NEWBORN SCREENING SAVES LIVES, WHAT’S NEW?

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  • PI of TXPOP and TXPOP II funded by Texas Department of State Health Services’ Children’s Outreach Heart Program.
  • Member of Texas Newborn Screening Advisory Committee.

Learning Objectives
• At the end of this presentation the participant will be able to
  1. Characterize Texas newborn screening program
  2. Understand tandem mass spectrometry (MS/MS)
  3. Know the major categories of diseases detected by Texas newborn screening
  4. Describe follow-up for an abnormal newborn screening result.

What is Newborn Screening?
• The practice of testing all babies in their first days of life for certain disorders and conditions that can hinder their normal development.
• Testing is required in every state and is typically performed before the baby leaves the hospital.
• The conditions included in newborn screening can cause serious health problems starting in infancy or childhood.
• Early detection and treatment can help prevent intellectual and physical disabilities and life-threatening illnesses.

Historical Background
• 1934 – Asbjorn Folling, Professor of nutrient research in Oslo, met Borgny Egeland, mother of 2 children with progressive mental retardation.
  • Urine - strong smell – id by Folling as phenylpyruvic acid (“the idiot acid”)
  • First association between a defect in the metabolic process of the body and the developmental retardation - changed the lives of patients from one of disability to one of ability
  • “Knowledge leads to humility”

• 1961 Robert Guthrie - Developed a sensitive, simple bacterial inhibition assay using filter paper that could be administered a few days after birth test thus making possible the early detection of PKU and management.

  • “The conquest of PKU is important not only for itself, but because it serves as an open door to a whole new era of preventive medicine based upon new understanding of medical genetics.”
1. Important health problem
2. Accepted treatment
3. Diagnosis and treatment facilities available
4. Recognizable latent or early symptomatic state
5. Suitable test or examination
6. Test is acceptable to the population
7. Natural disease history adequately understood
8. Agreed policy on whom to treat as patients
9. The cost balanced relative to possible expense for medical care
10. Case finding is a continuous process

Traditional Criteria for Newborn Screening
Wilson and Jungner – WHO, 1968
10 Criteria for Population Screening

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Congressional Interest - Equality
U.S. Government Accounting Office 2003
Response to Senate Request

HRSA Contract
National Policy Development for NBS Test Selection
American College of Medical Genetics
Completed January 2005

Sorting of Survey Scores

HRSA Recommended Uniform Screening Panel (RUSP) : Core Panel

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What is RUSP?
- Recommended Uniform Screening Panel
- Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children
  - Group of professionals and family advocates convened by Secretary of Health and Human Services.
  - To review evidence and public health impact of conditions that could be added to the newborn screening panel.
- Although Committee makes recommendations, each state decides for itself which conditions to include on their state’s panel.
**Newborn Screening Saves Lives Act**

- 2008 Established national newborn screening guidelines and support comprehensive state screening efforts.
- 2014 Passed reauthorization act
  - Improve and expand state-based programs
  - Educate providers and parents about newborn screening
  - Develop screening standards and surveillance efforts
  - New provision addressing research uses of newborn dried blood spots (NDBS)
  - Places NDBS under Federal Policy for Protection of Human Subjects

**Texas - 2011**

- HB 411 – required consent for storage and use of NDBS
  - Without consent, all specimens stored for up to 2 years and not allowed for external research use (certain internal uses including QA/CC allowed)
  - With consent, specimens stored up to 25 years and can be used for external research
  - Codified DSHS IRB and management approval requirements
  - New forms, collection kits
  - Effective June 1, 2012
  - Opt-in for long term storage of blood spot
  - Parents must complete “Parental Decision for Storage and Use of Newborn Screening Blood Spot Cards”

**Texas Newborn Screening is Opt-Out**

- Parents can only refuse to have their child screened if the screening conflicts with a parent’s religious tenets or practices (Texas Health & Safety Code Sec. 33.012).
- In order to refuse, a parent must sign a form stating he/she has a religious objection to newborn screening. Points to consider before refusing newborn screening:
  - There are important medical benefits of newborn screening.
  - Symptoms of a newborn screening disorder can appear much later, after a child’s health has already been injured by the disease.
  - The screen is mandated by law.
  - The only legal reason to refuse newborn screening is if it conflicts with your religious tenets or practices.
- Form # - EF14-13549 can be found: https://www.dshs.state.tx.us/lab/nbsFAQ.shtml

**What is Tandem Mass Spectrometer (MS/MS)?**

- Sophisticated detector – 5 elements:
  - Electro-spray ion source
  - First mass spectrometer (MS1)
    - Filters compounds based on molecular weight
  - Collision cell
    - Fragments compounds into smaller “daughter ions”
  - Second mass spectrometer (MS2)
    - Filters daughter fragments based on specified parameter (molecular weight)
  - Detector
    - Detects and measures abundance of filtered ions
MS/MS
- Detects 2 types compounds: acylcarnitines and amino acids
- Acylcarnitines – organic compound conjugated to carnitine (import of long-chain FA into mitochondria prior to β-oxidation)
  - Intermediates of FA oxidation and organic acid metabolism
  - Range from C2 to C18 as well as C0
- AA: aromatic (PA, Ty), branched-chain (leu, isoleu, val), sulfur-containing (met), intermediates of urea cycle (cit, orn, arg).

Texas NBS
- 2013 Taryn Kennedy, Nash Sievers & Rex Van de Putte act passed requiring all newborns be screened for Critical congenital heart disease.
- 2015 – 24 secondary conditions added
  - Some clinically significant
  - Others with unclear natural history or lack appropriate medical therapy that affects long-term outcome.

Texas NBS – Pompe’s not added
- Pompe (acid maltase deficiency)
  - Approved fro RUSP in March 2015
  - 2 tier approach – dried blood spot screened for acid maltase (GAA) enzyme. If screen suggest deficiency, blood is obtained for enzyme level and to detect mutation in acid maltase gene by DNA testing.
  - Since 2006, Myozyme has been approved for enzyme replacement therapy.
    - Early treatment saves lives and improves health for infantile-onset form
    - Not known whether treatment benefits late-onset form.

Newborn Screening Program - components
- Education
  - Prenatal education - parents
- Screening
  - Specimen collection, submission, testing
- Follow-up
  - Abnormal and unsatisfactory results
- Diagnostic confirmation
- Management
- Program evaluation
  - Quality assurance, program evaluation, validity of testing systems, efficiency of follow up and intervention, assessment of long-term benefits
Cystic Fibrosis

- Immunoreactive trypsinogen IRT/IRT/DNA approach
  - Indeterminate - IRT on 1st screen elevated, will be tied to 2nd screen, if both elevated or 2nd not available, then reflex to DNA
  - mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (1900 known mutations)
  - 40 of most common genes tested
  - If DNA negative, then result will be inconclusive (testing if clinically indicated)
  - If 1 mutation, CF cannot be ruled out, refer for confirmatory testing
  - If 2 mutation, refer for confirmatory testing

- Sweat chloride for diagnosis
- 322 cases to date
- CF centers
- https://www.cff.org/What-is-CF/About-Cystic-Fibrosis/

Severe Combined Immune Deficiency

- Screen detects evidence of lack of lymphocytes
- PCR to detect circular DNA made by lymphocytes
- When screen fails to pick up PCR then definitive testing is done via DNA analysis.
  - All SCID due to mutations in immune system genes.
  - Most sporadically
  - Babies initially normal and are protected by maternal antibodies
- Diagnosis before screening only when infections noted to be more frequent and persistent. Frequently accurate diagnosis delayed
- 20 cases have been identified in Texas
- www.scid.net

What are the 24 secondary conditions?

- Amino Acid disorders
  1. Argininemia (ARG)
  2. Citrullinemia, type II (CIT II)
  3. Hypermethioninemia (MET)
  4. Benign hyperphenylalaninemia (H_PHE)
  5. Biopterin defect in cofactor biosynthesis (BIOPT(BS))
  6. Biopterin defect in cofactor regeneration (BIOPT REG)
  7. Tyrosinemia, type II (TRY II)
  8. Tryosinemia, type III (TRY III)

Secondary conditions, continue

- Fatty Acid Disorders
  9. Short-chain acyl-CoA dehydrogenase deficiency (SCAD)
  10. Medium/short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency (M/SCHAD)
  11. Glutaric acidemia type II (GA2)
  12. Medium-chain ketoacyl-CoA thiolase deficiency (MCKAT)
  13. 2,4 Dienoyl-CoA reductase deficiency (DE RED)
  14. Carnitine palmitoyltransferase type I deficiency (CPT 1A)
  15. Carnitine palmitoyltransferase type II deficiency (CPT II)
  16. Carnitine acylcarnitine translocase deficiency (CACT)

Secondary conditions, continue

- Organic acid disorders
  17. Methylmalonic acidemia with homocystinuria (Cbl C, D)
  18. Malonic acidemia (MAL)
  19. Isobutyrylglycinuria (IBG)
  20. 2-Methylbutyrylglycinuria (2MBG)
  21. 3-Methylglutaconic aciduria (3MGA)
  22. 2-Methyl-3-hydroxybutyric aciduria (2M3HBA)

- Hemoglobin disorder
  23. Various other hemoglobinopathies (Var Hb)

- Other
  24. T-cell related lymphocyte deficiencies
How is Newborn Screening done?
- Blood spot – collected onto filter paper
  - 24-48 hours
  - 7-14 days
  - Sample collected by healthcare provider
- DSHS public health laboratory in Austin performs testing
- Hearing
  - 24 hours to before discharge
  - OAE – otoacoustic emissions
  - ABR – auditory brain stem response
  - Screened by 1 month, Diagnosed by 3 months, Intervention by 6 months.
- CCHD
  - 24 hours to before discharge
  - Pulse oximetry – pre and post ductal

Texas Early Hearing Detection and Intervention (TEHDI)
- Mandated by Health and Safety Code, Chapter 47
- Dedicated to ensure that newborns and young children with hearing loss are identified as early as possible
- Goal to provide appropriate intervention to prevent delays in communication and cognitive skill development
- Screening via 2 methods: OAE, ABR

Otoacoustic Emissions (OAE)
- Measurements obtained from ear canal with probe
- Records cochlear responses to acoustic stimuli
- Reflects status of peripheral auditory system to cochlear outer hair cells
- If cochlea hearing loss, either no or below normal
- Normal cochlear response may be attenuated by middle ear fluid or external canal abnormalities.
- Most widespread use for screening; if initial abnormal, bears repeating.
- Implemented with automatic response-detection algorithms
- Will not identify auditory neuropathy

Auditory Brainstem Response (ABR)
- Measurements obtained from surface electrodes
- Records neural activity in cochlea, auditory nerve, and brainstem response to auditory stimuli
- Reflects status of peripheral auditory system, 8th nerve, and brainstem auditory pathway
- Will identify auditory neuropathy
- Infant must be asleep for testing
- Implemented with automatic response-detection algorithms

Etiology of early childhood hearing loss
- 60% congenital deafness has primary genetic etiology
  - 70% non-syndromic
  - 75% autosomal recessive
- Connexin 26 mutations found in 40%
- Congenital Cytomegalovirus (CMV)
  - Accounts for 40% of early identified hearing abnormalities
TEDHI
- DSHS oversight of web-based hearing database, tracking, and intervention
- Certification of Newborn Hearing Screening Programs
- 99% newborns are screened
- 2014 – 13,789 failed screen (3.5%)
- Only 316 diagnosed (0.079% population)

Newborn Hearing Resource
- www.infanthearing.org
- National Center for Hearing Assessment and Management
- www.babyhearing.org

Texas CCHD reporting to date
- Since September, 2014 when mandated reporting, 164 cases have been reported
- 23 cases, 14% picked up with pulse oximetry screening
- 14, 8.5% had normal screens and then had detection by symptoms
**What you need to do!**

- Know about all the screens for newborns
- Educate potential parents about newborn screens
- Check for results of the screens on your newborns
- Screening does not mean the baby is free from a disease, it means the baby tested at the time did not fall within standard cutoffs.

**What to tell parents**

1. NBS – important state-mandated tests to check baby for rare diseases
2. Newborns can appear healthy
3. Detection avoids illness, developmental delays, death
4. Texas babies tested for blood twice, 24-48 h and 7-14 days – blood drops go on filter paper card
5. Texas babies are screened for hearing impairment and critical congenital heart disease
6. Test results go to birthing facility and to doctor, parents will be notified for out of range results
7. Some babies need more tests
8. Parents decide what to do with blood spots by completing and signing form.

**What happens then?**

- Out-of-range test result
  - DSHS Clinical Care Coordination will contact the baby’s primary care physician to ensure that the baby receives confirmatory testing and treatment, if needed.
  - Along with the condition, act and fact sheets will be sent
  - Early treatment of these disorders can prevent serious complications such as growth problems, developmental delays, deafness, blindness, intellectual disability, seizures, or even early death.
- Panic level Triage
  - NBS RN immediately notifies health-care provider and faxes out of range screen along with ACT and FACT sheets, list of appropriate specialists
  - Health care provider determines tertiary center
  - Will notify family if unable to get primary care provider and direct family to emergency department.

**For more information**

- [http://www.newbornscreening.info/index.html](http://www.newbornscreening.info/index.html)
- Disorder Fact sheets sheets for Primary Care providers
- Disorder Fact sheets for Parents
  - Explanation of disorder, etiology, symptoms, treatment, things to remember
- [https://www.acmg.net/ACMG/Publications/ACT_Sheets_and_Confirmatory_Algorithms](https://www.acmg.net/ACMG/Publications/ACT_Sheets_and_Confirmatory_Algorithms)
- Disorder Act Sheets and Algorithms
- Texas:
  - [http://www.dshs.state.tx.us/newborn/secondary_conditions.aspx](http://www.dshs.state.tx.us/newborn/secondary_conditions.aspx)
### How successful has NBS been?

- From December 2006 to June 2015, Texas NBS has identified and confirmed **5156 cases**.
  - 1954 cases of primary hypothyroidism
  - 781 sickle cell anemia
  - 322 Cystic fibrosis
  - 266 Partial biotinidase deficiency
  - 256 Classical CAH
  - 201 Non Classical CAH
  - 125 Hgb S Beta plus thalassemia
  - 90 Classical MCAD...

### Texas Resources

- [http://www.dshs.state.tx.us/newborn/](http://www.dshs.state.tx.us/newborn/)
- **Newborn Screening Benefits Program**
  - **Eligibility**
    - Infants, children, adults, prioritized by need as funds available
    - Income < 350% federal poverty level
    - Diagnosed with disorder identified by NBS program
    - Bona fide Texas resident
    - Annual recertification
    - No other program providing same service
  - Provides dietary supplements, medications, vitamins, confirmatory testing, evaluation, follow up care

### What’s next?

- Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) Recommended
  - Mucopolysaccharidosis Type I (MPSI) (Hurler’s) (2/14/2015)
  - Adrenoleukodystrophy (X-ALD) (8/27/2015)
  - Awaiting the decision of the Secretary of Health and Human Service, Sylvia Mathews Burwell.

### MPS I

- Autosomal recessive Lysosomal Storage Disorder (LSD) caused by deficiency of α-L-iduronidase (IUDA) enzyme
- Progressive, multisystem disorder
- MS/MS can detect low IDUA enzyme activity
- Diagnosis IDUA enzyme activity measured in leukocytes or skin fibroblasts, <1% activity
- Cannot predict phenotype
- Genotype helpful but >100 known mutations
- Treatment
  - Hematopoietic Stem Cell transplant – early enough can allow individuals to produce endogenous enzyme
  - Enzyme replacement available but does not cross blood brain barrier

### X-ALD

- Peroxisomal d/o affecting adrenal cortex and CNS with VLCFA build up
- Disrupts myelin
- 3 forms: childhood cerebral, adrenomyeloneuropathy, Addison
- Affects 1 in 17,000; more severe and common in males, X-linked
- 20-40% women carriers have symptoms in adulthood
- Mutation ABCD1 gene cause ALDP deficiency
- Treatment for adrenal insufficiency
- Stem cell transplantation may halt progression if diagnosed and treated early

### What’s on the horizon?

- Fabry’s Disease
  - Lysosomal storage disorder (LSD), defect in alpha galactosidase A (GLA) gene
  - X-linked, 1 in every 40-60,000 males
  - Renal failure
  - Onset childhood to adolescence
- Gaucher Disease
  - LSD, defect in beta glucocerebrosidase
  - Autosomal recessive
  - Wide variability in severity and onset
- Niemann Pick
  - LSD, defect acid sphingomyelinase, sphingomyelin accumulation
  - Autosomal recessive
  - 4 types
AAP policy: **Newborn Screening Expands: Recommendations for Pediatricians and Medical Homes—Implications for the System** (2008)

- Proactive role in supporting the performance of the newborn screening system
- Immediate access to clinical and diagnostic information and guidance
- Develop office policies and procedures to ensure that newborn screening is conducted and that results are transmitted in a timely fashion
- Develop strategies to use should these systems fail
- Collaborate with local, state, and national partners for promoting actions and policies that optimize the function of the newborn screening systems and ensure that families receive the full benefit of them.