NBS for Pompe Disease in Missouri

Legislation to Implementation

National Newborn Screening Meeting on New Disorders (Pompe, MPS I, X-ALD)

Patrick Hopkins; Newborn Screening Project Specialist

NEWBORN SCREENING NEWS & ANNOUNCEMENT LIST

Thursday, September 25, 2008

FAMILY FORMS CAUSE AS BABY SUFFERS FROM DEADLY DISEASE

By: Amenda Alexander

Krabbe Disease (in medical terms) 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.

As a reader, you might wonder, why all this information on such a disease.

Recently, 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. He was later diagnosed with an Immature Nervous System. His parents were told that it would disappear by the age of four months.

During the four-month time span, Brady had colds, ear infections, recurrent Thrush, and the shaking still plagued him. He also began to straighten out his body and arch his back, stiffening as if he were in a lot of pain while crying and not feeding from his bottle.

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.

According to the family, doctors told them early symptoms included hypertonicity, gastric reflux, irritability, and clasped thumbs. Later symptoms would also include blindness and deafness. They were also told that in the infantile form, there is a rapid mental deterioration, which usually leads to death before the age of two.

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

Research indicates, if the screening had been done when Brady was born then he could have received a bone marrow transplant or cord blood transfusion which would have stopped the progression of the disease, and he most likely would have had a normal life.

Because it took four months to diagnose this disease, it is too late to treat his condition, and he is expected to live about 13 months, in pain, while going deaf and blind.

According to Latoya Talley, 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

4 Months Later – A Flurry of Activity

- Courtesy Call from CDC providing a “heads up”
- Lab Director contacted by grandmother of Brady
- House Bill 716 is introduced
- Department heads needed quick answers to many questions…What, Why, How, & Cost
- They wanted informative answers that were heavy on fact and short on opinions
- Legislative Committee hearings at the Capitol

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

AN ACT

To amend chapter 191, RSMo, by adding thereto three new sections relating to newborn screenings.

Be it enacted by the General Assembly of the state of Missouri, as follows:

Section A. Chapter 191, RSMo, is amended by adding thereto three new sections, to be known as sections 191.333, 191.1127, and 191.1130 to read as follows:

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

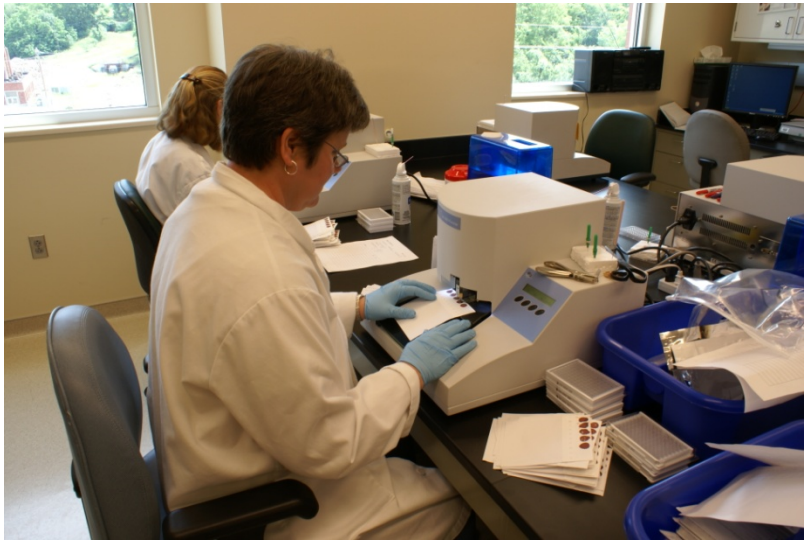
Genetic Advisory Committee Requested:

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

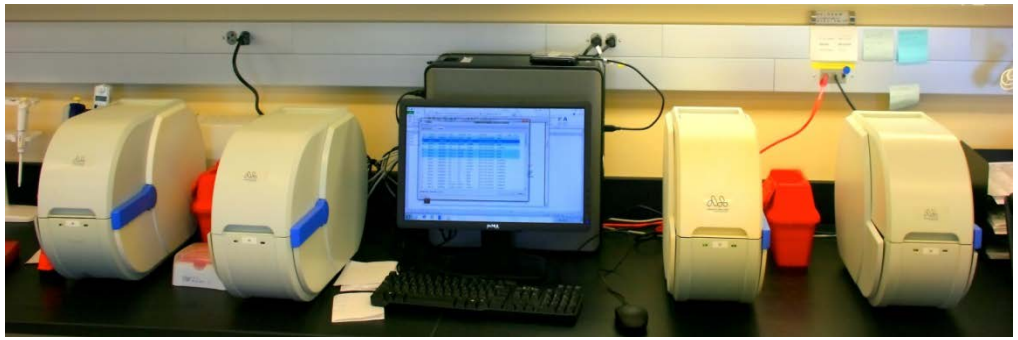
Road Blocks to Screening Implementation

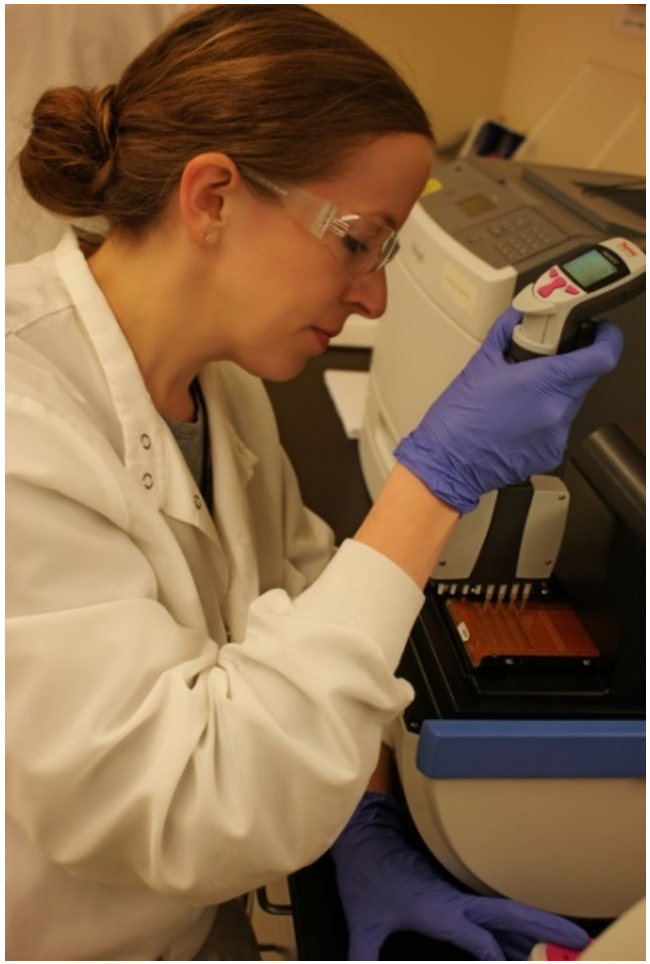
- Money! State budget situation was worst it had ever been
- Startup funds for NBS testing; MS/MS was costly
- Laboratory space and retrofitting of equipment, ventilation, electrical requirements, etc. (for MS/MS)
- Freeze on creating new FTE's
- Freeze on raising fees, including the NBS fee
- LSDs not yet recommended on Core Panel by ACHDNC at that time
- New York had significant trials with Krabbe screening
- Education for all involved regarding these disorders
- Many other issues popping up in the NBS arena at the same time

Staff and Lab Space Already Stretched



Made Decision to Utilize DMF





Tracy Klug, LSD Section Manager

Changes Needed for Lab and Staff?

- Needed to purchase a minus 80 degree freezer
- Was only able to add 1 FTE so needed to rearrange staff and workloads to free up another technician to support LSD screening
- Lots of encouragement needed (1st to screen for Pompe and 1st to screen with DMF)
- Lots of communication with Department Heads due to mandate scenario volatility

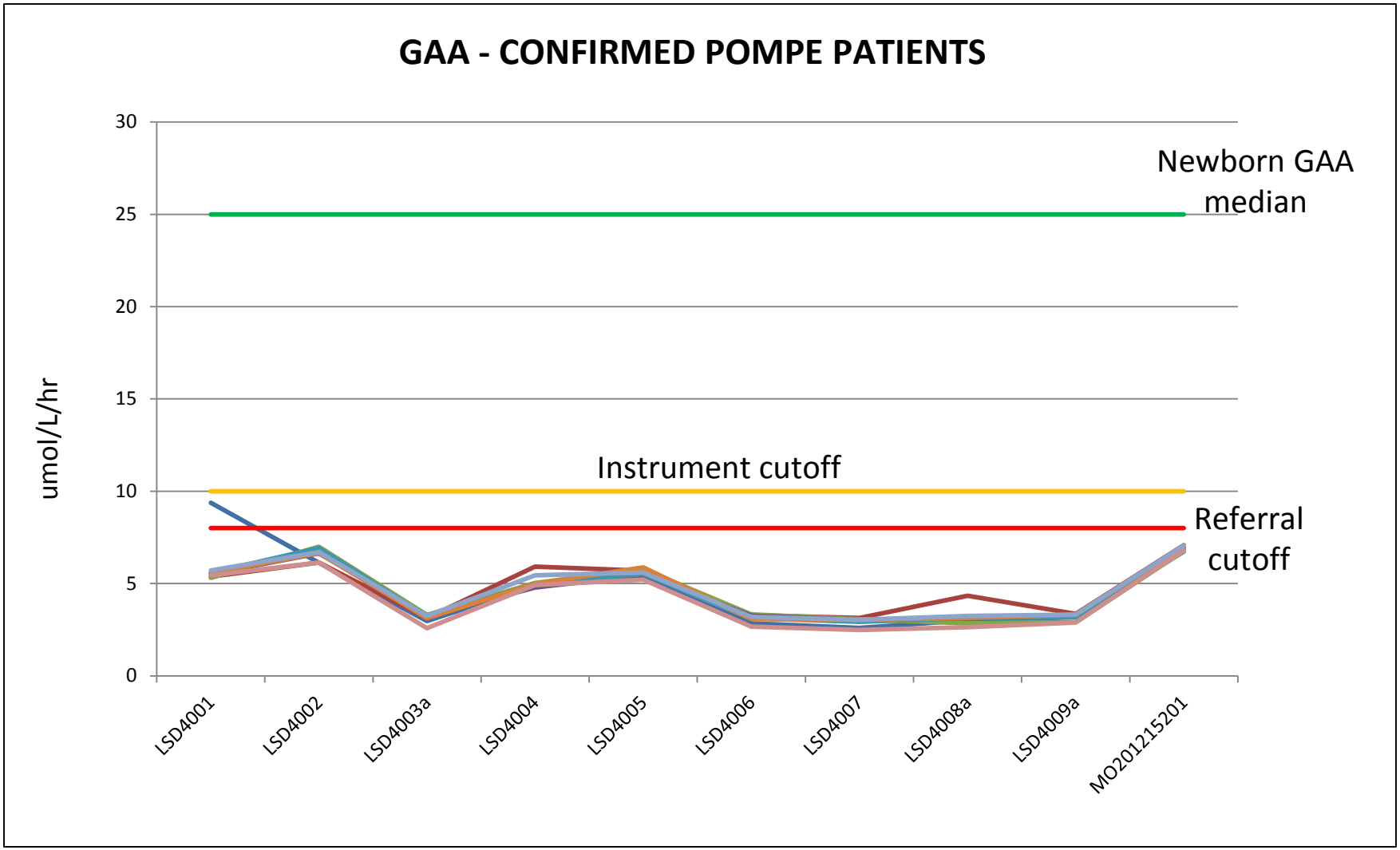
Several Unknowns at that Time

- How can we be sure of our cutoffs?
- What scenarios interfere with the assay results?
- How many false positives and false negatives?
- How many positive and borderline results with using only one tier?
- How many infantile cases will we find?
- How many variations and late onset forms?
- Treatment – When and when not to treat?
- How long should we stay in pilot phase?

How did we develop cutoffs?

- What is Normal? - Determine the normal population range
- What is Abnormal? – Determine the affected range
- Test true positive samples (genetically confirmed as affected) and false positive samples (carriers, pseudo-deficiencies and compromised samples)
- Look at the numbers that flag for various cutoffs using population data
- Are you able to include a borderline range during your pilot (request a second screen only) or will all that are abnormal get referred for diagnostic confirmation?
- Do you have to provide “normal” results on the lab reports during your pilot?
- Monthly feedback on referrals from our LSD Task Force helped us to scrutinize and tweak our cutoffs early in the pilot

Testing of Known Pompe Patients



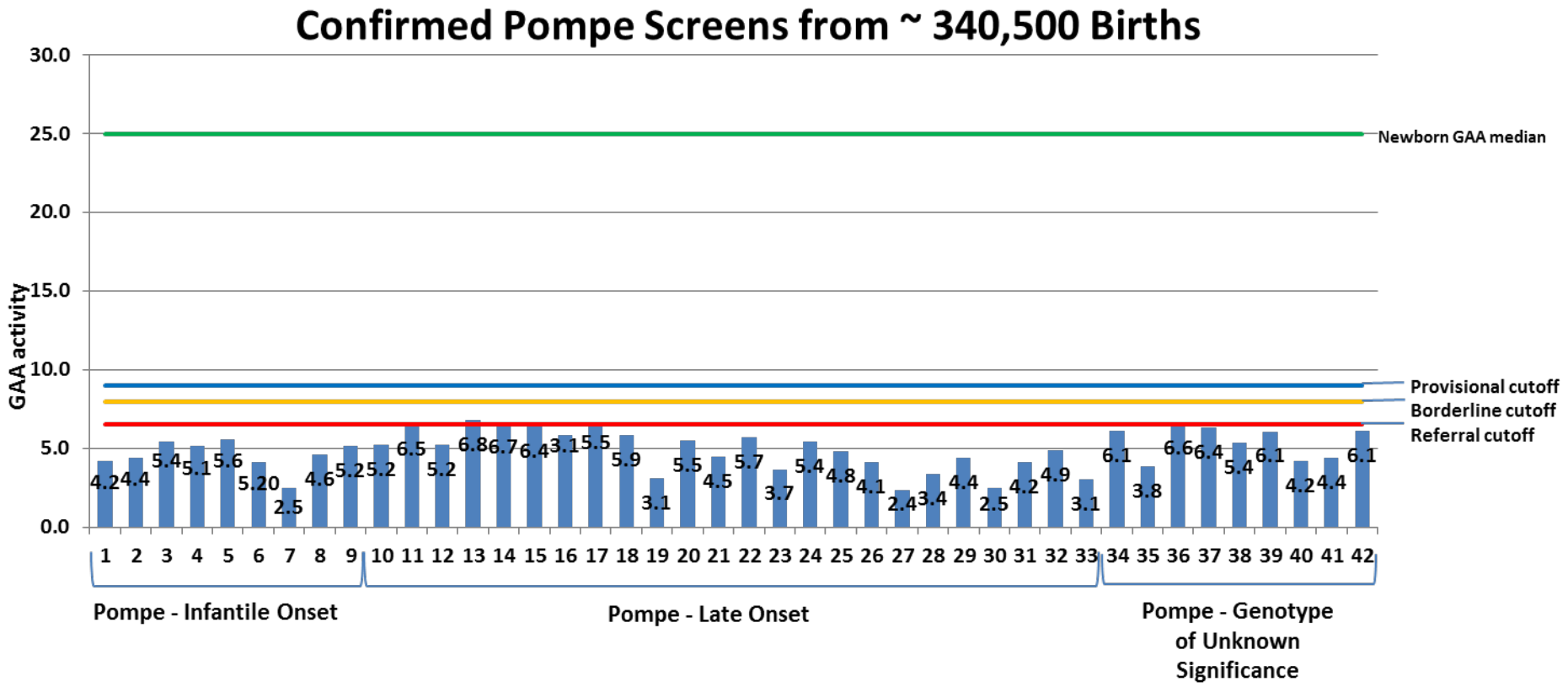
Pre-Pilot Phase Preparation

We used >13,000 de-identified DBS samples that had been stored for 6 months, but first we pre-separated them into specific categories :

- Collection time of > 24 hrs age and < 7 days age with normal health status
- ≥ 7 days-of-age collection, normal health status
- Early collection (< 24 hrs age), not transfused
- Premature, < 7 days of age, not transfused
- Transfused and < 7 days of age
- Transfused and ≥ 7 days of age

What Came Up That We Didn't Quite Expect

- The need for age-related cutoffs for Pompe but not MPS I
- The high incidence of Later Onset Pompe and the prevalence of genotypes of unknown significance
- The seasonal and environmental influences on LSD enzymes in the DBS samples
- Transfused babies not really a problem, but prematurity is an issue as typical in NBS
- The substantial benefit of multiplexing for several LSD's



Infantile Pompe Incidence = 1:37,833

Late Onset Pompe Incidence = 1:14,187

Combined Pompe Incidence = 1:10,318

Missouri LSD Screening Totals

Pompe, Gaucher, Fabry and MPS-1 – Jan. 11, 2013 through June 10, 2017 (**~340,500 Births**)

Krabbe – Aug. 22, 2012 through June 10, 2017 (**~369,500 Births**)

Disorder	Screen Positives	Confirmed Disorders	Conditions of ??? Significance or ??? Onset	Pseudo deficiencies	Carriers	False Positives	Refused Further Testing	Lost to Follow-up	Pending
Pompe	203	**33** (9 infantile) (24 late onset)	9	39	44	55	0	2	21
Gaucher	42	**5**	2	0	6	24	1	1	3
Fabry	210	**93**	8	0	0	72	5	7	25
MPS-1	152	**2**	2	72	8	47	1	4	16
Krabbe	103	**1**	10	2	75	6	4	0	5
Aggregate	**710**	**134**	31	113	133	204	11	14	70

Note: 2nd tier DNA testing may provide better Positive Predictive Values

Acknowledgements

- Tracy Klug, Lacey Vermette and the Missouri LSD laboratory team
- Dr. Sharmini Rogers, Julie Raburn-Miller, Jami Kiesling and the Missouri NBS follow-up team
- The Missouri LSD Task Force

“The secret of getting ahead is getting started”

Mark Twain