CDC's Thalassemia Activities

Cooley's Anemia Foundation 2018 Patient-Family Conference
July 7, 2018

Mary Hulihan, Division of Blood Disorders

DD07-010

- 2007-2012
  - Children’s Hospital of Philadelphia
  - Children’s Hospital Los Angeles
  - Children’s Hospital & Research Center Oakland
  - Cornell University
  - Children’s Memorial Hospital (Chicago)
  - Children’s Hospital Corporation (Boston)
  - Children’s Hospital of Atlanta

Human T Cell Lymphotropic Virus Type 1 Infection Among U.S. Thalassemia Patients

William M. Switzer,[1] Anupama Shankar,[1] Sean R. Trimble,[2] Alexis A. Thompson,[3] Patricia J. Giardina,[4] Alan R. Cohen,[5] Thomas D. Coates,[6] Elliott Vichinsky,[7] Ellis J. Neufeld,[8] Jeanne M. Boudreaux,[9] and Walid Heneine[1]

- Other sources of (HTLV) infection may be inferred, the most likely being unscreened blood product transfusion before 1988.
- Suggest that HTLV testing should be considered in thalassemia patients, particularly if they were recipients of unscreened transfusions.

CME **Transfusion complications in thalassemia patients: a report from the Centers for Disease Control and Prevention**

Elliott Vichinsky, Lynne Neumayr, Sean Trimble, Patricia J. Giardina, Alan R. Cohen, Thomas Coates, Jeanne Boudreaux, Ellis J. Neufeld, Kristy Kenney, Althea Grant, Alexis A. Thompson, and the CDC Thalassemia Investigators

- Hemosiderosis was the most common complication in this population.
- A history of transfusion reactions was reported in 48% of transfused patients.
- 19% of all transfused patients had alloantibodies.
- Autoantibodies occurred in 6.5% of patients.
- Local blood banking practices varied.
- ***This longitudinal surveillance project will enable the development of recommendations for interventions to prevent transfusion morbidity and evaluate long-term effectiveness.***

DD11-1108 Blood Safety Surveillance among People with Blood Disorders

- 2012-2014
  - The University of Mississippi Medical Center
  - Michigan Department of Health
  - Children's Hospital Los Angeles
  - Children's Memorial Hospital (Chicago)

Outcomes

- Expanded diagnosis list
- Improved data collection methods
- Continued specimen repository
- Planned Publication
  - Adherence to Treatment Recommendations in A Cohort of Thalassemia Patients
    - Evaluate the level of adherence to treatment recommendations, including iron assessment studies, iron overload status, and completion rate of hepatitis A and hepatitis B vaccination series.
    - Examine the relationship between patients' and/or parents' demographics, educational status, and adherence to treatment recommendations.

DD14-1406: Characterizing the Complications Associated with Therapeutic Blood Transfusions for Hemoglobinopathies

- 2014-2019
  - Georgia State University
  - Benioff Children's Hospital Oakland
  - University of Florida

Outcomes

- Interviews with patients and families regarding blood transfusion knowledge and attitudes
- Large payer claims database analysis of locations of care for patients with thalassemia
- *Transfusion Practices and Complications in Thalassemia* (accepted by Transfusion, June 2018)
- *Transfusion Service Knowledge and Practices Related to Transfusion in SCD and Thalassemia* (submitting to Transfusion Medicine, July 2018)
- Systematic literature review to expand on impact of extended phenotypic & genotypic cross-matching transfusions in SCD & thalassemia populations (submitted to Transfusion Medicine Reviews, April 2018)

Outcomes (con't)

- Patient identification cards
- Standard of care guideline development
- Educational materials for patients and families
- Educational materials for health care providers
  - Training webinar
  - Clinical consultations at Community Hospitals with highest patient numbers
- Scientific and lay publications and awareness raising, along with community and health care faculty education re. minority blood donation
  - Brochure, infographics, video
  - Be the Motivation campaign
  - Targeted blood drives

DD09-909/DD10-1017: Registry and Surveillance System for Hemoglobinopathies (RuSH)

- 2010-2012
  - California
  - Florida
  - Georgia
  - Michigan
  - New York
  - North Carolina
  - Pennsylvania

State-based surveillance for selected hemoglobinopathies

Mary M. Hulihan, MPH[1], Lisa Feuchtbaum, DrPH[2], Lanetta Jordan, MD[3], Russell S. Kirby, PhD[4], Angela Snyder, PhD[5], William Young, PhD[6], Yvonne Greene, MPH[7], Joseph Telfair, DrPH[8], Ying Wang, PhD[9], William Cramer, MPH[10], Ellen M. Werner, PhD[11], Kristy Kenney, MPH[1], Melissa Creary, MPH[1] and Althea M. Grant, PhD[1]

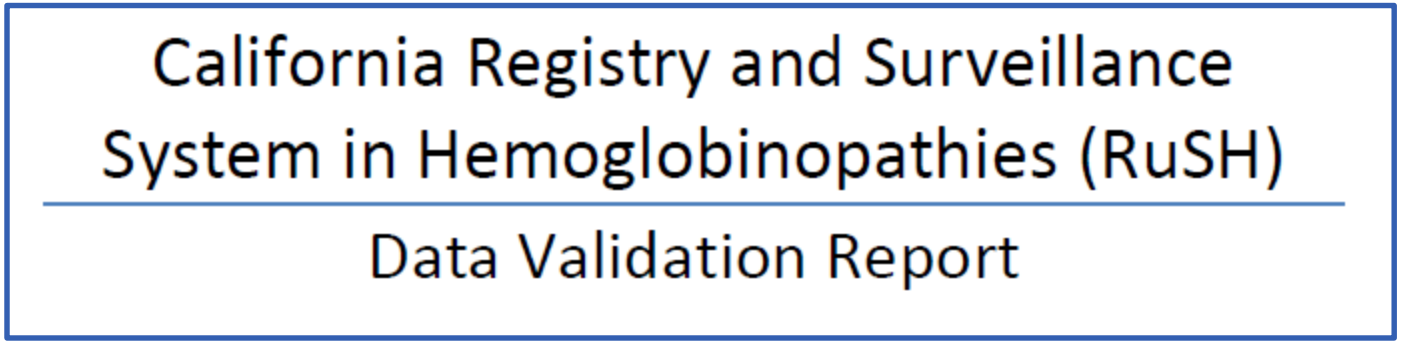
Table 3 Number of individuals with a thalassemia diagnosis by state and case definition level, 2004–2008

State	Level 1	Level 2	Level 3
California	836	1,915	14,534
Florida	14	1,620	6,731
Georgia	64	271	4,553
Michigan	6	31	1,354
New York	33	1,873	10,380
North Carolina	84	232	1,127

DD12-1206: Public Health Research, Education, and Surveillance for Hemoglobinopathies

- 2012-2014
  - California

Outcomes



- “We found significant problems in the results of data collection and linkage in describing the state’s thalassemia population.”
- “We suggest that future efforts to conduct surveillance for these two disorders be developed separately for this reason, make recommendations for such an effort, and note that recent changes in ICD 9 coding will improve future surveillance work in thalassemia.”

Outcomes (con't)

California Health Care Provider Fact Sheet: Thalassemias

Thalassemias are a group of inherited hemoglobin disorders screened for at birth in California and highly prevalent among many immigrant groups in the state.

While there are many different types of thalassemia, alpha thalassemia and beta thalassemia are the most important because of their potential adverse effects on health. These effects range from clinically insignificant or mild to life-threatening and many affected individuals require regular blood transfusions to maintain their health. Individuals born outside of California and adults born prior to the beginning of newborn screening for these disorders (1999 for all disorders, although screening for some disorders began in 1990) may have undiagnosed thalassemias.

Types of Thalassemia

Alpha Thalassemia is a deletion of one or more of the four genes that produce alpha globin chains. Clinical presentation ranges from benign to severe or incompatible with life, depending on the number of genes affected. In California these disorders are most common among Laotian (1 in every 240 live births) and Cambodian populations (1 in every 600 live births), but are seen in other Asian (including East Indian), Black/African American, Middle Eastern, Caucasian and Hispanic populations as well. On average, one alpha thalassemia case is identified out of every 11,000 live births in California, or about 45 new cases per year. Genetic testing of partner(s) is recommended for anyone with alpha thalassemia or alpha thalassemia trait.

- **Silent Carriers** have only one deleted gene. If an individual knows that she or he is a silent carrier, partners should be tested to determine if there is a risk of having a child with a clinically significant form of the disease.
- **Alpha Thalassemia Trait and Hemoglobin Constant Spring Trait** are typically benign conditions indicating deletion or dysfunction of two alpha globin genes. Mild microcytic anemia is often seen, sometimes mild hemolytic anemia.
- **Hemoglobin H Disease** is due to three missing or dysfunctional alpha globin genes, and typically causes moderate hemolytic anemia and splenomegaly. Patients with Hemoglobin H should be followed periodically by a hematologist in addition to a primary care provider.
- **Hemoglobin H/Constant Spring Disease** is typically a more severe thalassemia due to the Constant Spring gene mutation. As with Hemoglobin H, there may be moderate hemolytic anemia and/or splenomegaly; patients may become transfusion dependent. These individuals should be followed by a hematologist in addition to a primary care provider.
- **Alpha Thalassemia Major (Hydrops Fetalis or Hb Bart Syndrome)** manifests as fetal death or very severe hemolytic anemia in utero. All four genes are deleted or dysfunctional and normal hemoglobin cannot be produced. In-utero transfusions may be required to sustain the fetus, and on-going transfusions or bone marrow transplant thereafter.

Beta Thalassemia results from mutations in the HBB gene, which holds instructions for making beta-globin, an essential part of hemoglobin. Depending on the mutation, affected individuals have either a reduction in (beta thalassemia intermedia) or complete absence of (beta thalassemia major, the more severe form) beta-globin. In California these disorders are most common among Laotian (1 in every 1,300 live births) and Cambodian populations (1 in every 2,800 live births), but are seen in other Asian (including East Indian), Black/African American, Middle Eastern and Mediterranean populations as well. Genetic testing of partner(s) is recommended for anyone with beta thalassemia or beta thalassemia trait.

- **Beta Thalassemia Trait** does not cause significant health problems. Persons with trait may have mild microcytic anemia which, in the absence of other indications of iron deficiency, should not be treated with iron supplements. Persons with beta thalassemia trait are at risk for having a child with a more severe form of thalassemia or sickle cell disease if the other parent also has beta thalassemia or sickle cell trait or disease.

National Center on Birth Defects and Developmental Disabilities
Division of Blood Disorders (DBD)

CS203726

- **Beta Thalassemia Intermedia** is caused by mutations resulting in a less severe disorder that does not require chronic transfusion. However, individuals with this thalassemia may require intermittent transfusions and may have moderate to severe complications. These individuals should be followed by a hematologist in addition to a primary care provider.
- **Beta Thalassemia Major (Cooley's Anemia)** is the most severe form of beta thalassemia, and requires frequent chronic transfusions to survive along with iron chelation therapy to avoid iron overload complications. These individuals must be followed by a hematologist in conjunction with a primary care provider.

Hemoglobin E is a variant of normal (A) hemoglobin screened for at birth since 2005 in California. In conjunction with certain genetic globin mutations, Hemoglobin E may cause serious disease. Individuals born outside of California or born prior to 2005 may be unaware that they carry one or more genes for making hemoglobin E. Hb E is very common in Southeast Asian populations in California; benign (Hb E/E) and significant forms (Hb E/beta thalassemia) are seen in 1 of every 80 Laotian live births, 1 in every 100 Cambodian live births and 1 in every 700 other Southeast Asian live births, less frequently in other Asian populations, and occasionally in people of other races or ethnicities. Genetic testing of partners of anyone with Hb E trait or condition who is considering having children is recommended.

- **Hemoglobin E Trait** carriers have one gene for this variant and one for Hb A. These individuals do not have any symptoms other than mild microcytic anemia in some cases.
- **Hemoglobin EE** was added to California's Newborn Screening Hemoglobin Registry in 2005, and pediatricians of infants identified as having EE are notified. Persons with Hb EE make only E hemoglobin, but there are generally no significant clinical implications. Mild microcytic anemia and/or splenomegaly can occur. The microcytic anemia can be misdiagnosed as iron deficiency; however, iron supplementation should be avoided. Consequently, individuals of Southeast Asian origin with this form of anemia should be tested for a hemoglobinopathy.
- **Hemoglobin E/Beta Thalassemia** is caused by the pairing of genes for hemoglobin E and beta thalassemia, and may result in a more severe form of thalassemia that may require intermittent or chronic transfusions. Persons with Hb E/beta thalassemia should be followed by a hematologist along with a primary care provider.

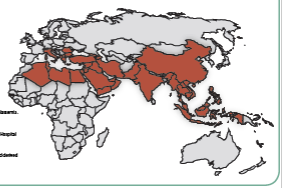
What are symptoms of thalassemias?

Mild to moderate anemia, brittle bones or other bone problems, and/or an enlarged spleen are characteristic of milder forms of thalassemia, and a pale and listless appearance, dark urine, jaundice or slowed growth can be indicative of a more severe form. Many forms of thalassemia can cause chronic iron overload even in non-transfused patients. The symptoms of iron overload (such as liver or heart disease, hypogonadism, hypothyroidism, diabetes or metabolic syndrome, osteoarthritis, and osteoporosis) are insidious and can result in serious problems later in life that are preventable with early diagnosis and treatment.

Who is at risk for thalassemias?

People born in or with ancestry in Asia (especially Southeast Asia, India and China), the Middle East, Northern Africa, or Mediterranean regions are more likely to have thalassemia, but anyone of any race can have one of these disorders.

Global Areas of Higher Risk for Thalassemias



Weatherall DJ. The definition and epidemiology of non-transfusion-dependent thalassemia. Blood Rev. 2012;26(suppl 1):S3-S6.

Northern California Comprehensive Thalassemia Center at UCSF Benioff Children's Hospital Oakland, http://thalassemia.com/demographics.aspx, accessed June 26, 2014.

Modell, B, Darlison, MW. (2008) Global epidemiology of haemoglobin disorders and derived service indicators. Bulletin of the World Health Organization, 86 (6): 480–487.

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Where are thalassemias most likely to be found in California?

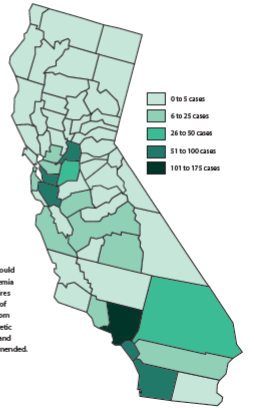
Thalassemias are most common in the most densely populated parts of the state and those with the largest populations of people from affected regions. But people with thalassemias and trait are found in every part of the state.

Why are thalassemias and thalassemia trait important to screen for and understand?

Patients with undiagnosed milder forms of thalassemia may present with microcytic anemia that can be mistaken for iron deficiency anemia, however, treatment with iron supplements is harmful to such patients. These patients and suspected patients with severe symptoms should be referred to a hematologist for diagnosis and care.

Individuals with ancestry in affected regions who are considering having children should be aware of their thalassemia and sickle cell trait status and that of their partners. Children born to two parents with these traits may inherit severe forms of thalassemia or sickle cell/thalassemia and may have significant health problems and shortened life expectancy.

California Newborn Screening (NBS) Thalassemia Cases 2000-2013



California Genetic Disease Screening Program Data

What steps should I take if I suspect thalassemia or thalassemia trait in a patient?

Patients with unexplained microcytic red cell indices should be referred to a hematologist experienced with thalassemia for diagnosis. The proper diagnosis of thalassemia requires DNA analysis of the patient's blood. If there is a history of thalassemia in the extended family or if the patient is from one of the highly affected ethnic groups, advice on genetic testing prior to pregnancy or birth should be provided and testing for all related family members should be recommended.

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Resources

UCSF Benioff Children's Hospital Oakland
Northern California Comprehensive Thalassemia Center
www.thalassemia.com

Cooley's Anemia Foundation
www.thalassemia.org

Thalassemia Support Foundation
www.helpthals.org

California Genetic Disease Screening Program
http://www.cdph.ca.gov/programs/GDSP/Pages/default.aspx

National Institutes of Health Genetics Home Reference
http://ghr.nlm.nih.gov/condition/beta-thalassemia

California Children's Services Approved Hemoglobinopathy Centers

NORTHERN CALIFORNIA

UC Davis Medical Center
2315 Stockton Boulevard
Sacramento, CA 95817
(916) 734-2781

UCSF Benioff Children's Hospital Oakland
747 52nd Street
Oakland, CA 94609
(510) 428-3376

Kaiser Permanente Oakland Medical Center
3779 Piedmont Avenue
Oakland, CA 94611
(510) 752-6592

UC San Francisco Medical Center
505 Parnassus Avenue, Box 0106
San Francisco, CA 94143
(415) 502-8054

Lucile S. Packard Children's Hospital at Stanford
725 Welch Road, Clinic E
Palo Alto, CA 94304
(650) 497-8053

Children's Hospital of Central California
9300 Valley Children's Place
Madera, CA 93638
(559) 353-5469

SOUTHERN CALIFORNIA

City of Hope Medical Center
1500 East Duarte Road
Duarte, CA 91010
(626) 301-8426

Children's Hospital Los Angeles
4650 Sunset Boulevard, MS54
Los Angeles, CA 90027
(323) 361-2352

LAC/USC Medical Center (Adults Only)
1240 North State Street
Los Angeles, CA 90033
(323) 226-3853

Kaiser Permanente West Los Angeles Medical Group Southern California Regional Hemoglobinopathy Center
6041 Cadillac Avenue
Los Angeles, CA 90034
(800) 734-5555 (323) 857-4462

Mattel Children's Hospital at UCLA Medical Center
10833 Le Conte Avenue
Los Angeles, CA 90095
(310) 825-6708

Cedars-Sinai Medical Center
8700 Beverly Blvd.
Los Angeles, CA 90048
(310) 423-4423

Children's Hospital of Orange County
455 South Main Street
Orange, CA 92868
(714) 532-8459

Harbor-UCLA Medical Center
1124 West Carson Street
Torrance, CA 90502
(310) 222-4154

Loma Linda University Medical Center
11234 Anderson Street
Loma Linda, CA 92354
(909) 651-1910

Miller Children's Hospital Long Beach Memorial Medical Center
2801 Atlantic Avenue
Long Beach, CA 90806
(562) 728-5500

Rady Children's Hospital San Diego
3020 Children's Way
San Diego, CA 92123-4282
(858) 966-5811

Thank you to the members of the PHRESH Thalassemia Advisory Committee and to our partners at Children's Hospital of Los Angeles and UCSF Benioff Children's Hospital Oakland for making this Thalassemia Fact Sheet possible.

September 2014

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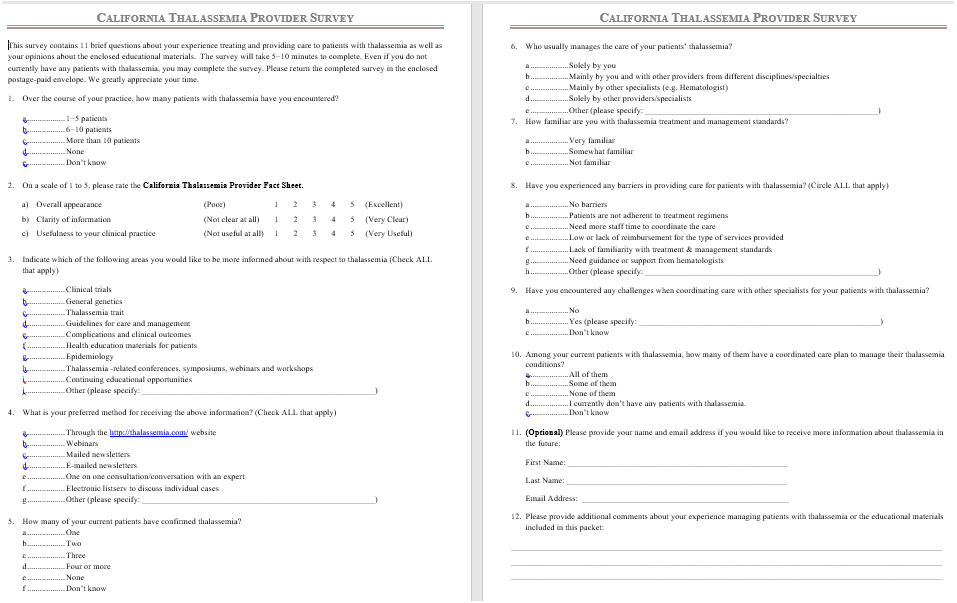
Outcomes (con't)



California Thalassemia Provider Survey

This survey contains 11 brief questions about your experience treating and providing care to patients with thalassemia as well as your opinions about the enclosed educational materials. The survey will take 5–10 minutes to complete. Even if you do not currently have any patients with thalassemia, you may complete the survey. Please return the completed survey in the enclosed postage-paid envelope. We greatly appreciate your time.

1. Over the course of your practice, how many patients with thalassemia have you encountered?

   a. 1–5 patients
   b. 6–10 patients
   c. More than 10 patients
   d. None
   e. Don't know

2. On a scale of 1 to 5, please rate the **California Thalassemia Provider Fact Sheet.**

   a) Overall appearance (Poor) 1 2 3 4 5 (Excellent)
   b) Clarity of information (Not clear at all) 1 2 3 4 5 (Very Clear)
   c) Usefulness to your clinical practice (Not useful at all) 1 2 3 4 5 (Very Useful)

3. Indicate which of the following areas you would like to be more informed about with respect to thalassemia (Check ALL that apply)

   a. Clinical trials
   b. General genetics
   c. Thalassemia trait
   d. Guidelines for care and management
   e. Complications and clinical outcomes
   f. Health education materials for patients
   g. Epidemiology
   h. Thalassemia -related conferences, symposiums, webinars and workshops
   i. Continuing educational opportunities
   j. Other (please specify: _____)

4. What is your preferred method for receiving the above information? (Check ALL that apply)

   a. Through the http://thalassemia.com/ website
   b. Webinars
   c. Mailed newsletters
   d. E-mailed newsletters
   e. One on one consultation/conversation with an expert
   f. Electronic listserv to discuss individual cases
   g. Other (please specify: _____)

5. How many of your current patients have confirmed thalassemia?

   a. One
   b. Two
   c. Three
   d. Four or more
   e. None
   f. Don't know

California Thalassemia Provider Survey

6. Who usually manages the care of your patients' thalassemia?

   a. Solely by you
   b. Mainly by you and with other providers from different disciplines/specialties
   c. Mainly by other specialists (e.g. Hematologist)
   d. Solely by other providers/specialists
   e. Other (please specify: _____)

7. How familiar are you with thalassemia treatment and management standards?

   a. Very familiar
   b. Somewhat familiar
   c. Not familiar

8. Have you experienced any barriers in providing care for patients with thalassemia? (Circle ALL that apply)

   a. No barriers
   b. Patients are not adherent to treatment regimens
   c. Need more staff time to coordinate the care
   e. Low or lack of reimbursement for the type of services provided
   f. Lack of familiarity with treatment & management standards
   g. Need guidance or support from hematologists
   h. Other (please specify: _____)

9. Have you encountered any challenges when coordinating care with other specialists for your patients with thalassemia?

   a. No
   b. Yes (please specify: _____)
   c. Don't know

10. Among your current patients with thalassemia, how many of them have a coordinated care plan to manage their thalassemia conditions?

    a. All of them
    b. Some of them
    c. None of them
    d. I currently don't have any patients with thalassemia.
    e. Don't know

11. **(Optional)** Please provide your name and email address if you would like to receive more information about thalassemia in the future:

    First Name: _____

    Last Name: _____

    Email Address: _____

12. Please provide additional comments about your experience managing patients with thalassemia or the educational materials included in this packet:

    _____

    _____

    _____

Table 1. Provider specialty and experience with thalassemia patients (N=574)

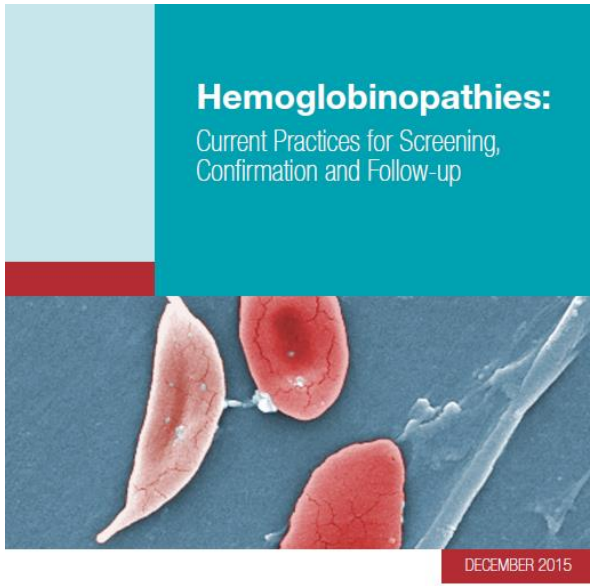
	n	%
Physician specialty[a]		
Pediatrics	204	35.7
Family practice	122	21.3
Obstetrics/Gynecology	98	17.1
Cardiology	37	6.5
General practice	36	6.3
Hematology	27	4.7
Other	79	13.8
No response	2	0.3
Number of patients with thalassemia encountered over the course of their practice		
1 – 5 patients	236	41.1
6 – 10 patients	95	16.6
More than 10 patients	215	37.5
Unknown	23	4.0
No response	5	0.9
Number of current thalassemia patients		
None	146	25.4
1 – 3 patients	164	28.6
4 or more patients	158	27.5
Unknown	93	16.2
No response	13	2.3

[a] Mark all that apply; the total percentage may add to more than 100.

OE15-1501: Newborn Screening and Genetics – Hemoglobinopathies Project

- 2015-2020
  - Association of Public Health Laboratories

Outcomes



Training Webinars

Module 1

Introduction, History, Specimen Collection

Module 2a

Hemoglobinopathy Screening Methods: Isoelectric Focusing (IEF), High Performance Liquid Chromatography (HPLC)

Module 2b

Molecular Methods, Tandem Mass Spectrometry, Overall Method Advantages and Limitations

Module 3

Screening and Reporting Algorithms, Quality Assurance, Follow-up

Outcomes (con't)

Two-part series: Thalassemia: Newborn Screening in the United States

This two-part webinar series is designed for medical professionals who are or may be responsible for screening, diagnosing, and treating hemoglobinopathies. The series was developed with expert guidance from the Hemoglobinopathy Laboratory Workgroup at the Association of Public Health Laboratories (APHL).

Part 1: Alpha Thalassemia: Clinical Aspects

Presenters:

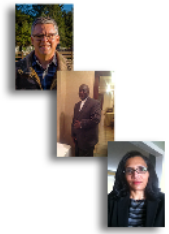
Tim Davis, Chair, BS
APHL Hemoglobinopathy Laboratory Workgroup, Microbiologist 3
Washington State Department of Health

Maria del Pilar Aguinaga, PhD, DLM (ASCP),
Co-Director, Sickle Cell Center
Meharry Medical College

A. Bender, MD,
Attending Physician, Seattle Children's Hospital
Director of Odessa Brown Comprehensive Sickle Cell Clinic

Part 2: Alpha Thalassemia Newborn Screening in the United States

Presenters:



Tim Davis, Chair, BS
APHL Hemoglobinopathy Laboratory Workgroup, Microbiologist 3,
Washington State Department of Health

Joseph Ubaike
Supervising Microbiologist,
Newborn Screening Section, Connecticut Department of Health

Christine Dorley, MSP, MT (ASCP),
Newborn Screening Division Manager,
Tennessee Department of Health Laboratory Services

- Alpha thalassemia survey results
- Beta thalassemia webinars
- Beta thalassemia survey dissemination and results

Thank you!

ibx5@cdc.gov