Report from Evidence Review

Advisory Committee on Heritable Disorders in Newborns and Children

May 14, 2010

Alex R. Kemper, MD, MPH, MS
Department of Pediatrics, Duke University

DUKE CHILDREN'S Hospital & Health Center

MassGeneral Hospital for Children℠

Recent Progress and Activities

- **Hemoglobin H (Hb H) Disease**
  - Final review submitted April 2010
  - Presentation will focus on
    - Update of evidence
    - Summary of key considerations for the Advisory Committee

- **Critical Congenital Cyanotic Heart Disease (CCCHD)**
  - Preliminary review submitted April 2010
  - Presentation will focus on
    - Summary of test characteristics of pulse oximetry
    - Improvements in the process of evidence review based on our experience, other approaches to review, and recommendations from the Advisory Committee

- Overview paper re ERG procedures published in *Genetics in Medicine*

- **Krabbe Disease**
  - Manuscript submitted to *Genetics in Medicine*

Workgroup Team Members

Key authors:

- Alex R. Kemper, MD, MPH, MS, Duke University
- Alixandra A. Knapp, MS, MGH/Harvard
- Danielle Metterville, MS, MGH/Harvard

Program director:

- James M. Perrin, MD, MGH/Harvard

Staff:

- Marsha Browning, MD, MPH, MGH/Harvard
- Anne Comeau, PhD, New England Newborn Screening Program/UMass Medical School
- Nancy Green, MD, Columbia University
- Lisa Prosser, PhD, University of Michigan Health System
- Denise Queally, JD, Consumer (PKU Family Coalition)

Hb H Disease Overview

- Inherited hemoglobinopathy, type of alpha-thalassemia
- Caused by deletions and/or nondeletional mutations of 3 of the 4 α-globin genes
- Variable clinical course
  - May include anemia, hepatosplenomegaly, cholelithiasis, or growth retardation
- Certain mutations associated with worse health outcomes

Alpha-Thalassemia Overview

Description & Terminology	α1 and α2 Genes Chromosome 16	Genotype
Normal	4 functional α-globin genes	αα/αα
Silent carrier	1 deletion	-α/αα
Alpha-thalassemia trait	2 deletions	-α/-α --/αα
Hb H disease (deletional)	***3 deletions***	***--/-α***
Hb H disease (nondeletional) ***Example:*** ***Hb H disease with CS****	***2 deletions + 1 mutation (T)*** ***2 deletions + CS mutation*** ***(α2 142 TAA→CAA or Ter→Gln)***	***--/$\alpha^{T}\alpha$*** ***--/$\alpha^{CS}\alpha$***
Hb Bart's hydrops fetalis	4 deletions	--/--

*CS = Constant Spring

Current Status of Hb H Screening

- Currently a secondary target
  - Conditions that are part of the differential diagnosis of a core panel condition or that would be identified in the process of screening for the core panel conditions
- At least 8 states report Hb Bart's (Jelili Ojodu, MPH; APHL)

Methods of Evidence Review

- Systematic literature review
  - Summarizes evidence from published studies
  - Presented at January 2010 AC Meeting
  - Updated for this meeting (2 additional case series related to natural history)
- Consultation with multiple newborn screening and Hb H disease experts to identify relevant unpublished data

Materials Included in Final Review

- Detailed literature review methods
- Summary of evidence from literature review and expert unpublished data
- Tables highlighting key data from abstracted articles
- Table of studies excluded because they report 4 or fewer cases
- Bibliography

Systematic Literature Review

- January 1989 – March 2010
  - 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
  - **1485** abstracts selected for preliminary review
  - **90** articles selected for in-depth review
  - **21** articles met all inclusion criteria for abstraction

Papers Meeting Review Criteria

Study Design	Number of papers
Experimental intervention	0
Cohort study	0
Case-control study	1
Case series	14
Sample size ≤ 10	0
Sample size 11 to 50	3
Sample size 51 to 100	2
Sample size ≥ 101	9
Economic Evaluation	0
Cross-sectional study	6
Total studies	21

Quality Assessment: Natural History

Type of evidence	Number of articles
Total (two articles overlap with screening)	**20**
Incidence (cases per 100,000), average within the U.S.	**3**
Data obtained from whole-population screening or comprehensive national surveys of clinically detected cases.	2
Ia. As in I but more limited in geographical coverage or methodology.	1
Extrapolated from class I data for non-U.S. populations.	0
Estimated from number of cases clinically diagnosed in U.S.	0
Genotype-Phenotype correlation	**14**
Data from retrospective screening studies in U.S. or similar population.	0
Data from systematic studies other than whole population screening.	10
Estimated from the known clinical features of the condition as described for individual cases or short series.	2
Other natural history of disease	**3**

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

Natural History: Incidence

Incidence	Method	Citation
1/15,000 for Hb H disease	Newborn screening in California from January 1998 to June 2000	Lorey et al. 2001
9/100,000 for Hb H disease 0.6/100,000 for Hb H with CS	Newborn screening in California from January 1998 to June 2006	Michlitsch et al. 2009

Deletional vs. Nondeletional Hb H Disease

Region	Citation	Deletional Hb H disease	Nondeletional Hb H disease
Hong Kong	Chen et al, 2000	87/114 (76%)	27/114 (24%)
Northern Thailand	Charoenkwan et al, 2005	44/102 (43%)	58/102 (57%)
Mediterranean area	Origa et al, 2007	216/251 (86%)	36/251 (14%)
Greece	Kanavakis et al, 2000 (14 subjects not counted with two non-deletions)	41/61 (67%)	20/61 (33%)
Sardinia	Gallano et al, 1992 (1 subject not counted with two non-deletions)	130/154 (84%)	24/154 (16%)
California, USA*	Lorey et al, 2001	69/89 (77.5%)	20/89 (22.5%)

*Population-based study, remaining studies are from clinically identified populations

Deletional vs. Nondeletional Hb H Disease

- Children with nondeletional Hb H disease
  - Diagnosed at younger ages
  - Higher rates of anemia and blood transfusion
  - Higher rates of hepatosplenomegaly

Natural History: Case Series

- *No population or screen-positive series*
- Newborn
  - Anemia, jaundice, hepatosplenomegaly (CS)
  - Reports of Hb H hydrops fetalis
- Infancy and childhood
  - Pallor, growth retardation, anemia
  - Pulmonary function defect, mild cardiac anomalies, hepatosplenomegaly
- Adult
  - Iron overload, cholelithiasis

Quality Assessment: Screening Test

Type of evidence	Number of articles
Total (two articles overlaps with condition/natural history)	**3**
Overall sensitivity and specificity of screening	**1**
Data obtained from screening programs in U.S. population or similar.	1
Data from systematic studies other than from whole population screening.	0
Estimated from the known biochemistry of the condition.	0
False positive rate	**0**
Data obtained from screening programs in U.S. population or similar.	0
Data from systematic studies other than from whole population screening.	0
Estimated from the known biochemistry of the condition.	0
Repeat specimen rate	**0**
Data obtained from screening programs in U.S. population or similar.	0
Data from systematic studies other than whole population screening.	0
Estimated from the known biochemistry of the condition.	0
Second-tier testing	**2**
Data obtained from screening programs in U.S. population or similar.	1
Data from systematic studies other than whole population screening.	0
Estimated from the known biochemistry of the condition.	1
Other screening test characteristics	**1**

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

California Screening Method

- First tier: Detect elevated Hb Bart's levels by HPLC
- Second tier: Confirmatory diagnostic α-globin genotyping for newborns with elevated Hb Bart's

Development of California Hb H Disease Newborn Screening Program

- “Trial period” June 1996 – September 1999
- Measure Hb Bart’s level by high-performance liquid chromatography (HPLC)
- Cutoff Hb Bart’s level set at 14% in June 1996
  - Lowest Hb Bart’s in newborn confirmed to have Hb H disease was 27%
- Cutoff Hb Bart’s level increased to 25% in August 1998
- Hb H Disease newborn screening mandated in October 1999

Diagnosis

- Multiple strategies for α-globin genotyping have been described
- For example, the California newborn screening program uses multiplexed gap-PCR assay to detect common deletional and nondeletional α-thalassemia mutations in their second tier screening

California Screening Experience

From Lorey et al. 2001

January 1998 - June 2000 data

Total newborns screened	1,320,000
Newborns with elevated Hb Bart's	101
Hb H disease	89
α-Thalassemia trait	9
α-Thalassemia silent carrier	1
Hb Bart's hydrops fetalis	1
Normal	1

Because most newborns with Hb Bart's levels *below* the cutoff value did not have confirmatory testing, an undetected case of Hb H disease in this range could not be ruled out

Quality Assessment: Treatment

Type of evidence	Number of articles
Total	**0**
Effectiveness of treatment	**0**
I. Well-designed RCTs.	0
I. Well-designed RCTs.	0
II-1. Well-designed controlled trials with pseudo randomization or no randomization.	0
II-2. Well-designed cohort studies:	0
A. prospective with concurrent controls	0
B. prospective with historical control	0
C. retrospective with concurrent controls.	0
II-3. Well-designed case-control (retrospective) studies.	0
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.	0
Other treatment characteristics	**0**

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

Follow-up and Treatment

- No peer-reviewed publications regarding presymptomatic treatment were identified
- No data published on follow-up of children identified in California

Economic Evidence

- No peer-reviewed publications relating to costs or cost-effectiveness of screening and treatment identified

Unpublished Data

- Contacted Hb H disease experts identified through:
  - Literature review
  - Discussion within workgroup
  - Recommendation by other experts
- Included experts from different Hb H disease domains:
  - Newborn screening
  - Clinical care

Experts & Advocates – Survey / Interview Completed

- Sylvia Au, MS, CGC
- Thomas Coates, MD
- Alan Cohen, MD
- Michael Glass, MS
- Patrick Hopkins
- Carolyn Hoppe, MD
- Ho-Wen Hsu, MD
- Fred Lorey, PhD
- Jennifer Marcy, MS, CGC
- Ellis Neufeld, MD, PhD
- Sarah Scollon, MS, CGC
- Sylvia Singer, MD
- Elliott Vichinsky, MD
- David Weatherall, MD, FRCP, FRS
- Kelley Woodruff, MD

Unpublished Data

- Experts corroborated literature findings
- No other data on the impact of pre- or early symptomatic treatment
- No systematic follow up data on any screen positive populations
- Insufficient data for economic analysis

Other State Screening Programs

State Lab	Starting Year	1st tier	1st tier cutoff	2nd tier	Reporting and confirmatory testing
Hawaii	July 1997	IEF	Hb Bart's	HPLC	**Hb Bart's ≥25%** - considered screen positive
Iowa	Iowa- 1988 North Dakota- 2003 South Dakota- 2007	IEF	Visually abnormal	HPLC Variant	**10% ≤ Hb Bart's < 25%** - reported **Hb Bart's ≥ 25% -** reported and follow up team is alerted that this infant may have Hb H disease

IEF=Iso-electric focusing

Other State Screening Programs

State Lab	Starting Year	1st tier	1st tier cutoff	2nd tier	Reporting and confirmatory testing
Missouri	1989	IEF	Two distinct Hb Bart's bands easily visible	HPLC	**3% ≤ Hb Bart's < 13%** - Within Normal Limits + Low Level Bart's Comment **13% ≤ Hb Bart's < 20%** - Abnormal: Slightly Elevated Hb Bart's, DNA DBS testing at Children's Hospital of Oakland Research Inst (CHORI) **Hb Bart's ≥ 20%** - Presumptive positive for Hb H disease, referred to Hemoglobinopathy Center and DBS DNA testing at CHORI
Washington	1991	IEF	Hb Bart's bands	HPLC	**6.5% ≤ Hb Bart's ≤ 18%** - reported as possible α-thalassemia trait **Hb Bart's > 18%** - reported as possible Hb H Disease, physician notified and sent information on follow up

Unpublished Data: California

- Common mutation panel identifies the majority of cases of Hb H disease in the California newborn population

- If no mutation detected:
  - DNA sequencing for other nondeletional mutation (99% sensitivity)
  - Multiplex ligation-dependent probe amplification (MLPA) for rare deletions

Unpublished Data: Hawaii

- 222,982 newborns screened in Hawaii from July 1997 – October 2009
- Newborn's physician receives test results
- Positive results accompanied by recommendation for referral to state Hemoglobinopathy Clinic for genetic counseling and α-globin testing
- Only about 25% of the 214 screen-positive children referred
- In 2008, Hawaii agreed to cover additional costs of the newborn's parents' genetic testing, and referrals have increased
- 48 confirmed cases of Hb H disease

Summary: Natural History and Screening

- Published natural history evidence
  - Studies on clinically identified populations
  - Older children and adults
- Children with nondeletional Hb H disease appear to have more jaundice, hepatosplenomegaly, growth retardation and blood transfusions than those with deletional Hb H disease
- California data suggest feasibility of newborn screening by HPLC for elevated Hb Bart's
- Data from other states suggest feasibility of IEF as a first tier screening method
- Validated methods for diagnosis of Hb H disease by confirmatory genotyping exist

Evidence Gaps

- What proportion of children with Hb H disease would benefit from condition-specific treatment?
  - Lack of systematic follow up data on screen-positive children
- How does this vary across the US?
- Does early identification improve the health of identified children?
- What harms are associated with delay in diagnosis?
- What is the cost-effectiveness of newborn screening for Hb H disease?

Key Questions for the Advisory Committee

- What is the threshold for moving a target from secondary to core?
- What are the potential advantages for such a move?
- What are the potential harms for such a move?
- What are the expectations for newborn screening laboratories, public health, clinicians, and families after such a move?

Questions for the ERW