Krabbe Disease

Evidence Review Group
Advisory Committee on Heritable Disorders in Newborns and Children
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Recent Progress and Activities

- Krabbe Disease
  - Draft report presented at May 12, 2009 ACHDNC meeting
  - Final report submitted in July 2009
  - AC Review today
- Overview paper describing ERG process submitted to MCHB

Workgroup Team Members

Key authors:

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- **James M. Perrin, MD**, MGH/Harvard

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- **Marsha Browning, MD, MPH**, MGH/Harvard
- **Anne Comeau, PhD**, New England Newborn Screening Program/UMass Medical School
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- **Ellen Lipstein, MD**, **MPH**, MGH/Harvard
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- **Denise Queally, JD**, Consumer (PKU Family Coalition)

Consultant:

- **Florian Eichler, MD**, MGH/Harvard (Neurology)

Krabbe Disease Overview

- Autosomal recessive lysosomal storage disease
- Mutations in galactocerebrosidase (GALC) gene
- Progressive damage occurs in white matter of peripheral and central nervous systems
- Four main clinical sub-types:
  - Early infantile (EIKD) – main focus of report
  - Late infantile
  - Juvenile
  - Adult

Rationale for Review

- Without treatment, most individuals with EIKD die by age two years
- Methods for NBS exist, by measuring enzyme activity and gene mutation analysis
- New York State began pilot population screening in August 2006
- Pre- or early-symptomatic hematopoietic stem cell transplant (HSCT) may decrease morbidity and mortality from EIKD

Methods of Evidence Review

- Systematic literature review to summarize evidence from published studies
- Assessment of important unpublished data from key investigators and advocates

Key Topics Reviewed: EIKD

- Incidence
- Natural history
- Testing
  - Screening
  - Diagnosis
- Treatment
- Economic evaluation
- Critical evidence needed

Materials Included in Final Report

- Detailed methods
- Summary of evidence
- Tables highlighting key data from abstracted articles
- Table of studies excluded due to ≤4 Krabbe disease subjects
- Bibliography of all identified articles

Systematic Literature Review

- January 1988 - July 2009
  - Medline, OVID In-Process and Other Non-Indexed Citations
  - English language only
  - Human studies only
- Reviewed references from nomination form and bibliography of review papers

- **330** abstracts selected for preliminary review
- **77** articles selected for in-depth review
- **29** articles met all inclusion criteria for abstraction

Papers Meeting Review Criteria

Study Design	Number of papers
Experimental intervention	0
Cohort study	1
Case-control study	4
Case series total	15
Sample size ≤ 10	5
Sample size 11 to 50	7
Sample size ≥ 51	3
Economic Evaluation	0
Other design	9
Total	29

Quality Assessment Methods Used

- By Study Design
  - Compare within, not between, study design categories
- By Study Goal
  - Natural history, Treatment, Screening test, Economic evaluation
    - Example: Sensitivity and specificity of screening
      - Data obtained from screening program in U.S. population or similar
      - Data from systematic studies other than whole population screening
      - Estimated from known biochemistry of the condition

Unpublished Data

- Contacted Krabbe experts identified through:
  - Literature review
  - Discussion within workgroup
  - Recommendation by other experts
- Included experts from different Krabbe disease domains:
  - Screening
  - Treatment
  - Advocacy groups – families' experiences represented by Hunter's Hope registry

Experts & Advocates Contacted

- Georgianne Arnold, MD*
- Scott Baker, MD, MS^
- Susan Berry, MD^
- Paula Brazeal#
- Barbara Burton, MD*
- Michele Caggana, ScD*
- Victor De Jesus, PhD *
- Patricia Duffner, MD*
- Florian Eichler, MD*
- Maria Escolar, MD*
- Bob & Sonja Evanosky#
- Michael Gelb, PhD^
- George Hoganson, MDx
- Rhona Jack, PhD^
- David Jinks, PhD**
- Joan Keutzer, PhD#
- Edwin Kolodny, MD#
- Kim Kubilus^
- Joanne Kurtzberg, MD*
- Jennifer Kwon, MD*
- Joe Orsini, PhD*
- Lawrence Shapiro, MD^
- Jakub Tolar, MD*
- Jacque Waggoner*
- Melissa Wasserstein, MDx
- Kenneth Weinberg, MDx
- David Wenger, PhD*

*Written survey and/or telephone interview
Unable to complete survey due to time constraints
xDid not respond

^ Deferred to other experts
** Unable to contribute due to internal policy

Natural History: EIKD

- Extreme irritability, spasticity, developmental delay before six months of age
- Decerebrate state in early infancy
- Most affected children die before age two years

Quality Assessment: Natural History

Genotype/Phenotype Correlation	**8**
I. Data from retrospective screening studies in US or similar population	0
II. Data from systematic studies other than whole population screening	2
III. Estimated from the known clinical features of the condition as described for individual cases or short series	6

Incidence (cases per 100,000), average within the US	**4**
I. Data obtained from whole-population screening or comprehensive national surveys of clinically detected cases	1
II. As in I, but more limited in geographical coverage or methodology	3
III. Extrapolated from class I data for non-U.S. populations	0
IV. Estimated from number of cases clinically diagnosed in US	0

Other natural history of disease	**8**

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

Incidence

Study	Incidence	Methods
Hagberg et al. (1969, Sweden)	1.9/100,000	▪32 cases collected from 1953-1967 considered representative of the occurrence of the disease in Sweden during this period ▪Median age at onset 4 months and death 13 months; clinical picture and course of disease uniform from case to case
Heim et al. (1997, Germany)	0.6/100,000	▪Survey of all departments of pediatrics, neurology, and neuropathology in Germany ▪Inclusion criteria - biochemically confirmed with clinical manifestations characteristic of neurodegenerative process
Poorthuis et al. (1999, Netherlands)	1.35/100,000	▪Calculated relative frequency and birth prevalence in The Netherlands based on all enzymatically confirmed cases diagnosed during 1970–1996

Screening Method

- Dried blood spot
  - GALC enzyme assay by MS/MS
- Followed by GALC mutation analysis

Genotype-Phenotype Correlations

- Homozygosity for 30-kb deletion is the only genotype strongly predictive of infantile Krabbe (EIKD)
- Over 60 mutations identified in the GALC gene

Quality Assessment: Screening Test Characteristics

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

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

Development of New York State Screening Program

- New York State newborn screening for Krabbe disease begun August 2006
- 550,000 newborns screened for Krabbe disease as of June 30, 2008

- Developed rapid/accurate technique for assessing GALC activity and performing DNA mutation analysis
- Standardized clinical evaluation protocol based on available literature
- Formulated criteria for transplantation for EIKD phenotype
- Developed clinical database and registry
- Studying developmental and functional outcomes
- New York Krabbe Consortium addresses need for clinical evaluation/follow-up for screen positive babies
- Of 550,000 babies screened: 4 high-risk, 6 moderate-risk, and 15 low-risk children identified

Duffner et al. 2009

New York Screening Experience

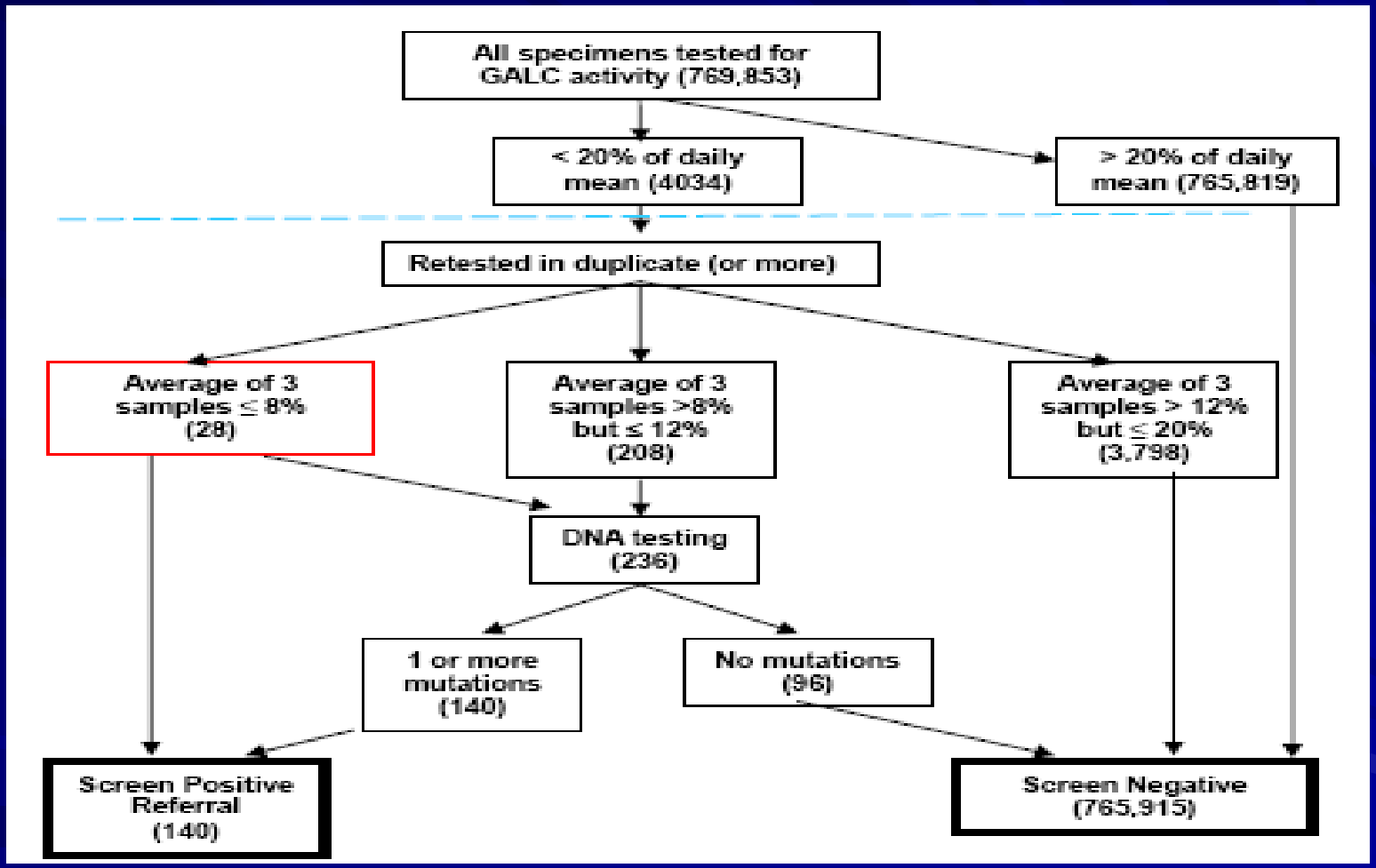
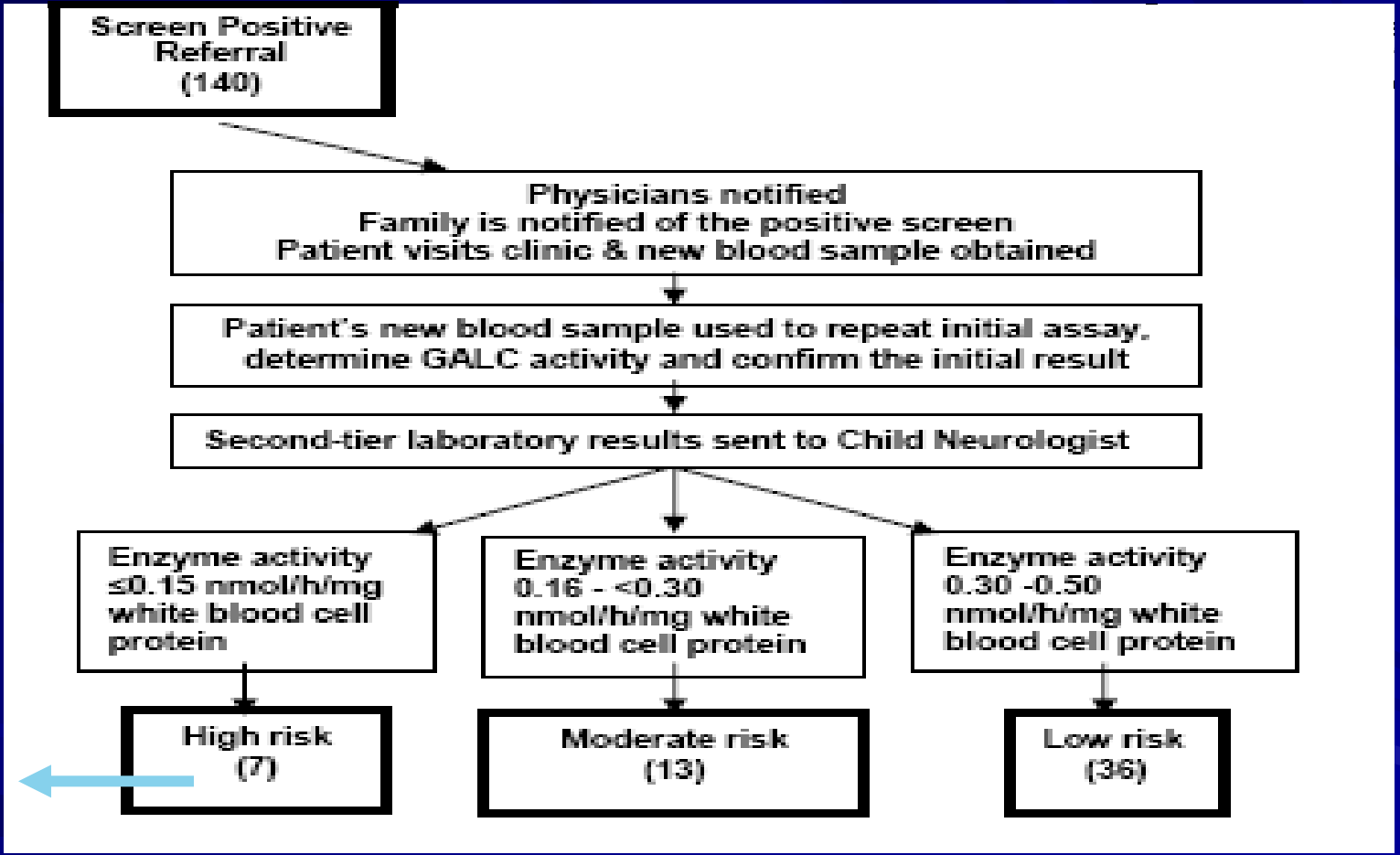


Figure adapted from the Management Guidelines: Krabbe disease published by the Wadsworth Center, New York State Department of Health (http://www.wadsworth.org/newborn/krabbe.htm), Duffner et al. 2009 and data from interviews with Dr. Caggana and Orsini

New York Screening Experience



2 HSCT

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

New York Screening Experience

	August 2006 - June 2009 data
Total newborns screened	769,853
Newborns referred for and completed diagnostic evaluations	140 (18.2/100,000)
High-risk newborns	7 (0.91/100,000)
Referred for HSCT (homozygous for 30-kb deletion; compound heterozygous for 30-kb deletion and novel mutation)	2/7 (0.26/100,000)
Moderate-risk newborns	13 (1.69/100,000)
Low-risk newborns	36 (4.68/100,000)

Data courtesy of Dr. Orsini and Dr. Caggana, New York State Department of Health

New York High-Risk Infants

Infant	Birth month	Outcome
1	Mar 2007	Following up, assumed asymptomatic
2	Mar 2007	Confirmed EIKD, underwent HSCT
3	Jul 2007	No follow-up, returned to country of origin
4	Aug 2008	No follow-up, family refused
5	Aug 2008	Confirmed EIKD, underwent HSCT, died approximately 11 days posttransplant*
6	Nov 2008	Following up, asymptomatic
7	Dec 2008	Following up, assumed asymptomatic

As described by Dr. Caggana and Orsini

**As described by Dr. Kurtzberg*

New York Program: Diagnosis

- Diagnosis based on GALC activity with either supportive genetic analysis (i.e., homozygosity for 30-kb deletion) or clinical findings
- Recommended follow-up schedule for screen positive infants

New York Screen Positive Follow-up

	Year One		Year Two	
	Neurologic Exam	Neurodiagnostic Tests*	Neurologic Exam	Neurodiagnostic Tests*
High Risk	Monthly	Every 3 months	Every 3 months	Every 6 months
Moderate Risk	Every 3 months	Annually unless exam abnormal	Every 3 months	Annually unless exam abnormal
Low Risk	Every 6 months	Only if exam abnormal	Every 6 months	Only if exam abnormal

*MRI, CSF, BAER, VEP, NCS

Treatment

- Allogeneic hematopoietic stem cell transplant (HSCT)
  - Sources include bone marrow and umbilical cord blood
  - Requires pre-conditioning with chemotherapy
  - Damage related to EIKD continues posttransplant until there is full engraftment and new glial cell development

Quality Assessment: Treatment

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

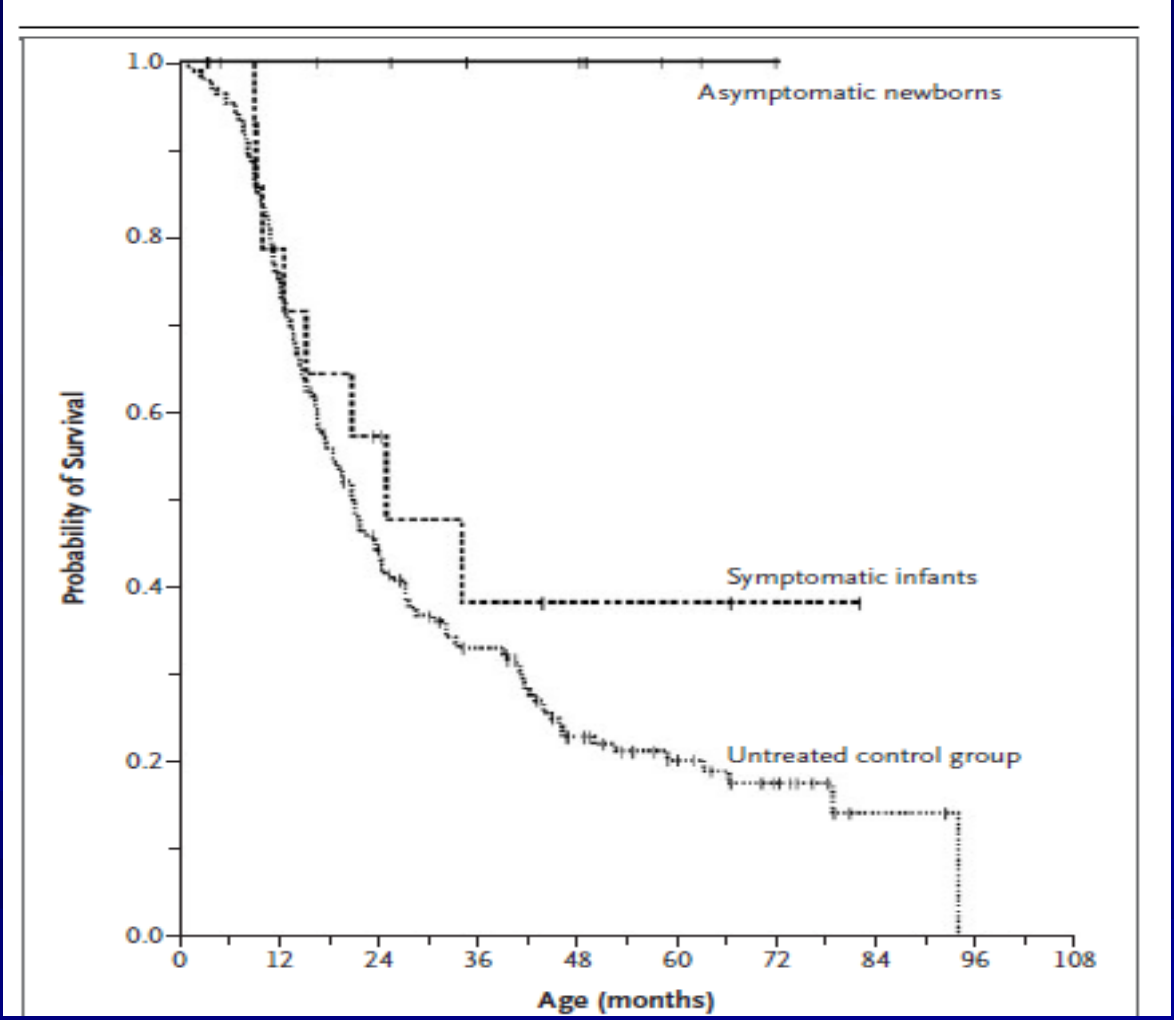
Adapted from Pandor et al. 2004, Pollitt et al. 1997

Treatment Evidence: Early HSCT

Escolar et al. 2005 & 2006 (USA)

Asymptomatic children: 2005:11 patients diagnosed prenatally or at birth 2006: 11 Stage 1 patients (appear developmentally normal but may have inconclusive neurological findings) **Symptomatic children:** 2005: 14 patients diagnosed between 4 and 9 months of age 2006: 4 Stage 2 patients 13 Stage 3 patients 1 Stage 4 patient	**Age:** 2005: 12-44 days 2006: Stated stage at transplant, but not age 2005: 142–352 days 2006: Stated stage at transplant, but not age	**Survival:** 2005: 100% survival at median of 36 months posttransplant (last data provided) 2006: 100% survival rate (follow-up between 24-108 months old) 2005: 6/14 at median of 41 months posttransplant (last data provided) 2006: Stage 2: 100% survival rate (follow-up between 24-108 months old) Stage 3: 61.5% survival rate	**Deaths:** 2005: None 2006: None 2005: 8/14 patients died 2006: Stage 3: 5/13 patients died, mean survival time 21.4 months posttransplant Stage 4: 1/1 patient died, a few weeks after procedure

Treatment: Mortality



- 11 asymptomatic newborns treated with HSCT
- 14 symptomatic newborns treated with HSCT
- Untreated control group from Hunter's Hope Registry

Escolar et al. New Engl J Med. 2005;352:2069-2081.

Treatment: Mortality

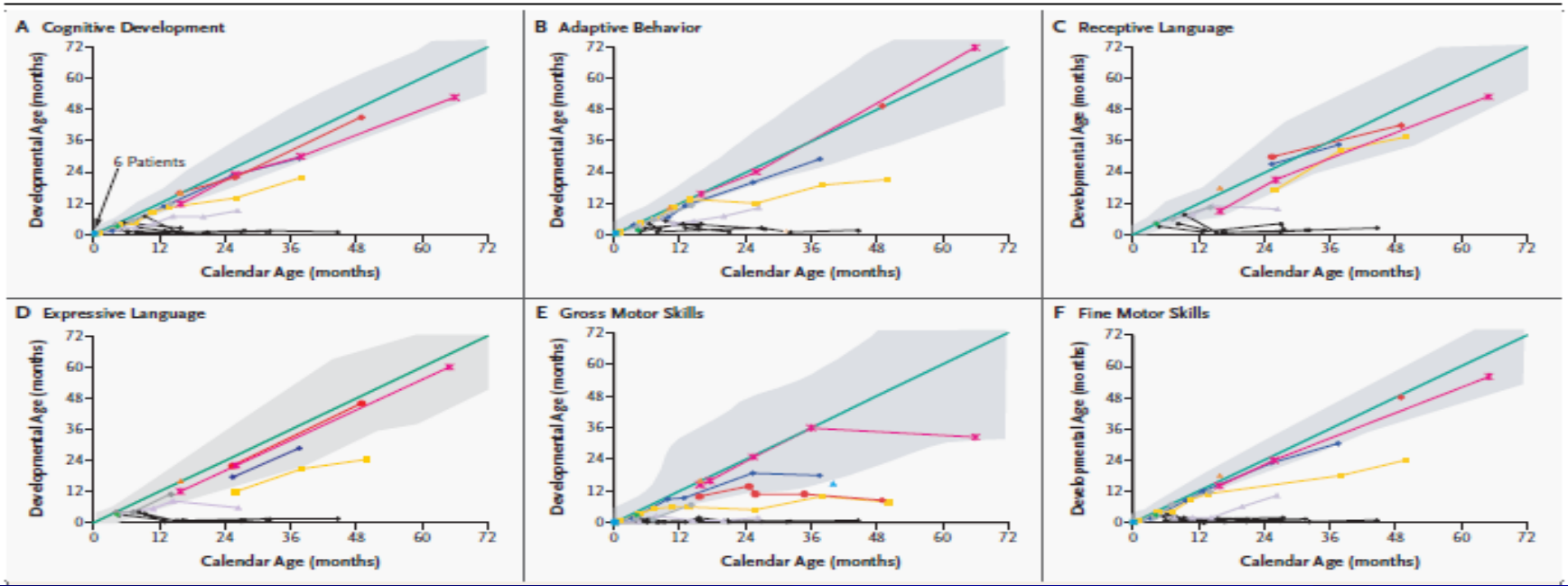
- Of two infants from New York Program transplanted, one died approximately 11 days post transplant

Treatment Evidence: Early HSCT

Escolar et al. 2005 & 2006 (USA)

Asymptomatic children: 2005: 11 patients diagnosed prenatally or at birth 2006: 11 Stage 1 patients (appear developmentally normal but may have inconclusive neurological findings) Symptomatic children: 2005: 14 patients diagnosed 4-9 months of age 2006: 4 Stage 2 patients 13 Stage 3 patients 1 Stage 4 patient	2005: ▪ Transplants prior to symptom onset maintained progressive central myelination, normal vision and hearing, and normal cognitive development except for gross motor development ▪ Transplants post symptom onset did not result in substantive neurologic improvement 2006: ▪ All Stage 1 children continued to show adequate rate of development in all domains except gross motor development ▪ Stage 2 patients showed gains in most developmental domains except gross motor function ▪ Stage 3 late infantile patients showed very minimal gains in most developmental areas and had no gains in motor function posttransplant ▪ Stage 3 early infantile patients showed no developmental gains

Treatment: Neurodevelopmental Outcomes



Among the early treatment group:

- Fine motor control interferes with cognitive function testing
- Motor involvement affects expressive language
- During the second and third year of life, progressive spasticity in the lower extremities and truncal weakness developed in 2 of 6 children
- 2 had severe delay in fine motor function

Escolar et al. New Engl J Med. 2005;352:2069-2081.

Treatment Evidence: Experts

Reporting physician	Number of patients transplanted	Morbidity	Neurodevelopmental Outcome
Dr. Escolar	17 surviving, ranging from 2 to 12 years posttransplant, oldest patient is now 13 years old 1 died of sepsis posttransplant	▪No further progress in motor skill development, no regression observed ▪Two or three can ambulate completely independently ▪Others need support for ambulation, some use wheelchairs ▪Peripheral neuropathy worsens over time	▪Less involved patients have normal cognitive abilities ▪More involved patients have difficultly with speed of processing
Dr. Kurtzberg		▪A third have normal motor function through the first decade of life ▪Another third are ambulatory but need devices to help them walk ▪Final third have severe spasticity and use wheelchairs	▪All have normal intelligence and communicate well
Dr. Burton	2, both under 1 month of age at transplant	▪One child received 2nd transplant at 3 months, developmentally delayed at 3 years of age ▪Other child symptomatic at time of transplant, ventilator dependent at 5 months of age	▪No additional information
Dr. Tolar	1, 3 months of age at transplant	▪Child is able to sit, but not walk, one year posttransplant	▪Child can vocalize but lacks understandable words

Availability of Treatment for Krabbe

- From Krabbe disease expert interviews:
  - Approximately 8 centers in the US experienced in transplantation of infants with Krabbe disease
    - Duke University and University of Minnesota are the most experienced sites for HSCT treatment of Krabbe disease
    - Additional sites in Illinois, Ohio, Missouri and Michigan
    - Mount Sinai in New York has begun transplanting patients with metabolic disorders
- HSCT protocol for Krabbe disease is similar to protocol for other childhood diseases, thus centers performing HSCT may be trained to transplant patients with metabolic disorders

Economic Evidence: Cost and cost-effectiveness

- No peer-reviewed publication relating to costs or cost-effectiveness of screening and treatment
- Insufficient data available for complete economic evaluation

Key Findings:
New York Pilot Screening

- No cases of EIKD have been reported to be missed
  - Sensitivity = 100%
- Observed prevalence of EIKD is less than predicted
  - 0.26/100,000 vs. approximately 1/100,000
- Overall specificity is >99.9% if positive screen is considered the point of family and physician notification and a positive result is the identification of a high risk newborn
- Specificity is still >99.9% if a positive result is considered to be referral to bone marrow transplantation

Key Findings: Treatment

- Evidence suggests that HSCT in presymptomatic or early symptomatic children with EIKD improves neurodevelopmental outcome
- Motor function appears to show less improvement

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

Critical Evidence Needed

- Are there appropriate ways to identify asymptomatic infants with low galactocerebrosidase levels who would benefit from bone marrow transplantation?
  - Clinical and radiological markers an area of current research
- What are the harms associated with screening, especially in the identification of asymptomatic infants with low galactocerebrosidase levels?
- What are the harms associated with chemotherapy used to pre-condition newborns for HSCT?
- What are the long-term neurodevelopmental outcomes for children who have received transplant?
- What is the cost-effectiveness of screening for Krabbe disease?

Thank you