?
ii. What are the costs associated with diagnosis, and the failure to diagnose in the presymptomatic period?
iii. What is the availability of treatment and what are the costs associated with treatment?

Literature review:
We found no economic evaluations of screening for Krabbe disease.

Expert information:
Dr. Caggana and Dr. Orsini report the startup cost of the New York State laboratory was approximately $1,000,000, which included three tandem mass spectrometers, two liquid handlers, evaporators, and two DNA fragment analyzers. The actual reagent screening costs for tandem mass spectrometry testing, reagents and consumables are $0.39 per baby, and $283,530 for the 727,000 screens completed. For diagnostic enzyme analysis, the cost is $12,500 per year, which has been derived from approximately 50 referrals annually at $250 per newborn. In terms of DNA costs, after screening 769,853 babies, 236 have had full DNA sequence analysis completed. The DNA analysis costs about $650 per newborn, and per infant screened it is approximately $0.20. There is no estimate available regarding medical work-up costs.

X. Key findings and summary

Children with EIKD develop profound neurologic deficits and typically die by two years of age. Advances in technology have made it possible to detect those with Krabbe disease in newborn screening blood spots. Direct enzyme replacement therapy is not available; however, galactocerebrosidase can be provided to affected individuals via HSCT.

The most comprehensive information about the birth incidence of Krabbe disease comes from the New York screening data, which could identify those with all forms of Krabbe disease. No cases of infantile Krabbe disease have been reported to be missed by that program (i.e., sensitivity = 100%). Population-based screening often uncovers a different spectrum of disease than epidemiology based on case-finding. For example, screening can detect those cases that would go undiagnosed, including those with severe disease leading to rapid death prior to diagnosis, those with typical disease that was never properly diagnosed, and those with minor disease for which diagnosis was never sought. In New York, the observed prevalence of infantile-onset Krabbe disease is less than that predicted based on other epidemiologic evaluations (0.26 cases per 100,000 vs. 0.9 cases per 100,000) but the overall prevalence of Krabbe disease, regardless of type, has been higher (5 per 100,000 vs. 1 per 100,000). The greatest challenge to understanding the epidemiology is the classification into type based on risk categorization. Because of the lack of genotype-phenotype correlation except for one specific mutation, complex criteria based on genotype, exam, and other neurologic tests have formed the basis for the case definition with regards to determining when HSCT should be offered.

The overall specificity of the New York screening program is >99.9% if a positive screen is considered the point of family and physician notification and a positive result is the identification of a high risk newborn (765,915 screened negative, 140 families and physicians notified leading to seven high risk newborns). The specificity is still >99.9% if a positive result is considered to be referral to bone marrow transplantation. The subsequent risk stratification leads to uncertainty about those who are high risk but not referred for bone marrow transplantation (which is five out of the seven identified in New York), those who are moderate risk (13 in New York), and low risk (36 in New York). Refining the process of risk stratification and subsequent follow-up, which is an active area of research, may decrease the uncertainty and decrease the amount of testing required. As described by the experts, this follow-up can be challenging (e.g., one high-risk child moved out of the country, one high-risk patient's family refused follow-up) which emphasizes the importance of the ongoing research to improve the process of diagnosis.

Currently only one laboratory provides diagnostic confirmation of GALC levels. The director of the laboratory believes that there is sufficient capacity to serve as a national confirmatory laboratory center as long as the false positive rate remains low. Experts believe that there are sufficient numbers of bone marrow transplantation programs for those with early-onset Krabbe disease, although families may have to travel far for

treatment. These different sites seem to use generally similar protocols (e.g., no radiation). However, efforts to standardize approaches are ongoing. If such standardized protocols are developed, other sites may be able to offer transplantation.

Evaluating the outcomes of treatment is challenging. Although bone marrow transplantation involves risk of morbidity and mortality, treatment of those with infantile Krabbe disease presymptomatically or at the first development of symptoms appears to decrease the risk of mortality.

Assessing the impact of transplantation on neurodevelopment is challenging. There are several challenges to evaluating this evidence:

1. Heterogeneity in how the disorder was diagnosed (e.g., newborn screening, sibling of affected individual)
2. Differences in the age at the time of HSCT
3. Variability in follow-up with few data extending into the second decade of life
4. Incomplete data with some loss to follow-up
5. Lack of standardized measures at specific time intervals

The evidence suggests that HSCT in presymptomatic or early symptomatic children with EIKD improves neurodevelopmental outcome. Motor function appears to be more affected after HSCT than cognitive development. At least one-third of children would need some ambulatory assistance. Insufficient long-term data are available to evaluate whether there is a plateau or regression in neurodevelopment.

We identified several questions that we were unable to answer from the available evidence. Most of these are active areas of research.

- What are the appropriate ways to identify asymptomatic infants with low galactocerebrosidase levels who would benefit from bone marrow transplantation?
- What are the harms associated with screening, especially in the identification of asymptomatic infants with low galactocerebrosidase levels?
- What are the long-term neurodevelopmental outcomes for children who have received transplant?
- What is the cost-effectiveness of screening for Krabbe disease?

XI. References

Aldosari M, Altuwaijri M, Husain AM. Brain-stem auditory and visual evoked potentials in children with Krabbe disease. *Clin Neurophysiol.* 2004 Jul; 115(7): 1653-1656.

Autti T, Joensuu R, Aberg L. Decreased T2 signal in the thalami may be a sign of lysosomal storage disease. *Neuroradiology.* 2007 Jul; 49(7): 571-578.

Bambach BJ, Moser HW, Blakemore K, Corson VL, Griffin CA, Noga SJ, Perlman EJ, Zuckerman R, Wenger DA, Jones RJ. Engraftment following in utero bone marrow transplantation for globoid cell leukodystrophy. *Bone Marrow Transplant.* 1997 Feb; 19(4): 399-402.

Barone R, Bruhl K, Stoeter P, Fiumara A, Pavone L, Beck M. Clinical and neuroradiological findings in classic infantile and late-onset globoid-cell leukodystrophy (Krabbe disease). *Am J Med Genet.* 1996 May 3; 63(1): 209-217.

Bernal OG, Lenn N. Multiple cranial nerve enhancement in early infantile Krabbe's disease. *Neurology.* 2000 Jun 27; 54(12): 2348-2349.

Beslow LA, Schwartz ES, Bonnemann CG. Thickening and enhancement of multiple cranial nerves in conjunction with cystic white matter lesions in early infantile Krabbe disease. *Pediatr Radiol.* 2008 Jun; 38(6): 694-696.

Boelens JJ. Trends in haematopoietic cell transplantation for inborn errors of metabolism. *J Inherit Metab Dis.* 2006 Apr-Jun; 29(2-3): 413-420.

Breningstall GN, Patterson RJ. Acquired obstructive hydrocephalus in globoid-cell leukodystrophy. *Pediatr Neurol.* 2008 Oct; 39(4): 279-280.

Callahan JW, Skomorowski MA. Diagnosis of Krabbe disease by use of a natural substrate. *Methods Mol Biol.* 2006; 347: 321-330.

Caniglia M, Rana I, Pinto RM, Fariello G, Caruso R, Angioni A, Dionisi Vici C, Sabetta G, De Rossi G. Allogeneic bone marrow transplantation for infantile globoid-cell leukodystrophy (Krabbe's disease). *Pediatr Transplant.* 2002 Oct; 6(5): 427-431.

Cesaro S. Will a reduced-toxicity conditioning regimen improve the results of stem cell transplantation in metabolic disease? . *Bone Marrow Transplant.* 2006 Mar; 37(6): 615.

Ceuterick C, Martin JJ. Krabbe globoid cell leukodystrophy. electron microscopy shows characteristic inclusions in eccrine sweat glands. *Pathol Res Pract.* 1993 May; 189(4): 384-386.

Corti P, Peters C, Balduzzi A, Bertagnolio B, Biondi A, Bugarin C, Dassi M, Furlan F, Gaipa G, Longoni D, Maglia O, Parini R, Perseghin P, Uderzo C, Uziel G, Masera G, Rovelli A. Reconstitution of lymphocyte subpopulations in children with inherited metabolic storage diseases after haematopoietic cell transplantation. *Br J Haematol.* 2005 Jul; 130(2): 249-255.

De Jesus VR, Zhang XK, Keutzer J, Bodamer OA, Muhl A, Orsini JJ, Caggana M, Vogt RF, Hannon WH. Development and evaluation of quality control dried blood spot materials in newborn screening for lysosomal storage disorders. *Clin Chem.* 2009 Jan; 55(1): 158-164.

De Meirleir LJ, Taylor MJ, Logan WJ. Multimodal evoked potential studies in leukodystrophies of children. *Can J Neurol Sci.* 1988 Feb; 15(1): 26-31.

Del Bigio MR, Chudley AE, Booth FA, Pacin S. Late infantile onset Krabbe disease in siblings with cortical degeneration and absence of cerebral globoid cells. *Neuropediatrics.* 2004 Oct; 35(5): 297-301.

Duffner PK, Caggana M, Orsini JJ, Wenger DA, Patterson MC, Crosley CJ, Kurtzberg J, Arnold GL, Escolar ML, Adams DJ, Andriola MR, Aron AM, Ciafaloni E, Djukic A, Erbe RW, Galvin-Parton P, Helton LE, Kolodny EH, Kosofsky BE, Kronn DF, Kwon JM, Levy PA, Miller-Horn J, Naidich TP, Pellegrino JE, Provenzale JM, Rothman SJ, Wasserstein MP. Newborn screening for Krabbe disease: The New York state model. *Pediatr Neurol.* 2009 Apr; 40(4): 245-252.

Duffner PK, Caviness VS,Jr, Erbe RW, Patterson MC, Schultz KR, Wenger DA, Whitley C. The long-term outcomes of presymptomatic infants transplanted for Krabbe disease: Report of the workshop held on July 11 and 12, 2008, Holiday Valley, New York. *Genet Med.* 2009 Jun; 11(6): 450-454.

Duffner PK, Jalal K, Carter RL. The Hunter's Hope Krabbe family database. *Pediatr Neurol.* 2009 Jan; 40(1): 13-18.

Escolar ML, Poe MD, Martin HR, Kurtzberg J. A staging system for infantile Krabbe disease to predict outcome after unrelated umbilical cord blood transplantation. *Pediatrics.* 2006 Sep; 118(3): e879-89.

Escolar ML, Poe MD, Provenzale JM, Richards KC, Allison J, Wood S, Wenger DA, Pietryga D, Wall D, Champagne M, Morse R, Krivit W, Kurtzberg J. Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease. *N Engl J Med.* 2005 May 19; 352(20): 2069-2081.

Escolar ML, Poe MD, Smith JK, Gilmore JH, Kurtzberg J, Lin W, Styner M. Diffusion tensor imaging detects abnormalities in the corticospinal tracts of neonates with infantile Krabbe disease. *Am J Neuroradiol.* 2009 May; 30(5): 1017-1021.

Eto Y, Shen JS, Meng XL, Ohashi T. Treatment of lysosomal storage disorders: Cell therapy and gene therapy. *J Inherit Metab Dis.* 2004; 27(3): 411-415.

Finelli DA, Tarr RW, Sawyer RN, Horwitz SJ. Deceptively normal MR in early infantile Krabbe disease. *Am J Neuroradiol.* 1994 Jan; 15(1): 167-171.

Fu L, Inui K, Nishigaki T, Tatsumi N, Tsukamoto H, Kokubu C, Muramatsu T, Okada S. Molecular heterogeneity of Krabbe disease. *J Inherit Metab Dis.* 1999 Apr; 22(2): 155-162.

Gaipa G, Dassi M, Perseghin P, Venturi N, Corti P, Bonanomi S, Balduzzi A, Longoni D, Uderzo C, Biondi A, Masera G, Parini R, Bertagnolio B, Uziel G, Peters C, Rovelli A. Allogeneic bone marrow stem cell transplantation following CD34+ immunomagnetic enrichment in patients with inherited metabolic storage diseases. *Bone Marrow Transplant.* 2003 May; 31(10): 857-860.

Galvin-Parton PA. Screening for GALC to make neonatal diagnosis and initial neonatal stem cell treatment with umbilical cord blood. *Pediatr Transplant.* 2003 Apr; 7(2): 83-85.

Gelb MH, Turecek F, Scott CR, Chamoles NA. Direct multiplex assay of enzymes in dried blood spots by tandem mass spectrometry for the newborn screening of lysosomal storage disorders. *J Inherit Metab Dis.* 2006 Apr-Jun; 29(2-3): 397-404.

Guzzetta F, Rodriguez J, Deodato M, Guzzetta A, Ferriere G. Demyelinating hereditary neuropathies in children: A morphometric and ultrastructural study. *Histol Histopathol.* 1995 Jan; 10(1): 91-104.

Heim P, Claussen M, Hoffmann B, Conzelmann E, Gartner J, Harzer K, Hunneman DH, Kohler W, Kurlemann G, Kohlschutter A. Leukodystrophy incidence in germany. *Am J Med Genet.* 1997 Sep 5; 71(4): 475-478.

Husain AM. Neurophysiologic studies in Krabbe disease. *Suppl Clin Neurophysiol.* 2006; 59: 289-298.

Husain AM, Altuwaijri M, Aldosari M. Krabbe disease: Neurophysiologic studies and MRI correlations. *Neurology.* 2004 Aug 24; 63(4): 617-620.

Ida H, Rennert OM, Watabe K, Eto Y, Maekawa K. Pathological and biochemical studies of fetal Krabbe disease. *Brain Dev.* 1994 Nov-Dec; 16(6): 480-484.

Kaye EM, Ullman MD, Kolodny EH, Krivit W, Rischert JC. Possible use of CSF glycosphingolipids for the diagnosis and therapeutic monitoring of lysosomal storage diseases. *Neurology.* 1992 Dec; 42(12): 2290-2294.

Kleijer WJ, Keulemans JL, van der Kraan M, Geilen GG, van der Helm RM, Rafi MA, Luzi P, Wenger DA, Halley DJ, van Diggelen OP. Prevalent mutations in the GALC gene of patients with Krabbe disease of Dutch and other European origin. *J Inherit Metab Dis.* 1997 Aug; 20(4): 587-594.

Korn-Lubetzki I, Dor-Wollman T, Soffer D, Raas-Rothschild A, Hurvitz H, Nevo Y. Early peripheral nervous system manifestations of infantile Krabbe disease. *Pediatr Neurol.* 2003 Feb; 28(2): 115-118.

Korn-Lubetzki I, Nevo Y. Infantile Krabbe disease. *Arch Neurol.* 2003 Nov; 60(11): 1643-1644.

Krabbe K. A new familial, infantile form of diffuse brain sclerosis. *Brain.* 1916; 39: 74-114.

Krivit W. Allogeneic stem cell transplantation for the treatment of lysosomal and peroxisomal metabolic diseases. *Springer Semin Immunopathol.* 2004 Nov; 26(1-2): 119-132.

Krivit W, Aubourg P, Shapiro E, Peters C. Bone marrow transplantation for globoid cell leukodystrophy, adrenoleukodystrophy, metachromatic leukodystrophy, and hurler syndrome. *Curr Opin Hematol.* 1999 Nov; 6(6): 377-382.

Krivit W, Lockman LA, Watkins PA, Hirsch J, Shapiro EG. The future for treatment by bone marrow transplantation for adrenoleukodystrophy, metachromatic leukodystrophy, globoid cell leukodystrophy and hurler syndrome. *J Inherit Metab Dis.* 1995; 18(4): 398-412.

Li Y, Brockmann K, Turecek F, Scott CR, Gelb MH. Tandem mass spectrometry for the direct assay of enzymes in dried blood spots: Application to newborn screening for Krabbe disease. *Clin Chem.* 2004 Mar; 50(3): 638-640.

Li Y, Scott CR, Chamoles NA, Ghavami A, Pinto BM, Turecek F, Gelb MH. Direct multiplex assay of lysosomal enzymes in dried blood spots for newborn screening. *Clin Chem.* 2004 Oct; 50(10): 1785-1796.

Lissens W, Arena A, Seneca S, Rafi M, Sorge G, Liebaers I, Wenger D, Fiumara A. A single mutation in the GALC gene is responsible for the majority of late onset Krabbe disease patients in the Catania (Sicily, Italy) region. *Hum Mutat.* 2007 Jul; 28(7): 742.

Loes DJ, Peters C, Krivit W. Globoid cell leukodystrophy: Distinguishing early-onset from late-onset disease using a brain MR imaging scoring method. *AJNR Am J Neuroradiol.* 1999 Feb; 20(2): 316-323.

Luzi P, Rafi MA, Wenger DA. Characterization of the large deletion in the GALC gene found in patients with Krabbe disease. *Hum Mol Genet.* 1995 Dec; 4(12): 2335-2338.

Martin PL, Carter SL, Kernan NA, Sahdev I, Wall D, Pietryga D, Wagner JE, Kurtzberg J. Results of the cord blood transplantation study (COBLT): Outcomes of unrelated donor umbilical cord blood transplantation in pediatric patients with lysosomal and peroxisomal storage diseases. *Biol Blood Marrow Transplant.* 2006 Feb; 12(2): 184-194.

McGraw P, Liang L, Escolar M, Mukundan S, Kurtzberg J, Provenzale JM. Krabbe disease treated with hematopoietic stem cell transplantation: Serial assessment of anisotropy measurements--initial experience. *Radiology.* 2005 Jul; 236(1): 221-230.

Meikle PJ, Ranieri E, Simonsen H, Rozaklis T, Ramsay SL, Whitfield PD, Fuller M, Christensen E, Skovby F, Hopwood JJ. Newborn screening for lysosomal storage disorders: Clinical evaluation of a two-tier strategy. *Pediatrics.* 2004 Oct; 114(4): 909-916.

Morse LE, Rosman NP. Myoclonic seizures in Krabbe disease: A unique presentation in late-onset type. *Pediatr Neurol.* 2006 Aug; 35(2): 154-157.

Moser HW. Peripheral nerve involvement in Krabbe disease: A guide to therapy selection and evaluation. *Neurology.* 2006 Jul 25; 67(2): 201-202.

NHS Center for Reviews and Dissemination. Undertaking systematic reviews of research on effectivemeness: CRD's guidance for those carrying out or commissioning reviews. CRD Report 4 (2nd Edition). http://www.york.ac.uk/inst/crd/report4.htm: March 2001, Accessed: October 17, 2008.

Orsini JJ, Morrissey MA, Slavin LN, Wojcik M, Biski C, Martin M, Keutzer J, Zhang XK, Chuang WL, Elbin C, Caggana M. Implementation of newborn screening for Krabbe disease: Population study and cutoff determination. *Clin Biochem.* 2009 Jun; 42(9): 877-884.

Pandor A, Eastham J, Beverley C, Chilcott J, Paisley S. Clinical effectiveness and cost-effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: A systematic review. *Health Technol Assess.* 2004 Mar; 8(12): iii, 1-121.

Percy AK, Odrezin GT, Knowles PD, Rouah E, Armstrong DD. Globoid cell leukodystrophy: Comparison of neuropathology with magnetic resonance imaging. *Acta Neuropathol (Berl).* 1994; 88(1): 26-32.

Pollitt RJ, Green A, McCabe CJ, Booth A, Cooper NJ, Leonard JV, Nicholl J, Nicholson P, Tunaley JR, Virdi NK. Neonatal screening for inborn errors of metabolism: Cost, yield and outcome. *Health Technol Assess.* 1997; 1(7): i-iv, 1-202.

Poorthuis BJ, Wevers RA, Kleijer WJ, Groener JE, de Jong JG, van Weely S, Niezen-Koning KE, van Diggelen OP. The frequency of lysosomal storage diseases in the Netherlands. *Hum Genet.* 1999 Jul-Aug; 105(1-2): 151-156.

Provenzale JM, Peddi S, Kurtzberg J, Poe MD, Mukundan S, Escolar M. Correlation of neurodevelopmental features and MRI findings in infantile Krabbe's disease. *Am J Roentgenol.* 2009 Jan; 192(1): 59-65.

Raghavan S, Zeng B, Torres PA, Pastores GM, Kolodny EH, Kurtzberg J, Krivit W. Globoid cell leukodystrophy (Krabbe disease): Normal umbilical cord blood galactocerebrosidase activity and polymorphic mutations. *J Inherit Metab Dis.* 2005; 28(6): 1005-1009.

Randell E, Connolly-Wilson M, Duff A, Skomorowski MA, Callahan J. Evaluation of the accuracy of enzymatically determined carrier status for Krabbe disease by DNA-based testing. *Clin Biochem.* 2000 Apr; 33(3): 217-220.

Sasaki M, Sakuragawa N, Takashima S, Hanaoka S, Arima M. MRI and CT findings in Krabbe disease. *Pediatr Neurol.* 1991 Jul-Aug; 7(4): 283-288.

Sauer M, Grewal S, Peters C. Hematopoietic stem cell transplantation for mucopolysaccharidoses and leukodystrophies. *Klin Padiatr.* 2004 May-Jun; 216(3): 163-168.

Selleri S, Torchiana E, Pareyson D, Lulli L, Bertagnolio B, Savoiardo M, Farina L, Carrara F, Filocamo M, Gatti R, Sghirlanzoni A, Uziel G, Finocchiaro G. Deletion of exons 11-17 and novel mutations of the galactocerebrosidase gene in adult- and early-onset patients with Krabbe disease. *J Neurol.* 2000 Nov; 247(11): 875-877.

Shapiro EG, Lockman LA, Balthazor M, Krivit W. Neuropsychological outcomes of several storage diseases with and without bone marrow transplantation. *J Inherit Metab Dis.* 1995; 18(4): 413-429.

Siddiqi ZA, Sanders DB, Massey JM. Peripheral neuropathy in Krabbe disease: Effect of hematopoietic stem cell transplantation. *Neurology.* 2006 Jul 25; 67(2): 268-272.

Siddiqi ZA, Sanders DB, Massey JM. Peripheral neuropathy in Krabbe disease: Electrodiagnostic findings. *Neurology.* 2006 Jul 25; 67(2): 263-267.

Stewart WA, Gordon KE, Camfield PR, Wood EP, Dooley JM. Irritability in Krabbe's disease: Dramatic response to low-dose morphine. *Pediatr Neurol.* 2001 Oct; 25(4): 344-345.

Suzuki K. Globoid cell leukodystrophy (Krabbe's disease): Update. *J Child Neurol.* 2003 Sep; 18(9): 595-603.

Suzuki K. Twenty five years of the "psychosine hypothesis": A personal perspective of its history and present status. *Neurochem Res.* 1998 Mar; 23(3): 251-259.

Tatsumi N, Inui K, Sakai N, Fukushima H, Nishimoto J, Yanagihara I, Nishigaki T, Tsukamoto H, Fu L, Taniike M. Molecular defects in Krabbe disease. *Hum Mol Genet.* 1995 Oct; 4(10): 1865-1868.

Tullu MS, Muranjan MN, Kondurkar PP, Bharucha BA. Krabbe disease--clinical profile. *Indian Pediatr.* 2000 Sep; 37(9): 939-946.

University of Washington. Krabbe disease online NIH gene tests [homepage on the Internet]. Funded by the NIH, developed at the University of Washington, Seattle. 2009, November 4, 2009. Available from: http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab/clinical_disease_id/3114?db=genetests.

Vanhanen SL, Raininko R, Santavuori P. Early differential diagnosis of infantile neuronal ceroid lipofuscinosis, Rett syndrome, and Krabbe disease by CT and MR. *AJNR Am J Neuroradiol.* 1994 Sep; 15(8): 1443-1453.

Wajner A, Michelin K, Burin MG, Pires RF, Pereira ML, Giugliani R, Coelho JC. Comparison between the biochemical properties of plasma chitotriosidase from normal individuals and from patients with Gaucher disease, GM1-gangliosidosis, Krabbe disease and heterozygotes for Gaucher disease. *Clin Biochem.* 2007 Mar; 40(5-6): 365-369.

Wang PJ, Wang TZ, Shen YZ. A study of genetic leukodystrophies in Chinese children. *Chung Hua Min Kuo Hsiao Erh Ko I Hsueh Hui Tsa Chih.* 1992 Jan-Feb; 33(1): 44-58.

Weinberg KI. Early use of drastic therapy. *N Engl J Med.* 2005 May 19; 352(20): 2124-2126.

Wenger DA. Krabbe disease online NIH Gene Review [homepage on the Internet]. Funded by the NIH, developed at the University of Washington, Seattle. 2008 August 5, 2008. Available from: http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=krabbe

Wenger DA, Rafi MA, Luzi P, Datto J, Costantino-Ceccarini E. Krabbe disease: Genetic aspects and progress toward therapy. *Mol Genet Metab.* 2000 May; 70(1): 1-9.

Wenger DA, Suzuki K, Suzuki Y, Suzuki K. Galactosylceramide lipidosis: Globoid cell leukodystrophy (Krabbe disease). In: Scriver C, Beaudet A, Sly W, et al, editors. *The Metabolic and Molecular Basis of Inherited Disease*. 8th ed. New York: McGraw-Hill; 2001. p. 3669-3694.

Wraith JE. The clinical presentation of lysosomal storage disorders. *Acta NeurolTtaiwan.* 2004 Sep; 13(3): 101-106.

Xu C, Sakai N, Taniike M, Inui K, Ozono K. Six novel mutations detected in the GALC gene in 17 Japanese patients with Krabbe disease, and new genotype-phenotype correlation. *J Hum Genet.* 2006; 51(6): 548-554.

Yamanouchi H, Kaga M, Iwasaki Y, Sakuragawa N, Arima M. Auditory evoked responses in Krabbe disease. *Pediatr Neurol.* 1993 Sep-Oct; 9(5): 387-390.

Zafeiriou DI, Anastasiou AL, Michelakaki EM, Augoustidou-Savvopoulou PA, Katzos GS, Kontopoulos EE. Early infantile Krabbe disease: Deceptively normal magnetic resonance imaging and serial neurophysiological studies. *Brain Dev.* 1997 Nov; 19(7): 488-491.

Zhang XK, Elbin CS, Chuang WL, Cooper SK, Marashio CA, Beauregard C, Keutzer JM. Multiplex enzyme assay screening of dried blood spots for lysosomal storage disorders by using tandem mass spectrometry. *Clin Chem.* 2008 Oct; 54(10): 1725-1728.

Zhou X, Turecek F, Scott CR, Gelb MH. Quantification of cellular acid sphingomyelinase and galactocerebroside beta-galactosidase activities by electrospray ionization mass spectrometry. *Clin Chem.* 2001 May; 47(5): 874-881.

Zlotogora J, Levy-Lahad E, Legum C, Iancu TC, Zeigler M, Bach G. Krabbe disease in israel. *Isr J Med Sci.* 1991 Apr; 27(4): 196-198.

XII. Appendix A - Krabbe disease evidence tables

Natural History

Authors/ Researcher Title of Paper Year	Study Population Description	Significant Findings
Aldosari,M.;Altuwaijri,M.;Husain,A. M. Brain-stem auditory and visual evoked potentials in children with Krabbe disease. 2004*	26 patients total 20 with EIKD, median age at diagnosis 6 months (range 2-12 months); 16 "symptomatic" and 4 "presymptomatic" - unclear how this is defined 6 with LOKD, median age at diagnosis 14 months (range 10-87 months) Ages at time of BAEP and/or VEP unclear.	• Prolonged or absent Bilateral Auditory Evoked Potentials (BAEP) were present in 88% (15/17) of those with EIKD • 40% of LOKD patients had abnormal BAEP • Abnormal BAEP is among first indication of disease onset in EIKD (may precede clinical symptoms) • Visual evoked potential (VEP) abnormalities were present in 53% (8/15) with EIKD • 0% of LOKD patients had abnormal VEP • VEP abnormality occurs later in illness progression
Barone,R.;Bruhl,K.;Stoeter,P.;Fiumara,A.;Pavone,L.;Beck,M. Clinical and neuroradiological findings in classic infantile and late-onset globoid-cell leukodystrophy (Krabbe disease). 1996	11 patients total 2 with EIKD 9 with LOKD age range 2 months - 5 years	• Variability of KD refers to clinical manifestations, CT and MRI findings • High density areas on CT exam is early and specific finding of EIKD • EIKD patients displayed cerebellar atrophy appearing during the first year of life • 2 patients with LOKD had follow-up MRI 18 months and 8 years after initial MRI • Follow-up MRIs displayed clear progression of white matter changes and clinically both had tetraplegic spasticity
Duffner,P. K.;Jalal,K.;Carter,R. L. The Hunter's Hope Krabbe family database 2009	334 families with children affected by Krabbe disease completed questionnaires as of June 2006	• Most common initial symptoms for age 0 to 12 months were crying and irritability, stiffness, and seizures • 71% developed symptoms at 0-6 months of age, 19% between 7-12 months of age, 10% at 13 months or more (13 months to 5.5 years of age) • Survival differed according to age of symptom onset: 0-6 months of age had worse survival than onset between 7-12 and 13 months or more • Three symptoms predictive of poor survival: stiffness, loss of vision, and poor feeding • Median survivals in the early infantile group: 17 months of age • Mean survival: 24.1 months of age • Neither GALC nor mutation analysis reliably predict disease severity

Escolar,M. L.;Poe,M. D.;Martin,H. R.;Kurtzberg,J. A staging system for infantile Krabbe disease to predict outcome after unrelated umbilical cord blood transplantation. 2006*	42 patients total 37/42 had sufficient data in medical chart (26 EIKD, 11 LIKD) 29/37 patients received a transplant 26 had unrelated CBT and 3 had BMT from sibling with conditioning	• Clinical staging system developed found to be predictive of neurodevelopmental outcome after CBT based on pretransplant progression of disease • Clinical interpretations of brain MRI, NCV, EEG, VEP, BAEP studies and CSF protein levels at initial evaluation were compared with age-equivalent normal controls, and all failed to correlate with disease stage • Clinical signs and symptoms alone sufficient in staging; undetectable GALC levels confirmed diagnosis in asymptomatic cases • Stage 1 and stage 2 patients had 100% survival rate (follow-up between 24-108 months old) • Stage 3 patients had 61.5% survival rate; mean survival time for 5 patients who died posttransplant was 21.4 months (range 7.5-50 months posttransplant) • Only 1 stage 4 patient received transplant and died weeks after; 8 patients at stage 4 were not transplanted and died
Escolar ML, Poe MD, Smith JK, Gilmore JH, Kurtzberg J, Lin W, Styner M. Diffusion tensor imaging detects abnormalities in the corticospinal tracts of neonates with infantile Krabbe disease. 2009	51 patients total 6 patients with KD: 4 infants with infantile Krabbe disease identified by family history with MRI in the first 4 weeks of life and 2 by NBS 45 controls	• After adjusting for gestational age, gestational age at birth, birth weight, sex, and race, those with Krabbe disease had significantly lower FA ratios than controls • In those with Krabbe disease, neurodevelopment in the motor area is associated with FA ratios
Guzzetta,F.;Rodriguez,J.;Deodato,M.;Guzzetta,A.;Ferriere,G. Demyelinating hereditary neuropathies in children: a morphometric and ultrastructural study. 1995	28 patients total 4 patients with KD: 12 months, 12 months, 18 months, 35 months of age at biopsy 5 normal age-matched controls (range 28 months - 17 years of age)	• Myelinated and unmyelinated number of fibers in KD patients were comparable to controls, but density in both fibers were comparatively low to controls • KD patients had: no nerve hypertrophy, relative loss of larger myelinated fibers, demyelination with significant low slope of the regression line of the ratio of myelin thickness to axon diameter, small onion bulb were evident • Typical inclusions in Schwann cells and macrophages found
Heim,P.;Claussen,M.;Hoffmann,B.;Conzelmann,E.;Gartner,J.;Harzer,K.;Hunneman,D.H.;Kohler,W.;Kurlemann,G.;Kohlschutter,A. Leukodystrophy incidence in Germany. 1997	All 439 pediatric, 463 neurology, and 41 neuropathology departments of Germany 353/439 (80%) pediatric centers replied 300/463 (65%) neurology centers replied 24/41 (58%) neuropathology centers replied	• A total of 617 leukodystrophy cases found • 80 patients with KD found, representing 14.4% of all leukodystrophies • In-depth national survey yielded an incidence of 0.6/100,000 for KD in Germany • Sweden reported 1/53,000 in 1970 (Hagberg et al. 1970) • Japan reported 1/100,000 in 1989 (Suzuki and Suzuki 1989)

Husain,A. M.;Altuwaijri,M.;Aldosari,M. Krabbe disease: neurophysiologic studies and MRI correlations 2004*	26 total patients 20/26 (77%) EIKD 16/20 EIKD (80%) symptomatic, 2 months at symptom onset (range 0.5-6 months) and 6 months at diagnosis (range 2-12 months) 4/20 EIKD presymptomatically diagnosed at birth; family history 6/20 LOKD 5/6 LOKD symptomatic, 12 months at symptom onset (range 10-60 months) and 14 months at diagnosis (range 10-87 months) 1/6 LOKD presymptomatically diagnosed at 48 months	• EIKD patients: all NCS abnormal, 88% of BAEPs abnormal, 65% of EEGs abnormal, 53% flash VEPs abnormal • Symptomatic EIKD patients more likely to have abnormal BAEPs, EEGs, and flash VEPs • In EIKD patients: NCS abnormality seen first, followed by BAEP, EEG and eventually flash VEP abnormalities • Findings show peripheral nervous system involved very early in EIKD disease process, even before CNS involvement and onset of symptoms • In LOKD patients, BAEPs most often abnormal (40%), followed by EEG abnormality (33%), NCS only abnormal in 20%, and all had normal flash VEPs
Kaye,E. M.;Ullman,M. D.;Kolodny,E. H.;Krivit,W.;Rischert,J. C. Possible use of CSF glycosphingolipids for the diagnosis and therapeutic monitoring of lysosomal storage diseases. 1992	59 total patients 2 patients with EIKD 2 patients with LOKD 23 patients: other LSDs 32 controls: 9 controls for ganglioside content, 12 for galactosylceramide, 11 for galactosylceramide sulfate	• All KD patients did not demonstrate higher levels of NFA- (non-hydroxy fatty acid) or HFA- (alpha-hydroxy fatty acid) galactosylceramide compared to control CSF • Trace amounts of lactosylceramide and globotriaosylceramide detected in KD compared to controls potentially due to myelin breakdown • CSF is not a pathway for galactosylceramide excretion in KD
Kleijer,W. J.;Keulemans,J. L.;van der Kraan,M.;Geilen,G. G.;van der Helm,R. M.;Rafi,M. A.;Luzi,P.;Wenger,D. A.;Halley,D. J.;van Diggelen,O. P. Prevalent mutations in the GALC gene of patients with Krabbe disease of Dutch and other European origin. 1997	111 total patients 41 Dutch with EIKD 23 of other European origin with EIKD 47 Dutch controls	• Of the 23 European EIKD patients, allele frequency of 30-kb deletion was 16/46 (35%), 502T polymorphism was 18/46 (39%) and the T513M base substitution was 0/46 (0%) • Of the 41 Dutch EIKD patients, allele frequency of 30-kb deletion was 43/82 (52%), 502T polymorphism was 55/82 (67%%) and the T513M base substitution was 7/82 (8.5%) • Of the 41 Dutch EIKD patients, coinheritance of the 30-kb deletion and 502T polymorphism was 41/43 30-kb deletion alleles and 41/55 of the 502T polymorphism alleles • Of the 47 controls, the allele frequency of the 502T polymorphism was 5/94 (5.3%)Together, the 502T polymorphism and 30-kb deletion are responsible for half of the GLD alleles in Caucasians in general, and 60% in Dutch patients

Korn-Lubetzki,I.;Dor-Wollman,T.;Soffer,D.;Raas-Rothschild,A.;Hurvitz,H.;Nevo,Y. Early peripheral nervous system manifestations of infantile Krabbe disease. 2003	8 patients total 2.5 - 5 months at symptom presentation, 2 weeks- 10 months until confirmed diagnosis of EIKD	• EIKD relatively frequent in Muslim-Arab population in Israel • 8/8 patients homozygous for same 1582 G-to-A mutation • 6/8 demonstrated CNS symptoms and signs of which seizures, poor focusing and irritability most common • 4/8 patients presented with hyperreflexia at first examination (4-5 months of age) • 2/8 patients detected with areflexia at first visit (3-5 months of age) • All 6/8 with CNS symptoms were blind and cognitively deteriorated 6-7 months after first visit • 2/8 patients had no CNS involvement for 9-10 months after initial symptom of peripheral neuropathy
Lissens,W.;Arena,A.;Seneca,S.;Rafi,M.;Sorge,G.;Liebaers,I.;Wenger,D.;Fiumara,A. A single mutation in the GALC gene is responsible for the majority of late onset Krabbe disease patients in the Catania (Sicily, Italy) region. 2007	8 families with a child affected by KD Ages not stated; LIKD, juvenile KD, and LOKD	• Identification of founder mutation in Italy of pGly41Ser (c.121 G>A) mutation in patients with LIKD, juvenile KD and LOKD
Loes,D. J.;Peters,C.;Krivit,W. Globoid cell leukodystrophy: distinguishing early-onset from late-onset disease using a brain MR imaging scoring method 1999	22 patients total 3 asymptomatic KD 10 EIKD over 2 years of age 9 LOKD under 2 years of age Age range: 1 month -18.5 years at exam; 3 months - 18 years old at onset of symptoms	• Identification of brain involvement among those with Krabbe is possible by MRI • Cerebellar white matter and deep gray matter involvement are present only in early onset Krabbe disease. • Pyramidal tract involvement is present in both early and late onset disease • All MRIs had abnormalities; KD has a characteristic pattern dependent on age of onset • The authors have developed a scoring method • Mean MRI severity scores of 8.1 for EIKD (range 3-18), 5.6 for LOKD (range 4-10) and 3.2 for asymptomatic (range 1.5-5)
Poorthuis,B. J.;Wevers,R. A.;Kleijer,W. J.;Groener,J. E.;de Jong,J. G.;van Weely,S.;Niezen-Koning,K.;E. van Diggelen,O. P. The frequency of lysosomal storage diseases in The Netherlands. 1999	963 enzymatically confirmed LSD cases between 1970-1996 in the Netherlands (assuming complete ascertainment) 70 with confirmed KD between 1971-1995	• The birth prevalence of Krabbe disease in the Netherlands is 1.35 per 100,000 between 1970-1996 • Combined birth prevalence in the Netherlands is 14 per 100,000 • KD diagnosed in 17% (70/424) of cases of lipidosis from 1970-1996

Provenzale,J. M.;Escolar,M.;Kurtzberg,J. Quantitative analysis of diffusion tensor imaging data in serial assessment of Krabbe disease 2005*	9 patients total All 9 infants with EIKD Ages at time of transplantation ranged from 3 weeks to 9 months of age, Pre and posttransplantation MR Images	• Very good correlation between clinical testing and Loes scores for entire brain • Moderately good correlation between clinical testing and Loes scores for specific brain regions • Loes scoring system from MRI likely provides reasonable assessment of prognosis and therapeutic response
Siddiqi,Z. A.;Sanders,D. B.;Massey,J. M. Peripheral neuropathy in Krabbe disease: electrodiagnostic findings 2006*	24 patients total All 24 with EIKD (others excluded) diagnosed between 1990 and 2002 seen at Duke for possible transplant	• Peripheral neuropathy occurs early in the disease • Nerve conduction tests provide a sensitive tool to "screen" this patient population - may reflect the degree of CNS involvement
Tatsumi,N.;Inui,K.;Sakai,N.; Fukushima,H.;Nishimoto,J.; Yanagihara,I.;Nishigaki,T.;Tsukamoto,H.;Fu,L.;Taniike,M. Molecular defects in Krabbe disease. 1995	11 patients total 7 Japanese, 4 non-Japanese patients Variable age of onset - difficult to tell from the paper; unclear how cases were assembled	• Mutations in infantile and late infantile patients are relatively heterogeneous
Tullu,M. S.;Muranjan,M. N.;Kondurkar,P. P.;Bharucha,B. A. Krabbe disease--clinical profile. 2000	9 patients total 5 "classical infantile", 3 "late infantile", and 1 juvenile KD Mean age of presentation 9.4 months (range 2.5-21 months); 1 case identified at 8 years of age	• Optic atrophy is uncommon • Most have elevated CSF protein • Most have peripheral neuropathy • Most have characteristic findings on MRI
Zlotogora,J.;Levy-Lahad,E.;Legum,C.;Iancu,T. C.;Zeigler,M.;Bach,G. Krabbe disease in Israel. 1991	26 patients total 18 patients with Krabbe disease diagnosed between 1975-1989, and 8 affected siblings who died without enzymatic confirmation 23 patients presented symptoms before age of 5 months; 3 patients presented symptoms between 6-11months of age	• Presenting symptoms are usually motor regression or irritability • All died before age 2 years

*Potential patient overlap between Aldosari et al. 2004, Escolar et al. 2006, Husain et al. 2004, Provenzale et al. 2005 and Siddiqi et al. 2006

Screening

Authors/Researcher Title of Paper Year	Study Population Description	Significant Findings
Duffner,P. K.; Caggana,M.; Orsini,J. J.;Wenger,D. A.; Patterson,M. C.;Crosley,C. J.;Kurtzberg,J.;Arnold,G. L.;Escolar,M. L.;Adams,D. J.;Andriola,M. R.;Aron,A. M.; Ciafaloni,E.;Djukic,A.;Erbe,R. W.;Galvin-Parton,P.; Helton,L. E.;Kolodny,E. H.;Kosofsky,B. E.;Kronn,D. F.;Kwon,J. M.;Levy,P. A.; Miller-Horn,J.;Naidich,T. P.;Pellegrino,J. E.; Provenzale,J. M.; Rothman,S. Newborn screening for Krabbe disease: the New York State model 2009	550,000 newborn babies screened for Krabbe disease as of June 30, 2008 Newborn screening program in New York state began in August 2006	• Formed the Krabbe Consortium for New York State to address the need for clinical evaluation and follow-up for screen positive babies • Developed a rapid and accurate technique for assessing GALC activity and performing DNA mutation analysis • Designed a standardized clinical evaluation protocol based on available literature • Formulated criteria for transplantation for EIKD phenotype • Developed a clinical database and registry • Instituted a study of developmental and functional outcomes • As of June 30, 2008, 550,000 babies have been screened: 4 high-risk, 6 moderate-risk, and 15 low-risk children have been identified to date
Kaye,E. M.;Ullman,M. D.;Kolodny,E. H.;Krivit,W.;Rischert,J. C. Possible use of CSF glycosphingolipids for the diagnosis and therapeutic monitoring of lysosomal storage diseases. 1992	59 total patients 2 patients with EIKD 2 patients with LOKD 23 patients: other LSDs 32 controls: 9 controls for ganglioside content, 12 for galactosylceramide, 11 for galactosylceramide sulfate	• All KD patients did not demonstrate higher levels of NFA- or HFA galactosylceramide compared to control CSF • Trace amounts of lactosylceramide and globotriaosylceramide detected in KD compared to controls potentially due to myelin breakdown • CSF is not a pathway for galactosylceramide excretion in KD
Kleijer,W. J.;Keulemans,J. L.;van der Kraan,M.;Geilen,G. G.;van der Helm,R. M.;Rafi,M. A.;Luzi,P.;Wenger,D. A.;Halley,D. J.;van Diggelen,O. P. Prevalent mutations in the GALC gene of patients with Krabbe disease of Dutch and other European origin. 1997	111 total patients 41 Dutch with EIKD 23 of other European origin with EIKD 47 Dutch controls	• Of the 23 European EIKD patients, allele frequency of 30-kb deletion was 16/46 (35%), 502T polymorphism was 18/46 (39%) and the T513M base substitution was 0/46 (0%) • Of the 41 Dutch EIKD patients, allele frequency of 30-kb deletion was 43/82 (52%), 502T polymorphism was 55/82 (67%%) and the T513M base substitution was 7/82 (8.5%) • Of the 41 Dutch EIKD patients, coinheritance of the 30-kb deletion and 502T polymorphism was 41/43 30-kb deletion alleles and 41/55 of the 502T polymorphism alleles • Of the 47 controls, the allele frequency of the 502T polymorphism was 5/94 (5.3%)Together, the 502T polymorphism and 30-kb deletion are responsible for half of the GLD alleles in Caucasians in general, and 60% in Dutch patients

Li,Y.;Brockmann,K.;Turecek, F.;Scott,C. R.;Gelb,M. H. Tandem mass spectrometry for the direct assay of enzymes in dried blood spots: application to newborn screening for Krabbe disease. 2004	28 total patient samples 4 KD, 4 Fabry, 3 Gaucher all diagnosed prior to use in assay 16 control samples	• Utilized dried blood 2mm punches and tandem mass spectrometry for direct enzyme assay • Activity in KD samples much lower with a range of 0.05-0.23 umol h-1 (L blood)-1 when compared to: controls (1.4-3.7), Fabry (range 1.28-5.34), and Gaucher (1.35-7.49) • The 5 actual KD results were 0.08, 0.05, 0.23, 0.07, 0.08 umol h-1 (L blood)-1 • C8-Cer (GALC) in MS/MS allows for high-sensitivity detection and quantification
Li,Y.;Scott,C. R.;Chamoles,N. A.;Ghavami,A.;Pinto,B. M.;Turecek,F.;Gelb,M. H. Direct multiplex assay of lysosomal enzymes in dried blood spots for newborn screening 2004	70 total patient samples 38 different lysosomal storage diseases 12/38 diagnosed with KD: 1 infant, 2 juvenile, 1 adult, 5 of unknown age Samples compared to 17 healthy adults and 15 healthy infant controls	• Used rehydrated DBS from NBS cards and tandem mass spectrometry for a multiplex of 5 lysosomal enzymes and corresponding diseases • GALC shows decrease in activity over a 4 year period; sufficient for a retrospective analysis only over a 4 year period • DBS from patients with KD had lower GALC levels than DBS from healthy patients collected in the same year • No data from KD heterozygotes available (only homozygous NBS cards) • GALC best identified using 2mm DBS punch alone instead of 5mm DBS punch and multiplex • Detection rate for affected patients in study was 100%
Meikle,P. J.;Ranieri,E.;Simonsen,H.;Rozaklis,T.;Ramsay,S. L.;Whitfield,P. D.;Fuller,M.;Christensen,E.;Skovby,F.;Hopwood,J. J. Newborn screening for lysosomal storage disorders: clinical evaluation of a two-tier strategy. 2004	547 total patient samples 47 Guthrie cards from newborns in Denmark collected from 1982-1997 who were diagnosed with a LSD (12 disorders represented) 227 control Guthrie cards from newborns in Denmark collected from 1982-1997 273 additional control cards from Australia	• The first tier of this two tiered strategy will not identify cases of Krabbe disease
Orsini JJ, Morrissey MA, Slavin LN, Wojcik M, Biski C, Martin M, Keutzer J, Zhang XK, Chuang WL, Elbin C, Caggana M. Implementation of newborn screening for Krabbe disease: Population study and cutoff determination. 2009	139,146 total patient samples Evaluate the % Daily Mean Activity (DMA) to set reasonable thresholds for the NY screening algorithm	• %DMA is approach to normalize for variability in reagents or other day-to-day changes • The main goal was to set %DMA for the first point to figure out who screens negative and who should be retested (from the same blood spot), and who (on the average of 3 samples in subsequent testing) should screen negative or go on to be considered to be a positive. • The range of activities was 0.17-335 micromol/L/H • Overall average DMA for Krabbe disease is 4.6% • The highest DMA% for Krabbe positive controls was 10.9%, therefore set to 20% to avoid missing any cases • "Immediate action" was set to 8% which overlapped with some controls • The 8-12% DMA threshold for DNA sequence analysis was set to assure no missed cases

Zhang,X. K.;Elbin,C. S.;Chuang,W. L.;Cooper,S. K.;Marashio,C. A.;Beauregard,C.;Keutzer,J. M. Multiplex enzyme assay screening of dried blood spots for lysosomal storage disorders by using tandem mass spectrometry 2008	309 total patient samples 149 DBS from healthy adults 100 DBS newborn screening cards 60 DBS from 60 patients with LSDs 10/60 LSD DBS samples previously diagnosed with KD	• Modified Li et al. assay: eluted GALC directly from NBS card punch directly into assay cocktail • Showed unambiguous distinction between samples from healthy individuals and corresponding samples from patients with LSDs • GALC assay separation between normal and disease samples became more pronounced than prior assay • Limits of detection observed were 2-fold below maximum observed disease activity, indicating higher precision • Assay was validated using CLSI standard protocol • Method works and could be implemented in high-throughput laboratory setting

Treatment

Authors/Researcher Title of Paper Year	Study Population Description	Significant Findings
Escolar,M. L.;Poe,M. D.;Martin,H. R.;Kurtzberg,J. A staging system for infantile Krabbe disease to predict outcome after unrelated umbilical cord blood transplantation. 2006*	42 patients total 37/42 had sufficient data in medical chart (26 EIKD, 11 LIKD) 29/37 patients received a transplant 26 had unrelated CBT and 3 had BMT from sibling with conditioning	• Clinical staging system developed found to be predictive of neurodevelopmental outcome after CBT based on pretransplant progression of disease • Clinical interpretations of brain MRI, NCV, EEG, VEP, BAEP studies and CSF protein levels at initial evaluation were compared with age-equivalent normal controls, and all failed to correlate with disease stage • Clinical signs and symptoms alone sufficient in staging; undetectable GALC levels confirmed diagnosis in asymptomatic cases • Stage 1 and stage 2 patients had 100% survival rate (follow-up between 24-108 months old) • Stage 3 patients had 61.5% survival rate; mean survival time for 5 patients who died posttransplant was 21.4 months (range 7.5-50 months posttransplant) • Only 1 stage 4 patient received transplant and died weeks after; 8 patients at stage 4 were not transplanted and died
Escolar,M. L.;Poe,M. D.;Provenzale,J. M.;Richards,K. C.;Allison,J.;Wood,S.;Wenger,D. A.;Pietryga,D.;Wall,D.;Champagne,M.;Morse,R.;Krivit,W.;Kurtzberg,J. Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease 2005*	215 patients total 190 untreated patient data from registry 25 infantile KD: 11/25 asymptomatic newborns (age range 12 to 44 days) 14/25 symptomatic infants (age range 142 to 352 days)	• Initiation of myeloablative chemotherapy for newborns was at a median of 18.5 days of age, transplant median of 28 days old • Transplanted umbilical cord blood from unrelated donors with partial HLA mismatches (4 to 6 /6 HLA loci matched) • Donor cell engraftment was 100% for both infants and newborns • Follow-up 4 months to 6 years posttransplantation (median 3 years) • At follow-up, survival rate was 100% for asymptomatic newborns, and 43% among symptomatic infants • Transplants prior to symptom onset maintained progressive central myelination, continued gains in developmental skills not present in controls • Transplants post symptom onset did not result in substantive neurologic improvement from transplant • GVHD developed in 8/11 newborns and 5/14 infants • Compared to affected siblings, 6/12 outlived untransplanted siblings by 8 to 48 months • The other 6/12 are still alive, but have yet to surpass the age of their deceased sibling

Gaipa,G.;Dassi,M.;Perseghin,P.;Venturi,N.;Corti,P.;Bonanomi,S.;Balduzzi,A.;Longoni,D.;Uderzo,C.;Biondi,A.;Masera,G.;Parini,R.;Bertagnolio,B.;Uziel,G.;Peters,C.;Rovelli,A. Allogeneic bone marrow stem cell transplantation following CD34+ immunomagnetic enrichment in patients with inherited metabolic storage diseases 2003	9 patients total 11 HSCTs completed with conditioning but no irradiation 3 GLD (KD) patients each received 1 haploidentical HSCT from unrelated donors GLD patients were 74, 79 and 109 months of age at HSCT 6 other metabolic storage diseases	• All 3 GLD (KD) patients achieved 100% donor chimerism post one HSCT each • All 3 alive at 68, 708, 384 days post-HSCT (last follow-up for each patient prior to publication) • One KD patients' GALC activity was equal to that of donor's post-HSCT • No patients developed acute or chronic GVHD
McGraw,P.;Liang,L.;Escolar,M.;Mukundan,S.;Kurtzberg,J.;Provenzale,J. M. Krabbe disease treated with hematopoietic stem cell transplantation: serial assessment of anisotropy measurements--initial experience 2005*	12 patients total 7 patients diagnosed with EIKD: 3 received HSCT by 1 month of life, and 4 who received HSCT in first year of life (range 5-8 months of age at HSCT) 5 age-matched retrospective controls for MR Imaging comparison	• Pretransplantation fractional anisotropy ratios (marker of myelination) for early transplanted were normal • Pretransplantation fractional anisotropy ratios for the later treated were decreased • After 1 year, there was increases in the fractional anisotropy ratio among the early treated • In the late treated group, the change in fractional anisotropy ratio was variable
Siddiqi,Z. A.;Sanders,D. B.;Massey,J. M. Peripheral neuropathy in Krabbe disease: effect of hematopoietic stem cell transplantation 2006*	12 patients total All 12 patients diagnosed with KD and treated with HSCT: 9 with EIKD, 2 juvenile KD, 1 LOKD	• Average follow-up was 18 months (6 months to 3 years) after HSCT • Results indicate that HSCT may have a beneficial effect on the neuropathy in that most nerve conduction abnormalities improve after transplantation and some previously absent responses become obtainable • Sural sensory responses most robust indication of improvement • However, nerve conduction can worsen after an initial improvement • One year after transplant the average peroneal motor conduction velocity and FWL improved in both early and late onset disease though significantly more in the early than the late onset cases

*Potential patient overlap between Escolar et al. 2005, Escolar et al. 2006, McGraw et al. 2005 and Siddiqi et al. 2006

XIII. Appendix B - Articles excluded due to ≤4 Krabbe disease subjects

Authors	Title	Journal	Year
Bambach,B. J.;Moser,H. W.;Blakemore,K.;Corson,V. L.;Griffin,C. A.;Noga,S. J.;Perlman,E. J.;Zuckerman,R.;Wenger,D. A.;Jones,R. J.	Engraftment following in utero bone marrow transplantation for globoid cell leukodystrophy.	Bone marrow transplantation	1997
Bernal,O. G.;Lenn,N.	Multiple cranial nerve enhancement in early infantile Krabbe's disease.	Neurology	2000
Beslow,L. A.;Schwartz,E. S.;Bonnemann,C. G.	Thickening and enhancement of multiple cranial nerves in conjunction with cystic white matter lesions in early infantile Krabbe disease.	Pediatric radiology	2008
Breningstall,G. N.;Patterson,R. J.	Acquired obstructive hydrocephalus in globoid-cell leukodystrophy	Pediatric neurology	2008
Caniglia,M.;Rana,I.;Pinto,R. M.;Fariello,G.;Caruso,R.;Angioni,A .;Dionisi Vici,C.;Sabetta,G.;De Rossi,G.	Allogeneic bone marrow transplantation for infantile globoid-cell leukodystrophy (Krabbe's disease).	Pediatric transplantation	2002
De Meirleir,L. J.;Taylor,M. J.;Logan,W. J.	Multimodal evoked potential studies in leukodystrophies of children.	Canadian Journal of Neurological Sciences	1988
Del Bigio,M. R.;Chudley,A. E.;Booth,F. A.;Pacin,S.	Late infantile onset Krabbe disease in siblings with cortical degeneration and absence of cerebral globoid cells.	Neuropediatrics	2004
Finelli,D. A.;Tarr,R. W.;Sawyer,R. N.;Horwitz,S. J.	Deceptively normal MR in early infantile Krabbe disease.	Ajnr: American Journal of Neuroradiology	1994
Percy,A. K.;Odrezin,G. T.;Knowles,P. D.;Rouah,E.;Armstrong,D. D.	Globoid cell leukodystrophy: comparison of neuropathology with magnetic resonance imaging.	Acta Neuropathologica	1994
Randell,E.;Connolly-Wilson,M.;Duff,A.;Skomorowski,M. A.;Callahan,J.	Evaluation of the accuracy of enzymatically determined carrier status for Krabbe disease by DNA-based testing.	Clinical biochemistry	2000
Sasaki,M.;Sakuragawa,N.;Takashi ma,S.;Hanaoka,S.;Arima,M.	MRI and CT findings in Krabbe disease.	Pediatric neurology	1991
Vanhanen,S. L.;Raininko,R.;Santavuori,P.	Early differential diagnosis of infantile neuronal ceroid lipofuscinosis, Rett syndrome, and Krabbe disease by CT and MR.	Ajnr: American Journal of Neuroradiology	1994
Wang,P. J.;Wang,T. Z.;Shen,Y. Z.	A study of genetic leukodystrophies in Chinese children.	Chung-Hua Min Kuo Hsiao Erh Ko i Hsueh Hui Tsa Chih	1992
Yamanouchi,H.;Kaga,M.;Iwasaki,Y .;Sakuragawa,N.;Arima,M.	Auditory evoked responses in Krabbe disease.	Pediatric neurology	1993
Zafeiriou,D. I.;Anastasiou,A. L.;Michelakaki,E. M.;Augoustidou-Savvopoulou,P. A.;Katzos,G. S.;Kontopoulos,E. E.	Early infantile Krabbe disease: deceptively normal magnetic resonance imaging and serial neurophysiological studies.	Brain & development	1997

The Committee identified the following evidence gaps:

(1) **EIKD, The Condition:** need consensus about the case definition of what constitutes Early Infantile Krabbe Disease (EIKD)

(2) **Test for EIKD, Screening and Diagnosis:** there is a need for additional information about the testing algorithm for EIKD. It is important to ascertain whether testing for Krabbe disease would be a stand alone test or done with multiplex testing, in part because of the cost implications.

(3) **Treatment for EIKD:** More information is needed about the specific benefits of Hematopoietic Stem Cell Transplant (HSCT) to treat patients and what mutations would benefit most from HSCT.

The Committee understands that additional states will be adding Krabbe Disease to their NBS panel. It is anticipated that some data will be available from those states that could address the evidence gaps, and highly recommended that the data be made available to the Committee and its external evidence review workgroup. A potential strategy to addressing the gaps would be to develop a research partnership with the National Institutes of Health's newly established Newborn Screening Translational Research Network, under the leadership of the American College of Medical Genetics.

The Committee will reconsider its recommendation after the new evidence addressing the above issues are made available for the Committee's review and re-evaluation.

Sincerely yours,

/s/

R. Rodney Howell, M.D.
Chairman

Enclosure- Final Krabbe External Evidence Review Workgroup Report

cc: Joanne Kurtzberg, M.D.
Michele Caggana, Sc.D., FACMG
Maria Luisa Escolar, M.D.
Ms. Micki Gartzke

SCID

Newborn Screening Advisory Committee
September 24, 2014

SCID Estimates for Arizona (~$10/screen)

		AZ FY2016				
		Projected	Expected Cases		$10.14	
Population[1]	Incidence	1st screens	Cases/year	Years to 1st case	SCID Revenue/Year[6]	Cost to 1st Case[7]
General (not including below)	1/100,000	**48,203**	**0.48**	**2.07**	**$488,786**	$1,014,021
Hispanic[2]	1/25,000	**33,254**	**1.33**	**0.75**	**$337,202**	$253,505
AIAN (non-Athabascan)[3]	1/100,000	**2,396**	**0.02**	**41.74**	**$24,293**	$1,014,021
AIAN Athabascan (Off reservation births)[4]	1/2,000	**2,261**	**1.13**	**0.88**	**$22,924**	$20,280
Total:		**86,113**	**2.97**	**0.34**	**$873,204**	**$294,357**
AIAN Athabascan (on-reservation)[5]	1/2,000	**1,328**	0.66	1.51	**$13,468**	N/A

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. American Indian Alaska Native **(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. Revenue assumes cost per newborn billed to first screen.
7. Cost based on average annual cost over five years: $873,204

KEY POINTS

- Washington State: "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. Their value of one life saved is estimated at $ 7.7 million. (the last baby born with SCID in California prior to starting screening generated more than $4 million in medical bills - Puck 2012)."
- Washington State's assumed incidence was 1:49,827, which is less than Arizona's combined incidence, due to the contribution of Athabascan AIANs.
- Perkin Elmer's SCID testing kit is expected to be approved by FDA in early 2015. Current ***program*** costs are estimated at ~$10 per screen in-house, while sendout to Perkin Elmer is ~ $6.50 per screen (which does not include follow-up, education, billing and sample handling).

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.

References

Appelbaum, B. (2011). *As U.S. Agencies Put More Value on a Life, Businesses Fret.* The New York Times, February 16, 2011.

Baker, M. W. (2011). *Newborn Screening for Severe Combined Immunodeficiency in Wisconsin: 2008-2011*. Newborn Screening and Genetic Testing Symposium, San Diego, CA; November 10, 2011.

Brown, L., J. Xu-Bayford, et al. (2011). "Neonatal diagnosis of severe combined immunodeficiency leads to significantly improved survival outcome: the case for newborn screening." Blood **117**(11): 3243-6.

Buckley, R. H. (2010) "Long term clinical and immunologic outcomes of bone marrow transplantation in SCID." Center for Disease Control and Prevention Meeting on Newborn Screening for SCID, Atlanta, GA; October 28, 2010.

Buckley, R. H. (2012) "The long quest for neonatal screening for severe combined immunodeficiency." J Allergy Clin Immunol (epub ahead of print).

Caggana, M. (2011). *New York's Experience: Summary of the First Six Months of SCID Screening*. Newborn Screening and Genetic Testing Symposium, San Diego, CA; November 10, 2011.

Chan, A., C. Scalchunes, et al. "Early vs. delayed diagnosis of severe combined immunodeficiency: a family perspective survey." Clin Immunol **138**(1): 3-8.

Comeau, A. M. (2011). *Establishing Follow-up Protocols for Low Frequency Events in SCID NBS: Working with Specialists New to Newborn Screening*. Newborn Screening and Genetic Testing Symposium, San Diego, CA; November 10, 2011.

Hague, R. A., S. Rassam, et al. (1994). "Early diagnosis of severe combined immunodeficiency syndrome." Arch Dis Child **70**(4): 260-3.

Lorey, F. (2012). Personal communication (email sent January 13, 2011).

Myers, L. A., D. D. Patel, et al. (2002). "Hematopoietic stem cell transplantation for severe combined immunodeficiency in the neonatal period leads to superior thymic output and improved survival." Blood **99**(3): 872-8.

OFM (2011). *November 2011 Components of April 1 Population Change*. Office of Financial Management, Olympia, WA.

Puck, J. (2012). Personal communication (email sent April 4, 2012).

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

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

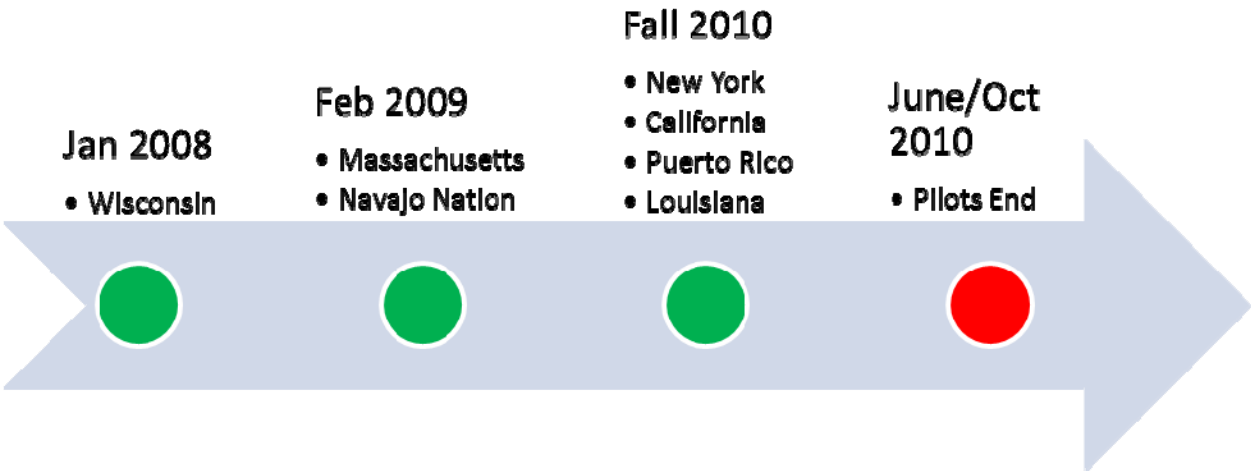


Figure 2: Cumulative Number of Newborns Screened and SCID Cases Diagnosed

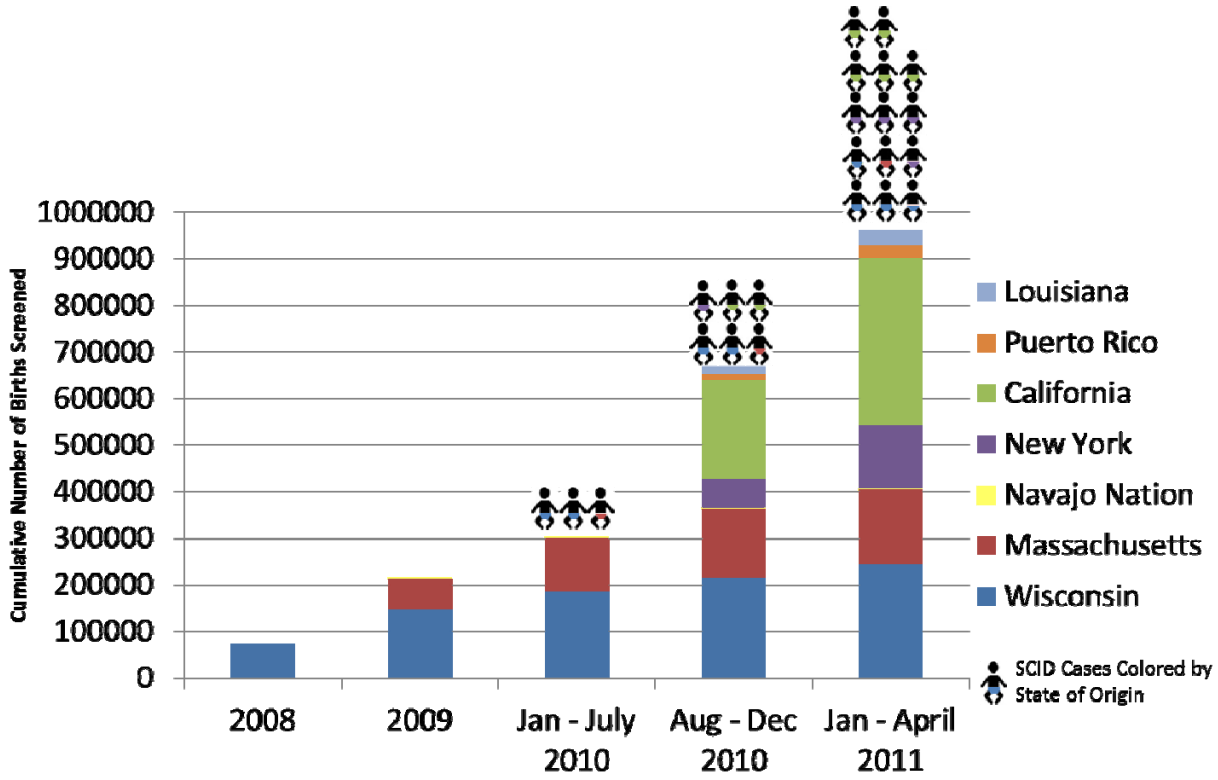


Figure 3: Type of Treatment for SCID Cases (N=14) in All Pilots

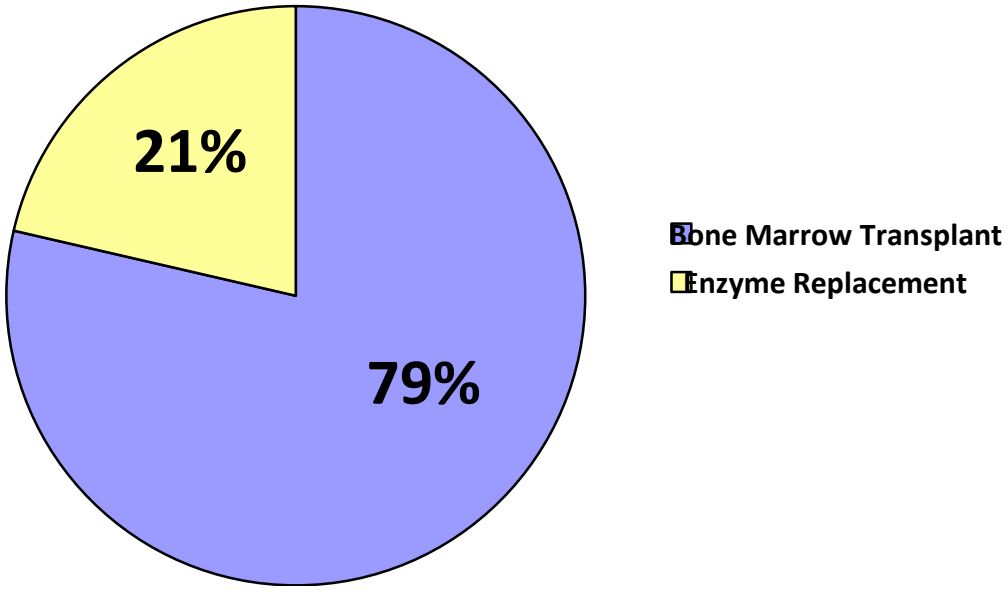


Figure 4: Diagnosis for Non SCID Cases for All Pilots (N=40)

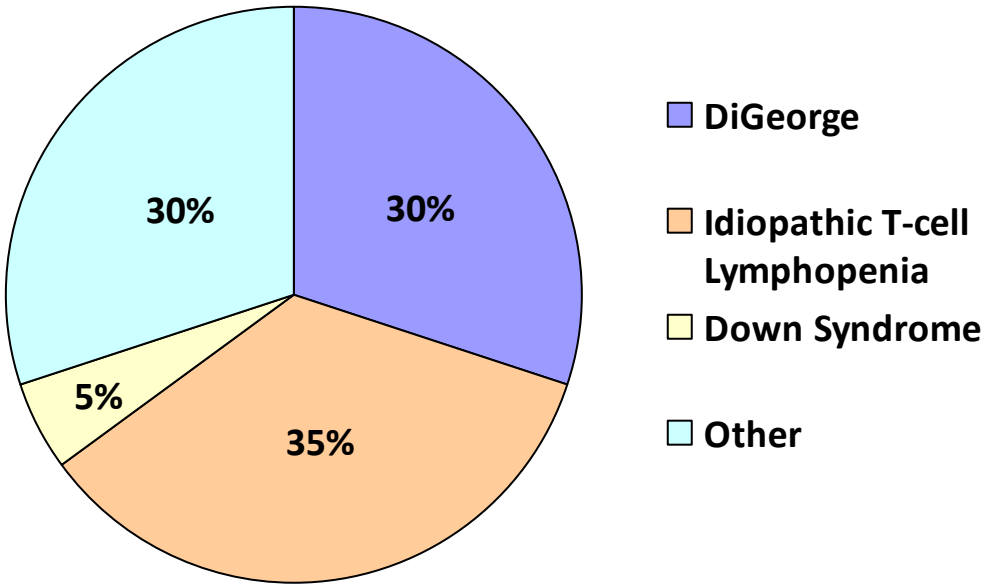
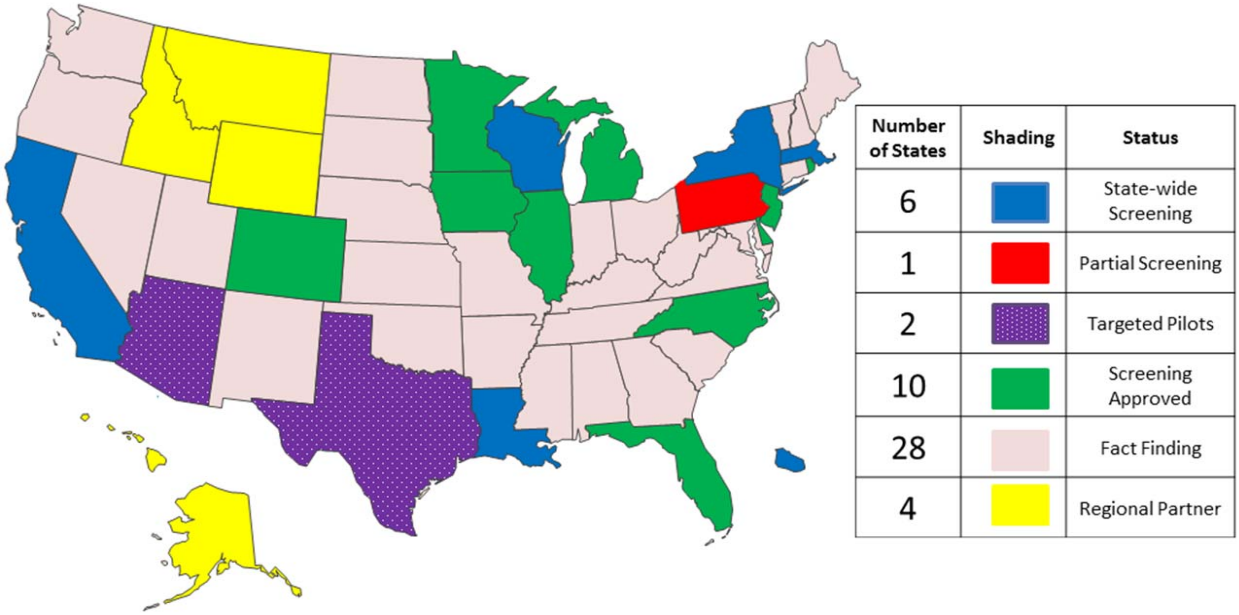


Figure 5. Map of Newborn Screening for SCID Implementation Status



References

1. Howell, R. R. (2010, February 25). Letter to the Secretary, U.S. Department of Health and Human Services. Retrieved May 3, 2011, from http://www.hrsa.gov/heritabledisorderscommittee/correspondence/feb2010letter.htm.
2. Sebelius, K. (2010, May 21). Letter to R. Rodney Howell. Retrieved May 3, 2011, from http://www.hrsa.gov/heritabledisorderscommittee/correspondence/.
3. Railey, M. D., Lokhnygina, Y., & Buckley, R. H. (2009). Long-term clinical outcome of patients with severe combined immunodeficiency who received related donor bone marrow transplants without pretransplant chemotherapy or post-transplant GVHD prophylaxis. *Journal of Pediatrics, 155*, 834–840.
4. Buckley, R. H. (2011). Transplantation of hematopoietic stem cells in human severe combined immunodeficiency: Long-term outcomes. *Immunologic Research, 49*, 25–43.
5. Centers for Disease Control and Prevention. (2004). Applying public health strategies to primary immunodeficiency diseases: A potential approach to genetic disorders. *MMWR—Recommendations and Reports, 53*, 1–29.
6. Chan, K., & Puck, J. M. (2005, February). Development of population-based newborn screening for severe combined immunodeficiency. *Journal of Allergy and Clinical Immunology, 115*(2), 391–398.
7. Gerstel-Thompson, J. L., Wilkey, J. F., Baptiste, J. C., Navas, J. S., Pai, S. Y., Pass, K. A., et al. (2010, September). High-throughput multiplexed T cell receptor excision circle quantitative PCR assay with internal controls for detection of severe combined immunodeficiency in population-based newborn screening. *Clinical Chemistry, 56*(9), 1466–1474.
8. Baker, M. W., Grossman, W. J., Laessig, R. H., Hoffman, G. L., Brokopp, C. D., Kurtycz, D. F., et al. (2009, September). Development of a routine newborn screening protocol for severe combined immunodeficiency. *Journal of Allergy and Clinical Immunology, 124*(3), 522–527.
9. Routes, J. M., Grossman, W. J., Verbsky, J., Laessig, R. H., Hoffman, G. L., Brokopp, C. D., et al. (2009, December). Statewide newborn screening for severe T cell lymphopenia. *JAMA, 302*(22), 2465–2470.
10. Comeau, A. M., Hale, J. E., Pai, S. Y., Bonilla, F. A., Notarangelo, L. D., Pasternack, M. S., et al. (2010, October). Guidelines for implementation of population-based newborn screening for severe combined immunodeficiency. *Journal of Inherited Metabolic Disease, 33*(Suppl 2), S273–S281.
11. Hale, J. E., Bonilla, F. A., Pai, S. Y., Gerstel-Thompson, J. L., Notarangelo, L. D., Eaton, R. B., et al. (2010, November). Identification of an infant with severe combined immunodeficiency by newborn screening. *Journal of Allergy and Clinical Immunology,* 126(5), 1073–1074.
12. Baker, M. W., Laessig, R. H., et al. (2010, May–June). Implementing routine testing for severe combined immunodeficiency within Wisconsin's newborn screening program. *Public Health Reports,* 125(Suppl 2), 88–95.
13. U.S. Department of Health and Human Services, Food and Drug Administration. (2007, September 14). *Guidance for industry and FDA staff—Commercially distributed analyte-specific reagents (ASRs): Frequently asked questions.* Retrieved May 3, 2011, from http://www.fda.gov/.

14. U.S. Department of Health and Human Services, Centers for Medicare & Medicaid Services. (2011, January 18). *Overview*. Retrieved May 3, 2011, from https://www.cms.gov/clia/.
15. McHugh, D. M., Cameron, C. A., Abdenur, J. E., Abdulrahman, M., Adair, O., Al Nuaimi, S. A., et al. (2011). Clinical validation of cutoff target ranges in newborn screening of metabolic disorders by tandem mass spectrometry: A worldwide collaborative project. *Genetics in Medicine, 13*(3), 230–254.
16. Howell, R. R. (2011). Quality improvement of newborn screening in real time. *Genetics in Medicine*, 13(3), 205.
17. Logical Observation Identifiers Names and Codes. *Newborn screening.* Retrieved May 3, 2011, from http://loinc.org/newborn-screening.
18. Association of Public Health Laboratories. *Newborn screening and genetics.* Retrieved May 3, 2011, from http://www.aphl.org/aphlprograms/nsg/.
19. IDF and NBSTRN Telephone Survey (February 2010 to March 2011).
20. Immune Deficiency Foundation. *Infants with severe combined immune deficiency should not receive live rotavirus vaccines.* Retrieved May 3, 2011, from http://www.primaryimmune.org/advocacy_center/scid/scid_docs/LiveRotavirusVaccines.pdf.
21. California educational materials available at ftp://ftp.acmg.net/.
22. Wisconsin educational materials available at ftp://ftp.acmg.net/.
23. Massachusetts educational materials available at ftp://ftp.acmg.net/.
24. New York educational materials available at ftp://ftp.acmg.net/.
25. American College of Medical Genetics. (2011). *Home*. Retrieved May 3, 2011, from http://www.acmg.net/.
26. Grants.gov. (2011, March 17). *Program to support new implementation of State or Territorial public health laboratory capacity for newborn bloodspot screening of severe combined immune deficiency (SCID)*. Retrieved May 3, 2011, from http://www.grants.gov/search/search.do?mode=VIEW&oppId=80113.
27. Rare Clinical Disease Research Network. *Primary Immune Deficiency Treatment Consortium*. Retrieved May 3, 2011, from http://rarediseasesnetwork.epi.usf.edu/PIDTC/index.htm.
28. Green, N. S., Rinaldo, P., Brower, A., Boyle, C., Dougherty, D., Lloyd-Puryear, M., et al. (2007). Committee report: Advancing the current recommended panel of conditions for newborn screening. *Genetics in Medicine*, 9(11), 792–796.
29. Calonge, N., Green, N. S., Rinaldo, P., Lloyd-Puryear, M., Dougherty, D., Boyle, C., et al. (2010). Committee report: Method for evaluating conditions nominated for population-based screening of newborns and children. *Genetics in Medicine*, 12(3), 153–159.