Newborn Screening for Lysosomal Storage Diseases in Missouri

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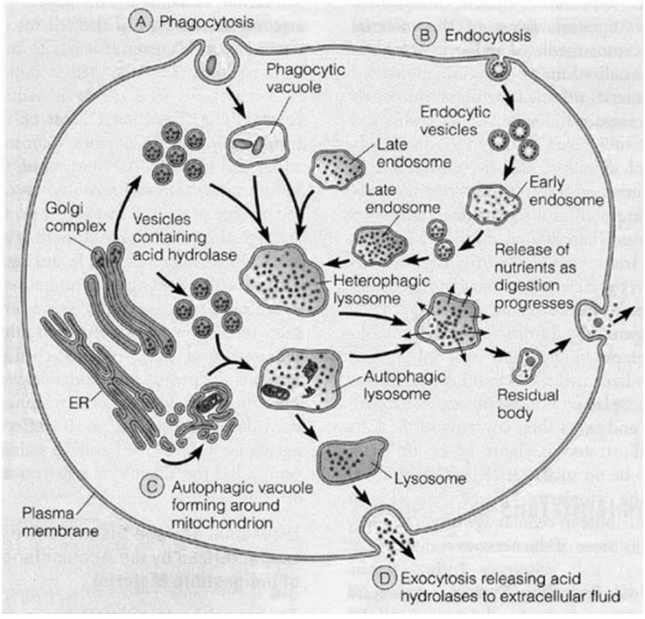
Outline

- Brief overview of clinical features of the LSDs that will be screened for in Missouri and other states
- Legislation for LSDs in the US
- Screening programs in US states
- Planning for follow-up of abnormal screens for LSDs in MO

Function of the Lysosomes

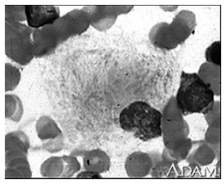
- Lysosomes are membrane-enclosed organelles that contain an array of enzymes capable of breaking down all types of macromolecules—proteins, nucleic acids, complex carbohydrates, lipids, sulfates and phosphates
- Lysosomes function as the "digestive system" of the cell:
  - degrade material taken up from outside the cell
  - digest obsolete components of the cell itself
- They are also involved in cell autolysis or programmed cellular self-destruction

Lysosomes: The "Recycle Bins" of the Cell

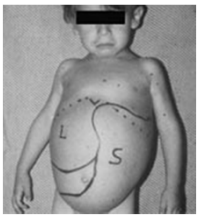


What Are Lysosomal Storage Disorders?

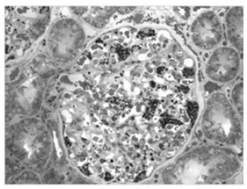
- Lysosomal enzyme defects
  - Over 40 different types
  - Most are autosomal recessive
  - Hunter syndrome and Fabry disease are X-linked
  - Enzyme dysfunction leads to storage material within cells and subsequent tissue damage
- Symptomatically diverse
  - Many different organ systems involved
- Usually not apparent at birth
  - Signs and symptoms develop progressively
  - Variable age of onset



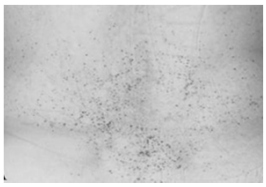
Gaucher Disease



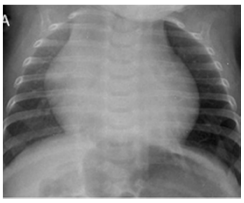
- Deficiency of glucocerebrosidase
- Hepatosplenomegaly
- Anemia, thrombocytopenia
- Bone disease due to storage material in the bone marrow cells
- Type I: Non-neuropathic, most common in Ashkenazi Jewish population
- Type II: Severe infantile form, neuropathic
- Type III: Later childhood onset, neuropathic
- Enzyme replacement therapy available but not effective for CNS disease



Fabry Disease



- Deficiency of alpha galactosidase A
- X-linked disorder
- Neuropathy, angiokeratomas, renal insufficiency, cardiac disease, hearing loss, GI disturbance, eye disease, anhidrosis
- Females variably affected
- Age of onset variable, adult or childhood
- Enzyme replacement therapy available



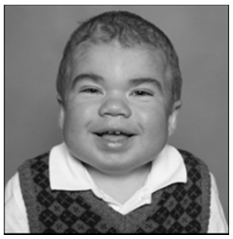
Pompe Disease

- Glycogen storage disease type II
- Acid alpha-glucosidase (GAA) deficiency
- Severe infantile and later onset forms
- Progressive muscle disease
- Cardiomyopathy
- Skeletal muscle myopathy
- Enzyme replacement therapy is available

Hurler Syndrome (MPS I)

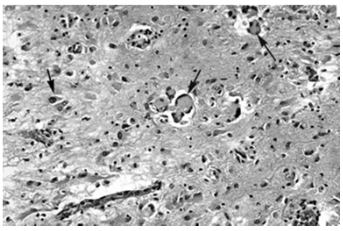
- Deficiency of alpha-iduronidase
- Progressive neurologic deterioration, hepatosplenomegaly, skeletal and heart abnormalities, cloudy corneas
- Severe infantile form best treated with stem cell transplant as early as possible
- Milder forms with later onset
- Enzyme replacement therapy is available

Hunter Syndrome (MPS II)

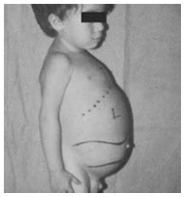


- Iduronate-2-sulfatase deficiency
- X-linked disorder
- Similar features to Hurler syndrome except there is no corneal clouding
- Enzyme replacement therapy is available
- Stem cell or bone marrow transplants have not shown consistent benefit

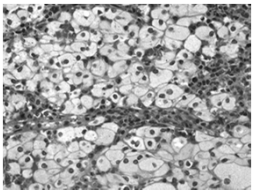
Krabbe Disease



- Globoid Cell Leukodystrophy
- Autosomal recessive
- Galactocerebrosidase deficiency
- GALC needed for the production of normal myelin in the central and peripheral nervous systems
- General irritability, stiffness, arrest of motor and mental development, loss of previously milestones, difficulty in feeding, and seizures.
- Symptoms usually begin at two to six months
- Average age of death is 13 months
- Early stem cell transplant has been shown to improve outcomes



Niemann-Pick Disease A/B



- Deficiency of sphingomyelinase
- Enlargement of the liver and spleen
- Thrombocytopenia
- Sphingomyelin accumulation in the central nervous system results in ataxia, dysarthria and discoordinated swallowing
- Basal ganglia dysfunction causes dystonia
- Gradual loss of intellectual abilities, dementia and seizures
- No effective therapy at this time

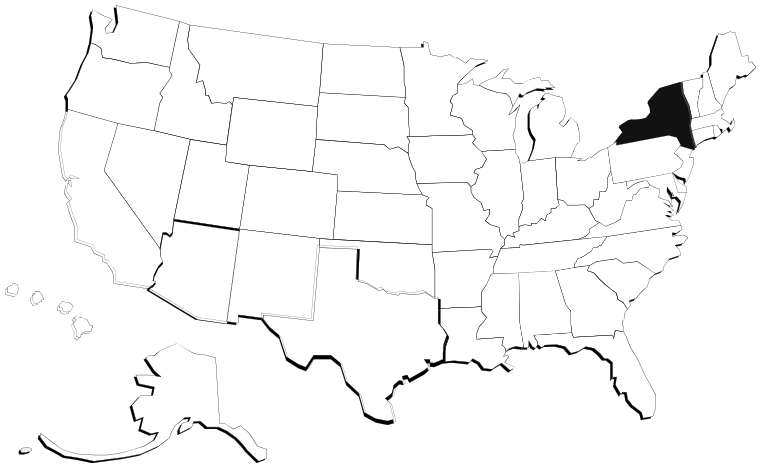
Why Screen for LSDs?

- Most LSDs are not apparent at birth, however irreversible damage to affected organs may be progressing
- Early detection offers the best opportunity for therapeutic or corrective intervention (ERT or HSCT).
- Therapeutic options are increasing
- Multiplex screening methods have been developed
- Can save the family from undergoing months or even years of a "diagnostic odyssey"
- Public Advocacy

Hunter's Hope Foundation

- Legislation passed in 2005 in New York specifically for Krabbe disease newborn screening
- Screening implemented in August 2006
- Screening is done with a combination of enzyme assay and molecular genetic testing

States Screening or Planning to Screen for LSDs - 2005



Mandated screening (Krabbe)

CDC

What is Krabbe?

Globoid Cell Leukodystrophy, more commonly known as Krabbe (crab ā) disease, is an inherited disorder that affects the central and peripheral nervous systems. Children who inherit the disorder lack an important enzyme (GALC) that is needed for the production of normal myelin (white matter). Myelin is the protective covering of the nerve cells. It is essential to normal bodily function.

For more information about Krabbe disease, please visit www.huntershope.org/krabbeNBS

Photos courtesy of www.photohome.com

Hunter James Kelly

Hunter's Hope was established in 1997 by Jim Kelly, Hall of Fame Quarterback, and his wife Jill, after their infant son, Hunter (2/14/97—8/5/05) was diagnosed with Krabbe Leukodystrophy.

The mission of the Foundation includes education, awareness, research, and family support.

Hunter's Hope
P.O. Box 643
Orchard Park, NY 14127
(716) 667-1200, info@huntershope.org
www.huntershope.org

Thank you to NYMAC (New York-Mid-Atlantic Consortium) for funding the creation and printing of this brochure.

Krabbe

Newborn Screening

Evanosky Foundation
Advocacy for LSD Screening in Illinois

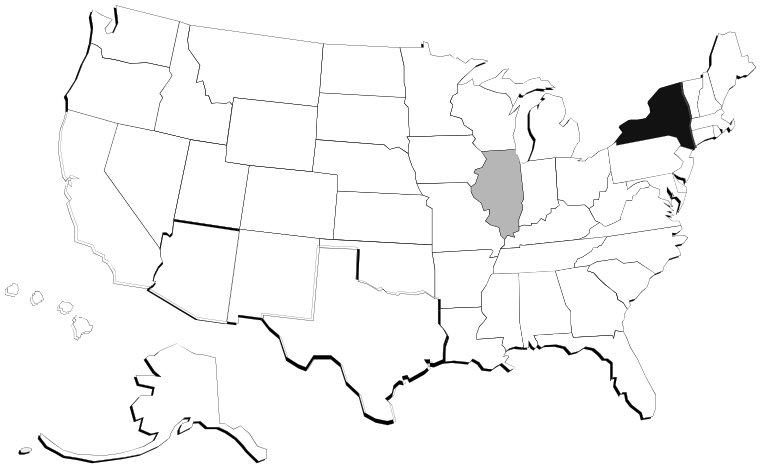
Bob and Sonya Evanosky with sons John, Christopher and Jack

Metachromatic Leukodystrophy (MLD)

Illinois Legislation

- Mandates screening for:
  - Gaucher disease
  - Fabry disease
  - Pompe disease
  - Niemann-Pick A/B
  - Krabbe disease
- Choices of disorders to screen for made because testing was possible via MS/MS methodology

States Screening or Planning to Screen for LSDs - 2008



Legislated but not yet implemented

Mandated screening (Krabbe)

CDC

NEWBORN SCREENING NEWS & ANNOUNCEMENT LIST

Thursday, September 25, 2008

FAMILY FORMS CAUSE AS BABY SUFFERS FROM DEADLY DISEASE

Krabbe Disease is a rare genetic disorder of the nervous system, resulting from a deficiency in an enzyme known as galactocerebrosidase (GALC). A defect in the GALC gene causes the disease. According to research, the body needs GALC to make the substance myelin which cover the nerves in the body. Without it, myelin breaks down, brain cells die, and nerves in the brain and other body areas do not work properly.

Brady Alan Cunningham was born on April 16, 2008 in Cape Girardeau, Mo., with all the standard newborn screenings, indicating normal results. However, his parents and hospital staff noticed Baby Brady shaking a lot after being born. The decision was made to take Brady to the Children's Hospital in St. Louis, Mo. While there, many of the previous tests were re-examined until illness after illness was ruled out. Finally the doctors decided to test for a rare lysosomal disease. It took only one week for the results to return with the news that Baby Brady had Krabbe Disease.

His parents are asking, why not add this disease to the routing screenings done on newborns, to prevent this from happening to another infant.

According to a family friend, the family is going to work hard to get this disease put on the list of routine screenings which are done at birth.

Save Babies Through Screening Foundation

The Power of Advocacy

Jessy, Dustin (parents) and Brady Cunningham
with Bob Evanosky

FIRST REGULAR SESSION
[TRULY AGREED TO AND FINALLY PASSED]

SENATE COMMITTEE SUBSTITUTE FOR
HOUSE BILL NO. 716
95TH GENERAL ASSEMBLY
1522S.03T 2009

191.333. 1. This section shall be known and may be cited as the **"Brady Alan Cunningham Newborn Screening Act".**

2**. By July 1, 2012**, the department of health and senior services **shall** expand the newborn screening requirements in section 191.331 to include the following lysosomal storage diseases: **Krabbe disease, Pompe disease, Gaucher disease, Niemann-Pick disease, and Fabry disease.**

The department may by rule screen for additional lysosomal storage disorders when the following occurs:
(1) The registration of the necessary reagents with the federal Food and Drug Administration;
(2) The availability of the necessary reagents from the Centers for Disease Control and Prevention;
(3) The availability of quality assurance testing methodology for such processes; and
(4) The acquisition and installment by the department of equipment necessary to implement the expanded screening tests.

3. The department may promulgate rules to implement the provisions of this section. Any rule or portion of a rule, as that term is defined in section 536.010, RSMo, that is created under the authority delegated in this section shall become effective only if it complies with and is subject to all of the provisions of chapter 536, RSMo, and, if applicable, section 536.028, RSMo. This section and chapter 536, RSMo, are nonseverable and if any of the powers vested with the general assembly pursuant to chapter 536, RSMo, to review, to delay the effective date, or to disapprove and annul a rule are subsequently held unconstitutional, then the grant of rulemaking authority and any rule proposed or adopted after August 28, 2009, shall be invalid and void.

4. The department may increase the fee authorized in subsection 6 of section 191.331 to cover the additional cost of the expanded newborn screening test required in this section.

LSDs to be Screened in Missouri

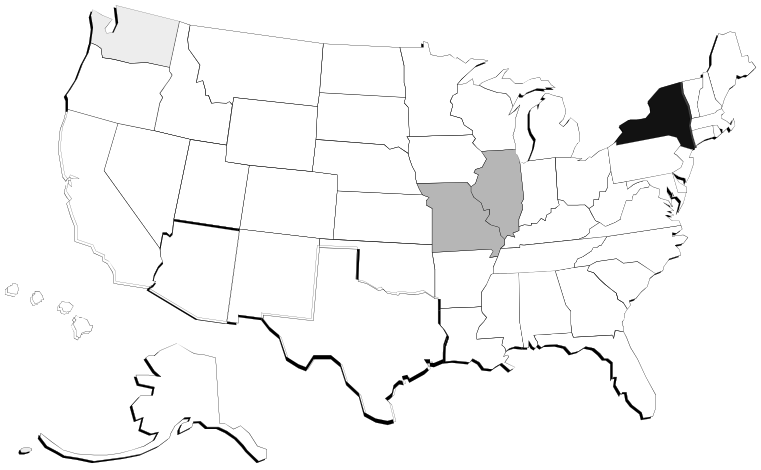
Mandated by LSD Law:

- Krabbe
- Pompe
- Gaucher
- Fabry
- Niemann-Pick A/B

Genetic Advisory Committee Requested:

- MPS I (Hurler)
- MPS II (Hunter)

States Screening or Planning to Screen for LSDs - 2009



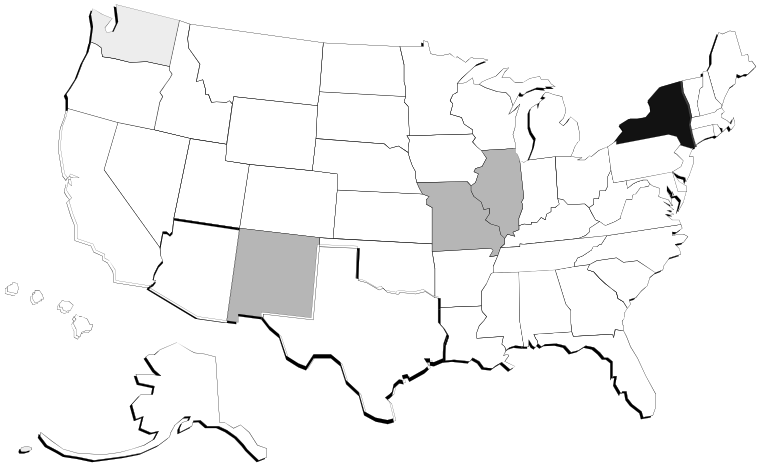
Pilot study

Legislated but not yet implemented

Mandated screening (Krabbe)

CDC

States Screening or Planning to Screen for LSDs - 2010



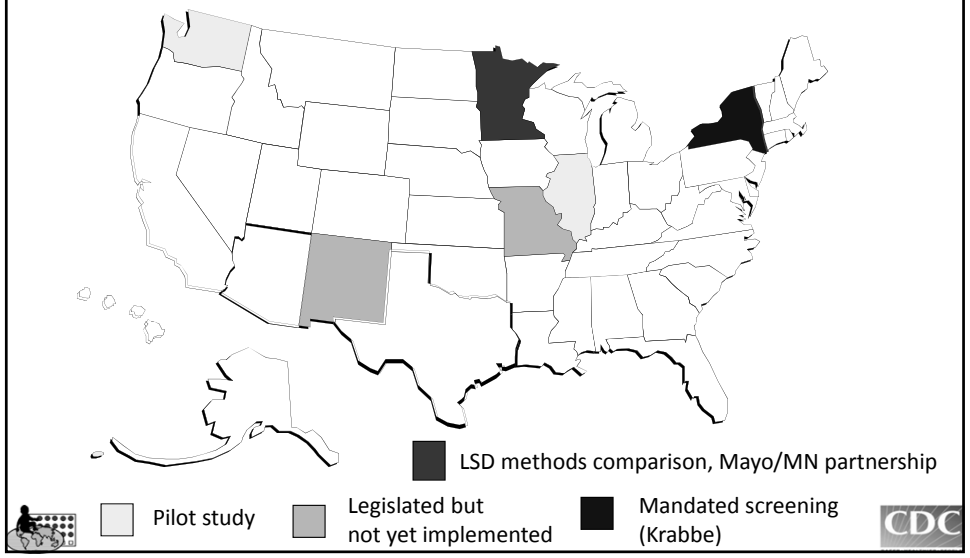
Pilot study

Legislated but not yet implemented

Mandated screening (Krabbe)

CDC

States Screening or Planning to Screen for LSDs - 2011



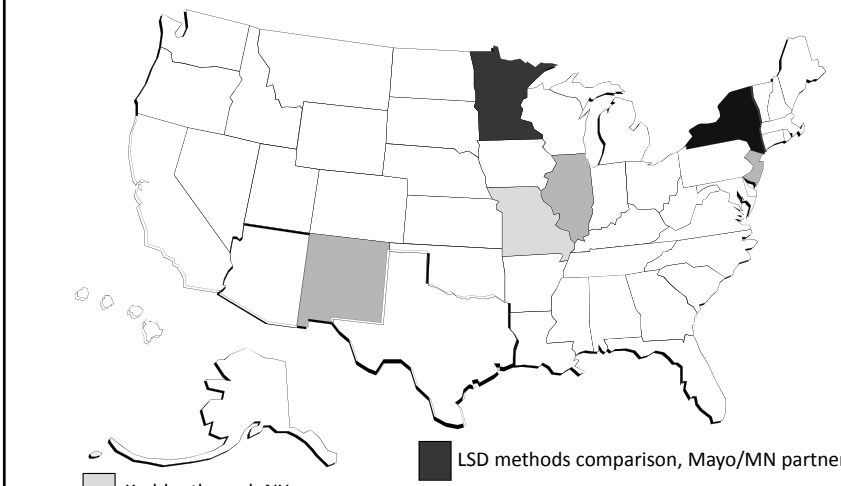
Illinois Screening Pilot

- Piloted screening in the Chicago area hospitals for Pompe, Gaucher and Fabry diseases
- Used Advanced Liquid Logic enzyme assay methodology
- Pilot stopped because of technical difficulties with the assay, primarily for Gaucher
- Illinois is now planning to use the MS/MS methodology and has not yet restarted screening
- Legislation was expanded to include Hurler and Hunter syndromes

Krabbe Disease Screening in Missouri

- Screening began a couple of weeks ago in September 2012
- We are currently sending samples to the New York state lab
- Enzyme assay and DNA analysis for the common 35 kb deletion as well as sequencing
- First abnormal this week!

States Screening or Planning to Screen for LSDs - 2012



Road Blocks to Screening Implementation

- Money! State budget issues.
- Startup funds for NBS testing
- Laboratory space and equipment
- Freeze on creating new FTE's at the lab
- Freeze on raising fees of any kind---will require additional legislation
- Education for all involved regarding the disorders

Missouri LSD Screening Plans

- Planning for the screening of 5 LSDs utilizing the Advanced Liquid Logic (ALL) microfluidics platform.
- Formation of an LSD task force – April 2011.
- Installation and validation of ALL systems – spring and summer of 2012.
- Full population pilot study – January through July 2013.
- Utilize the 4 contracted tertiary genetics centers for follow-up, confirmation and treatment.
- Go live with LSD reporting – July 2013.

Responding to Abnormal LSD Screens

- LSD task force has been formed with geneticists from each of the 4 Missouri tertiary care centers
- We are currently developing follow-up protocols for each disorder
- We obtained draft protocols from the Illinois screening program to modify
- We also modified the New York Krabbe disease follow-up protocol
- We are including neurologists and hematologists/transplanters in our follow-up planning discussions

Unknowns…

- How many variants and late onset forms?
- How many false positives and false negatives?
- How many borderlines?
- What scenarios interfere with the assay results?
- When to treat and when not to treat?
- Long term follow-up – NBSTRN working on nationally harmonized data sets.