2014-0202

PETITION TO ADDRESS THE COUNCIL

St. Charles Parish Council Chairman
P. O. Box 302
Hahnville, LA 70057
(985) 783-5000

Today's Date: July 23, 2014

RECEIVED
JUN 24 2014
PARISH COUNCIL

Dear Chairman:

Please place my name to address the Council on:

DATE: July 7, 2014

SPECIFIC TOPIC: Adrenoleukodystrophy (ALD) newborn screening, ALD awareness month in Sept., and Rare Genes day February 28.

(*See specific guidelines on the reverse side and refer to Parish Charter Article VII Sec. I)

DOCUMENTS, IF ANY: (YES) / NO

NAME: Carissa & Marvin Oxford

COMPANY/ ORGANIZATION: Alex's Angels

MAILING ADDRESS: 72 Saint Anthony St., Luling, La. 70070

PHONE: (504) 289-4409

SIGNATURE: Coxford

Dear Constituent:

Thank you for your active participation. Your views and comments will be considered by the Council in making our decisions. The Council has a considerable amount of business to conduct in a limited amount of time, therefore, please note the following items that are expected of you:

- The Home Rule Charter provides for citizens to address the Council. It makes no provision for initiating debate, discussion, or question and answer sessions with Councilmembers or Administration Officials. Your right is also guaranteed to examine public documents as you prepare your presentation. Should you have any questions for Councilmembers and/or Department Heads as you prepare, please forward such inquiries to the Council Office to insure a timely response. Should you wish to speak to any Official or Department personally, a complete list of contact information will be furnished at your request.
- Please be brief and limit your comments to the specific subject matter on which you have requested to address the Council. Please reference the Council guidelines for time limit specifications.
- **Please forward supporting documents to the Council Secretary for distribution to the Parish Council BEFORE your scheduled appearance in order for the Council to prepare themselves, if necessary.**
- Upon completion of your allotted time to address the Council, please respect the time given to Councilmembers to respond to your comments by not interrupting or interjecting remarks.
- **Slanderous remarks and comments will not be tolerated.** If slanderous remarks or comments are made, your opportunity to address the Council will end, regardless of the remaining time left to address the Council.
- **Repetitious comments and subject matter will be strictly limited.**

A confirmation letter will follow when your name is placed on the agenda.

Sincerely,

JULIA FISHER-PERRIER
COUNCIL CHAIRMAN

(OVER)

What is ALD?

Some background information about chromosomes and genes is helpful for understanding the genetics of X-linked Adrenoleukodystrophy (X-ALD). We all have billions of cells throughout our body. These cells contain chromosomes, which are the carriers of our genetic information. Chromosomes come in 23 pairs; so we have 46 in total - 1 member of each pair comes from our mother's egg cell, and one member of each pair comes from our father's sperm cell at the time of conception. Our chromosomes contain approximately 20,000 genes, of which we have two copies. Our genes are made up of the genetic information that tells our bodies how to grow and develop. Genes help determine traits like eye color and hair color, they help form our personality, and they help protect and make us susceptible to different diseases and genetic conditions (such as the *ABCD1* gene and X-ALD). The *ABCD1* gene is the gene that, when altered or changed, can cause X-ALD. This is the only gene that is known to be associated with this condition and it is located on the X chromosome.

X-ALD is an X-linked condition. This means that it is passed down in families as a mutation, or genetic change, on the X chromosome. With our 46 chromosomes, 2 are comprised of sex chromosomes. Females generally have two X chromosomes and males generally have one X and one Y chromosome. X-ALD historically was referred to as an X-linked recessive condition, implying that females are not affected but are called "carriers" of the condition and males are affected with the condition. In males, one altered copy of the *ABCD1* gene is sufficient to cause disease. Since carrier females have two X chromosomes, the unaltered *ABCD1* gene can somewhat compensate for the one that is altered. Males only have one X chromosome so this is not possible. However, since a significant number of women do have related symptoms (walking difficulties and urinary incontinence for example) it is more appropriate to refer to the inheritance as "X-linked." In almost all cases, females are not at risk for the cerebral form of the disease or adrenal insufficiency (resources below include illustrations of inheritance pattern).

With a carrier mother, there's a 50% chance that with each pregnancy, the *ABCD1* mutation will be passed down. This is a 50/50 chance; like a coin toss. Therefore, if a carrier woman has a son, there's a 50% chance that he'll inherit the *ABCD1* mutation and could develop signs and symptoms of X-ALD. If the carrier mother has a daughter, there's a 50% chance that the *ABCD1* mutation is passed down making her a carrier female also.

A male with X-ALD will pass down the mutation to ALL of his daughters (who will be carriers) and NONE of his sons (since they inherit his Y chromosome and not the X chromosome which carries the mutation).

Most of the time, X-ALD is something that is inherited, or passed down in the family. The act of passing down our genetic information in an egg or sperm is something that is completely out of our control. Approximately 7% of males that have X-ALD have it because of a de novo, or a "new mutation." This is due to an accident that happens in the egg cell or the fertilized egg at a very early stage of development. Again, we have no

personal control over this type of genetic alteration. Once a mutation is created, it is then passed down in families in an X-linked manner. A carrier female may also present this way.

Some resources that might be helpful:

Genetics fact sheets:
http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets

See specifically the fact sheet on X-linked recessive inheritance (again, keep in mind that carrier females can be affected and that it's best to refer to X-ALD as X-linked and not X-linked recessive; I include this resource however because it gives a lot of good background info and explanations of inheritance)
http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/x-linked-recessive-inheritance-2013-traditional-patterns-of-inheritance-3-1

Genetics home reference: (for general information on genetics related topics)
http://ghr.nlm.nih.gov/

ALD Connect:

http://aldconnect.org/index.php

http://aldconnect.org/what_is_ald.php (for specific information on inheritance and aspects of the disease)

X-linked Adrenoleukodystrophy Database:

http://www.x-ald.nl/ (see the clinical and diagnosis section for helpful facts on X-ALD and genetic counseling info) * 5

very resourceful site.

It is highly recommended that you meet with a local genetic counselor for a face-to-face discussion about your family history and genetic counseling for support, information and resources that are specific to your situation.

To find a local genetic counselor please refer to The National Society of Genetic Counselors' website: www.nsgc.org
Go to the "find a genetic counselor" link; located at the bottom right of the page. You can search by different criteria. I would recommend selecting the pediatric option (many pediatric genetic counselors also see adults). If not or if they have someone that's more appropriate at their institution you will be referred on).

-Maria Ronningen Johnson, MS, CGC
Genetic Counselor at University of MN Health

Alex Oxford's ALD story and New Born Screening Benefits.

Alex was born August 14, 2003. He was born a happy, healthy, vibrant little boy. Absolutely perfect. Little did we know there was something fatal lurking inside. Alex played sports from the time he could walk and swing a bat. He made very good grades in school and eventually excelled greatly in athletics. However, Alex has always gotten extremely car sick and complained of leg pain. I took him to the Doctor and they told me to give him Dramamine before we travel anywhere and that his leg pain was nothing more than growing pains. When Alex started Kindergarten, his teacher suggested that we put Alex on medication for ADHD. ADHD is the most common misdiagnosis for ALD. We tried all ADHD meds in 2 years. Alex always did well in school until the 3rd grade. We started to notice that he was forgetting work he always knew how to do. Then at the start of baseball season we noticed that he was having some issues. We chalked it up to the ADHD. Then one day in April 2012 Alex vomited and went lethargic. His Father rushed him to Kenner Regional where they did a flu test (that came back negative) but still gave us a diagnosis of the flu. He couldn't walk or talk. We asked for an MRI and they laughed at us and said that wasn't financially justified. They sent us home with a prescription for Phenergan (a vomiting medication.) Two weeks later, I received a call from Alex's school stating that he had vomited and needed to be picked up from school. I went to pick him up and he seemed fine until we got home. Then he vomited and once again went lethargic, totally nonresponsive. At that point we rushed him to Children's Hospital where a nurse immediately informed us that he was having a seizure. This lead to a CAT scan which showed swelling in the white matter in the back of his brain. They then admitted him and did an MRI the next day. At that point, they knew it was bad. Most of the myelin sheath of his brain was missing. A blood test had to be performed to confirm the diagnosis. The doctor told us she was very sorry but ALD is a fatal non-curable brain disease and he had less than 2 years to live. Luckily, we had done our own research and found out that there is an option. The only possibility was a bone marrow transplant. The transplant is not a cure as it doesn't reverse the damage already caused to the brain but it is designed to halt the progression of the disease. We were diagnosed Wednesday, May 9, 2012. By the following Monday we were in Minnesota to see if Alex was a candidate for a bone marrow transplant. If the damage to the brain is too great, they will not perform the transplant. By the grace of God, Alex was a candidate. Little did we know we were about to embark on the most hellacious journey of our lives. We had to move to Minnesota to have the transplant done as that is where the only ALD SPECIALISTS in the WORLD are. During the first transplant Alex lost most of his vision, hearing, needed assistance with walking and eating but could still talk and understand but with slowed processed thinking. Unfortunately, the first transplant was not successful. Hearing that news was as devastating as the diagnosis. We had to put him through this to him again. In the second transplant Alex lost the rest of his vision, hearing, ability to talk, walk, and is now in diapers. We didn't expect him to do so poorly during the transplants. But, with ALD there are so many unknowns that it is impossible to predict how well a child will handle a transplant. Not all children tank the way Alex did. It's so unfair, it's like we have to mourn the loss of our child twice. Once when they lose all function and are no longer the bright vibrant little boys we knew and loved and again when they get their wings. We do however know that the earlier the child is diagnosed and the sooner a transplant is performed, the better the results. ALD is a time sensitive disease. It slowly eats away the myelin sheath of the brain over time. ALD is also NOT currently a part of new born screening here in the United States. New York is the only state that I

know of that has added it to its panel. When you are able to find out through New Born Screening that your child has ALD, time is then on your side. You do yearly MRI's until age 3 then every 6 months afterwards. As soon as they doctors see the slightest change in the MRI they can do a bone marrow transplant to halt the progression of the disease. It truly is immoral that such a devastating disease could be tested in new born babies and avoids these boys from suffering the horrific death they are subjected too. ALD only affects boys, usually young boys between the ages of 6-8. The cost of the test is approximately $1.50 and only boys need to be tested, though New York tests both boys and girls (to see if they are carriers for the disease). The cost of the machine to test here in state is upward of 1 million dollars. Otherwise the test is sent to John Hopkins in New York. Since testing in New York has started 8 children have been diagnosed.

OPEN * This is a copy of "Aiden's Law" (the New Born Screening in New York.

Bill S2386-2013

Enacts Aidan's law to require adrenoleukodystrophy screening of newborns

Enacts Aidan's law to require adrenoleukodystrophy screening of newborns.

Details

- Same as: A211-2013
- Versions S2386-2013
- Sponsor:ADAMS
- Multi-sponsor(s): None
- Co-sponsor(s): GOLDEN, LANZA, PARKER, STAVISKY
- Committee: FINANCE
- Law Section: Public Health Law
- Law: Amd §2500-a, Pub Health L

Actions

- Feb 28, 2013: REPORTED AND COMMITTED TO FINANCE
- Jan 17, 2013: REFERRED TO HEALTH

Meetings

- Health: Feb 28, 2013

Votes

VOTE: COMMITTEE VOTE: - Health - Feb 28, 2013
Ayes (16): Hannon, Farley, Felder, Fuschillo, Golden, Larkin, Savino, Seward, Young, Rivera, Montgomery, Sampson, Hassell-Thompson, Adams, Peralta, O'Brien
Nays (1): Ball

Memo

BILL NUMBER:S2386

TITLE OF BILL: An act to amend the public health law, in relation to requiring adrenoleukodystrophy screening of newborns

PURPOSE: Enacts Aidan's Law to require adrenoleukodystrophy screening of newborns

SUMMARY OF PROVISIONS: Section 1. This act shall be known and may be cited as "Aidan's Law". § 2. Subdivision (a) of section 2500-a of the public health law, as amended by chapter 863 of the laws of 1986, is amended to read as follows: (a) It shall be the duty of the administrative Officer or other person in charge of each institution caring for infants twenty-eight days or less of age and the person required in pursuance of the provisions of section forty-one hundred thirty of this chapter to register the birth of a child, to cause to have administered to every such infant or child in its or his care a test for phenylketonuria, homozygous sickle cell disease, hypothyroidism, branched-chain ketonuria, galactosemia, homocystinuria, adrenoleukodystrophy, and such other diseases and conditions as may from time to time be designated by the commissioner in accordance with rules or regulations prescribed by the commissioner. Testing, the recording of the results of such tests, tracking, follow-up reviews and educational activities shall be performed at such times and in such manner as may be prescribed by the commissioner. The commissioner shall promulgate regulations setting forth the manner in which information describing the purposes of the requirements of this section shall be disseminated to parents or a guardian of the infant tested.

JUSTIFICATION: Aidan Jack Seeger, was diagnosed with ALD (adrenoleukodystrophy) on June 2, 2011; he was just 6 years old. ALD is a horrific metabolic disease, which affects the myelin sheath in the brain and affects all neurological functioning, eventually leading to death. Aidan was in 1st grade, above grade level and running and playing as any other child his age. He started having vision problems around April and it was assumed he needed glasses.

After many doctors and finally an MRI and VLCFA blood test, Aidan was diagnosed with ALD. The only option to possibly stop the progression of the disease is a bone marrow transplant. Aidan received his unrelated cord blood transplant at Duke University in North Carolina on July 21, 2011, also his 7th birthday. The months that followed were grueling, the bone marrow transplant was a success, but unfortunately, since he was already symptomatic and with the effects of the chemotherapy and the disease progression, Aidan lost his ability to see, hear, eat, walk and communicate. After 10 months in the hospital, Aiden lost his battle with the disease on April 29, 2012.

If New York and the rest of the nation had newborn screening for ALD, Aidan and so many other children's prognosis would be different. Children who have undergone bone marrow transplants before the onset

of symptoms have had a much better prognosis and most are perfectly healthy today.

The urgency for these families to find out about this genetic disease at birth so they can be monitored and treated before symptoms arise is paramount. Unfortunately, many parents have never heard of this disease until diagnosed after the onset of symptoms. There are horror stories of the families that have had 1 child diagnosed, often too late for treatment, and then miracles, often bittersweet of brothers, cousins, etc. being tested after the tragedy, getting treatment and living full normal lives. We can save lives with a simple test.

PRIOR LEGISLATIVE HISTORY: None.

FISCAL IMPLICATIONS: To be determined.

LOCAL FISCAL IMPLICATIONS: To be determined.

EFFECTIVE DATE: This act shall take effect on the one hundred eightieth day after it shall have become a law; provided, however, that effective immediately the addition amendment and/or repeal of any rule or regulation necessary for the implementation of this act on its effective date are authorized and directed to be made and completed on or before such effective date.

Text

STATE OF NEW YORK

2386

2013-2014 Regular Sessions

IN SENATE

January 17, 2013

Introduced by Sen. ADAMS -- read twice and ordered printed, and when printed to be committed to the Committee on Health

AN ACT to amend the public health law, in relation to requiring adrenoleukodystrophy screening of newborns

THE PEOPLE OF THE STATE OF NEW YORK, REPRESENTED IN SENATE AND ASSEMBLY, DO ENACT AS FOLLOWS:

Section 1. This act shall be known and may be cited as "Aidan's Law".

S 2. Subdivision (a) of section 2500-a of the public health law, as amended by chapter 863 of the laws of 1986, is amended to read as follows:

(a) It shall be the duty of the administrative officer or other person in charge of each institution caring for infants twenty-eight days or less of age and the person required in pursuance of the provisions of section forty-one hundred thirty of this chapter to register the birth of a child, to cause to have administered to every such infant or child in its or his care a test for phenylketonuria, homozygous sickle cell disease, hypothyroidism, branched-chain ketonuria, galactosemia, homocystinuria, ADRENOLEUKODYSTROPHY and such other diseases and conditions as may from time to time be designated by the commissioner in accordance with rules or regulations prescribed by the commissioner. Testing, the recording of the results of such tests, tracking, follow-up reviews and educational activities shall be performed at such times and in such manner as may be prescribed by the commissioner. The commissioner shall promulgate regulations setting forth the manner in which information describing the purposes of the requirements of this section shall be disseminated to parents or a guardian of the infant tested.

S 3. This act shall take effect on the one hundred eightieth day after it shall have become a law; provided, however, that effective immediately, the addition, amendment and/or repeal of any rule or regulation necessary for the implementation of this act on its effective date are authorized and directed to be made and completed on or before such effective date.

EXPLANATION--Matter in ITALICS (underscored) is new; matter in brackets [ ] is old law to be omitted.

LBD03768-01-3

Comments

This is some pwk. used to pass New Born Screening in New York.

SECTION 1. Section 124977 of the Health and Safety Code is amended to read:

124977. (a) It is the intent of the Legislature that, unless otherwise specified, the genetic disease testing program carried out pursuant to this chapter be fully supported from fees collected for services provided by the program.

(b) (1) The department shall charge a fee to all payers for any tests or activities performed pursuant to this chapter. The amount of the fee shall be established by regulation and periodically adjusted by the director in order to meet the costs of this chapter. Notwithstanding any other provision of law, any fees charged for prenatal screening and followup services provided to persons enrolled in the Medi-Cal program, health care service plan enrollees, or persons covered by health insurance policies, shall be paid in full and deposited in the Genetic Disease Testing Fund or the Birth Defects Monitoring Fund consistent with this section, subject to all terms and conditions of each enrollee's or insured's health care service plan or insurance coverage, whichever is applicable, including, but not limited to, copayments and deductibles applicable to these services, and only if these copayments, deductibles, or limitations are disclosed to the subscriber or enrollee pursuant to the disclosure provisions of Section 1363.

(2) The department shall expeditiously undertake all steps necessary to implement the fee collection process, including personnel, contracts, and data processing, so as to initiate the fee collection process at the earliest opportunity.

(3) Effective for services provided on and after July 1, 2002, the department shall charge a fee to the hospital of birth, or, for births not occurring in a hospital, to families of the newborn, for newborn screening and followup services. The hospital of birth and families of newborns born outside the hospital shall make payment in full to the Genetic Disease Testing Fund. The department shall not charge or bill Medi-Cal beneficiaries for services provided under this chapter.

(4) (A) The department shall charge a fee for prenatal screening to support the pregnancy blood sample storage, testing, and research activities of the Birth Defects Monitoring Program.

(B) The prenatal screening fee for activities of the Birth Defects Monitoring Program shall be ten dollars ($10).

(5) The department shall set guidelines for invoicing, charging, and collecting from approved researchers the amount necessary to cover all expenses associated with research application requests made under this section, data linkage, retrieval, data processing, data entry, reinventory, and shipping of blood samples or their components and related data management.

(6) The only funds from the Genetic Disease Testing Fund that may be used for the purpose of supporting the pregnancy blood sample storage, testing, and research activities of the Birth Defects Monitoring Program are those prenatal screening fees assessed and collected prior to the creation of the Birth Defects Monitoring Program Fund specifically to support those Birth Defects Monitoring Program activities.

(7) The Birth Defects Monitoring Program Fund is hereby created as a special fund in the State Treasury. Fee revenues that are collected pursuant to paragraph (4) shall be deposited into the fund and shall be available upon appropriation by the Legislature to support the pregnancy blood sample storage, testing,

and research activities of the Birth Defects Monitoring Program. Notwithstanding Section 16305.7 of the Government Code, interest earned on funds in the Birth Defects Monitoring Program Fund shall be deposited as revenue into the fund to support the Birth Defects Monitoring Program.

(c) (1) The Legislature finds that timely implementation of changes in genetic screening programs and continuous maintenance of quality statewide services requires expeditious regulatory and administrative procedures to obtain the most cost-effective electronic data processing, hardware, software services, testing equipment, and testing and followup services.

(2) The expenditure of funds from the Genetic Disease Testing Fund for these purposes shall not be subject to Section 12102 of, and Chapter 2 (commencing with Section 10290) of Part 2 of Division 2 of, the Public Contract Code, or to Division 25.2 (commencing with Section 38070). The department shall provide the Department of Finance with documentation that equipment and services have been obtained at the lowest cost consistent with technical requirements for a comprehensive high-quality program.

(3) The expenditure of funds from the Genetic Disease Testing Fund for implementation of the Tandem Mass Spectrometry screening for fatty acid oxidation, amino acid, and organic acid disorders, and screening for congenital adrenal hyperplasia may be implemented through the amendment of the Genetic Disease Branch Screening Information System contracts and shall not be subject to Chapter 3 (commencing with Section 12100) of Part 2 of Division 2 of the Public Contract Code, Article 4 (commencing with Section 19130) of Chapter 5 of Part 2 of Division 5 of Title 2 of the Government Code, and any policies, procedures, regulations or manuals authorized by those laws.

(4) The expenditure of funds from the Genetic Disease Testing Fund for the expansion of the Genetic Disease Branch Screening Information System to include cystic fibrosis, biotinidase, severe combined immunodeficiency (SCID***), and adrenoleukodystrophy (ALD)*** may be implemented through the amendment of the Genetic Disease Branch Screening Information System contracts, and shall not be subject to Chapter 2 (commencing with Section 10290) or Chapter 3 (commencing with Section 12100) of Part 2 of Division 2 of the Public Contract Code, Article 4 (commencing with Section 19130) of Chapter 5 of Part 2 of Division 5 of Title 2 of the Government Code, or Sections 4800 to 5180, inclusive, of the State Administrative Manual as they relate to approval of information technology projects or approval of increases in the duration or costs of information technology projects. This paragraph shall apply to the design, development, and implementation of the expansion, and to the maintenance and operation of the Genetic Disease Branch Screening Information System, including change requests, once the expansion is implemented.

(d) (1) The department may adopt emergency regulations to implement and make specific this chapter in accordance with Chapter 3.5 (commencing with Section 11340) of Part 1 of Division 3 of Title 2 of the Government Code. For the purposes of the Administrative Procedure Act, the adoption of regulations shall be deemed an emergency and necessary for the immediate preservation of the public peace, health and safety, or general welfare. Notwithstanding Chapter 3.5 (commencing with Section 11340) of Part 1 of Division 3 of Title 2 of the Government Code, these emergency regulations shall not be subject to the review and approval of the Office of Administrative Law. Notwithstanding Sections 11346.1 and 11349.6 of the Government Code, the department shall submit these regulations directly to the Secretary of State for filing. The regulations shall become effective immediately upon filing by

the Secretary of State. Regulations shall be subject to public hearing within 120 days of filing with the Secretary of State and shall comply with Sections 11346.8 and 11346.9 of the Government Code or shall be repealed.

(2) The Office of Administrative Law shall provide for the printing and publication of these regulations in the California Code of Regulations. Notwithstanding Chapter 3.5 (commencing with Section 11340) of Part 1 of Division 3 of Title 2 of the Government Code, the regulations adopted pursuant to this chapter shall not be repealed by the Office of Administrative Law and shall remain in effect until revised or repealed by the department.

(3) The Legislature finds and declares that the health and safety of California newborns is in part dependent on an effective and adequately staffed genetic disease program, the cost of which shall be supported by the fees generated by the program.

SEC. 2. Section 125001 of the Health and Safety Code is amended to read:

125001. (a) The department shall establish a program for the development, provision, and evaluation of genetic disease testing, and may provide laboratory testing facilities or make grants to, contract with, or make payments to, any laboratory that it deems qualified and cost-effective to conduct testing or with any metabolic specialty clinic to provide necessary treatment with qualified specialists. The program shall provide genetic screening and followup services for persons who have the screening.

(b) The department shall expand statewide screening of newborns to include tandem mass spectrometry screening for fatty acid oxidation, amino acid, and organic acid disorders and congenital adrenal hyperplasia as soon as possible. The department shall provide information with respect to these disorders and available testing resources to all women receiving prenatal care and to all women admitted to a hospital for delivery. If the department is unable to provide this statewide screening by August 1, 2005, the department shall temporarily obtain these testing services through a competitive bid process from one or more public or private laboratories that meet the department's requirements for testing, quality assurance, and reporting. If the department determines that contracting for these services is more cost-effective, and meets the other requirements of this chapter, than purchasing the tandem mass spectrometry equipment themselves, the department shall contract with one or more public or private laboratories.

(c) The department shall expand statewide screening of newborns to include screening for severe combined immunodeficiency (SCID) as soon as possible. In implementing the SCID screening test, the department shall also screen for other T-cell lymphopenias that are detectable as a result of screening for SCID, insofar as it does not require additional costs or equipment beyond that needed to test for SCID.

(d) The department shall expand statewide screening of newborns to include screening for adrenoleukodystrophy (ALD) as soon as possible.

Newborn Screening for Adrenoleukodystrophy

Gerald Raymond
Ann Moser
Kennedy Krieger Institute
Baltimore, MD

Peroxisomal Disorders

Assembly Disorders

Zellweger Syndrome
Neonatal Adrenoleukodystrophy
Infantile Refsum
Rhizomelic Chondrodysplasia Punctata

Single Peroxisomal Protein Disorders

X-linked Adrenoleukodystrophy
Acyl-CoA Oxidase Deficiency
Multifunctional Enzyme Deficiency
Thiolase Deficiency
DHAP Alkyltransferase Deficiency
Alkyl DHAP Synthetase Deficiency
Glutaric aciduria type III
Refsum Disease
Hyperoxaluria type I

Adrenoleukodystrophy (ALD)

X-linked disorder - Xq28

incidence 1:17,000, all races affected

Peroxisomal ATPase Binding Cassette Protein (ABCD1)

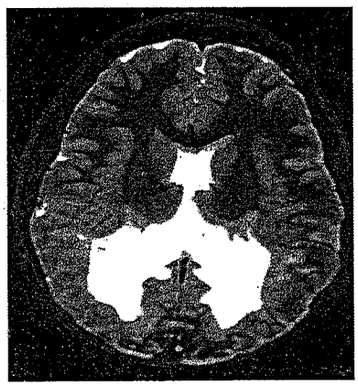
Defect in peroxisomal beta oxidation

Accumulation of very long chain fatty acids (VLCFA)

Affects myelin, adrenal cortex, Leydig cells of the testes

ALD Phenotypes

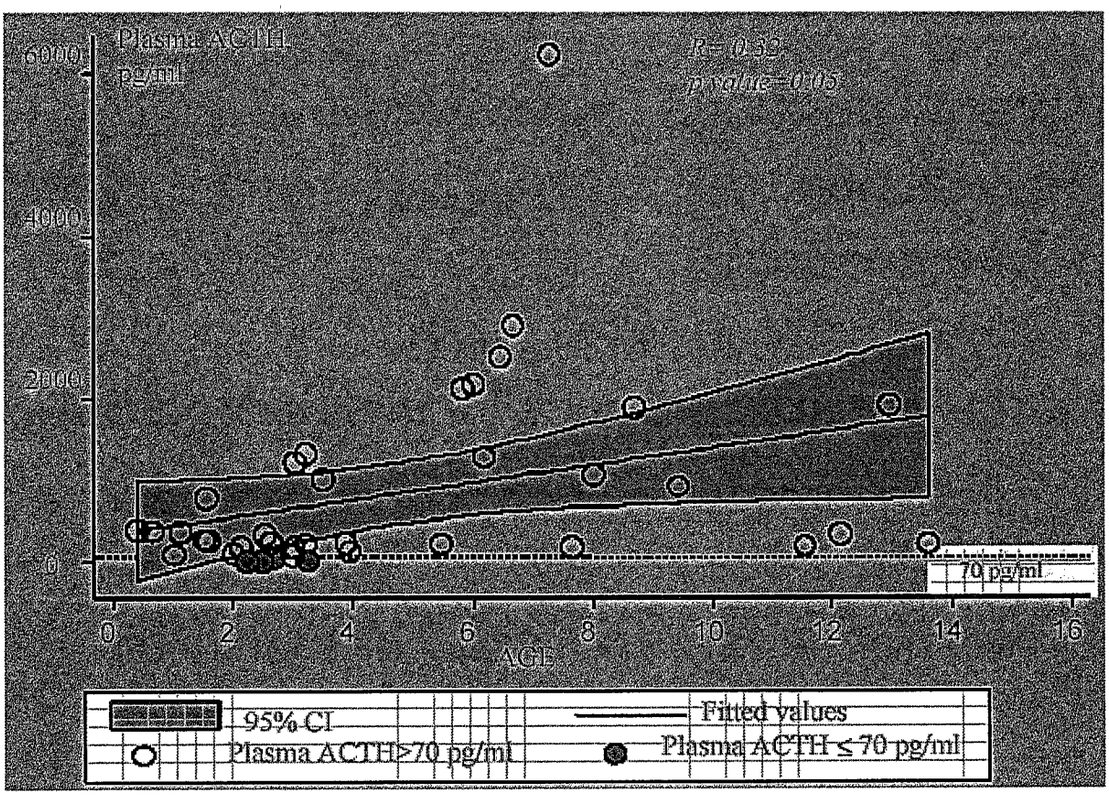
- Childhood Cerebral
  - Diffuse inflammatory demyelination
  - MRI abnormality precedes disease
  - Rapid progression
- Addison Disease
  - Significant cause of morbidity
  - Does not correlate with neurologic disease
- Adrenomyeloneuropathy (AMN)
  - Spastic Paraparesis
- Asymptomatic
- >50% of heterozygous women develop spinal cord features in adult years
- Neither the genetic mutation nor the degree of biochemical abnormality predicts the manifestations, but they can be clinically monitored



Adrenal insufficiency (Addison disease)

- Primary adrenocortical dysfunction
- May present acutely or chronically
- Hypoglycemia
- Difficulty fighting infections
- Dehydration
- Hyperpigmentation (elevation in ACTH)
- Rarely low Na, high K
- A leading cause of adrenal insufficiency in males
- Majority will develop neurologic manifestations

Plasma ACTH in X-ALD identified by VLCFA screen



MRI Progression

Fig 1. Axial FLAIR (A) and sagital T1-weighted MRI after contrast administration (B) demonstrate a focal area of high signal in the splenium of corpus calosum, which shows enhancement after contrast administration.

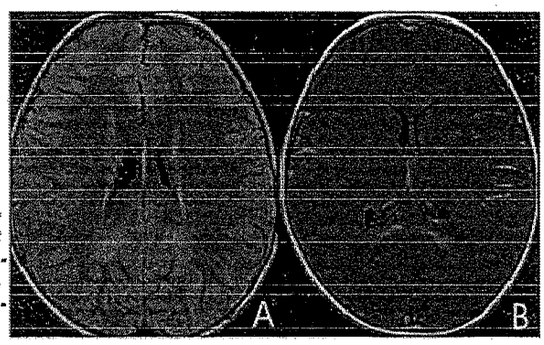


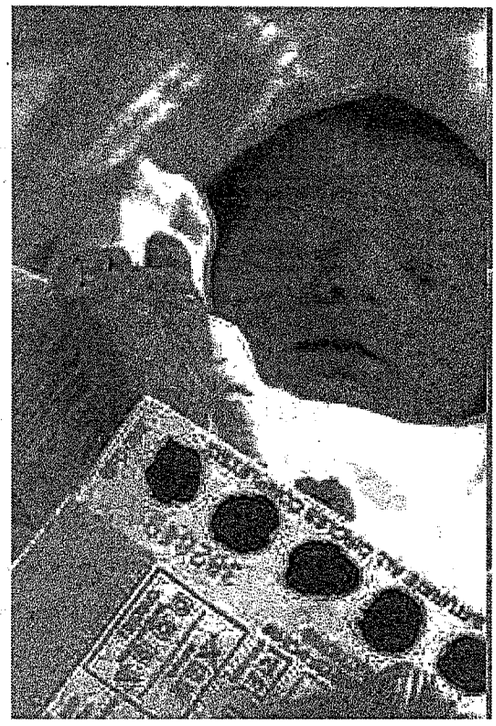
Fig 2. Axial FLAIR (A) and axial T1-weighted MRI after contrast administration (B) show progression of the corpus calosum lesion, as well as other lesions in the parietal white matter.

Current ALD Therapies

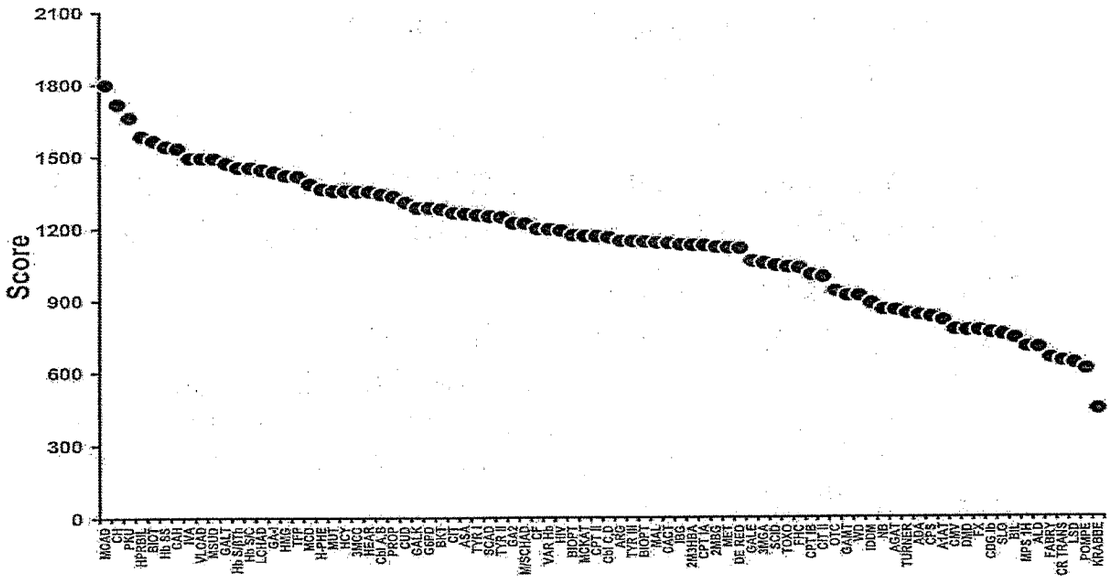
- Adrenal hormone replacement
  - Life-saving
  - Oral medication
  - Need for stress doses
- Hematopoietic stem cell transplant (HSCT)
  - Early cerebral disease
- Gene Therapy
- Preventative therapy with Lorenzo's oil

Newborn Screening for ALD

- Advantages
  - Identify and monitor individuals at risk for adrenal insufficiency
  - Monitor for early cerebral disease and refer when appropriate for therapy
  - Identify extended family members
- Issues
  - Determination of methodology
  - Sensitivity and specificity of the method

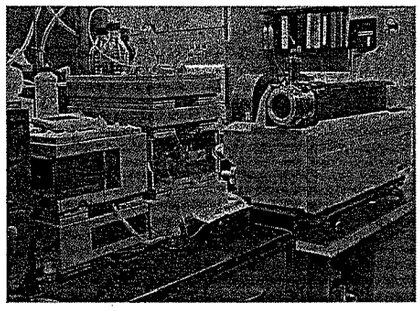


Newborn Screening: Toward a Uniform Screening Panel and System (2006)



Methodology of Newborn screening for ALD – Initial Concerns

- Biochemical determination rather than genetic (DNA) based
  - Elevation of VLCFA defines all males
  - >500 mutations
- Desire to use existing methods
  - Neonatal screening cards (Guthrie Cards)
  - Tandem mass spectroscopy
- VLCFA measurement of dried whole blood spots did not allow diagnosis



Preliminary attempts

- Total VLCFA in whole blood spots did not differentiate ALD from controls
  - High content of sphingolipids in red blood cells
  - Elevated levels of VLCFA in the blank
- Acylcarnitine profiles not diagnostic (Rizzo et al)
- Sphingomyelin and ceramide fraction is increased, but increase is only 2-3 fold and overlaps with controls
- Tested other lipid fractions
  - Lysophosphatidyl choline (lyso-PC) fraction
  - Combined Liquid Chromatography Tandem Mass Spectroscopy as an analytical method for high throughput screening for X-linked adrenoleukodystrophy (Hubbard WC, et al. Mol Genet Metab 89:185-187, 2006)

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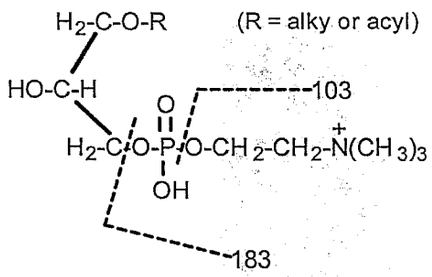
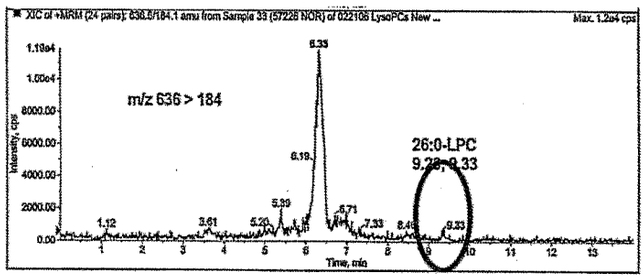
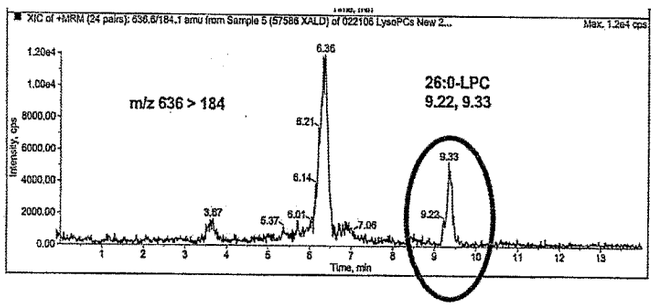


1-acyl-lyso phosphatidylcholine

Normal

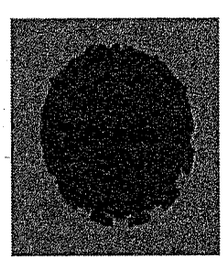


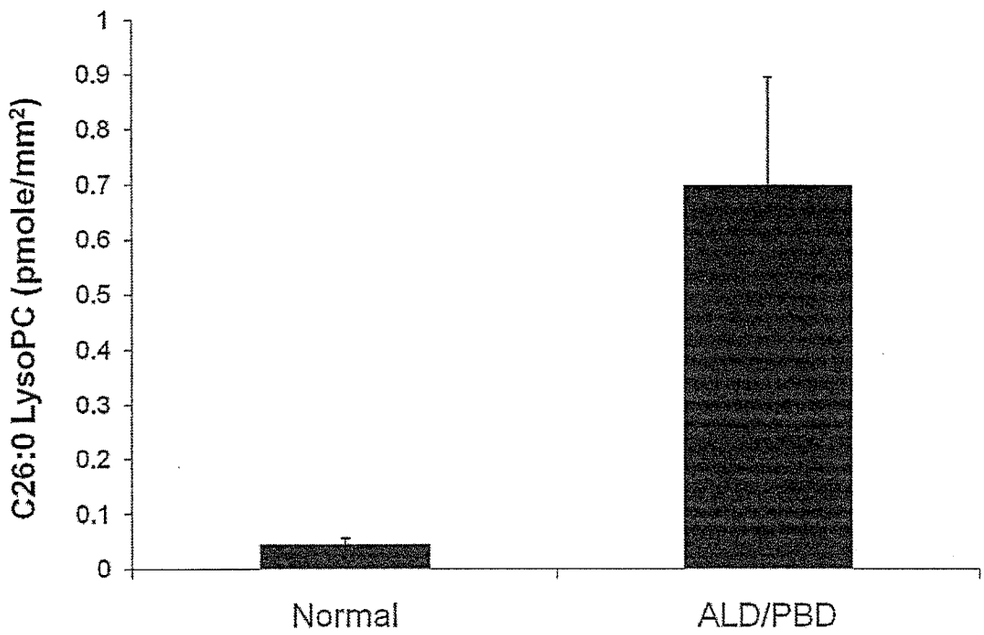
ALD



Determine Sensitivity of Assay

- Retrieve and run newborn banked samples with a known number of identified affected individuals (ALD and PBD)
- In cooperation with NBS programs retrieved 17 samples of known individuals
- Performed masked analysis with 663 anonymous newborn controls





Range 0.016-0.095
N=663

Range 0.482-1.228
N=16

Sample Identifier	Diagnosis	C26:0 Lyso-PC (pmoles/mm^2)
1	ALD	0.724
2	ALD	0.665
3	ALD	0.083
4	ALD	0.931
5	ALD	0.799
6	ALD	0.592
7	PBD	0.713
8	PBD	0.948
9	PBD	1.228
10	ALD	0.611
11	ALD	0.482
12	ALD	0.590
13	ALD	0.667
14	ALD	0.503
15	ALD	0.616
16	ALD	0.578
17	ALD	0.548

Is Sample Number 3 a "False Negative" Result?

Test	Result
Targeted DNA mutation (bloodspot)	No mutation found
Targeted DNA mutation (venous blood)	Family mutation present

CONCLUSION:

- Bloodspot is not from this ALD patient
- This is not a □False Negative□result

Determine Specificity of Assay

- 5000 samples collected in Maryland over a year
- Obtain consent from parent at participating hospital
  - Johns Hopkins Hospital
  - Frederick Memorial Hospital
  - Greater Baltimore Medical Center
- Identify sample and obtain punch at State Laboratory
- Run sample at JHH/KKI MS facility
- Follow up of positives using standard methodology in collaboration with State Newborn Screening program

Pilot newborn screening for X-linked ALD in Maryland

- Period of study
  - November 26, 2008 – August 27, 2010
  - Hopkins □ GBMC □ FMH

	Males	Females	Totals
JHH	519	479	998
GBMC	1503	1416	2919
FMH	586	497	1083
	2608	2392	5000

Methods

- Neonatal dried blood spots (DBS) on filter paper cards
- Stored @ -20° C until sampling with a 1/8" punch into test tube or 96 well plates
- Add a 10µl of purified water
- Add 150 µl isopropanol:hexane 2:3 containing internal standard
  - 10.56 pmoles D-4-26:0 Lyso-PC
- Mix gently for 1 hour at room temp
- Centrifuge and transfer supernatant to glass injection vials with 100ul inserts for LC-MSMS,
- Inject into LC-MSMS
  - 5µl API 4000
  - 10µl API 3200

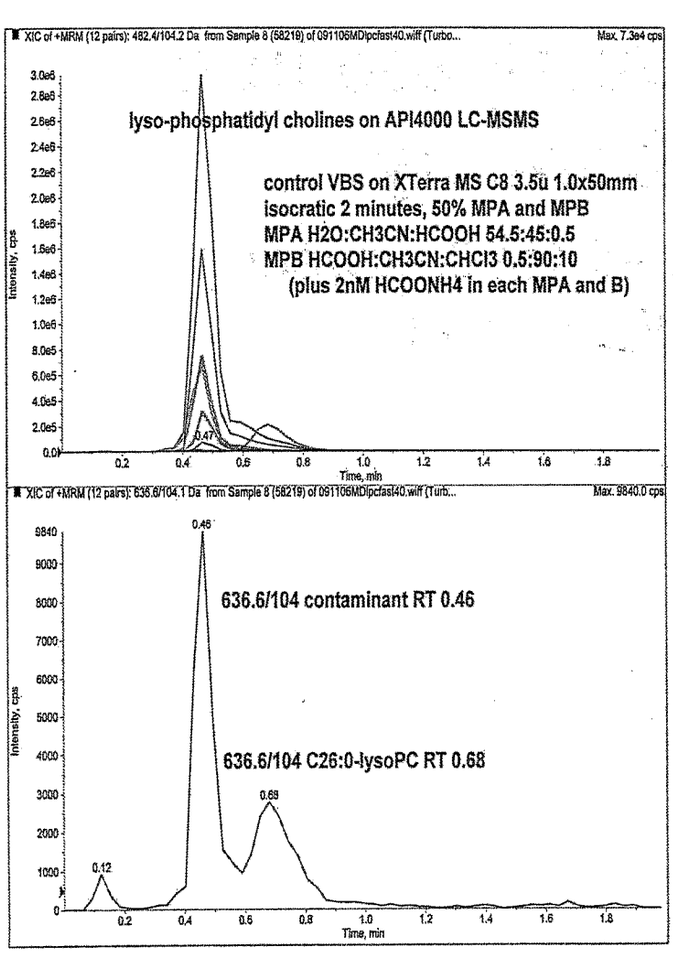
Methods

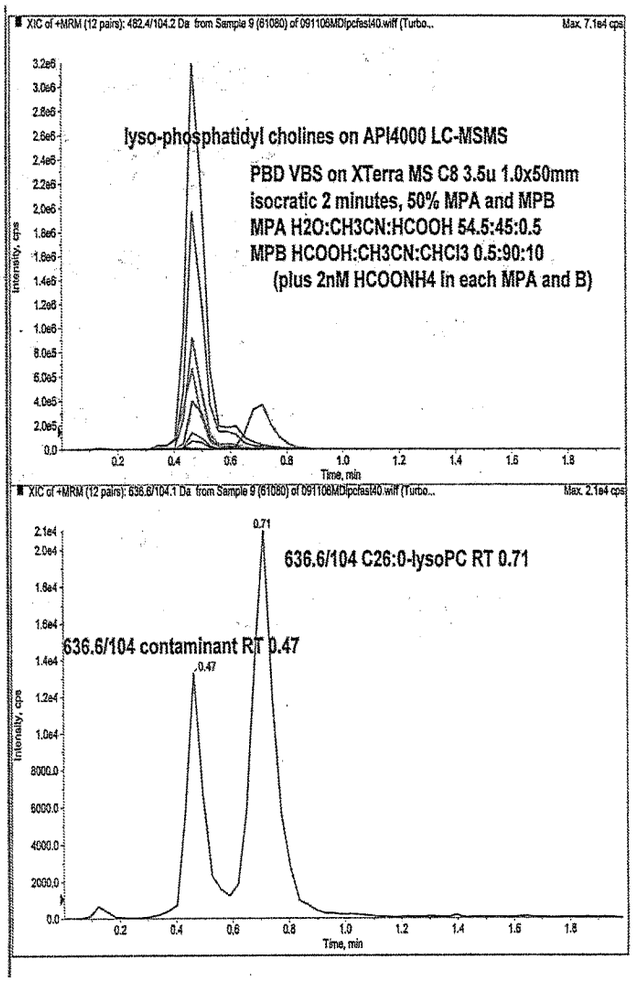
Liquid Chromatography Tandem Mass Spectroscopy

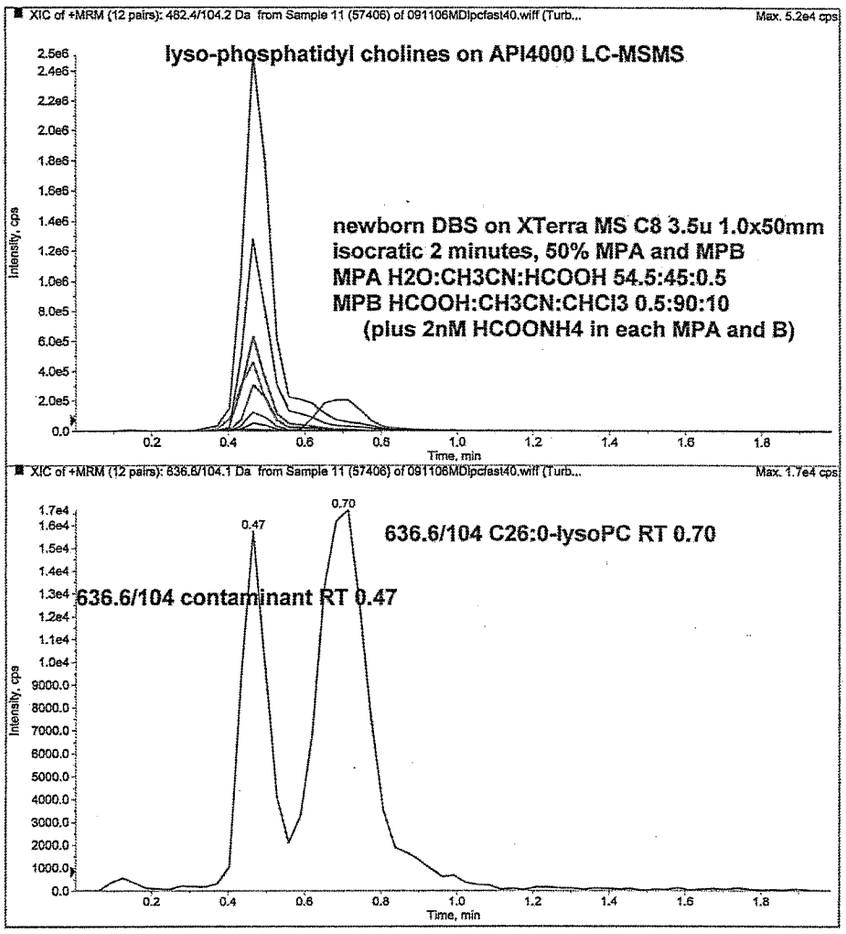
Electrospray ionization (ESI) LC-MS/MS MRM Analysis:

Instruments: Applied Biosystems API 4000 or 3200

- MRM transitions
  - » 1-acyl-lyso-PCs =[M+H]$^+$ >m/z 104
  - » 1-alkyl-lyso-PCs =[M+H]$^+$ >m/z 104
- Reversed phase column: C8-MS, Waters XTerra, 3.5u particle, 1.0x50mm for 2 min isocratic analysis.
- HPLC Solvents:
  - » MPA H_20:CH_3CN:HCOOH 54.5:45:0.5
  - » MPB HCOOH:CH_3CN:$CHCl_3$ 0.5:90:10 (2mM $HCOONH_4$)
- Flow: 0.18ml/minute for 1.0x50mm column 50% MPA and MPB isocratic for 2 min for high throughput analysis.
- Optimized: declustering potential (DP), collision energy (CE), collision exit potential (CXP)





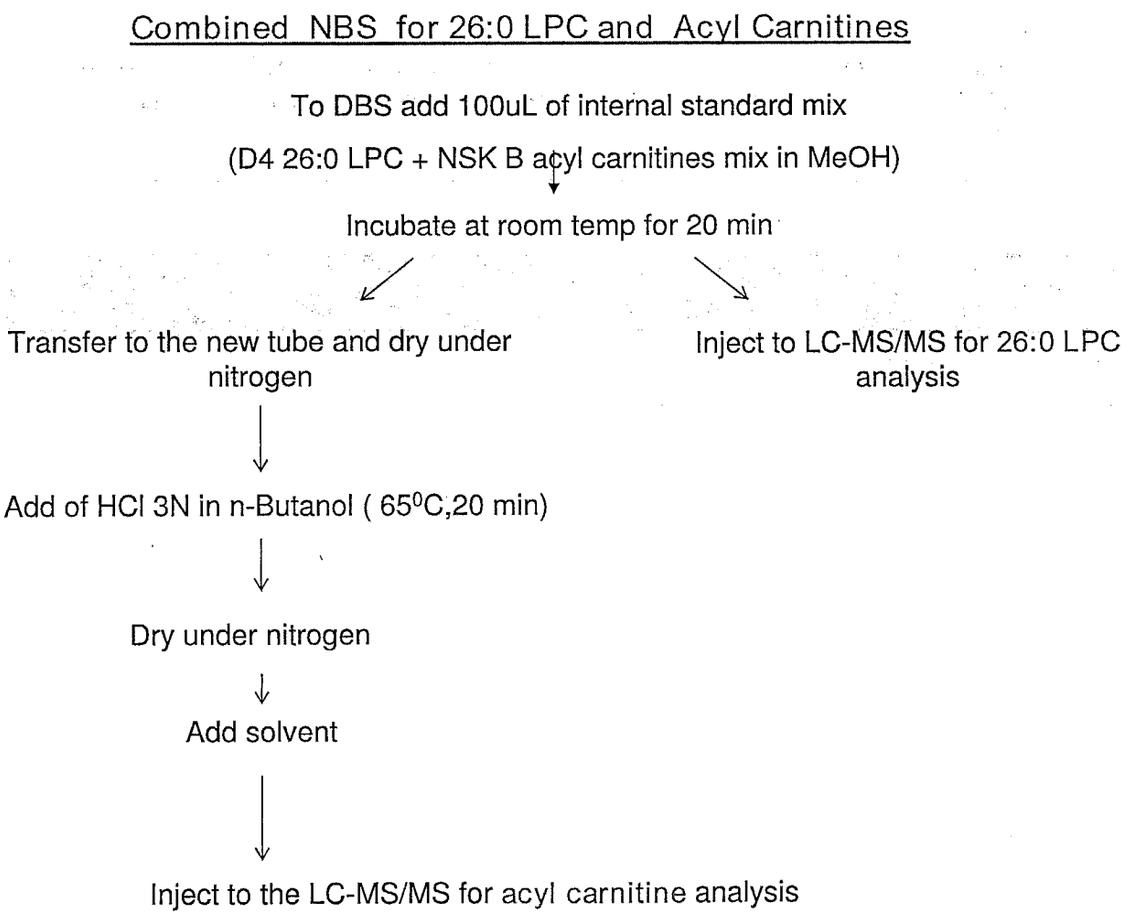


Retrieved and Analyzed from State Laboratory

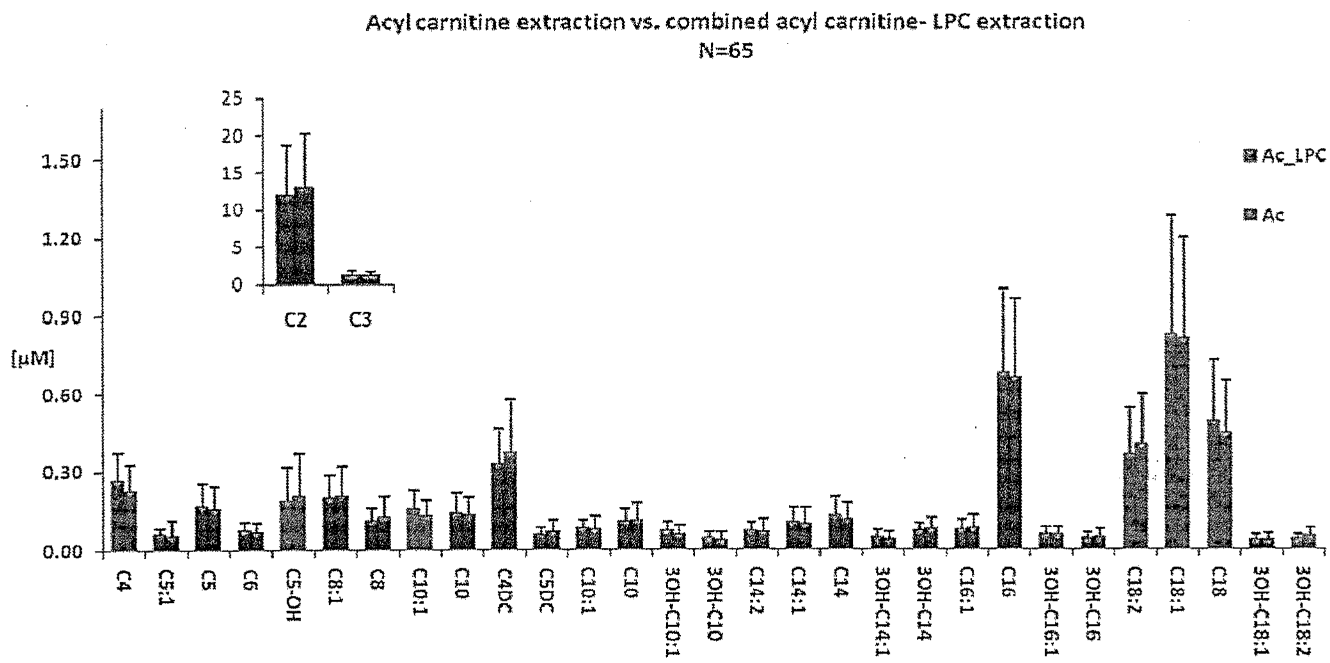
- Received and analyzed 4696 newborn blood spots out of 5000 consented
  - ~6 % not analyzed
    - 293 identified as insufficient
    - 18 not retrieved
- No positives to date

Summary of LC-MS/MS Data Obtained From Newborn Blood Spots:
26:0-Lyso-PC Levels Expressed as Picomoles per 1/8□Blood Spot

	MD pilot study	X-ALD/PBD newborns
Mean	0.365	6.53
Standard Deviation	0.149	1.62
Range	0.11 □1.14	4.69 □9.71
Number of Subjects	4688	16



Method comparison:
Conducted comparison of randomly collected dried blood spots that were extracted with and without lysophosphatidyl choline modification. Acyl carnitines concentrations in both of these experiments compared very well with no diagnostically significant differences.



Summary of data obtained from combined acyl carnitines - lysophosphatidyl choline extraction of DBS. Concentration of 26:0 LPC is expressed as picomoles per 1/8□DBS

	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]

Detection of other peroxisomal disorders

Proposed methodology will detect other peroxisomal disorders that affect beta oxidation of long-chain fatty acids

- Zellweger spectrum disorders
- Single enzyme disorders including Acyl CoA Oxidase and D-bifunctional

Potentially adaptable to other peroxisomal disorders

Total incidence may be comparable to ALD

Presently no available treatment

Summary of Newborn Screening in ALD

- Developed and refined a methodology for determining elevation in very long-chain fatty acids in blood spots
  - Further refinements are expected and run times as short as 2 minutes are possible
  - Possible to combine with other assays
    - Acylcarnitines
    - Amino acids
- Identifies individuals with Adrenoleukodystrophy and other peroxisomal disorders with high sensitivity
- Excellent specificity
- If implemented, the impact on disease is unknown and will require further study, but present clinical experience suggests that it will have significant impact and improve the health of identified individuals

Acknowledgements

- Kennedy Krieger Institute
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- Antonie Kline and staff at GBMC
- Fred Lorey
- Robert Vogt
- Daniela Macaya

- European Leukodystrophy Association
- Myelin Project
- United Leukodystrophy Foundation

Dedicated to Hugo Moser (1924-2007) and our patients and their families

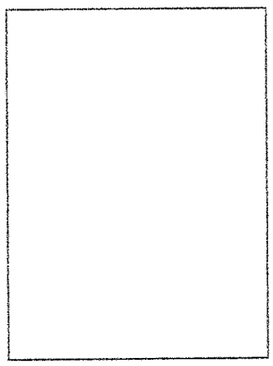
Gmail by Google *This is the story of a mother from New York whose son has been diagnosed thanks to New Born Screening (NBS)

Carissa Oxford <carissaoxford@gmail.com>

NBS letter

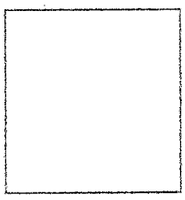
Lindsay <mrshunter122@gmail.com> Tue, Jun 3, 2014 at 7:20 PM
To: "carissaoxford@gmail.com" <carissaoxford@gmail.com>

Adrenoleukodystrophy. ALD for short. What I would give to go back and never learn what this monster of a word means. I would give the world to live a day, even an hour without ALD in my life. But I can't. ALD is a monster that doesn't leave.Adrenoleukodystrophy enters innocent lives unnoticed, often until it's too late for treatment and never leaves. There is no cure for ALD. But there is treatment. The only problem with that is many doctors wrongly diagnose patients because eachpatient's symptoms can greatly vary, and are easily confused with other health issues.

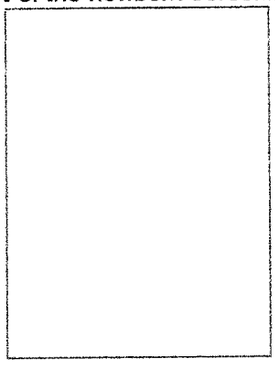


I was going to sit here and go through all the facts, symptoms and sadness this disease brings to families worldwide. I decided not to. I'm sure you'll hear all the nasty things ALD can do. How fast it can change a perfect little boy into severely disabled boy. I'm sure you'll get the sad stories, the ones that will never leave your heart. You'll get the ones that bring a tear to your eye and heaviness on your heart. You'll see the innocent children who once played, ran, heard and saw, who had that stolen from them. You may not sleep well for a few nights after hearing the gruesome details of the nightmare some ALD parents have been living. I don't have that kind of story. But I am a parent of an ALD baby. Just like the rest of the stories you will hear, my baby has the same monster growing inside of him. The only difference is my baby boy, has a chance to walk, talk, speak, run, jump, see and hear the rest of his life. We don't have a magiccure; we don't have access to special treatment. Nothing like that. We were blessed to be screened for this deadly disease when our son was less than 48 hours old. All because we live in New York.
Although ALD has struck my life by surprise tore it up and spit it out with no concern for my families feelings I am lucky. Not because I've learned what ALD is, but because my perfect little boy has a chance to fight this beast. We will have the opportunity to use the tools that are readily available to monitor, treat and take all necessary actions needed to survive our battle with ALD.

Matthew was born January 29th, 2014 in Syracuse New York. He weighed 7lbs 1oz measuring in at 21 inches long. Matthew was healthy and thriving and continues to do so at 6 weeks old. If you look at my dear son you wouldn't know anything was wrong with him. You wouldn't know he has been diagnosed with a deadly disease that attacks some of his most important body parts, his spinal cord and his brain. Matthew hasAdrenoleukodystrophy. Do you know how terrifying it is to hear that your perfect little boy's genes have a mutation that attacks his brain and spinal cord? That even though Matthewwill learn how to walk and talk likes a "normal" boy that can be taken from him as young as 4 years old? I hope you don't, but I do. And that's why I'm writing to you



After hearing the devastating news that Matthews Newborn screening test came back positive for ALD Matthews father and I also found out more information that will forever change our lives, this time for the better. Matthew was the 4th child in the United States to test positive for ALD through the Newborn Screening Program. Not because ALD is that rare but because New York was the first state to mandate ALD screening in newborns. And to make it even more shocking, the law tookeffect just 28 short days before Matthews's birth. For a disease that is so rare in 28 days New York has already received 4positive ALD infants. How rare? Only 1 in ever y 17,000 people have ALD. Soon after learning of this, we learned why ALD was added to the New York newborn screening panel. We learned all about this little blonde curly hair, bright blue eyed boy named Aidan Seeger.
Unlike Matthew, Aidan didn't gettested for ALD as a newborn, and didn't survive his fight against ALD. ALD may have won that battle, but the parents of Aidan fought on in Aidan's name. So much in his name that "Aidan's law" is the reason my 6 week old son has a chance to live a normal healthy life. Without the hours, the dedication, the fighting and the will to beat this monster that so carelessly stole their bright eyed little boy, I would still not know that that huge scary word Adrenoleukodystrophy means, but my little Matthew would still have it. Like I said before I would give anything to live a day without ALD constantly haunting my every thought and action, I am grateful that my son had the opportunity to fight his fight with ALD with the time andresources needed. Aida n's law didn't get passed because someone felt bad for the Seeger's, Aidans law got passed because there's no reason that any child shouldn't have the chance Matthew has. Because ALD is treatable, if the patient has the key to lock ALD away forever. And that key is time. Matthew has his key to his fight; thankfully he was born in the right state. Sadly, so many more innocent children don't have this chance. Won't ever have this chance, without mandatory ALD screening as part of the newborn screening panel.



You are probably wondering how that could possibly be good news to a parent. Well; in life you have two choices be happy or be sad. Starring into my perfect 7 pound 2 week old babies eyes we decided to take the happy road. Even though we just had the worst news a parent can ever receive, Matthew would have ALD even if we didn't get the newborn screening. If that was the case,Matthew wouldn't have a chance. Matthew at 6 weeks old already has a team of specialists working to monitor his health every step of the way so he can take on ALD with the chance at retaining a normal life. Today Matthew is a healthy baby boy meeting all of his milestones, but someday he may not be. He may go backwards physically and mentally. When will that happen? We don't know, doctors don't know. All we know is that Matthew has the mutation in his ABCD1 gene. How he will be affected and when is a medical mystery. There is no test to pinpoint how severe Matthews ALD will be. The only way to conquer ALD's battle is by giving the doctors adequate time to monitor his health and be prepared for treatment. Without the tool of newborn detection patients of ALD don't have the chance they deserve. They don't have the chance my littleMatthew has.

Even though we have only know ALD for a month, it already has killed me to see and hear other stories, some including the death of their sons, and some that found out to late and their 7 or 8 year old is fully dependant on others for care all because of where they live. There are countless families out there right now fighting the fight of their baby's lives and they don't even realize it because their child was born in the wrong zip code. There are families struggling to care for their sons because they weren't tested as a newborn and because of that they had little to no time for treatment as ALD is a very fast moving disease. Every day I wake up and I look into my sons eyes and I thank God for ALD newborn screening. When people hear me tell my story they always say "I'm so sorry", I tell them "don't be,Matthew would have ALD with or without newborn screening, but because of newborn screening he has a chance and we have a chance as his parents to give him the medical care he needs to take on ALD and come out okay!" As heartbroken I am that a family lost their son because they didn't have the test for ALD when he was born, I will forever be thankful for the hard work and dedication the Seegers of Brooklyn New York put into mandating Adrenoleukodystrophy testing for all newborns in new York state. Matthew may not be the first positive ALD test- but without a single doubt, he will not be the last. And until there is a cure there's no excuse any human could live with as to why one babies life is worth being able to have the chance my son has and another baby doesn't, just because of where he was born.
Sent from my iPhone