

The Changing Landscape of Newborn Screening

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- Commercial Support

This educational activity received no commercial support.

- Disclosure of Conflict of Interest

Dr. Wasserstein has a consulting relationship and has received reimbursement for travel as well as research support from Sanofi Genzyme Corporation.

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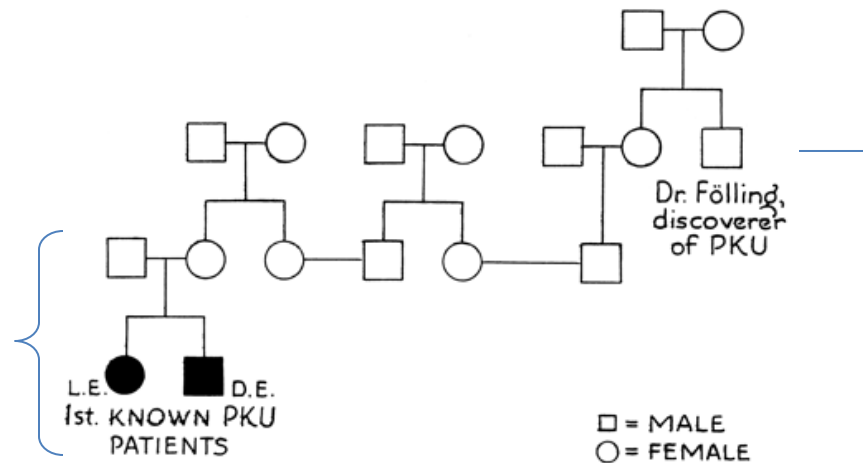
What is newborn screening?

A public health program to identify children at increased risk for selected diseases in order to prevent

- Death
- Irreversible neurological and mental sequelae



PKU: Initial Discovery



“These parents were intelligent and educated, and the children were attractive but severely retarded and irritable with destructive behavior. “

Jervis G.

Phenylpyruvic oligophrenia: a clinical and laboratory study of 50 cases of mental deficiency associated with excretion of phenylpyruvic acid.

COMMON

Archives of Neurology and Psychiatry 1937;38:944.

Bickle H, Gerrard J, Hickmott FM

Influence of phenylalanine intake on phenylketonuria.

Lancet 1953;2:812.

TREATABLE

DETECTABLE



Dr. Robert Guthrie, 1916-1995

NYS Newborn Screening Panel: 2016

Inborn Errors of Metabolism: Fatty Oxidation Disorders

2,4-Dienoyl-CoA reductase (2,4-Di) deficiency
 Carnitine acylcarnitine translocase (CAT) deficiency
 Carnitine palmitoyltransferase 2 (CPT-II) deficiency
 Carnitine palmitoyltransferase I (CPT-I) deficiency
 Carnitine Uptake Defect (CUD)
 Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency
 Medium-chain 3-ketoacyl-CoA thiolase (MCKAT) deficiency
 Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency
 Medium/short-chain 3-hydroxyacyl-CoA dehydrogenase (M/SCHAD) deficiency
 Multiple acyl-CoA dehydrogenase deficiency (MADD)
 Short-chain acyl-CoA dehydrogenase (SCAD) deficiency
 Trifunctional Protein (TFP) Deficiency
 Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency

Inborn Errors of Metabolism: Organic Acid Disorders

2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency (MHBD)
 2-Methylbutyryl-CoA dehydrogenase (2-MBCD) deficiency
 3-hydroxy-3-methylglutaryl-CoA lyase (HMG-CoA lyase) deficiency
 3-Methylcrotonyl-CoA carboxylase deficiency (3-MCC)
 3-methylglutaconic acidemia, type 1 (3-MGA)
 Beta-ketothiolase (BKT) deficiency
 Cobalamin A,B cofactor deficiency (Cbl A,B)
 Cobalamin C,D cofactor deficiency (Cbl C,D)
 Galactosemia (GALT)
 Glutaric acidemia, type I (GA-I)
 Isobutyryl-CoA dehydrogenase (IBCD) deficiency
 Isovaleric Acidemia (IVA)
 Malonic Aciduria (MA)
 Methylmalonyl-CoA mutase deficiency (MUT)
 Multiple carboxylase deficiency (MCD)
 Propionic Acidemia (PA)

NYS Newborn Screening Panel 2016 (Cont'd)

Inborn Errors of Metabolism: Urea Cycle Disorders

Argininemia (ARG)
Argininosuccinic aciduria (ASA) deficiency
Citrullinemia (CIT)
Human Immunodeficiency Virus (HIV)

Infectious Diseases

Inborn Errors of Metabolism: Amino Acid Disorders

Homocystinuria (HCY)
Hypermethionemia (HMET)
Maple Syrup Urine Disease (MSUD)
Phenylketonuria (PKU)
Tyrosinemia type I
Tyrosinemia type II
Tyrosinemia type III

Hemoglobinopathies

Sickle Cell Disease (S/S and S/C) and Sickle Cell Trait (carrier)

Endocrine disorders

Congenital Adrenal Hyperplasia (CAH)
Congenital Hypothyroidism (CH)

Other Genetic Conditions

Krabbe Disease
Adrenoleukodystrophy (ALD)
Biotinidase Deficiency (BIOT)
Cystic Fibrosis (CF)
Pompe Disease (GAA)
Severe Combined Immunodeficiency (SCID)

Wilson and Jungner Criteria for inclusion on NBS panel

- Accurate screening test
- Regular review of scientific and medical rationale
- Significant life-challenging risk of morbidity if the disorder is untreated
- Total costs of the system from diagnosis to follow-up must be reasonably priced
- Significant prevalence of the disorder
- Natural history of the disease understood
- Consumer involvement, physician and public health acceptance in the decision to mandate screening
- Positive health benefits must outweigh risks and burdens
- The disorder must be treatable and require early treatment
- Resources for and access to confirmatory testing, treatment and counseling.

The ACHDNC and the RUSP

- The Advisory Committee on Heritable Disorders in Newborns and Children (“the ACHDNC”) was established under the Public Health Service Act, Title XI, § 1109 (42 U.S.C. 300b-10), as amended by the Newborn Screening Saves Lives Reauthorization Act of 2014 (P.L. 113-240).
- The Committee recommends that every newborn screening program include a Uniform Screening Panel that screens for 32 core disorders and 26 secondary disorders (aka “the RUSP”)
- While the RUSP provides recommendations, states are free to choose their own NBS panels

NY State Newborn Screening for Krabbe Disease

Krabbe disease

- Progressive neurodegenerative leukodystrophy caused by inherited deficiency of galactocerebrosidase (GALC)
- Infantile form (85-90%)
 - Early infantile Krabbe disease presents before six months of age
 - Irritability, dysphagia, progressive spasticity, developmental regression, blindness, deafness, seizures, and death before 2 years of age
 - Late infantile Krabbe disease presents between six and twelve months of age
 - Progressive neurodegenerative course
- Late-Onset form (10-15%)
 - Variable age of onset from 6 months to 60 years of age
 - Weakness, vision loss, intellectual regression, ataxia

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Transplantation of Umbilical-Cord Blood in Babies with Infantile Krabbe's Disease

Maria L. Escolar, M.D., Michele D. Poe, Ph.D., James M. Provenzale, M.D.,
Karen C. Richards, M.D., June Allison, R.N., Susan Wood, P.N.P.,
David A. Wenger, Ph.D., Daniel Pietryga, M.D., Donna Wall, M.D.,
Martin Champagne, M.D., Richard Morse, M.D., William Krivit, M.D., Ph.D.,
and Joanne Kurtzberg, M.D.

UCB Transplantation For Infantile Krabbe disease

- 25 patients with a form of infantile Krabbe disease
 - GALC activity and genotype not reported
 - Many diagnosed in utero because of + family history
 - 11 asymptomatic newborns (12-44 days of age)
 - 14 symptomatic infants (142-352 days of age)

- Underwent myeloablative chemotherapy and umbilical cord blood transplantation at Duke University
 - Newborn transplants:
 - No deaths, many had progressive myelination and most acquired developmental skills
 - Symptomatic transplants:
 - 57% died, no survivors showed improvement

Newborn Screening for Krabbe Disease

➤ Rationale:

- Based on NEJM paper, bone marrow transplantation can favorably alter the outcome of infantile Krabbe disease if performed presymptomatically
- As untreated infantile Krabbe disease is uniformly fatal, NBS for Krabbe disease was advocated by family support groups

➤ In 2006, NY was mandated to screen all newborns for Krabbe disease

But....

- The ACHDNC advised *against* including Krabbe disease on the RUSP, citing insufficient knowledge about:
 - Accuracy of screening
 - Screening can't differentiate early vs later onset phenotype
 - Diagnostic strategy
 - How do you know which asymptomatic newborn needs treatment?
 - Benefits and harms of treatment
 - Bone marrow transplant has high morbidity and mortality
 - Long term prognosis of bone marrow transplantation
 - NEJM study had median follow up of 3 years
 - Reports of progressive gross motor delay in children with Krabbe disease after successful transplantation

The New York State Krabbe Consortium

- Established in 2006, prior to “live screening”
- Diverse group of experts in NBS, neurology, bone marrow transplantation, biochemical genetics, neuroradiologists, patient advocates, ethicists
- Initial Tasks
 - Develop risk category
 - To distinguish which asymptomatic newborns need further evaluation
 - Create neurodiagnostic algorithm and scoring system
 - To determine which “at risk” infants need emergent transplantation

Risk categorization

- Risk category based on GALC activity in leukocytes
 - Always performed at the Thomas Jefferson Lysosomal Diseases Testing Laboratory using a tritium-labeled galactosylceramide
 - Infants with the lowest enzyme activity were predicted to have the highest risk of developing Krabbe disease

Risk Category	GALC Activity (nmol/hr/mg)	
	2006-2011	After 2012
High	0-0.15	0-0.15
Moderate	0.16-0.29	0.16-0.29 or 0.30-0.50 + two mutations
Low	0.30-0.50	Eliminated
Not at risk	>0.50	≥0.30

Neurodiagnostic evaluation for high risk infants

➤ Components

- Brain MRI
- Lumbar puncture to measure CSF protein
- Nerve conduction velocity
- Brainstem auditory evoked response

Assessment schedule

	0-12 months	13-36 months	37-60 months	Years 6-10
High Risk				
Neurological Examinations	Every month	Every 3 months	Every 6 months	Annual
Neurodiagnostic Evaluations	0, 4, 8, 12 months	As needed	As needed	As needed
Moderate Risk				
Neurological Examinations	Every 3 months	Every 3 months	Every 6 months	Annual
Neurodiagnostic Evaluations	At 12 months	As needed	As needed	As needed

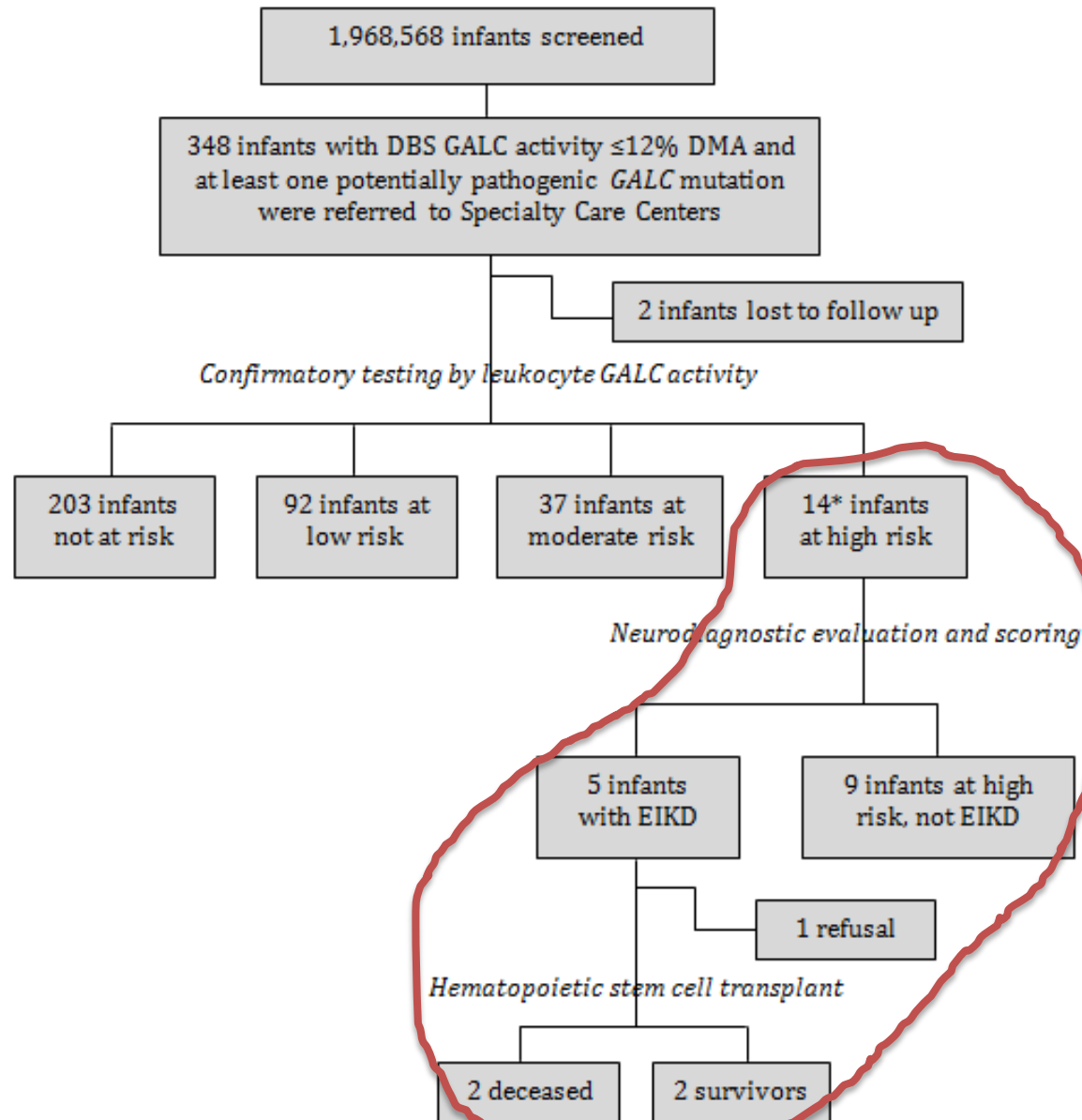
Krabbe Scoring System

- Based on neurodiagnostic scoring system

Parameter	Points
Abnormal Neurologic Exam	2
Abnormal MRI	2
Elevated CSF Protein	2
Abnormal Nerve Conduction Velocity	2
Abnormal Brainstem Auditory Evoked Response	1
30KB Homozygous Deletion	4

Infants with a score ≥ 4 are candidates
for bone marrow transplantation

Flow Diagram, 2006-2014



Outcomes of Infants with Early Infantile Krabbe Disease Identified Through NYS Newborn Screening

- Patient 1 (del30kb /p.I546T+ p.*670Qext42)
 - Transplanted at 32 days of age
 - Z score weight -6.65, Z score height -4.23, HC 2.7th percentile at ~8 years of age
 - Lansky performance score 70, significant delays in all domains but has good receptive language

- Patient 2 (del30kb/del30kb)
 - Transplanted at 31 days of age
 - Died at 84 days from multi-organ failure

- Patient 3 (del30kb/del30kb)
 - Not transplanted
 - Died at ~18 months of age of Krabbe disease

- Patient 4 (del30kb/p.G360Dfs*2)
 - Transplanted at 41 days of age
 - Z score weight -4.3, Z score height -2.06, HC 60th percentile at ~3 years of age
 - Lansky score 40, severe global developmental delay

- Patient 5 (del30kb/del30kb)
 - Transplanted at 24 days of age
 - Died at 69 days of age from progressive respiratory failure

High Risk Infants (2006-2014)

- 9 additional high risk infants, NOT infantile Krabbe disease
- All had
 - Low leukocyte GALC in high risk range
 - Two potentially disease-causing variants
- All underwent at least one neurodiagnostic evaluation
- Current age range 18 months to 9 years of age
 - All remain clinically asymptomatic
 - Some return for neurologic follow up; most do not
 - None have completed all neurodiagnostic evaluations on schedule

	0-12 months	13-36 months	37-60 months	Years 6-10
High Risk				
Neurological Examinations	Every month	Every 3 months	Every 6 months	Annual
Neuro-diagnostic Evaluations	0, 4, 8, 12 months	As needed	As needed	As needed
Moderate Risk				
Neurological Examinations	Every 3 months	Every 3 months	Every 6 months	Annual
Neuro-diagnostic Evaluations	At 12 months	As needed	As needed	As needed

The NY Numbers (2006-2014)

	Expected	Actual
Incidence	1:100,000	1:394,000*
Infantile phenotype	90%	10%
Later onset phenotype	10%	90%**

*Early infantile Krabbe disease only

**Based on moderate and high risk categories. Might take decades to ascertain if there is a phenotype

	Positive Predictive Value of NBS
Early onset Krabbe	1.4%
Later onset Krabbe	?**
MCAD	58.7%

Conclusions of NY State Krabbe Screening

- Morbidity and mortality of transplantation are significant
 - 50% mortality in NY
 - Developmental delays are present in survivors
- Efficacy of transplantation is arguable
 - Progressive motor deterioration has been noted in successfully transplanted children
 - Abnormal myelination in 17-20 week fetuses with early infantile disease suggests prenatal onset of disease, which would limit efficacy

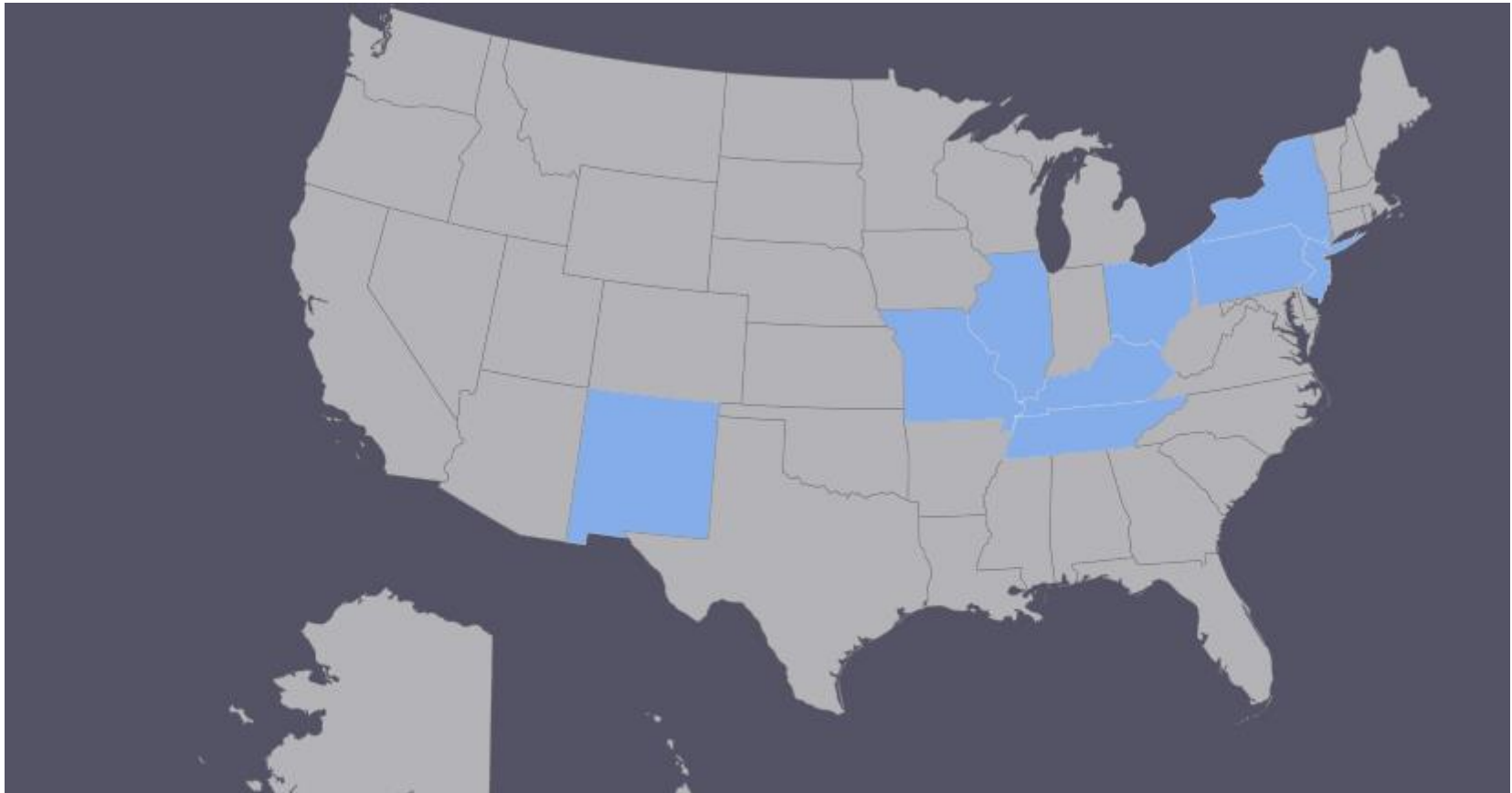
More conclusions...

- There are risks of screening
 - Identification of higher than expected numbers of “at risk” children suggests that we are screening for a predominantly later onset disease
 - Lack of adherence to evaluation schedule suggests that this is stressful to families

Has NY's experience with Krabbe disease influenced other state programs?

- States that are actively screening all newborns for Krabbe disease
 - Missouri
 - Kentucky
- States that recently passed legislation requiring screening all newborns for Krabbe disease:
 - Illinois
 - New Mexico
 - New Jersey
 - Pennsylvania
 - Ohio
 - Tennessee

Status of Krabbe NBS in Other States



Recently Passed Legislation to Mandate Krabbe Screening: IL, NM, NJ, PA, OH, TN

Newborn Screening for X-linked Adrenoleukodystrophy in NYS

Childhood Cerebral X-linked Adrenoleukodystrophy (CCALD)

- “A high-spirited and precocious boy who spoke three languages”
- At about 4 years of age, he “suddenly begun slurring his speech, stumbling and having temper tantrums at school.”
- At age 8, he was paralyzed and blind, unable to speak, dependent on a feeding tube and kept alive by round-the-clock nursing care and the nearly full-time ministrations of his parents.



<http://www.nytimes.com/2013/10/29/world/europe/augusto-odone-father-behind-real-life-lorenzos-oil-dies-at-80.html>

DAILY NEWS

“Brooklyn family fights to pass ‘Aidan’s Law’ which would require screening newborns for rare brain disorder ALD

- Rationale: CCALD is a life-threatening disease. Early treatment with bone marrow transplantation and endocrine therapy may be life-saving.
- NY started screening all newborns in December 2013

Other X-ALD phenotypes

- **Adrenomyeloneuropathy (AMN)**
 - Age of onset: 20-50
 - Characterized by progressive “dying back” distal axonopathy
 - Stiffness and clumsiness in legs, can progress to wheelchair
 - Weight loss, weakness, hyperpigmentation, nausea and vomiting
- **Adult Cerebral**
 - Similar to CCALD but with later onset, typically between 20-50 years of age
 - May present with mania, dementia or psychiatric symptoms
 - Majority also have adrenal symptoms
 - Rapid (3-4 years) progression to death
- **Addison’s Only**
 - Adult onset, adrenal insufficiency without CNS involvement
- **Olivocerebellar Degeneration**
 - Adult onset, CNS phenotype
- **Asymptomatic males**
- **Female heterozygotes**
 - Some develop overt neurologic disturbances similar to AMN
 - Some women have diffuse pain and are misdiagnosed with fibromyalgia
 - Adrenal insufficiency rare

Newborn Screening for X-ALD

➤ Method

- First tier C26:0 by MS/MS.
- Second tier C26:0 LPC using HPLC-MS/MS.
- Third tier: *ABCD1* sequencing

But- it is impossible to predict X-ALD phenotype based on C26:0 and mutation

Phenotypes (males)	Estimated Relative Frequency
Childhood Cerebral	31-35% ← Goal of NBS
Adolescent	4-7%
Adrenomyeloneuropathy	40-46%
Adult Cerebral	2-5%
Olivo-ponto-cerebellar	1-2%
Addison only	Varies with age
Asymptomatic	Varies with age

Majority of cases

Adapted from OMMBID Table 131-1: X-ALD Phenotypes

Surveillance Protocol

- Protocol developed for the context of newborn screening
- Developed based on expert consultation, literature review and input from metabolic specialists and neurologists at NYS NBS Specialty Care Centers

Recommendations for Monitoring At Diagnosis

Evaluation	Timing
Endocrine	
Enter practice and Initial clinical evaluation	At Diagnosis
Serum ACTH	At Diagnosis
Cortisol	At Diagnosis
Neurology	
Enter practice and Initial clinical evaluation	At Diagnosis
Genetic Counseling	At Diagnosis

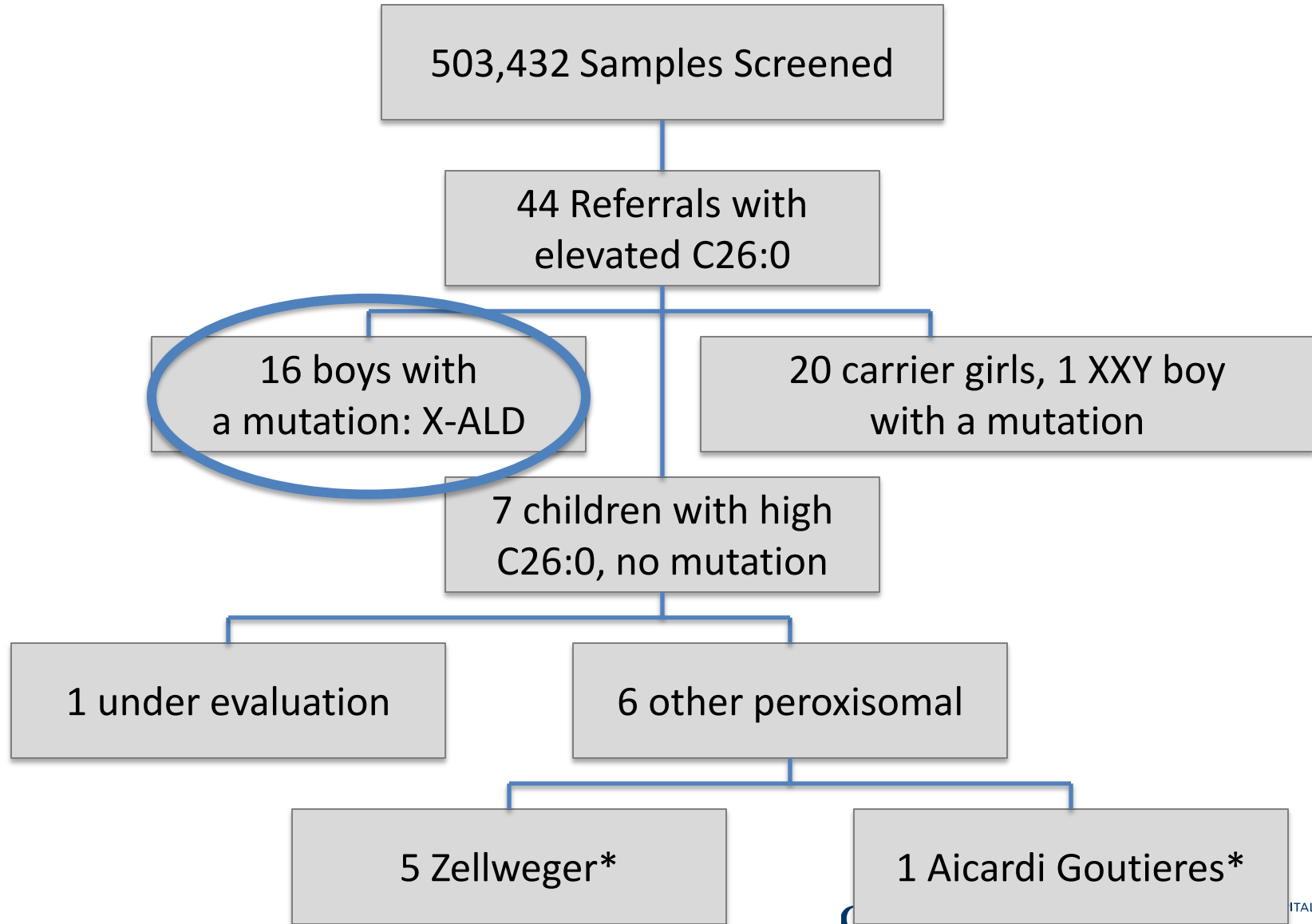
Recommendations for Monitoring: Asymptomatic Boys in Childhood

Evaluation	Age	Frequency
Endocrine evaluation	Age 12 months - 18 years	At least annually
Serum ACTH	Age 6 months- 18 years	Every 6 months
Cortisol	Age 6 months- 18 years	Every 6 months
Neurology evaluation	Age 6 months - 18 years	Annually
Brain MRI without contrast	Age 6 months	Initial
Brain MRI without contrast	Age 18 months - 30 months	Annually
Brain MRI without contrast	Age 36 months - 10 years	Every 6 months
Brain MRI without contrast	Age 10 years - 18 years	Annually
Genetic evaluation and counseling	Age 12 months - 18 years	At discretion of specialist

Recommendations for Monitoring Asymptomatic Men in Adulthood

Evaluation	Age	Frequency
Clinical evaluation with adult endocrinology	Starting at 18 years	At least every other year
Serum ACTH*	Starting at 18 years	Annually
Cortisol*	Starting at 18 years	Annually
Clinical evaluation with adult neurology	Starting at 18 years	Annually
Brain MRI without contrast**	Starting at 18 years	Annually
Genetics evaluation and counseling	Starting at 18 years	At discretion of specialist

The NY Numbers: December 2013- December 2015



Clinical Outcomes of Boys at Risk for X-ALD

- One boy had a bone marrow transplant at ~9 months of age based on MRI changes
- One boy on hormone replacement for adrenal insufficiency since about six months of age
- 14 non-transplanted boys are being watched under surveillance protocol

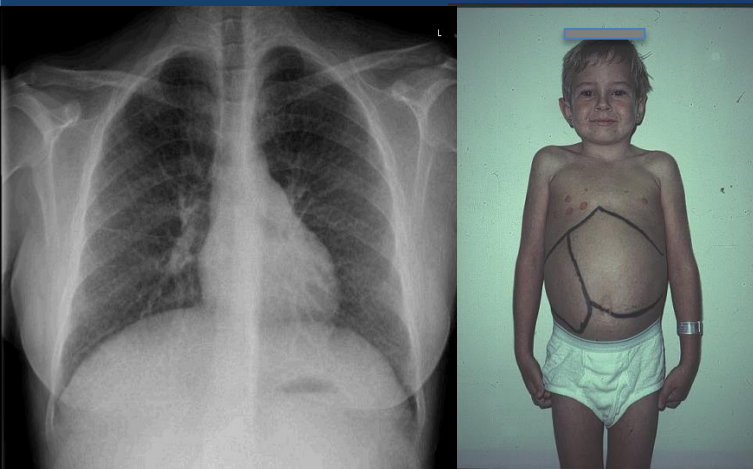
How's X-ALD going for the NBS teams?



- At risk family members can present at any age with any X-ALD phenotype
 - What are the obligations of the NBS team to notify all at risk males?
 - What are the medicolegal implications if a relative can't be located?
 - What are the HIPAA implications?
- Long term follow up
 - How do we ensure follow up over years in *asymptomatic children*?
 - Girls who are carriers will need reminders when they're of child-bearing age
 - Who's responsible for ensuring these individuals are aware of their health status and reproductive risks when they reach the age of majority?



Pilot Newborn Screen for Lysosomal Storage Disorders



	SUB-TYPES	AGE OF ONSET	CLINICAL MANIFESTATIONS	TREATMENT
Gaucher disease	Type 1	Childhood to never	Hepatosplenomegaly, Osteopenia, Pancytopenia, Variable neurodegeneration	FDA approved
	Type 2	Birth to months		
	Type 3	Six months		
Fabry disease	Classic Cardiac	Childhood met		
Niemann Pick A				
MPS1		to four months	Variable intellectual disability, HSM, Dysotosis multiplex, cataracts	FDA approved ERT + bone Marrow Transplant
	Scheie	Childhood to adulthood		

Later-onset disease

\$\$\$\$\$\$\$\$

~\$350K per year for an adult for life

\$\$\$\$\$\$\$\$

No effective

How will newborn screening work for these disorders?
Should we be doing it?

What is a pilot newborn screen?

ROUTINE NBS	PILOT NBS STUDY
Mandatory for all newborns (opt out for religious purposes)	Optional research study
Diseases on the routine panel are determined at the level of the state government	Diseases on the pilot panel are determined by the study investigators
Parental education provided, usually passively	Education provided, actively
Informed consent not required	Informed consent required

Why aren't pilot studies always done with new disorders?

- Informed consent is necessary
 - It is daunting to obtain appropriate informed consent when working with very large numbers
- IRB approval necessary at each participating hospital
- Expensive

The Lysosomal Storage Disorders: A Pilot Newborn Screen and Examination of the Associated Ethical, Legal and Social Issues

- Funded by NICHD
- Multi-Program Collaboration
 - New York State Newborn Screening Program
 - Albert Einstein College of Medicine
 - Newborn Screening Translational Research Network
 - 4 high birth rate, ethnically diverse NYC Hospitals
 - IRB approved research study that requires informed consent to participate

Informed Consent in a Pilot NBS

- IRB approval for a “Waiver of Written Consent with Documentation of Verbal Consent”
- This is a model of informed consent that has since been recommended by the Newborn Screening Translational Research Network
 - Onsite coordinator discusses study with each family
 - Provides educational materials including multilingual brochures, videos
 - Answers questions
 - Documents verbal consent

Participation

- Enrolled (as of December October 1, 2016): 51,179
- Overall consent rate: 72%
- Average enrolled/month: 1,475

	# Screened	# Referred	False Positives	True Positives		PPV
				Later onset phenotype	Early onset phenotype	
Pompe	19,197	6	5	1	0	.17
Gaucher	51,179	11	1	10	0	.90
ASMD	51,179	2	0	2	0	1.0
MPS1	21,503	6	6	0	0	0
Fabry	51,179	18*	4	12	0	0.67

Great positive predictive value!

Currently on the Recommended Uniform Screening Panel

Pilot Study Part 2:

Defining Natural History

- Standard clinical management
- Longitudinal natural history studies to capture data about earliest signs and symptoms of disease with the goal of developing prognostic and treatment algorithms
- We created a long-term follow up shareable database of infants in collaboration with the Newborn Screening Translational Research Network (NBSTRN)
- Goal is to identify clinical and/or biochemical parameters that we can use as guidelines about when to start treatment

Pilot Study Part 3:

Ethical Implications of NBS for the LSDs

- Does screening newborns for later onset disease cause harm?
- Is it beneficial?
 - Current Study: What is the psychological impact on *parents*?
 - Structured, anonymous, online questionnaire
 - Guided, open interview
 - Questionnaire is open to parents from all states currently screening for late onset diseases (Krabbe, LSDs, X-ALD)
 - Future Study: What is the psychological impact on the children themselves?

What's the next step in NBS?

NIH program explores the use of genomic sequencing in newborn healthcare



Can sequencing of newborns' genomes provide useful medical information beyond what current newborn screening already provides? Pilot projects to examine this important question are being funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Human Genome Research Institute (NHGRI), both parts of the National Institutes of Health. Awards of \$5 million to four grantees have been made in fiscal year 2013 under the Genomic Sequencing and Newborn Screening Disorders research program. The program will be funded at \$25 million over five years, as funds are made available.

"Genomic sequencing has potential to diagnose a vast array of disorders and conditions at the very start of life," said Alan E. Guttmacher, M.D., director of NICHD. "But the ability to decipher an individual's genetic code rapidly also brings with it a host of clinical and ethical issues, which is why it is important that this program explores the trio of technical, clinical, and ethical aspects of genomics research in the newborn period."



In conclusion

- Newborn screening was developed to prevent morbidity and mortality by early detection of treatable disorders
- Newborn screening is evolving at a dramatic rate
- The technical ability to screen for so many disorders is introducing novel clinical and ethical issues

Acknowledgements

Children's Hospital at Montefiore

Nicole Kelly, BA, MPH, Project Manager

Aliza Quinones
Paul Levy, MD
Molly Regelman, MD
Deborah Campbell, MD

Mount Sinai Medical Center

Amy Yang, MD
Robert J. Desnick, MD, PhD
Kurt Hirschhorn, MD
George Diaz, MD, PhD
Ian Holzman, MD
Alex Kenigsberg, BA, MST
Ruth Kornreich, PhD
Aliza Quinones
Rosamond Rhodes, PhD
Saskia Sanderson, PhD
Ed Schuchman, PhD
Chunli Yu, MD
Jinglan Zhang, PhD
Manisha Balwani, MD
Lissette Estrella, NP

Newborn Screening Translational Network

Amy Brower, PhD
Mike Watson PhD
Jen Loutrel

New York State Department of Health: Newborn Screening Laboratory

Joseph Orsini, PhD
Michele Caggana, ScD
Beth Vogel, MS, GC
Denise Kay, PhD

Maimonides Medical Center

Gabriel Kupchik, MD
Tori Velez

New York University Medical Center

Sean Bailey MD
Katherine Carome
Rebecca Zarchin

Elmhurst Medical Center

Randi Wasserman, MD
Dalia Makarem, MPH

Duke University Medical Center

Priya Kishnani, MD
Deeksha Bali, PhD

And All Members of the New York Krabbe Consortium

The Pilot NBS is supported by the Eunice Kennedy Shriver NICHD of the NIH under Award Number 5R01HD073292-04