A New Era in Newborn Screening
Saving Lives, Improving Outcomes

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Program Description
Hear stories from four families whose children's lives were saved from life-threatening diseases by newborn screening, early diagnosis, and effective management. Learn how these children have thrived through actions taken by informed parents working with medical care teams. Meet a star student and athlete with homocystinuria and hear from a mother whose energetic little boy has medium-chain acyl-coA dehydrogenase (MCAD) deficiency. Hear from a woman with Phenylketonuria (PKU) who had a healthy baby because she followed a specific diet and visit children with sickle cell disease (SCD) who are leading active lives due to early detection and good management. Witness the progress of a heelstick blood spot from the hospital, to the laboratory, to the follow-up process. Pediatricians and experts in the field of medical genetics will speak on the diagnosis and management of children with disorders detected by newborn screening programs and the challenges that yet remain. By the end of the program, the panelists will have explored multiple areas of the newborn screening program in the United States, from past and current practices to working toward the development of a national agenda.

Goals
To improve recognition, detection, and diagnosis leading to early intervention and effective management of metabolic disease, endocrine disorders, and hemoglobinopathies in newborns.

Objectives
After viewing this program, participants will be able to:

- Describe the evolution of newborn screening programs in the U.S.
- Discuss the current newborn screening environment and the national agenda.
- Identify newly recognized metabolic disorders for which screening tests are now available.
- Discuss the effect of disorders detected by newborn screening on affected children and families.
- Identify collection, handling and shipping factors that affect test results.
- List three examples of newborn screening tests.
- Explain the significance of an effective follow-up component in the newborn screening system.
- Discuss the diagnosis and management of children detected by these programs.

Target Audience
This program is designed for physicians, nurses, laboratorians, and other health care

professionals serving newborns and their parents in physician offices, hospitals, clinics, and public health settings. It should also of interest to the general public, parents, and policy makers.

Faculty

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Program Guide

I. Medium-chain acyl-coA dehydrogenase (MCAD) deficiency

Listen to Lisa describe Matthew's brush with death in the newborn nursery. Learn how well he is doing now and how easy MCADD is to manage when the child is diagnosed early enough.

II. Evolution of Newborn Screening

Dr. Harvey Levy

In 1934, Dr. Asbjörn Fölling (1888-1973) discovered phenylketonuria (PKU) as a biochemical cause for one type of mental retardation.

In 1953, Dr. Horst Bickel (1918-2000) developed a diet that could prevent the mental retardation of PKU.

The diagnosis of PKU must be made very early in infancy, before signs of developmental delay appear.

In 1961, Dr. Robert Guthrie (1916-1995) developed a simple test to make routine newborn screening for PKU possible. He used the idea of a bacterial inhibition assay that would detect an increase in phenylalanine (Guthrie test) and the filter paper blood specimen (Guthrie specimen).

Dr. Guthrie worked with Dr. Robert MacCready, Director of the Diagnostic Division of the Massachusetts Public Health Laboratories, to try the new test out on a routine basis. Of 53,000 newborns tested in Mass. in 1962, nine infants with PKU were identified (1:6000). At that time the incidence of PKU was assumed to be 1:20,000. Soon, routine screening for PKU spread to other states.

Dr. Guthrie developed other bacterial assays for newborn screening:

- Leucine for Maple Syrup Urine Disease (MSUD)
- Galactose for Galactosemia
- Methionine for Homocystinuria (HCU)

Other newborn screening tests developed over the years include tests for congenital hypothyroidism, sickle cell disease, congenital adrenal hyperplasia, biotinidase deficiency. Today there are more than 30 genetic diseases that can be tested for in the newborn.

III. Current Newborn Screening Environment and the National Agenda

Dr. Michele Lloyd-Puryear

Every state has its own newborn screening (NBS) program that should include testing, information retrieval for screened-positive infants, follow-up, confirmatory diagnosis, treatment plans for long-term care, quality assurance, and education of health care providers and infants.

States differ in how their public health system supports the newborn screening system:

- Some operate within a public health agency, other contract out to academic centers
- All states must maintain quality control for their program
- Different newborn screening policies
- Different laboratory capacities
- Different funding for programs
- All states universally screen for PKU and congenital hypothyroidism
- Most states universally screen for galactosemia
- 45 states universally screen for sickle cell diseases
- States vary considerably for any other conditions

Challenges to state newborn screening programs:

- Ability to screen for many disorders at one time with new technologies – tandem mass spectrometry and DNA-based technology
- Expertise for using new technology?
- Expertise in treating infants identified?

The American Academy of Pediatrics, in 1998, gathered together families, public and private health care professionals, scientists, health policy experts, and industry professionals, called the "Newborn Screening Task Force" to make recommendations that would strengthen the newborn screening system. The report, *Serving the Family From Birth to the Medical Home* was published in the American Academy of Pediatrics, "Pediatrics" supplement, August 2000, Volume 106, Number 2.

The Task Force discovered there was:

- No national oversight
- No consistent approach for follow-up, diagnosis, patient management
- No national standards for treatment, follow-up, quality assurance
- Many state NBS weren't ready for new technologies – lack of funding or expertise
- Treatment of the infants identified by new technologies was a big issue

The Task Force Report contains a national agenda to strengthen NBS programs and suggests that public and private health professionals partner with consumers to continue a national process that:

- Defines responsibilities for federal and state agencies
- Develops regulatory models for NBS systems
- Defines minimum standards
- Creates guidelines and protocol models for health professionals
- Outlines systems of care from infancy to adulthood
- Designs strategies to inform and involve families and the general public
- Provides funds for demonstration projects to evaluate technology, quality assurance, and health outcomes

Disparities between the states are considered the top priority item for the Task Force which recommended the establishment of national standards for:

- Conditions screened in each state
- Storage and use of residual blood spots
- The informed consent/dissent process
- Uniform treatment standards
- Assurances of access to treatment and third party payment

The Task Force Report is the basis for many federal and state activities in NBS:

- Expanding newborn hearing screening programs
- Creating more coordinated infant health programs & information systems
- Increasing pilot newborn screenings for new tests and technologies
- Adding more DNA testing (SCD, CF, congenital hearing loss)
- Researching later-onset disorder screenings (e.g. asthma, diabetes)
- Using tandem mass spectrometry (one sample → many conditions)

Additional questions with new technologies:

- Testing for disorders we can't treat?
- Redefining treatment?
- Testing for disorders we don't understand?

On the national level, funding is now going to the states to evaluate the use of newer technologies and to expert groups to develop policies to bring more uniformity to state screening programs.

Title 26 of the Children's Health Act of 2000 established a new program, "Screening for Heritable Disorders". The Act establishes Federal grant programs that can directly target state programs to enhance, improve, or expand the ability of state and local public health agencies. The states can then provide screening, counseling, and services to newborns and children at risk for heritable diseases. It also establishes grants to states for evaluating the effectiveness of these services in reducing morbidity and mortality rates.

IV. Sickle Cell Disease

Maria describes the effect that sickle cell disease has had on her daughters, Sasha and Kaitlyn Hear how well they are doing thanks to her vigilance and prompt and regular medical care.

V. Heelstick Collection & the Newborn Screening Laboratory

Dr. Kenneth Pass

The three most recent disorders to be added to the NBS screening panels in many states:

1. Cystic fibrosis (CF) – affects lungs and other body systems

2. Congenital adrenal hyperplasia (CAH) – disorder of the adrenal glands that disrupts the Infant's ability to produce hormones that respond to stress and other hormones that regulate sodium and potassium ions. Therefore the baby has a hard time regulating water and electrolyte balance.
3. Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) – deficiency of the enzyme acyl-CoA disrupts the body's ability to mobilize energy from fats during a stressful event, like fasting.

Metabolic disorders detectable by tandem mass spectrometry (MS/MS):

Fatty Acids
- Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency
- Short-chain acyl-CoA dehydrogenase (SCAD) deficiency
- Long-chain hydroxy acyl-CoA dehydrogenase (LCHAD) deficiency
- Very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency
- & others . . .

Organic Acids
- Propionic academia (PPA)
- Glutaric academia, Type I (GA-I)
- Methylmalonic academia (MMA)
- & others . . .

Amino Acids
- Phenylketonuria (PKU)
- Maple Syrup Urine Disease (MSUD)
- Tyrosinemia, types I & II (TYR)
- & others . . .

Multiplex testing – using one blood spot to obtain many results

Some tests look at red blood cell components:
- Transferase = Galactosemia
- Hemoglobin = Sickle Cell Disease (SCD)
- Biotinidase = Biotinidase deficiency

Other tests are serum based:
- Phenylalanine = Phenylketonuria (PKU)
- 17 a-Hydroxyprogesterone = Congenital Adrenal Hyperplasia (CAH)
- Immunoreactive trypsinogen = Cystic Fibrosis (CF)
- T_4 + TSH = Congenital Hypothyroidism (CH)

Analytical tests used:
- Enzyme Immunoassay (EIA)
- Bacterial Inhibition Assay (BIA)
- Isoelectric Focusing (IEF)
- Tandem Mass Spectrometry (MS/MS)
- & others . . .

Small amounts of blood used for testing, from 12 microliters for PKU testing to less than one microliter for DNA testing.

Proper specimen collection is key to obtaining an accurate test result. A short segment of the NCCLS video, *Making a Difference Through Newborn Screening: Blood Collection on Filter Paper* demonstrates a heelstick collection and how to avoid problems in applying blood to filter paper.

Specimen collection for newborn screening generally need to be taken:
- At least 24 hours after birth. Some states require 48 hours.
- Before any transfusions take place

Before discharge from the hospital

Substances that can interfere with test results:
- Antibiotics
- Alcohol on skin
- Carnitine
- Total Parental Nutrition (TPN)
- Latex
- Cake/Coffee/Sugar

Fill in all information requested on the filter paper form.
Dry the specimen properly.
Mail the specimen to the lab promptly – don't hold or batch samples for several days.
Confirm that the specimen has arrived at the lab.

The average time for a screening lab to process results is two days.
In most labs, two different tests are done on the Guthrie spot before abnormal results are reported.
Rapid testing requires rapid notification to start the follow-up process.

VI. Homocystinuria

Listen to Benjamin, a star student and athlete, as he talks about living well with homocystinuria. His parents, Katrina and David, describe his diagnosis and management of the disorder.

VII. Follow-up in Newborn Screening

Sharon Quary

Key factors and components of effective follow-up:
- Appropriately trained personnel knowledgeable about the laboratory and conditions screened for
- Interpretation of screening results
- Make appropriate decisions based on clinical picture
- Communication & customer service skills to explain details about the screening tests and conditions to parents, nurse, and the primary care provider (PCP)
- Resourcefulness to quickly locate the infant and have child assessed for symptoms of condition in question

Case study #1
- 3-day-old female
- TSH > 200 μ IU/mL
- High probability of primary hypothyroidism

Case study #2
- Male, 5 days old @collection
- Positive result for galactosemia
- Elevated metabolites

Establish designated contacts with doctors' offices, health departments, NICU's, medical records, etc.

Obtain follow-up help from parents, relatives, friends, neighbors, hospital departments, health departments, law enforcement agencies, correctional facilities, adoption agencies, businesses, other state NBS programs.

Form an alliance with specialty consultants – geneticist, endocrinologists, metabolic nutritionists, diagnostic testing laboratories.

Patience and persistence are also necessary ingredients for thorough follow-up care.

For some conditions, the follow-up process is essentially a race against the onset of symptoms, especially for:

- Galactosemia
- Maple Syrup Urine Disease (MSUD)
- Congential Adrenal Hyperplasia (CAH)

Case Study #3

- Male, 7 days old @ time of collection
- MSUD = 10 mg/mL
- CAH > 200 ng/dL

VII. Prevention of Maternal Phenylketonuria

Julie discusses living with PKU and how she was able to deliver a healthy son, Luke.

VIII. Diagnosis and Management

Dr. Paul Fernhoff

Newborn screening is a five-part program:

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

The final diagnosis of a disorder usually involves:

- Evaluation by the primary care provider
- Blood sample
- Urine sample

The diagnostic specimens are sent to specialized laboratories, where accurate results can be obtained quickly. For some conditions, such as Maple Syrup Urine Disease, results are need quickly so treatment can begin immediately. For other conditions, such as congenital adrenal hyperplasia, it may be necessary to begin treatment before the final diagnosis is confirmed.

Treatment for the conditions you saw today usually requires lifelong treatment with special medications and often need highly specialized diets as well. Management of these disorders requires the help of many health care specialists who understand the complex medical, nutritional, and psychosocial issues surrounding each disease:

- Clinical and laboratory biochemical geneticists
- Endocrinologists.
- Hematologists
- Metabolic nutritionists
- Neurodevelopmental specialists
- Social workers
- Genetic counselors

Close communication among the families, the primary health care providers and specialists is essential. The goal is to achieve optimal health, growth, and development for the child.

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A child with PKU who is missed by screening is fairly normal for the first several months of life. However, the parents and doctors soon recognize that the child is not growing or developing normally. The untreated, older infant develops:

- Severe skin problems
- Unpleasant "wet fur" odor
- Small head size.
- Irreversible brain damage
- Seizures
- Severe mental retardation.

Immediately after the diagnosis of PKU is confirmed, the child must begin a diet with:

- Very reduced amounts of all natural protein
- Special formula with very low phenylalanine and extra amounts of tyrosine

As a PKU child gets older, his or her diet must be closely monitored. The diet resembles that of a strict vegetarian:

- Little to no meats
- No dairy products
- No eggs
- No fish
- No fowl.

We now know that this diet needs to be followed for life, since if the older child or adult goes off their diet, their blood levels of phenylalanine rise and they may experience late onset neurological and psychiatric problems.

Maternal PKU

It is critical that women with PKU, while in the reproductive age range, stay on diet before and during a pregnancy to prevent damage to their baby: a situation called "Maternal PKU". Although the baby of a PKU mother will usually not have PKU, the high blood phenylalanine levels of a poorly controlled pregnant woman with PKU cross into the fetal circulation and fetal brain and lead to devastating effects. It's been estimated that there is a nearly 90% chance of having either a miscarriage or causing severe damage to the developing baby. With good diet control before and during a pregnancy, women with PKU can have an excellent pregnancy outcome.

Homocystinuria

Homocystinuria is another disorder of amino acid metabolism. If not treated early, affected children appear normal for the first year of life. They then present with:

- Poor growth and development delays
- May have severe seizures
- May develop recurrent blood clots
- Tall and thin body build
- Severe back curvature (scoliosis)
- Dislocated lenses (causing painful glaucoma and eye damage)

Treatment is with a life-long special metabolic formula, a protein restricted diet, extra vitamins and other nutritional supplements.

MCADD

This is the most common disorder of fatty acid metabolism. Most of the babies do well in the nursery and early on at home as long as they are fed regularly they may remain healthy.

If a child with MCADD develops a routine illness and is unable to eat or hold down food:

- Death may occur (previously thought to have Sudden Infant Death Syndrome, SIDS)
- Very low blood sugar and ketones
- Very high ammonia
- Brain swelling and coma

Permanent brain damage

Treatment:

Feed child frequently - reduced fat, high carbohydrate diet
Frequently check the blood glucose
When necessary bring child quickly to the hospital for intravenous glucose and calories
Extra amounts of carnitine.

Carnitine is a naturally occurring substance required in cellular energy metabolism. It helps transfer long-chain fatty acids into the mitochondria or the “power-plants” of cells to increase cellular energy production.

Sickle Cell Disease

Children with sickle cell disease require many specialists and much education of the family. Sickle Cell Disease and its related disorders are not only found in African-American children - all children are tested.

Children with Sickle Cell Disease do well during the first few months of life; however prophylactic penicillin should start by two months of age to prevent infections or sepsis.
As Sickle hemoglobin builds up in their bodies, they begin to have:

Chronic anemia
Recurrent pain attacks or crises due to a blockage of blood flow in vessels anywhere in the body (if a blockage occurs in the brain – transient ischemic attack (TIA) or stroke)
Susceptibility to life-threatening bacterial infections

In addition to care by their primary care provider, children and adults with Sickle Cell Disease are often managed in specialized centers by experienced hematologists.

Parents of children with Sickle Cell Disease learn to recognize the early signs of attacks, make sure that their children get plenty of rest and fluids. The children take prophylactic antibiotics for the first few years of life, get special immunizations to prevent against pneumococcal and other bacterial infections and they take extra folic acid which is needed because of the increased destruction of red blood cells.

Child's transition to adulthood.

During late childhood and early adolescence, the child must begin to assume responsibility for management of their own disorder

Prepare their formula
Take their medications
Comply regularly with record keeping
Keep medical and nutritional appointments
Prepare their special diets
Order out in restaurants
Discuss their special diet and medications with friends

Evaluation

Someone, usually public health officials from each state, needs to evaluate the whole process and effectiveness of the newborn screening program:

Are all babies being screened?
How long does it take for filter paper card samples to reach the screening laboratory?
What percentage of cards is unsatisfactory to test?
How long does it take to find the child, confirm the diagnosis and begin treatment?
How successful is the treatment over the long-term?

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Association of Public Health Laboratories

National Laboratory Training Network

March of Dimes

National Newborn Screening and Genetics Resource Center

American College of Medical Genetics

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Newborn Screening Link List

National and State News

National Newborn Screening and Genetics Resource Center
http://GeNeS-R-US.uthscsa.edu

Maternal and Child Health Bureau
http://www.mchb.hrsa.gov/

Newborn Screening Report Addresses Inconsistencies and Controversies
News Release, American Academy of Pediatrics – August 7, 2000
http://www.aap.org/advocacy/archives/augscreening.htm

Centers for Disease Control and Prevention (CDC)

CDC Newborn Screening Quality Assurance Program
National Center for Environmental Health, Division of Laboratory Sciences
http://www.cdc.gov/nceh/dls/newborn_screening.htm

National Laboratory Training Network
Provides laboratory training courses and an online lending library
http://www.phppo.cdc.gov/nltn/default.asp

Morbidity and Mortality Weekly Report (MMWR)
Using Tandem Mass Spectrometry for Metabolic Disease Screening Among Newborns
http://www.cdc.gov/mmwr/PDF/RR/RR5003.pdf

National Center on Birth Defects and Developmental Disabilities
http://www.cdc.gov/ncbddd/

Information on Disorders and Support Groups

Save Babies Through Screening
http://www.savebabies.org/

Exceptional Parent
http://www.eparent.com/healthcare

Fatty Oxidation Disorders Family Support Group
http://www.fodsupport.org/index.htm

National Coalition for PKU and Allied Disorders
http://www.pku-allieddisorders.org/home.htm

National PKU News
http://www.pkunews.org

Organic Acidemia Association
http://www.oaanews.org/

The Sickle Cell Information Center
The Georgia Comprehensive Sickle Cell Center at Grady Health System
http://www.emory.edu/PEDS/SICKLE/

American Academy of Pediatrics

Health Supervision for Children With Sickle Cell Disease
American Academy of Pediatrics, Pediatrics, Vol 109, #3 March 2002
http://www.aap.org/policy/re1011.html

Maternal Phenylketonuria
American Academy of Pediatrics, *Pediatrics*. Vol 107, #2 February 2001
http://www.aap.org/policy/re0024.html

Association of Public Health Laboratories
http://www.aphl.org

American College of Medical Genetics
http://www.acmg.net

NCCLS
http://www.nccls.org/

March of Dimes

Genetic Education Programs: Online descriptions
http://www.modimes.org/Programs/428.htm

Fact Sheets for consumers and professionals on Newborn Screening, birth defects and genetic disorders. Downloadable at:
http://www.modimes.org/HealthLibrary/fact_sheets.htm

History

PKU Basics on the Net
http://www.fesoc.com/pku/history.htm

PKU - The Beginnings
http://www.pku-allieddisorders.org/guthrie.htm