Report from Evidence Review

Advisory Committee on Heritable Disorders in Newborns and Children

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Recent Progress and Activities

- Hemoglobin H (Hb H) Disease
  - Preliminary review submitted in January 2009
  - Presentation today limited to published materials

- Krabbe Disease
  - Final report presented in September 2009
  - Revised final report submitted in December 2009
  - Manuscript undergoing clearance review; will be submitted to *Genetics in Medicine*

- Overview paper describing ERG process in press at *Genetics in Medicine,* as well as brief summaries of three final reports

Workgroup Team Members

Key authors:

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- **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
  - Symptoms include anemia, hepatosplenomegaly, cholelithiasis, or growth retardation
- Certain mutations associated with worse health outcomes

Hemoglobin Overview

Hemoglobin	Subunits	Timing
Hb F (Fetal)	2 α, 2 γ	Predominant Hb in fetal life
Hb A (Adult)	2 α, 2 β	Predominant Hb soon after birth
Hb Bart's	4 γ	Present in newborns with α-globin deficiency
Hb H	4 β	Present in individuals with α-globin deficiency

Normal

α-Globin deficiency

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

Rationale for Review

1. Individuals with Hb H disease may experience significant anemia and growth retardation

2. Presymptomatic identification of infants with Hb H disease may improve health outcomes

3. Newborn screening is possible using dried blood spots
   a) California has screened for Hb H disease since October 1999
   b) Newborn screening occurs in critical window for Hb Bart's detection
   c) Current state hemoglobinopathy screening technologies could be used for Hb H disease

Methods of Evidence Review

- Preliminary report (today)
  - Systematic literature review to summarize evidence from published studies
- Final report
  - Consultation with multiple Hb H disease investigators and advocates and assessment of unpublished data

Key Topics Reviewed: Hb H Disease

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

Materials Included in Preliminary Review

- Detailed literature review methods
- Summary of evidence from literature review
- Tables highlighting key data from abstracted articles
- Table of studies excluded because they are based on 4 or fewer cases
- Bibliography

Systematic Literature Review

- January 1989 – October 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

- **1362** abstracts selected for preliminary review
- **88** articles selected for in-depth review
- **19** 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	12
Sample size ≤ 10	0
Sample size 11 to 50	3
Sample size 51 to 100	2
Sample size ≥ 101	7
Economic Evaluation	0
Cross-sectional study	6
Total studies	19

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

Quality Assessment: Natural History

Type of evidence	Number of articles
Total (two articles overlap with screening)	**18**
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	**12**
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**

Natural History: Case Series Reports

- 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

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

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

Screening Method

- First tier: Detect elevated Hb Bart's levels
- 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

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

Diagnosis

- Multiple strategies for α-globin genotyping have been described

- California newborn screening program uses a multiplexed gap-PCR assay to detect common deletional and nondeletional α-thalassemia mutations in newborns with elevated Hb Bart's

Quality Assessment: Treatment

Type of evidence	Number of articles
Total	**0**
Effectiveness of treatment	**0**
I. Well-designed RCTs.	0
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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

- Insufficient data available for an economic evaluation

Key Findings

- Compared to children with deletional Hb H disease, those with nondeletional Hb H disease more often had:
  - Jaundice
  - Hepatosplenomegaly
  - Growth retardation
  - Blood transfusions

- Most published natural history evidence is from studies on clinically identified populations in older children and adults

Key Findings

- California data suggests HPLC for elevated Hb Bart's is a feasible Hb H disease newborn screening method
- Validated methods for diagnosis of Hb H disease by confirmatory genotyping exist

Critical Evidence Needed: Hb H Disease

- What is the natural history during the newborn period and first five years of life?
- What are the benefits of early diagnosis?
  - What treatment methods are available?
  - What is the effectiveness of treatment?

Hb H Disease and Newborn Screening Experts to Consult

- Charles Brokopp, PhD, Wisconsin State Laboratory of Hygiene
- Michele Caggana, ScD, New York State Department of Health
- David Chui, MD, Boston Medical Center
- Thomas Coates, MD, Children's Hospital Los Angeles
- Alan Cohen, MD, Children's Hospital of Philadelphia
- Roger Eaton, PhD, New England Regional Newborn Screening Program
- Carolyn Hoppe, MD, Children's Hospital Oakland Research Institute
- Franz Kuypers, PhD, Children's Hospital Oakland Research Institute
- Fred Lorey, PhD, California State Newborn Screening Laboratory
- Robert Mignacca, MD, Children’s Hospital Central California
- Ellis Neufeld, MD, PhD, Children's Hospital Boston
- Nancy Olivieri, BSc, MD, Toronto General Research Institute
- Sylvia Singer, MD,Children's Hospital Oakland Research Institute
- Elliott Vichinsky, MD, Children’s Hospital and Research Center at Oakland
- David Weatherall, MD, University of Oxford

Thank you