The Evolving Landscape of Newborn Screening: What Pediatricians Need To Know

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Department of Pediatrics
Louisiana State University Health Sciences Center – Shreveport

LA AAP Acadiana Potpourri
Lafayette, LA
August 20, 2017
Financial Disclosure

During the past 12 months, I have not had a significant financial interest or other relationship with the manufacturers of the products or providers of the services that will be discussed in this presentation.
Objectives

- Describe the evolution of the Newborn Screening Program
- Describe the expanding role of the primary care physician
- Describe the Louisiana newborn screening program
The beginning of newborn screening

- 1961 – pilot studies
- 1963 – MA
- 1968 – 43 states

A SIMPLE PHENYLALANINE METHOD FOR DETECTING PHENYLKETONURIA IN LARGE POPULATIONS OF NEWBORN INFANTS

Robert Guthrie, Ph.D., M.D., and Ada Susi
Department of Pediatrics, School of Medicine State University of New York at Buffalo and Children’s Hospital, Buffalo 22, New York

PRINCIPLE

The inhibition of growth of Bacillus subtilis ATCC 6051 by B-2-thienylalanine in a minimal culture medium is prevented by phenylalanine, phenylpyruvic acid, and phenyllactic acid. This finding has permitted the development of a convenient agar diffusion microbial assay for phenylketonuria (PKU), employing small filter paper discs, impregnated with blood by heel puncture is applied immediately to a piece of thick, very absorbent filter paper (Schleicher & Schuell #903). The blood spot when air dried should be at least ½ inch in diameter (but not more than ⅛ inch) and close enough to the edge of the paper to facilitate punching out the disc. This paper is so absorbent that even very viscous blood from a young infant spreads through the paper, so that the appearance of the
Newborn screening

- State based public health program
- Advancing technology
  - Mass spectrometry
- 2003 – individual states newborn screening panels varied from 3 to 45 conditions
- AAP, ACMG, Health Resources Services Administration (HRSA) recommended the establishment of a standardized evidence based approach to newborn screening and conditions included on the screening panel
Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children

- Federal Advisory Committee
  - Established by Congress in 2003 (SACHDNC)
  - Reauthorized in 2015 (ACHDNC)
  - 15 members
    - NIH, FDA, CDC
    - HRSA, AHRQ
  - Organizations
    - AAP, AAFP, ACMG, APHL, ASTHO, MOD, SIMD
ACHDNC

- Advisory to the Secretary of Health and Human Services

- Mission:
  - To reduce morbidity and mortality in newborns and children who have, or are at risk for, heritable disorders
  - To enhance the ability of state and local health agencies to provide for newborn and child screening, counseling, and health care services.
  - Determine by evidence review whether a nominated condition meets criteria to be recommended for newborn screening (RUSP)
Routine Uniform Screening Panel (RUSP)

- 2005 – American College of Medical Genetics expert panel recommended screening for 29 core conditions with reporting of 25 additional secondary conditions

- 2005 - SACHDNC recommended the panel to the Secretary of Health and Human Services
  - 2006 - Approved
States screening for the core bloodspot conditions in the RUSP
Results of newborn screening, 2009

- >98% of the ~4 million infants born in the US were screened
- ~12,500 infants were diagnosed with one of the 29 core conditions
- Most common
  - Hearing loss
  - Primary congenital hypothyroidism
  - Cystic fibrosis
  - Sickle cell disease
  - Medium chain acyl-CoA dehydrogenase deficiency
- Overall cost: $30/infant
Conditions reviewed by ACHDNC since 2006

<table>
<thead>
<tr>
<th>Recommended</th>
<th>Not-recommended</th>
</tr>
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<tbody>
<tr>
<td>Severe Combined Immunodeficiency (2009)</td>
<td>22q11.2 Deletion Syndrome</td>
</tr>
<tr>
<td>Critical Congenital Cyanotic Heart Disease (2010)</td>
<td>Fabry Disease</td>
</tr>
<tr>
<td>Adrenoleukodystrophy (2012)</td>
<td>Hemoglobin H</td>
</tr>
<tr>
<td>Pompe Disease (2013)</td>
<td>Krabbe Disease</td>
</tr>
<tr>
<td>Mucopolysaccharidosis Type 1 (2015)</td>
<td>Neonatal Hyperbilirubinemia</td>
</tr>
<tr>
<td></td>
<td>Niemann-Pick Disease</td>
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<tr>
<td></td>
<td>Pompe (2008)</td>
</tr>
<tr>
<td></td>
<td>Spinal Muscular Atrophy</td>
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</table>

RUSP: Core and secondary conditions (as of Nov, 2016)

<table>
<thead>
<tr>
<th>ACMO Code</th>
<th>Core Condition</th>
<th>Metabolite Disorder</th>
<th>Endocrine Disorder</th>
<th>Hemoglobin Disorder</th>
<th>Other Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRCP</td>
<td>Prolactinemia</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MUT</td>
<td>Methylmalonicemia (methyloxaloacetateuria)</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CAIA</td>
<td>Malek syndrome</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>IVFA</td>
<td>Isovaleric acidemia</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2-HMG</td>
<td>2-Methylglutaric acidemia</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>MCD</td>
<td>Medium-chain length acyl-CoA dehydrogenase deficiency</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>GKT</td>
<td>Glycerol kinase deficiency</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QXL</td>
<td>Glutaric acidemia</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CUP</td>
<td>Carnitine uptake defect/carnitine transport defect</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MCAD</td>
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</tr>
<tr>
<td>VLCAD</td>
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<td>X</td>
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<td></td>
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<tr>
<td>LOHAD</td>
<td>Long-chain-length fatty acid-CoA ligase deficiency</td>
<td>X</td>
<td></td>
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</tr>
<tr>
<td>TPR</td>
<td>Transcriptional protein deficiency</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABA</td>
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<td>X</td>
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</tr>
<tr>
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<tr>
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<td>X</td>
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<tr>
<td>HOCH</td>
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<tr>
<td>CYF</td>
<td>Cystinemia, congenital</td>
<td>X</td>
<td></td>
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<tr>
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<td>High serum bilirubinemia</td>
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<tr>
<td>HIS</td>
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1. Selection of conditions based upon Newborn Screening for A Uniform Panel and System. Genetic Test. 2006; 8(8) Suppl: 830-8332 as authored by the American College of Medical Genetics (ACMG) and commissioned by the Health Resourcxs and Services Administration (HRSA).
2. Disorders that should be included in every Newborn Screening Program.
Universal Screening Status of the 34 Core Disorders (April 2017)
Cystic Fibrosis was the last condition to be added to the Louisiana Newborn Screening Panel (2007)

Subsequent ACHDNC recommendations approved by the Secretary:

- SCID, Pompe, MPS I and X-ALD have not been added to the Louisiana panel due to lack of funding to initiate and maintain testing.

- Critical Congenital Heart Disease
  - Legislature approved statute mandating that all infants are screened before hospital discharge
    - Data not kept by genetics or birth defects programs.
Criteria for consideration for newborn screening

- Disorder is medically serious
- Spectrum is well described (case definition)
  - Able to predict the phenotypic range of identified newborns
  - Those who will benefit can be identified
- Effective treatment
- Evidence that diagnosis at birth leads to improved health outcomes
Criteria for consideration for newborn screening

- Effective screening test
  - Uses dried blood spots
  - Analytic validity
  - Performance characteristics should be reasonable for the newborn screening system
    - False positive and false negative rates, able to be performed in a high throughput laboratory
  - Inexpensive

- Widely available confirmatory test

- Prospective pilot data from population-based assessment
### Louisiana Newborn Screening Program, 2016: Results

<table>
<thead>
<tr>
<th>Number Receiving at Least One Screen</th>
<th>% of LA births</th>
<th>Number with a Presumptive Positive Screen (%)</th>
<th>Number of Confirmed Cases (%)</th>
<th>Confirmed Cases Referred for Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>63,754</td>
<td>99.7%</td>
<td>2028 (3.2%)</td>
<td>154 (0.24%)</td>
<td>100%</td>
</tr>
</tbody>
</table>

1 in 13 presumptive positives are confirmed

1 in 414 screened are identified with a screened-for condition
## Louisiana Newborn Screening Program, 2016: Results

<table>
<thead>
<tr>
<th>Condition</th>
<th>Confirmed Cases</th>
</tr>
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<tbody>
<tr>
<td>Glutaric acidemia type I</td>
<td>1</td>
</tr>
<tr>
<td>Medium-chain acyl-CoA dehydrogenase deficiency</td>
<td>2</td>
</tr>
<tr>
<td>Citrullinemia, type I</td>
<td>1</td>
</tr>
<tr>
<td>Classic phenylketonuria</td>
<td>3</td>
</tr>
<tr>
<td>Primary congenital hypothyroidism</td>
<td>37</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td>4</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>55</td>
</tr>
<tr>
<td>Sickle-beta-thalassemia</td>
<td>8</td>
</tr>
<tr>
<td>S,C disease</td>
<td>18</td>
</tr>
<tr>
<td>Biotinidase deficiency</td>
<td>7</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>17</td>
</tr>
<tr>
<td>Classic galactosemia</td>
<td>1</td>
</tr>
</tbody>
</table>
### Louisiana Hearing Screening Program: Results

<table>
<thead>
<tr>
<th></th>
<th>2015</th>
<th></th>
<th>2016</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Rate</td>
<td>Number</td>
<td>Rate</td>
</tr>
<tr>
<td>Occurrent Births</td>
<td>64266</td>
<td></td>
<td>62817</td>
<td></td>
</tr>
<tr>
<td>Total Newborns To Be Screened</td>
<td>63883</td>
<td></td>
<td>62452</td>
<td></td>
</tr>
<tr>
<td>Inpatient Hearing Screenings Completed</td>
<td>63253</td>
<td>99.0% Screening Rate</td>
<td>61760</td>
<td>98.9% Screening Rate</td>
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<tr>
<td>Passed</td>
<td>60004</td>
<td></td>
<td>58871</td>
<td></td>
</tr>
<tr>
<td>Did Not Pass (Refer)</td>
<td>3249</td>
<td>5.1% Refer Rate</td>
<td>2889</td>
<td>4.7% Refer Rate</td>
</tr>
<tr>
<td>Inpatient Hearing Screenings Not Completed</td>
<td>630</td>
<td></td>
<td>692</td>
<td></td>
</tr>
<tr>
<td>Total confirmed hearing loss</td>
<td>101</td>
<td>1.6 per 1,000 live births</td>
<td>100</td>
<td>1.6 per 1,000 live births</td>
</tr>
</tbody>
</table>

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Melinda M. Peat, MCD  
Hearing, Speech & Vision Program Manager  
LA EHDI Principal Investigator  
Office: 504-568-5028  
Fax: 504-568-5854  

LOUISIANA DEPARTMENT OF HEALTH
Louisiana EDHI Program

75% of infants failing the screen return for follow-up care

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1 screening
Hearing screening on all infants before 1 month of age

3 diagnosis
Audiological diagnosis before 3 months of age if the infant does not pass the screening

6 intervention
Medical, educational, and audologic intervention before 6 months of age if diagnosed with hearing loss
Newborn Screening Expands: Recommendations for Pediatricians and Medical Homes—Implications for the System

Newborn Screening Authoring Committee

ABSTRACT
Advances in newborn screening technology, coupled with recent advances in the diagnosis and treatment of rare but serious congenital conditions that affect newborn infants, provide increased opportunities for positively affecting the lives of children and their families. These advantages also pose new challenges to primary care pediatricians, both educationally and in response to the management of affected infants. Primary care pediatricians require immediate access to clinical and diagnostic information and guidance and have a proactive role to play in
Office Policies and Procedures

- **3-5 day old visit**
  - Assure NBS was conducted
    - Home birth, hospital transport, refusal, adoption

- **1 month visit**
  - Assure results received and within range
  - Document results and inform family
  - Follow-up with lab if not received

- **Special circumstances**
  - Repeat, preterm infant, TPN or post transfusion, international adoption, older child, PCP different from nursery provider, etc.

What do you do when you receive a report of an out-of-range result?
Out-of-range result

- >50% of pediatricians prefer that the state NBS program manage the diagnostic workup of a positive newborn screen (Kemper, Pediatrics 2006;118:1836)
Out-of-range result

- Office should be prepared to take prompt action following a call (FAX) from lab
  - LA NBS Program provides
    - Information on urgency
    - Next steps
    - ACT Sheet and Algorithm
    - Identifies specialist for referral, if needed
ACT Sheets and Algorithms

- Developed by American College of Medical Genetics
- Continuously review process by the Board of Directors
- As new conditions introduced, additional materials are added
- Available
  - http://www.acmg.net/Admin/ACT_Sheets_and_Confirmatory_Algorithms/NBS_ACT_Sheets_and_Algorithm_Table/ACMG/Resources/ACT_Sheets_and_Confirmatory_Algorithms/NBS_ACT_Sheets_and_Algorithms_Table.aspx?hkey=aa84b9b4
  - Smartphone or tablet on the ACT Sheet Mobile App
American College of Medical Genetics: ACT Sheets/Algorithms

- Brief description of condition
- Short term actions for communicating with family
- Appropriate steps in the follow-up of the infant
  - Diagnostic evaluation
  - Clinical considerations
- Links to additional information sources
American College of Medical Genetics: ACT Sheets/Algorithms

- Algorithm with basic steps for determining the final diagnosis in the infant
- LA NBS Program provides referral information for testing and clinical services
Newborn Screening ACT Sheet

[Sickle Cell Anemia (HbSS Disease or HbS/Beta Zero Thalassemia)]

Differential Diagnosis: Homozygous sickle cell disease (Hb SS), sickle beta-zero thalassemia, or sickle hereditary persistence of fetal hemoglobin (Hb S-HPFH)

Condition Description: A red blood cell disorder characterized by presence of fetal hemoglobin (F) and hemoglobin S in the absence of hemoglobin A. The hemoglobins are listed in order of the amount of hemoglobin present (F>S). This result is different from FAS which is consistent with sickle carrier.

YOU SHOULD TAKE THE FOLLOWING ACTIONS:
- Contact the family to inform them of the screening result.
- Consult a specialist in hemoglobin disorders; refer if needed.
- Evaluate infant and assess for splenomegaly; do complete blood count (CBC) with mean corpuscular volume (MCV), and reticulocyte count.
- Order hemoglobin profile analysis (usually performed by electrophoresis).
- Initiate timely confirmatory/diagnostic testing as recommended by consultant.
- Initiate daily penicillin VK (125mg po bid) prophylaxis and other treatment as recommended by the consultant.
- Educate parents/caregivers regarding the risk of sepsis, the need for urgent evaluation if fever of ≥ 38.5°C (101° F) or signs and symptoms of splenic sequestration.

Diagnostic Evaluation: CBC, MCV, and reticulocyte count. Hemoglobin separation by electrophoresis, isoelectric focusing or high performance liquid chromatography (HPLC) shows F pattern. DNA studies may be used to confirm genotype. Sicklex is not appropriate for confirmation of diagnosis in infants.

Clinical Considerations: Newborn infants are usually well. Hemolytic anemia and vaso-occlusive complications develop during infancy or early childhood. Complications include life-threatening infection, splenic sequestration, pneumonia, acute chest syndrome, pain episodes, aplastic crises, dactylitis, priapism, and stroke. Comprehensive care including family education, immunizations, prophylactic penicillin, and prompt treatment of acute illness reduces morbidity and mortality. S-HPFH is typically benign.

Additional Information:
- Grady Comprehensive Sickle Cell Center
- Management and Therapy of Sickle Cell Disease
- Sickle Cell Disease in Children and Adolescents: Diagnosis, Guidelines for Comprehensive Care, and Protocols for Management of Acute and Chronic Complications
- American Academy of Pediatrics
- Sickle Cell Disease Association of America

Referral (local, state, regional and national):
- Testing
- Clinical Services
- Comprehensive Sickle Cell Center Directory
- Sickle Cell Information Center
- Find Genetic Services

Hb S Screening

Hb S Screening

NBS Hb S on screen by HPLC or IEF

Confirm by alternative method (IEF, HPLC, electrophoresis or DNA studies)

CBC, Hb, and Penicillin

Confirm by alternative method (IEF, HPLC, electrophoresis or DNA studies)

[FS] Hb SS

Hb SC disease

[FAA] Hb S-thalassemia

[FAV] Hb S/Arthrogryposis

[FS] Hb AS

Refer to specialist in hemoglobin disorders

Refer to specialist in hemoglobin disorders

Refer to specialist in hemoglobin disorders

Refer to specialist in hemoglobin disorders

No further testing required

* Offer family members referral for hemoglobin disorders testing and genetic counseling.

Action steps are shown in shaded boxes; results are in the unshaded boxes.

Abbreviations Key:
- F, S, A, C, and V: The hemoglobins seen in neonatal screening,
- HPLC: High performance liquid chromatography
- IEF: Isoelectric focusing

Disclaimer: This guideline is designed primarily as an educational resource for clinicians to help them provide quality medical care. It should not be considered a statement of the standard of care; nor an endorsement of particular procedures or tests that are recommended or not recommended by the guideline. The guideline does not necessarily ensure a successful medical outcome. In determining the propriety of any specific procedure or test, the clinician should consider the specific clinician and circumstances presented by the individual patient or patient. Clinicians are encouraged to consider the measures for the use of a particular procedure or test, whether or not it is in conformance with this guideline. Clinicians are also advised to take notice of the date this guideline was adopted, and to consider other medical and scientific information that becomes available after that date.

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(Funded in part through NICHD/HD5/HD5 grant R22/HD03975)
Newborn Screening ACT Sheet
[Elevated IRT +/- DNA]
Cystic Fibrosis

Differential Diagnosis: Cystic fibrosis (CF); gastrointestinal abnormalities are also causes of increased IRT.

Condition Description: The cystic fibrosis transmembrane conductance regulator (CFTR) protein regulates chloride transport that is important for function of lungs, upper respiratory tract, pancreas, liver, sweat glands, and genitourinary tract. CF affects multiple body systems and is associated with progressive damage to respiratory and digestive systems.

YOU SHOULD TAKE THE FOLLOWING ACTIONS:
- Contact family to inform them of the newborn screening result and to ascertain clinical status (meconium ileus, failure to thrive, recurrent cough, wheezing and chronic abdominal pain).
- Contact CF Center for consultation with CF specialist.
- Determine sweat chloride (sweat test) through experienced sweat test laboratory.
- If cystic fibrosis is confirmed, clinical evaluation and genetic counseling are indicated.
- Report findings to newborn screening program.

Diagnostic Evaluation: Varies with screening test. Infants with highly elevated immunoreactive trypsinogen (IRT) may be considered screen positive. Elevated IRT results are followed with second tier tests for either additional IRT measurement or CFTR mutation panels. If screen positive, follow up with sweat chloride test to confirm diagnosis.

Clinical Considerations: Deficient chloride transport in lungs causes production of abnormally thick mucous leading to airway obstruction, neutrophil dominated inflammation and recurrent and progressive pulmonary infections. Pancreatic insufficiency found in 80 – 90% of cases. Some males may be infertile in adulthood.

Additional Information:
- Gene Reviews
  Cystic Fibrosis Foundation
  OMIM
  Genetics Home Reference
  American College of Medical Genetics

Referral (local, state, regional and national):
- Testing
  Clinical Services
  Find Genetic Services

Immunoreactive Trypsinogen (IRT Elevated)

- Immunoreactive Trypsinogen (IRT) Screening
  - Moderately elevated IRT
  - Highly elevated IRT

  Repeat IRT
  - Elevated 2nd IRT
  - Single mutation
  - Two mutations
    - Expanded mutation panel testing
      - One or two mutations
        - Determine sweat chloride
          - 60mEq/L is Positive for cystic fibrosis (CF)

* Mutational analysis if not already done

Actions are shown in shaded boxes; results are in the unshaded boxes.

Disclaimer: These guidelines are designed primarily as an educational resource for physicians to help them provide quality clinical services. Adherence to these standards and guidelines does not necessarily ensure a successful medical outcome. These standards and guidelines should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, the healthcare provider should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the patient record the rationale for any significant deviation from these standards and guidelines.

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Parent education for false out-of-range results

- 5-20% of parents will persist in having concerns about the health of the infant for months to years
- Effective discussion by PCP on subsequent visits may ameliorate concerns
Confirmatory test result indeterminate

- Subspecialist input and ongoing collaboration
- Monitor infant for signs and symptoms of suspected condition
- Example: Cystic Fibrosis
Cystic Fibrosis: Consensus guidelines from CF Foundation

- Diagnosis associated with Cystic Fibrosis transmembrane conductance regulator (CFTR) mutations in all individuals, from newborn to adult, is established by evaluation of CFTR function with a sweat chloride test.

- Genetic analysis included as part of the NBS program must not be relied upon for conclusive diagnosis or genotyping.
Cystic Fibrosis: Confirmatory test

- Qualitative Sweat Conductivity Test – NOT ACCEPTABLE

- Required: Quantitative Pilocarpine Iontophoresis Sweat Chloride Test
  - LA AAP will refer to one of 5 institutions in LA
Newborns with a high immunoreactive trypsinogen level and inconclusive CFTR functional (Sweat Cl ≥30 but ≤60mmol/L) and genetic testing may be designated CFTR-related metabolic syndrome or CF screen positive, inconclusive diagnosis.
Carrier identification

- Implications
  - Autosomal-recessive condition: If both parents are carriers, subsequent pregnancies have 1-in-4 risk of disorder
    - Parents may wish genetic testing
  - Additional genetic counseling may be needed for affected child when reaching reproductive age
Limitations of Newborn Screening

- Condition may present before notification of NBS results
- In-range NBS result is not diagnostic
  - Does not eliminate the possibility of presence of a condition
  - Conditions must be considered in differential diagnosis when infant has signs or symptoms suggestive or consistent with one of the disorders that can be detected by NBS
What is “Critical” Congenital Heart Disease (CCHD)?

- Specific heart defects that require prompt detection to avoid crises

- **Primary screening targets:**
  - Hypoplastic left heart syndrome
  - Tetralogy of Fallot
  - Total anomalous pulmonary venous connection
  - Tricuspid stenosis and atresia
  - D-transposition of the great arteries
  - Pulmonary atresia
  - Truncus arteriosus

- **Secondary screening targets:**
  - Coarctation of the aorta
  - Double-outlet right ventricle
  - Aortic arch interruption/atresia
  - Ebstein anomaly
  - Single ventricle
Key Findings – Effects of Screening Policies

- Birth and death records, 2017-2013
- Relative reductions in CCHD and Other CHD deaths compared to births in months with no state policy, adjusted for state factors and time trends
  - Mandatory screening
    - CCHD deaths to age 6 months fell by one-third (33.4%)
    - Other CHD deaths fell by one-fifth (21.4%)
    - Both changes were statistically significant
Severe Combined Immunodeficiency (SCID)

- Genetically heterogeneous disorder
  - At least 13 different genetic defects

- Characterized by
  - T-cell lymphopenia
  - Lack of antigen-specific T-cell
  - May also lack B-cells/responses
  - May also have lack of NK cells/function

- Uniformly fatal in infancy
  - Extreme susceptibility to infections
SCID: Diagnostic pediatric emergency

- No live vaccines
- Only CMV-neg, irradiated blood products
- Avoid infection
- Transplantation before infant develops infection has best outcome

Problem: Presymptomatic treatment is only possible for the child born to a family known to be at risk
Key findings:

- Screening period: Jan, 2008-July, 2013
- Newborns screened: 3,030,083
- Cases Detected: 52 Total (42 typical SCID, 9 leaky SCID, 1 Omenn syndrome)
- Incidence: 1 in 58,000 (95% CI, 1/46,000-1/80,000)
- Survival: 87%; 92% for infants who received transplantation, enzyme replacement, and/or gene therapy
Non-SCID Lymphopenophasias Identified

Table 5. Diagnoses of 411 Infants With Non-SCID T-Cell Lymphopenia Identified by Newborn Screening

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syndromes with T-cell impairmenta</td>
<td>136</td>
</tr>
<tr>
<td>DiGeorge</td>
<td>78b</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>21</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>4</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>4</td>
</tr>
<tr>
<td>CHARGE</td>
<td>3</td>
</tr>
<tr>
<td>Jacobsen</td>
<td>2</td>
</tr>
<tr>
<td>CLOVES</td>
<td>1</td>
</tr>
<tr>
<td>ECC</td>
<td>1</td>
</tr>
<tr>
<td>Fryns</td>
<td>1</td>
</tr>
<tr>
<td>Nijmegen breakage</td>
<td>1</td>
</tr>
<tr>
<td>Noonan</td>
<td>1</td>
</tr>
<tr>
<td>Rac2 defect</td>
<td>1c</td>
</tr>
<tr>
<td>Renpenning</td>
<td>1</td>
</tr>
<tr>
<td>TAR</td>
<td>1</td>
</tr>
<tr>
<td>Not specified</td>
<td>10</td>
</tr>
<tr>
<td>Cytogenetic abnormalitiesd</td>
<td>6</td>
</tr>
<tr>
<td>Secondary T-cell impairment</td>
<td>117</td>
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<tr>
<td>Cardiac anomalies</td>
<td>30</td>
</tr>
<tr>
<td>Multiple congenital anomalies</td>
<td>23</td>
</tr>
<tr>
<td>Loss into third space</td>
<td>15</td>
</tr>
<tr>
<td>Gastrointestinal anomalies</td>
<td>15</td>
</tr>
<tr>
<td>Neonatal leukemia</td>
<td>4</td>
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<tr>
<td>Not specified</td>
<td>30</td>
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<tr>
<td>Preterm birth alone</td>
<td>29</td>
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<tr>
<td>Variant SCID</td>
<td>12e</td>
</tr>
<tr>
<td>Unspecified T-cell lymphopenophasia</td>
<td>117</td>
</tr>
</tbody>
</table>

Abbreviations: CHARGE, coloboma, heart defect, atresia choanae, retarded growth and development, genital and ear abnormality; CLOVES, congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and spinal/skeletal anomalies; ECC, ectodermal dysplasia, ectrodyctalyly and cleftling; SCID, severe combined immunodeficiency; TAR, thrombocytopenia and absent radius.

a Eponymous syndromes: DiGeorge, cardiac defects, hypocalcemia, thymus dysplasia, and other anomalies, most often with chromosome 22q11.2 interstitial deletion. Jacobsen, growth and psychomotor retardation and congenital anomalies with chromosome 11qter deletion; Fryns, diaphragmatic hernia and other congenital anomalies; Noonan, multiple congenital anomalies. Renpenning, X chromosome-linked mental retardation with distinctive facies.

b Included 3 infants with complete DiGeorge syndrome and absent T cells, 2 of whom received a thymus transplant.

c Eventual hematopoietic cell transplant performed.17

d Included chromosome 6p deletion, ring chromosome 14, ring chromosome 17, chromosome 17q duplication, and 2 siblings with unspecified chromosome abnormalities.

e Eventual hematopoietic cell transplant performed for 1 case.

f Includes infants from Michigan (46), New York (30), Massachusetts (25), Wisconsin (13), Connecticut (2), and Delaware (1); further information was not available for these infants, although those from New York were reported to require ongoing monitoring or treatment for a deficiency of T cells.30
2016

SOURCE: PRESENTED TO THE SECRETARY’S ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN BY JELILI OJODU, MPH, ASSOCIATION OF PUBLIC HEALTH LABORATORIES AND MARCI SONTAG, PHD, COLORADO SCHOOL OF PUBLIC HEALTH. AUGUST 2015.
**Future?**

- **Whole Genome/Exome Sequencing**
  - NIH has awarded 4 grants to investigate possible benefits of WGS/WES, either as primary or secondary testing
    - **WGS** – determining the complete DNA sequence of a person (chromosomal and mitochondrial)
    - **WES** – sequencing all expressed genes (exons = encode proteins) to identify genetic variants that alter protein sequences
  - Non-invasive maternal testing
Louisiana Genetics Program

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Key Additional Resources

- AAP Clinical Report – Recommendations for Pediatricians
  - Pediatrics 2008;121:192

- Baby’s First Test
  - http://www.babysfirsttest.org/newborn-screening/responding-to-results