

# Newborn Screening: Metabolic Conditions

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# Agenda

- NBS history
- Parent stories
- Metabolic disorders overview
  - Genetics
  - Pathophysiology
- How NBS changes lives of people
  - Natural history with and without treatment
  - Treatment options available
- Communicating results to parents
  - Clinical pearls

## **Learning objective:**

- Develop a framework to explain positive NBS test results for a:
  - rare metabolic condition
  - rare endocrine condition
  - rare hematologic condition
  - new condition added to RUSP



# Newborn Screening

- Public health initiative
- Aimed at preventing
  - Mortality
  - Morbidity
  - Disabilities
- Metabolic screening on blood spots
- Other types of screening (e.g. hearing)

# Learning About a NBS Result: a Parent's Perspective



# Why NBS Matters: a Parent's Perspective



# Talking to Parents: An Examples

- *“One of the things I regret is not being here at the time... That’s something I can’t really change and wish I could, because that’s an experience that no mom should have to go through on their own and I’d like to have been here for that”*
  - Father of child with cystic fibrosis
- *“We had a look online... that was quite scary as well, because if you read some of the stuff online, it’s not good and it tells you about life expectancy. That’s one of the first things that comes up and then you start to think....”*
  - Mother of child with cystic fibrosis

# The NBS Starting Point: PKU

- 1930's
  - PKU identified as a cause of intellectual disability (George Jervis)
  - Early treatment could prevent symptoms (Horst Bickel)
- 1958: bacterial inhibition assay developed (Robert Guthrie)
- 1961: local (NY) newborn screening for PKU started
- 1962: state-wide screening for PKU began in MA with support from the National Association for Retarded Children



# Core Recommended Uniform Screening panel (RUSP)

## Metabolic disorders:

- Propionic acidemia
- Methylmalonic acidemia
- Isovaleric acidemia
- 3-Methylcrotonyl-CoA carboxylase deficiency
- 3-Hydroxy-3-methylglutaric aciduria
- Holocarboxylase synthase deficiency
- $\beta$ -Ketothiolase deficiency
- Glutaric acidemia type I
- Carnitine uptake defect/carnitine transport defect
- Medium-chain acyl-CoA dehydrogenase deficiency
- Very long-chain acyl-CoA dehydrogenase deficiency

- Long-chain L-3 hydroxyacyl-CoA dehydrogenase def.
- Trifunctional protein deficiency
- Argininosuccinic aciduria
- Citrullinemia, type I
- Maple syrup urine disease
- Homocystinuria
- Classic phenylketonuria
- Tyrosinemia, type I

## Endocrine Disorders

- Primary congenital hypothyroidism
- Congenital adrenal hyperplasia

## Hematological Disorders

- S,S disease (Sickle cell anemia)
- S,  $\beta$  thalassemia
- S,C disease

## Other

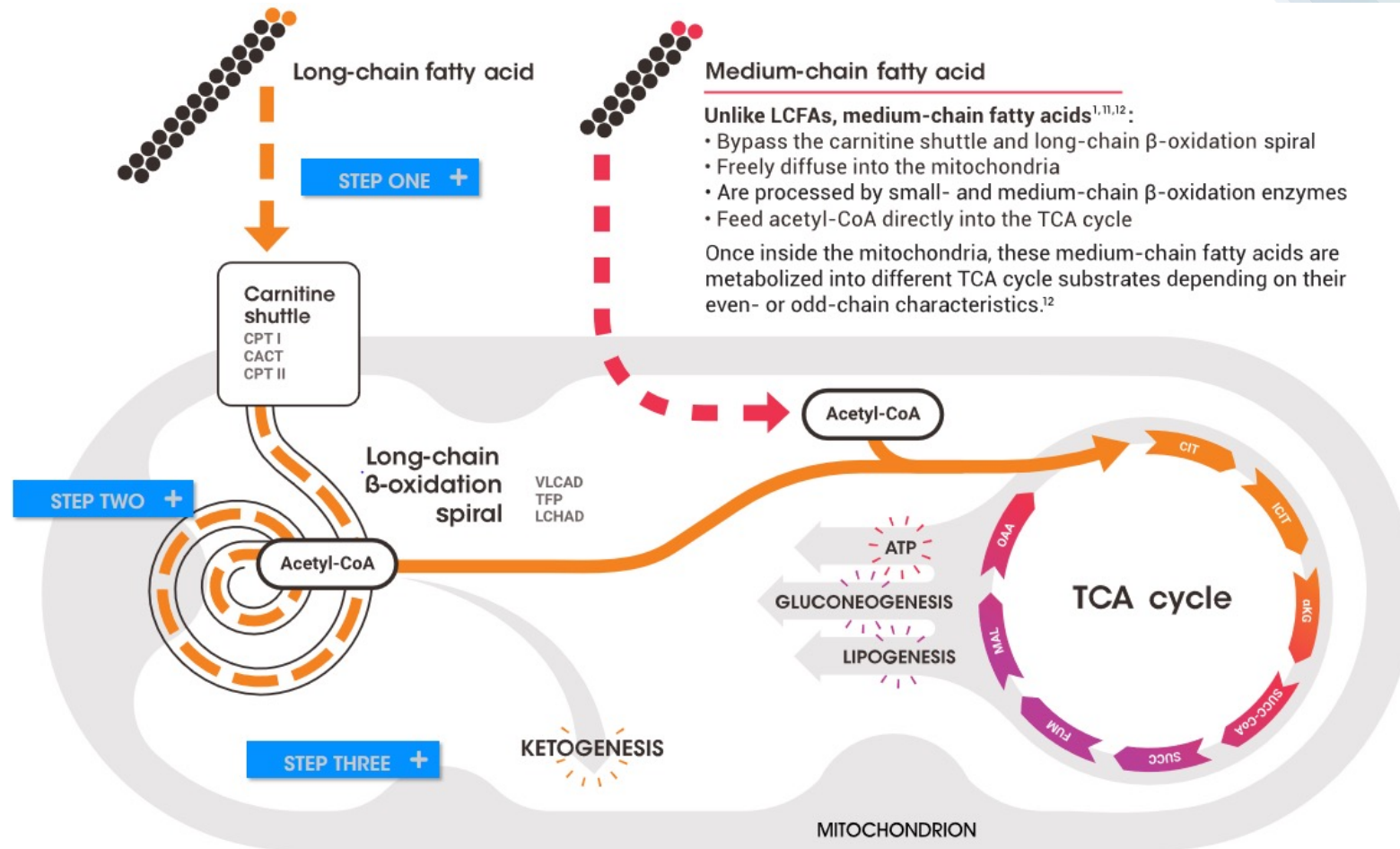
- Biotinidase deficiency
- Critical congenital heart disease
- Cystic fibrosis
- Classic galactosemia
- *Pompe disease*
- Hearing loss
- *Severe combined Immunodeficiencies*
- *MPS Type 1*
- *X-linked Adrenoleukodystrophy*
- *Spinal Muscular Atrophy*

# Metabolic Disorders

## Metabolic disorders:

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# Metabolic Disorders are Complicated



# NBS Changes Lives: PKU

- Prevents devastating neurologic symptoms
- Treatment is lifelong
- Impacts patient and family
- Requires a knowledgeable team to optimize outcome
- New medicines on the horizon

## Phenylalanine hydroxylase deficiency: diagnosis and management guideline

Jerry Vockley, MD, PhD<sup>1,2</sup>, Hans C. Andersson, MD<sup>3</sup>, Kevin M. Antshel, PhD<sup>4</sup>, Nancy E. Braverman, MD<sup>5</sup>, Barbara K. Burton, MD<sup>6</sup>, Dianne M. Frazier, PhD, MPH<sup>7</sup>, John Mitchell, MD<sup>8</sup>, Wendy E. Smith, MD<sup>9</sup>, Barry H. Thompson, MD<sup>9</sup> and Susan A. Berry, MD<sup>10</sup>; For the American College of Medical Genetics and Genomics Therapeutic Committee

**Disclaimer:** This guideline is designed primarily as an educational resource for clinicians to help them provide quality medical services. Adherence to this guideline is completely voluntary and does not necessarily assure a successful medical outcome. This guideline 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 clinician should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. Clinicians are encouraged to document the reasons 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. It also would be prudent to consider whether intellectual property interests may restrict the performance of certain tests and other procedures.

Phenylalanine hydroxylase deficiency, traditionally known as phenylketonuria, results in the accumulation of phenylalanine in the blood of affected individuals and was the first inborn error of metabolism to be identified through population screening. Early identification and treatment prevent the most dramatic clinical sequelae of the disorder, but new neurodevelopmental and psychological problems have emerged in individuals treated from birth. The additional unanticipated recognition of a toxic effect of elevated maternal phenylalanine on fetal development has added to a general call in the field for treatment for life. Two major conferences sponsored by the National Institutes of Health held >10 years apart reviewed the state of knowledge in the field of phenylalanine hydroxylase deficiency, but there are no generally accepted recommendations for therapy. The purpose of this guideline is to review the strength of the medical literature relative to the treatment of phenylalanine hydroxylase deficiency and to develop recommendations for diagnosis and therapy of this disorder. Evidence review from the original National Institutes of Health consensus conference and a recent update by the Agency for Healthcare Research and Quality was used to address key questions in the diagnosis and treatment of phenylalanine hydroxylase deficiency by a working group established by the American College of Medical Genetics and Genomics. The group met by phone and in person over the course of a year to review these reports, develop recommendations, and identify key gaps in our knowledge of this disorder.

Above all, treatment of phenylalanine hydroxylase deficiency must be life long, with a goal of maintaining blood phenylalanine in the range of 120–360  $\mu\text{mol/L}$ . Treatment has predominantly been dietary manipulation, and use of low protein and phenylalanine medical foods is likely to remain a major component of therapy for the immediate future. Pharmacotherapy for phenylalanine hydroxylase deficiency is in early stages with one approved medication (sapropterin, a derivative of the natural cofactor of phenylalanine hydroxylase) and others under development. Eventually, treatment of phenylalanine hydroxylase deficiency will be individualized with multiple medications and alternative medical foods available to tailor therapy. The primary goal of therapy should be to lower blood phenylalanine, and any interventions, including medications, or combination of therapies that help to achieve that goal in an individual, without other negative consequences, should be considered appropriate therapy. Significant evidence gaps remain in our understanding of the optimal therapies for phenylalanine hydroxylase deficiency, nonphenylalanine effects of these therapies, and long-term sequelae of even well-treated disease in children and adults.

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**Key Words:** maternal PKU; phenylalanine hydroxylase deficiency; phenylketonuria; sapropterin; therapy

Phenylalanine hydroxylase (PAH) deficiency, traditionally called phenylketonuria (PKU) due to characteristic phenylketones accumulating in the urine of affected individuals, has a significant place in history as the first inborn error of metabolism identified through population-based screening, initiating

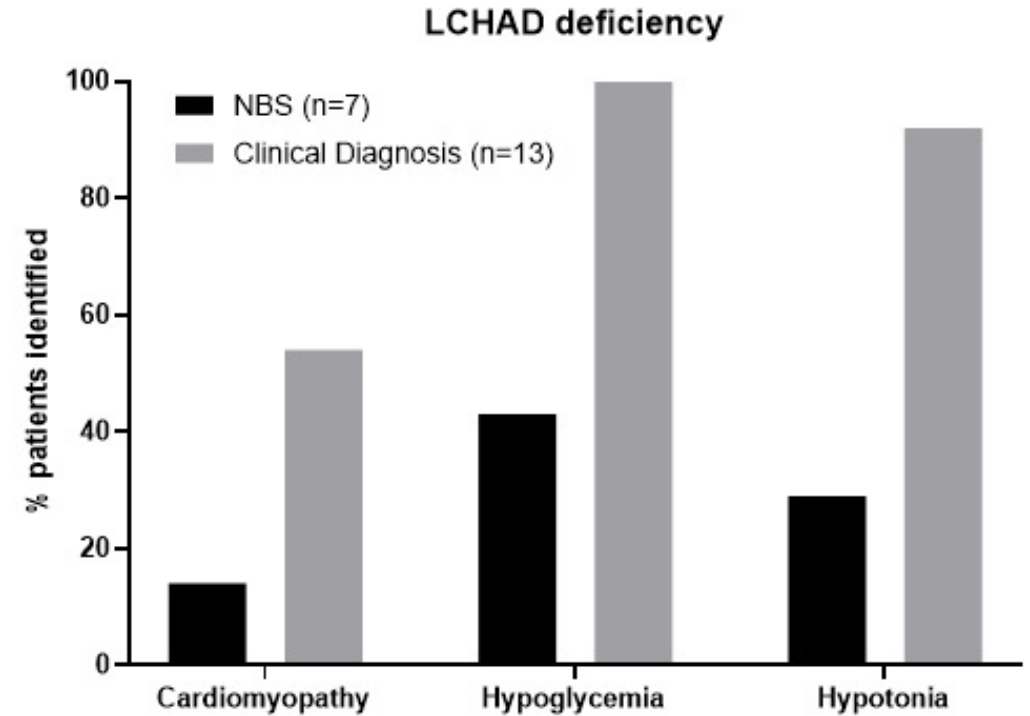
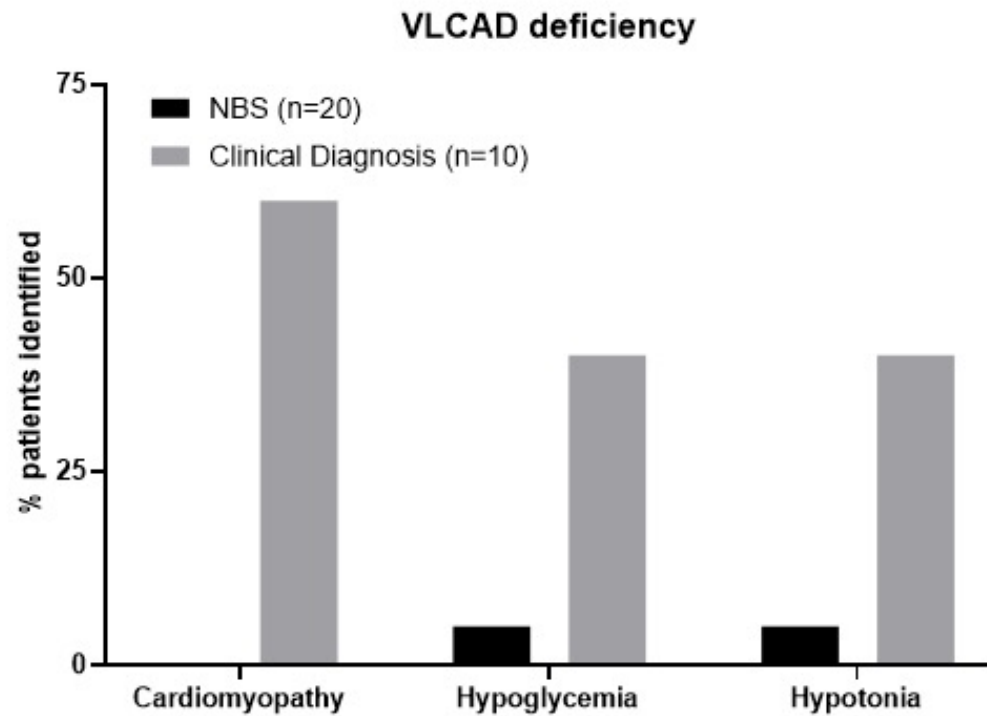
a new era in the diagnosis and treatment of genetic disorders. PKU was first described in 1934 by the Norwegian physician Asbjørn Fölling, but it was not until the mid-1950s that a patient with PAH deficiency was treated with a low phenylalanine (PHE) diet. Although this first patient already had irreversible

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# NBS Improves Outcomes



Marsden D, Bedrosian CL, and Vockley J. Impact of newborn screening on the reported incidence and clinical outcomes associated with medium- and long-chain fatty acid oxidation disorders. *Genet Med.* 2021;23(5):816-29.

# Responding to the Call

- Experts involved in newborn screening for endocrine, hematological, genetic, and metabolic diseases
- ACT sheets and diagnostic algorithms
- ACT sheets include
  - Information about the analytes and their clinical significance
  - Links to informational resources
  - Links to websites of regional subspecialists for consultation and referral
- You may need to be the front line returning results

The screenshot shows the homepage of the American College of Medical Genetics (ACMG). The header includes the ACMG logo and the tagline "Medical Genetics: Translating Genes Into Health®". A search bar is located in the top right corner. Below the header is a navigation menu with links for HOME, JOIN ACMG, FOUNDATION, LINKS, CALENDAR, FIND A GENETICIST, LOGIN, and LOGOFF. A secondary menu includes About ACMG, Newsroom, ACMG Events, Publications, Education, Products, Resources, Committees, and Members Only.

The main content area features a "Welcome" message: "Welcome to the American College of Medical Genetics. The ACMG provides education, resources and voice for the medical genetics profession." Below this are two columns: "SPOTLIGHT" and "ACMG WEBINAR".

**SPOTLIGHT:** A section titled "FREE PUBLIC/PROFESSIONAL FORUM ON NBS BLOOD SPOTS, GENETIC RESEARCH AND PRIVACY". It describes a forum sponsored by the ACMG and Genetic Alliance, held in Bethesda, MD, and broadcasted online. It also mentions a new ACMG radio program titled "New ACMG Radio Program Tackles NBS Dried Blood Spot Issue" featuring ACMG Executive Director Michael S. Watson, PhD, FACMG and Dr. Alan Fleischman, Medical Director of the March of Dimes Foundation.

**ACMG WEBINAR:** A section titled "ACMG Efforts Help Public to Better Understand Genetics". It states that it is important for both the public and healthcare professionals to have accurate information about genetics and to understand how genes affect our health. It mentions that the ACMG continues its efforts to raise awareness about genetic healthcare through media, educational opportunities, and its regional and advocacy efforts. It also includes a play button icon and text: "Click the play button, above, to view the ACMG webinar 'How Genetic Discoveries are Being Translated Into Better Health.' This lively discussion, moderated by executive director Michael S. Watson, PhD, FACMG; president-elect Bruce R. Korf MD, PhD, FACMG; and genetic counselor and Special Assistant to the Director, ACMG Judith Benkendorf, MS, CGC, illustrates what is currently happening in genetic medicine. The webinar included discussions about some of the most exciting developments on the front lines of clinical genetics from the ACMG for 2009 and beyond."

On the right side of the page, there is a "NEWS RELEASES" section with several headlines, including "The HRSA Genetics Collaboratives Are Bringing Genetic and NBS Services to Local Communities Around the US", "Newborn Screening Blood Spots: How Can We Preserve Both This National Treasure and Patient Privacy?", and "Jane Dabroth, CEM, CMP joins American College of Medical Genetics Staff". Below the news releases are several call-to-action buttons: "ACT Sheets & Confirmatory Algorithms", "Order your 2009 GRC Syllabus", "National Coordinating Center", "Donate to the ACMG Foundation", and "ACMG 2007 Salary Survey Final Report".

# Best practices to talk to parents (PCP)

- First contact is likely to be by phone
- Have your info on the disease available (ACT sheet)
- Know your referral lines
- Keep details to a minimum
- Defer to specialist
- Remind them that a NBS positive test is only preliminary
- Remind them that NBS panel is for conditions that can be treated

# Best practices to talk to parents

- First meeting is overwhelming. Don't add to the problem!
  - Information on the web may be outdated. It will be extensive
  - Parents will likely only hear a small portion of what you say
- NBS response should be a team approach
  - MD (Geneticist, endocrinologist, neurologists, etc)
  - Genetic Counselor
  - Metabolic Dietitian
- Some diseases need urgent treatment, which should be the focus of the initial meeting
- “No one in my family has ever had anything like this.”

# Clinical Pearls

- Metabolic disorders are a major part of NBS
- NBS can change lives of people with metabolic disorders
- Past experiences with parents shows there is room for improvement in communication
- Parents hear what they hear, not necessarily what you say
- Communicating results to parents
  - Do your homework
  - Empathy
  - Best practices