Newborn Metabolic Screening

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Brief Newborn Screening History

1. 1934: PKU identified by Dr. Asbjorn Folling in Norway
2. 1954: Dr. Horst Bickel published a paper on the dietary treatment of PKU
3. Attempts made in Europe, New Zealand and the U.S. to screen urine
4. 1961: Dr. Robert Guthrie developed filter paper test for PKU (identified newborns with PKU whose diet could be modified thus preventing mental retardation)
5. Parents pressed for testing through organized lobbying
6. 1963: Labs in Portland, Boston, and Los Angeles start newborn screening for PKU
7. Legislatures began to pass mandatory newborn screening laws

Brief Newborn Screening History in the U.S.

Rationale

- State funds support mental institutions
- Persons with PKU end up in mental institutions
- Preventing PKU keeps people out of mental institutions
- Mandating screening for PKU ultimately saves State funds

Brief Newborn Screening History In the United States

1970s

- Other tests became available on filter paper.
- Technology improved allowing program expansion.
- Programs began expanding to higher incidence disorders – congenital hypothyroidism – and disorders that result in death – CAH, GAL.
- Legislatures began asking programs to become self-supporting.

Brief History of Newborn Screening In the United States

1980s

- Programs became computerized.
- Expansion continued including DNA studies.

1990s

- DNA tests used as second tier – Sickle Cell Disease screening, Cystic Fibrosis screening.
- Tandem mass spectrometry developed allowing simultaneous detection of multiple disorders.

History of NBMS in Alaska

- Began in Massachusetts and Oregon in 1963
- Screening for PKU began in AK in 1968
- All states test for PKU and hypothyroidism
- Alaska has added tests over time to include screening for 6 disorders during the 80's and 90's and expansion in October 2003 to screening for more than 30 disorders and now Cystic Fibrosis in 2007

Core Public Health Roles in Newborn Screening

- Assessment – assessing whether testing for specific disorders is beneficial
- Policy – based on assessment, modify program by adding or deleting a disorder from screening program
- Assurance – ensuring screening program is in place, all newborns are screened, treatment and services are received; follow-up
- Evaluation

Newborn Screening is a System

- Screening
- Follow-up
- Diagnosis
- Management
- Education
- Evaluation

Sample Collection

Transport

Screening Tests

Normal

Abnormal

Report

Normal

Follow-up Tracking

Confirmatory Testing

Positive

Report

Medical Consultant

Practitioner

Infant Parents

NW Regional Screening Meeting 2008

OPHL New Building in Hillsboro

Regulations for NBMS

- First specimen must be obtained before discharge or transfer from birthing facility (also guarantees at least one test is obtained)
- Required to obtain a 2nd sample if first is collected before 48 hours of age
- Refusals only allowed on religious grounds or personal belief
- When refusing, the front of the form must be filled in, back of form must be signed by parent, and form sent to testing lab
- Parents must be informed of what they are refusing and consequences of the disorders

Recommendations for NBMS

- Collect first sample between 24 & 48 hours of age because of urgent need for treatment of some disorders
- Obtain a sample before giving a transfusion (GALT, Biotinidase, and Hemoglobinopathies affected by transfusions)
- Second samples are ALWAYS recommended regardless of when first is obtained due to late onset of some disorders
- OPHL found that 17% of the disorders were found on the 2nd sample in study years 1962-1994 (12% have late onset hypothyroidism)
- Second tests should be collected at approximately 2-3 weeks of age (OPHL will accept specimens on infants up to 6 months of age)

Fees for Testing

- Alaska charges a fee per baby (currently this is $75)
- No additional charge for 2nd specimens
- No additional charge for any follow-up serum testing if done through OPHL
- Medical consultation from OHSU at no charge
- This fee does not include the sweat testing confirmation for Cystic Fibrosis

Disorders Screened for in Alaska Before October 2003

- Phenylketonuria (PKU)
- Hypothyroidism
- Biotinidase deficiency
- Galactosemia
- Maple Syrup Urine Disease
- Congenital Adrenal Hyperplasia
- Hemoglobinopathies (by request only)

Phenylketonuria

- Infants appear normal at birth
- Delayed developmental milestones
- Untreated leads to mental retardation, seizures, cerebral palsy, hyperactivity
- Deficiency of a liver enzyme
- Treated with low phenylalanine formula
- Virtually 100% can be detected within first 24 hrs of life regardless of protein intake due to new testing methodologies; does not capture late onset

Hypothyroidism

- Deficiency of thyroid hormone
- Untreated leads to mental and growth retardation
- No clinical signs often for first year of life
- Treated with Synthyroid with dosage changing with infant growth
- Does not depend upon protein or lactose ingestion
- App. 10% are diagnosed from a 2nd specimen

Biotinidase Deficiency

- Defect in biotin re-utilization or recycling
- Normal at birth but develop symptoms within weeks or months
- Feeding and breathing difficulties, excema, hair loss, seizures, and lethargy that can progress to coma
- Treated with oral biotin
- Does not depend on protein or lactose ingestion

Maple Syrup Urine Disease

- Inherited disorder of protein metabolism
- Hyperammonemia leads to progressive neurological damage within days - considered a neonatal emergency
- Appear normal until 3-5 days
- Signs include poor feeding, vomiting, listlessness leading to convulsions & coma
- Urine and sweat smell like maple syrup
- Treatment with diet restricted in branched chain amino acids (leucine,isoleucine,and valine)

Congenital Adrenal Hyperplasia

- Inborn error of steroid synthesis preventing normal production of cortisol
- Androgens may virilize female external genitalia
- Untreated leads to rapid growth w/ advanced skeletal age, early puberty, & short stature as adults
- Treatment w/ hydrocortisone & mineralocorticoids
- Testing not dependent on protein or lactose ingestion

Galactosemia

- Inherited defect of galactose (carbohydrate) metabolism
- Untreated yields high morbidity and mortality in first months of life
- Signs include gram negative sepsis, liver disease, jaundice, failure to thrive
- Treated with a galactose-free diet for life
- Diagnosis NOT dependent on galactose intake

Hemoglobinopathies

- Originally offered to detect sickle cell anemia
- Also detects other abnormal hemoglobins, i.e. sickle beta thalassemia, Hgb SC disease
- May be life threatening or lead to a number of crisis situations
- Treatment with penicillin prophylaxis

Expanded Testing with MS/MS

- NBMS Advisory Committee recommended starting with expanded screening to begin 7/1/03; actually began 10/1/03
- Current panel includes 5 additional amino acid disorders, 6 fatty acid oxidation disorders, and 13 organic acid disorders
- All tests from old panel continued
- Hemoglobinopathies done on all infants
- No additional blood needed
- CF screening was added 2/1/07

Tandem Mass Spectrometry

- Simple sample preparation
- Rapid quantitative analysis
- High sensitivity & specificity
- High throughput
- Semi-automated
- Multiple simultaneous tests

Expanded Screening Panel Began on October 1, 2003

- Endocrine Disorders
  - Hypothyroidism
  - Congenital Adrenal Hyperplasia
- Hemoglobinopathies
- Biotinidase Deficiency
- Galactosemia
- Cystic Fibrosis screening began 2/1/07 using the IRT methodology

Expanded Screening (cont'd) Tandem Mass Spec Disorders

Amino Acid Disorders

- Phenylketonuria (PKU)
- Tyrosinemia (types I and II)
- Homocystinuria
- Arginase deficiency
- Argininosuccinate lyase deficiency
- Citrullinemia

Expanded Screening (cont'd)

Organic Acidemias

- Beta-ketothiolase deficiency
- Glutaric acidemia, Type 1
- Isobutyryl CoA dehydrogenase deficiency
- Isovaleric acidemia
- Malonic aciduria
- Maple Syrup Urine Disease (MSUD)
- Methymalonic acidemias (8 types)
- Multiple carboxylase deficiency

Expanded Screening (cont'd)

Organic Acidemias (cont'd)

- Proprionic acidemia
- 2-Methyl-3-hydroxybutryl CoA dehydrogenase deficiency
- 2-Methybutyryl CoA dehydrogenase deficiency
- 3-Hydroxy-3-methylglutaryl (HMG) CoA lyase deficiency
- 3-Methylcrotonyl CoA carboxylase deficiency (3-MCC)
- 3-Methylglutaconyl CoA hydrolase deficiency

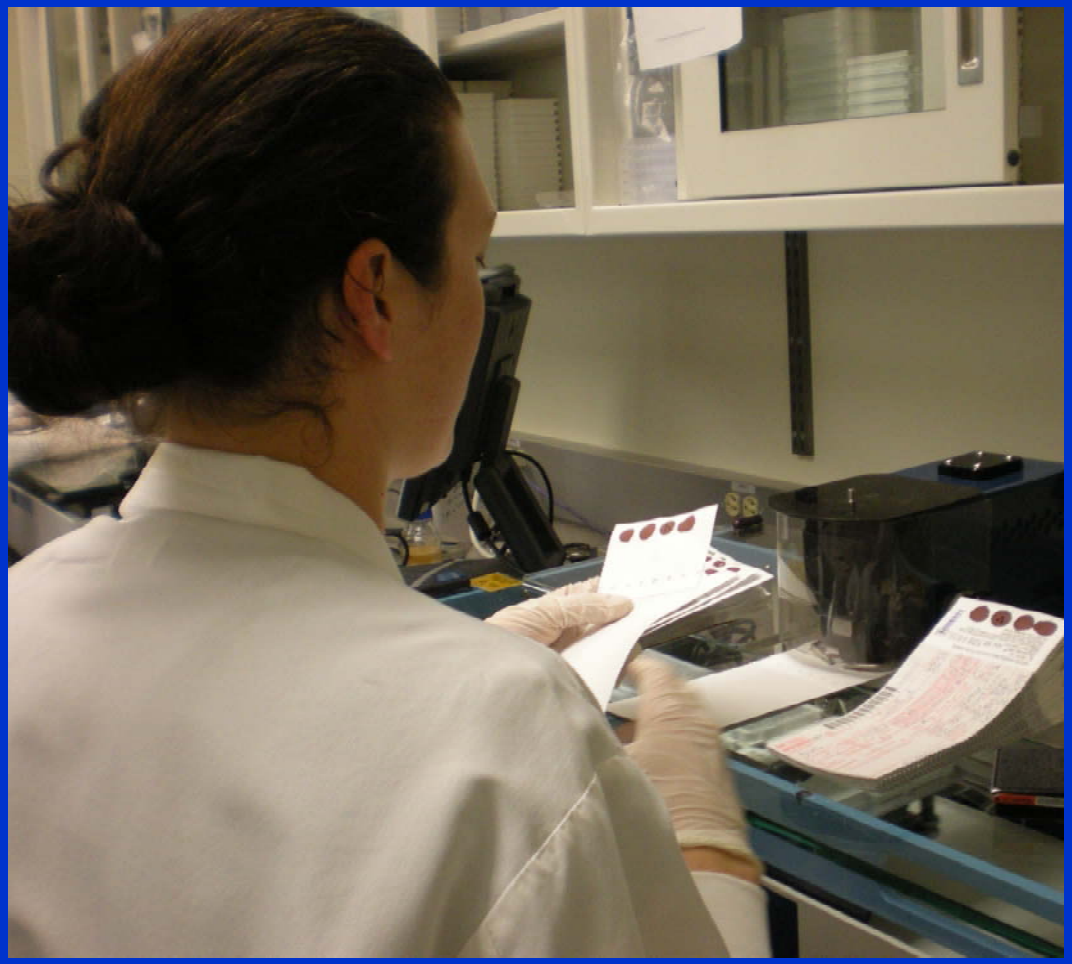
Expanded Screening (cont'd)

Fatty Acid Oxidation Disorders

- Very long chain acyl-CoA dehydrogenase deficiency (VLCADD)
- Long chain -3 hydroxyacyl-CoA dehydrogenase deficiency (LCHADD)
- Medium chain acyl-CoA dehydrogenase deficiency (MCADD)
- Short chain acyl-CoA dehydrogenase deficiency (SCADD)
- Carnitine uptake/transport defects
- Multiple acyl-CoA dehydrogenase deficiency (MADD, aka Glutaric acidemia Type 2)

The Screening Lab

Preparing Blood Spots



Common Collection Errors

- Quantity not sufficient
- Contaminated - this can be powder from gloves, urine, or anything spilled on the filter paper
- Uneven saturation - this is the most common error; the filter paper must be evenly saturated for the TMS extraction
- Transfused - all NICUs have been advised to collect a specimen before transfusion

Case Studies:

Maple Syrup Urine Disease

- Baby boy born 9/12/02
- First specimen 9/14/02
- Leucine = 6mg/dl on 9/19/02 with repeat on 9/20/02 and same result
- Baby seen by pediatrician on day 5, looked fine, regained weight, breast fed
- Baby in crisis on day 8 when results were reported;serum drawn with leucine = 3342 uM (normal at 61-183 uM)
- Fortunately this infant was tested in the birthing facility
- Has since received a liver transplant and is doing very well

Congenital Hypothyroidism

- **Baby girl born 5/9/02**
- **First specimen not obtained at birthing facility and no signed refusal submitted**
- **Tested on 5/13/02 at a medical clinic**
- **Specimen was QNS for T4 and TSH; repeat requested**
- **Repeat obtained 6/3/02 (baby 25 days old)**
- **TSH >200 uIL/ml so serum requested**
- **Serum collected 6/13/02 with TSH 578.48 uIU/ml**
- **Treatment started on day 34**
- **A good reason for testing in birthing facility**

Congenital Hypothyroidism

- Baby boy born 5/14/04
- First specimen normal 5/15/04
- Second specimen 5/27/04 TSH elevated at 165.09
- Treatment started on day 27
- A good reason to get a second specimen

MCAD: Medium Chain Acyl-CoA Dehydrogenase Deficiency

- White Hispanic male born 10/3/03
- First sample 10/4/03 with elevated C8
- Request for plasma acylcarnitine, plasma carnitine, and urine organic acids
- Profile suggestive of MCAD
- Mutation analysis confirmed diagnosis
- Treatment already begun on day 10
- MCAD screening began on 10/1/03!

Carnitine Palmitoyl Transferase 1A (CPT-1A) Deficiency

- Alaska Native male born 1/16/04
- First specimen normal on 1/17/04
- Second specimen 2/5/04 with elevated C0/C16 and C0/C18 ratios
- Plasma acylcarnitine profile normal
- Skin biopsy performed and results consistent with CPT1A deficiency
- Treatment already begun on day 48

Abnormal Screening Results with an Unclear Etiology

- Male born 8/15/04 at ANMC
- Abnormal acylcarnitines on 1st screen
- Urine organic acids & serum acylcarnitines ordered
- Urine organic acids were odd but not diagnostic
- 2nd specimen at 15 days still with abnormal acylcarnitines
- VLCFA ordered but not diagnostic
- What is this?

3-Methylcrotonyl Co-A Carboxylase (3-MCC) Deficiency

- Abnormal acylcarnitines on newborn screening (elevated C5-OH acylcarnitine)
- Serum acylcarnitines and urine organic acids analyzed on infant
- Urine organic acids were ordered on the mother
- Increased urine 3-MCC indicated the Mom had 3-MCC deficiency, baby was unaffected
- Seen in Genetics Clinic for counseling

2005 Newborn Screening Data

- 3 Hypothyroidism
- 1 TBG and 1 TBG excess
- 1 Glutaric acidemia Type 1
- 1 Partial Biotinidase Deficiency
- 4 CAH (one was late onset)
- 20 CPT-1A

2005 Abnormal Hemoglobins

- 70 Alpha thalassemia
- 42 S traits
- 16 C traits
- 11 Unknown Hgb variant
- 4 D or G trait
- 4 S trait & Alpha thalassemia
- 3 E trait & Alpha thalassemia
- 1 C trait & Alpha thalassemia
- 1 CC disease
- 1 Hgb H disease

2006 Data

- 5 Hypothyroidism (3 dx'd from a 2nd specimen)
- 1 CAH
- 3 TBG
- 28 CPT-1A
- 2 CPT-1A carriers
- 1 VLCAD
- 1 Biotinidase carrier
- 1 Benign MAT deficiency

2006 Abnormal Hemoglobins

- 54 Alpha thalassemia
- 44 S trait
- 32 E trait
- 15 C trait
- 12 Unknown Hemoglobin
- 4 D or G trait
- 2 E trait & Alpha thalassemia
- 2 S trait & Alpha thalassemia
- 1 Sickle Cell Disease
- 1 CC Disease

2007 Data

- 7 Hypothyroidism
- 1 CAH
- 1 TBG Deficiency
- 29 CPT-1A
- 2 PKU
- 1 MCAD
- 1 GA-1
- 1 VLCAD
- 1 Galactosemia
- 1 Propionic Acidemia
- 1 Cystic Fibrosis

2007 Abnormal Hemoglobins

- 2 Sickle Cell Disease
- 1 EE Disease
- 66 Alpha thalassemia
- 59 S trait
- 35 E trait
- 25 C trait
- 2 D or G trait
- 15 Unknown Hemoglobin
- 6 E trait & Alpha thal
- 6 S trait & Alpha thal
- 1 Unk Hgb & Alpha thal

We Have the Data You Need for Action

- NBMS Data is used to educate health care professionals and parents to ensure that all newborns are screened before leaving the birth facility in order to prevent lifelong disabilities and even death.

- Presentations made to areas of the State where there is a high rate of parental refusal for discharge screening.

Incidence of Disorders in AK 2006

- Primary hypothyroidism 1:2178
- CAH 1:10,892
- Metabolic disorders 1:350 (28 CPT-1A in this category)
- Hemoglobin disease 1:5444
- Hemoglobin traits 1:66

Logistics of Newborn Screening:

- The Oregon State Public Health lab processes ~ 1,000 screening cards daily
- Samples come from Oregon, Alaska, Idaho, Hawaii, New Mexico, and Nevada
- Punched samples are analyzed via multiple technologies

What Happens if a Test is Abnormal?

- Abnormal results:
  - Repeat test on a new sample from <u>same</u> screening card
    - If normal then stop
    - If abnormal next steps are determined based upon SOPs
- Non-urgent condition:
    - Await second screen or request repeat screening card
- Urgent Condition:
    - Contact PCP and responsible State personnel
    - Contact appropriate medical consultant
    - Obtain confirmatory samples
    - Begin appropriate therapy

Newborn Screening Basics for PCPs

- What does an abnormal screen mean?
  - Abnormal metabolite levels are present
  - Further evaluation and testing is necessary
- What are the PCP's responsibilities?
  - Contact the family
    - Ascertain status of infant
    - Advise on any immediate therapy required
    - Arrange to obtain confirmatory studies

Newborn Screening Basics for PCPs

- Educate office staff
  - Get the FAX!
  - Read the FAX!
- The FAX outlines what's needed for confirmation
- The information in the FAX will also help you know what questions to ask the consultant when he calls.

The Future:

Promises

Threats

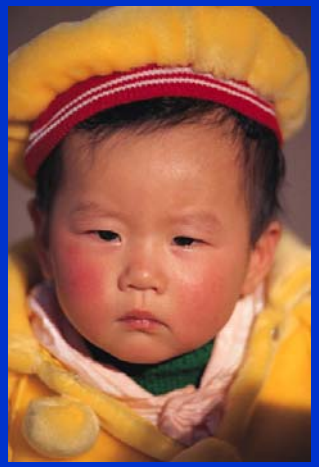
- Promises
  - Earlier intervention for treatable disorders
    - Wilson disease, Hemochromatosis
  - Early identification allows for genetic counseling

- Threats:
  - Abnormalities with uncertain implications can be identified
  - There are few evidence based treatments
  - False positives have negative consequences
  - Expanded screening can have economic impacts on State Public Health resources

What’s on the Horizon?

- Lysosomal storage diseases
  - Mucopolysaccharidoses
  - Gaucher
  - Fabry
- CMV
- SCID
- Wilsons disease

Why We Care



Alaska Newborn Metabolic Screening Program

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