Newborn Screening: Talking to Parents

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Disclosures

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Rationale of NBS

"The goal of newborn screening is early detection of children at increased risk for selected metabolic or genetic diseases so that medical treatment can be promptly initiated to avert metabolic crises and prevent irreversible neurological and developmental sequelae"

Newborn Screening in New York -
A Guide for Health Professionals 1991

Core Recommended Uniform Screening panel (RUSP)

Metabolic disorders:

- Organic Acidemias
- Propionic acidemia
- Methylmalonic acidemia
- Isovaleric acidemia
- 3-Methylcrotonyl-CoA carboxylase deficiency
- 3-Hydroxy-3-methyglutaric aciduria
- Holocarboxylase synthase deficiency
- ß-Ketothiolase deficiency
- Glutaric acidemia type I
- Fatty Acid Oxidations Disorders
- 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
- Aminoacidopathies
- Argininosuccinic aciduria
- Citrullinemia, type I
- Maple syrup urine disease
- Homocystinuria
- Classic phenylketonuria
- Tyrosinemia, type I

Endocrine Disorders

- Primary congenital hypothyroidism
- Congenital adrenal hyperplasia

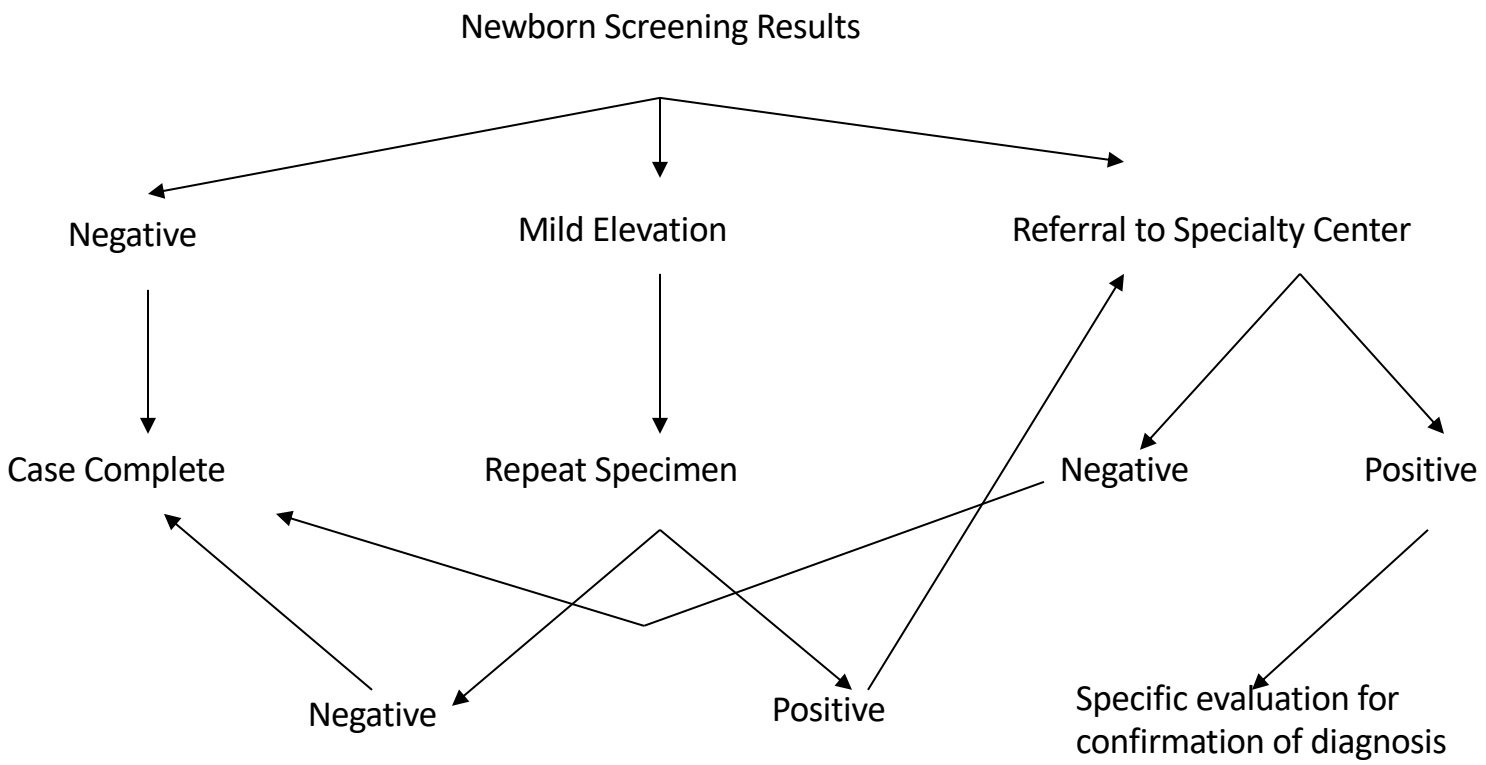
Hematological Disorders

- S,S disease (Sickle cell anemia)
- S, βeta-thalassemia
- S,C disease

Other

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

The Algorithm

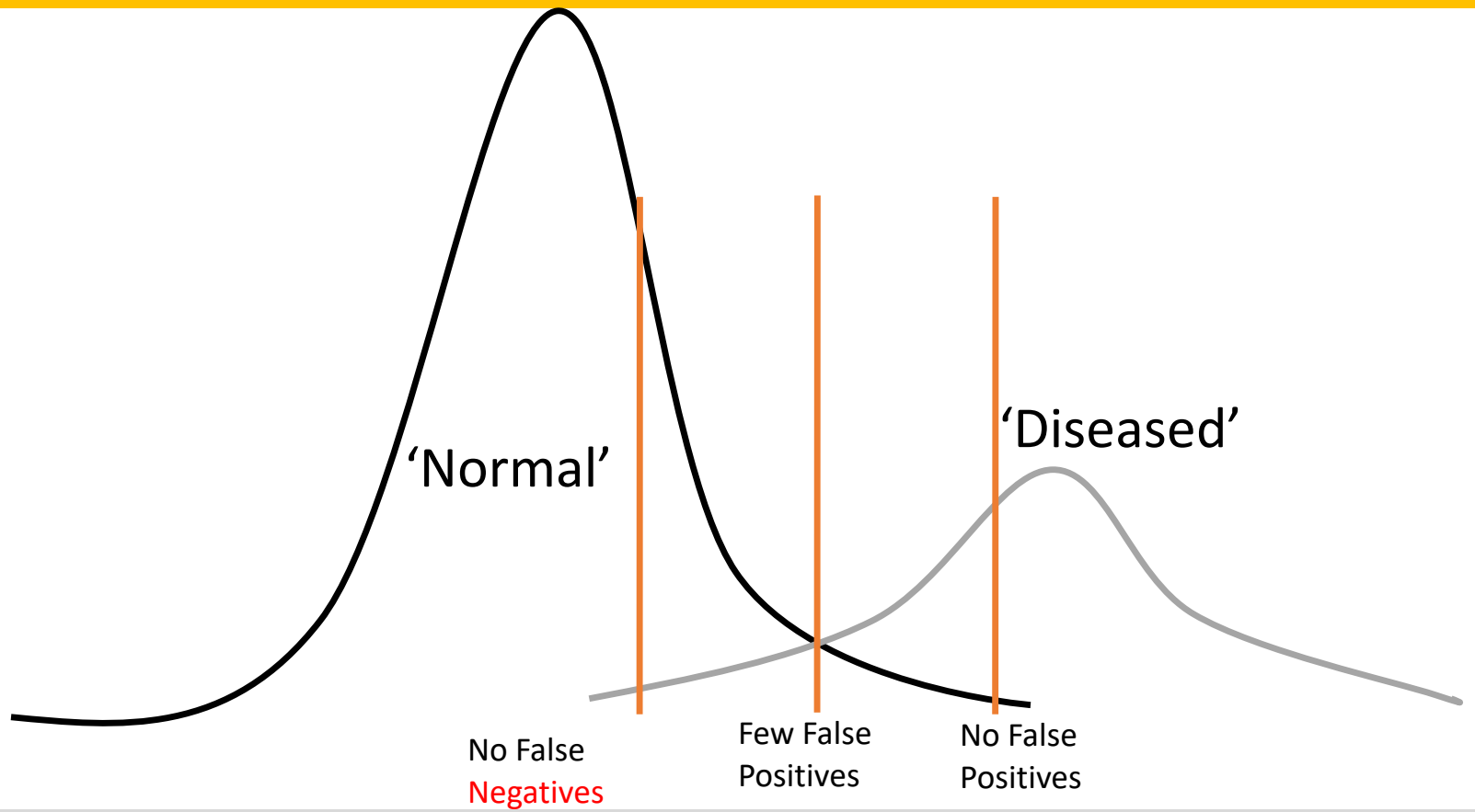


Accuracy

- Sensitivity = likelihood infant who HAS the disease will have POSITIVE test result[1,2]
  - Ideally, a test should approach 100% sensitivity (0 false negative results) by reliably detecting almost all true cases – TP/TP+FP
- Specificity = likelihood infant who does NOT HAVE the disease will have NEGATIVE test result[1,2]
  - As sensitivity increases, false-positive tests increase, resulting in unnecessary follow-up tests (higher costs) and cause parents undue worry – TN/TN + FN
- Positive predictive value (PPV) = proportion of infants with positive test results who HAVE the disease[1,2]
  - eg, a PPV of 10% = 10 patients require follow-up test for 1 infant who HAS the disease to be diagnosed
  - PPV varies by disease; depends on cutoff values (which may vary by state)
  - We don't want to miss a case, but that comes at the cost of an increased number of false positives!

1. Kronn D. *Neoreviews*. 2019;20(5):e280. **2.** Kwon C and Farrell PM. *Arch Pediatr Med*. 2000;154:714.

Accuracy



Kronn D. *Neoreviews*. 2019;20(5):e280-e291.

Accuracy: New York State 2014 (2016)

Screening Results	Actionable 2014 / 2016	Screen Positive 2014 only	Confirmed Cases 2014 / 2016
Phenylketonuria	21 / 22	144	11 / 11
Sickle Cell	145 / 117	144	132 / 93
Severe combined immunodeficiency	109 / 120	532	5 / 9
Krabbe disease	44 / 45	44	1 / 7
Congenital adrenal hyperplasia	290 / 143	2015	15 / 10
Pompe disease	9 / 35	-	1 / 9 (2 infantile, 7 adult-onset)
Aldrenoleukodystophy	19 / 15	-	8 / 5 (3 male, 1 female carrier, 1 other)

Newborn screening program: 2014 annual report. New York State Department of Health. Accessed Jan 7, 2022. https://www.wadsworth.org/sites/default/files/WebDoc/329548136/NBS_annual_2014.pdf .
Newborn screening program: 2016 annual report. New York State Department of Health. Accessed Jan 7, 2022. https://www.wadsworth.org/sites/default/files/WebDoc/445034535/2016%20Annual%20final%20May.pdf

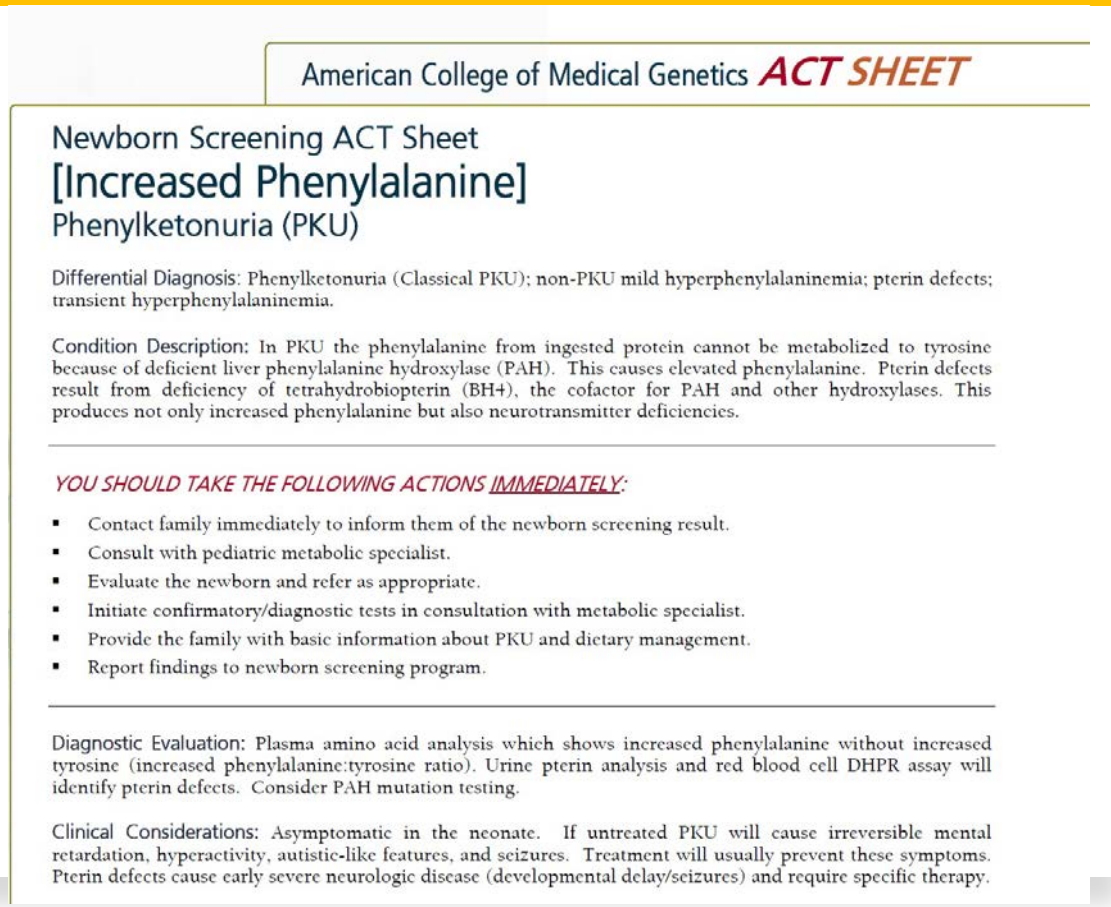
Timliness

- Presumptive positive results for time-critical conditions should be communicated immediately to the newborn's healthcare provider but no later than five days of life.
- Presumptive positive results for all other conditions should be communicated to the newborn's healthcare provider as soon as possible but no later than seven days of life.
- All NBS tests should be completed within seven days of life with results reported to the healthcare provider as soon as possible.

- In order to achieve the above goals:
  - Initial NBS specimens should be collected in the appropriate time frame for the newborn's condition but no later than 48 hours after birth, and
  - NBS specimens should be received at the laboratory as soon as possible; ideally within 24 hours of collection.

Timliness

- The American College of Medical Genetics has created “ACT Sheets” which provide concise guidance on immediate next steps for many NBS conditions
- https://www.acmg.net/



American College of Medical Genetics **ACT SHEET**

Newborn Screening ACT Sheet

[Increased Phenylalanine]

Phenylketonuria (PKU)

Differential Diagnosis: Phenylketonuria (Classical PKU); non-PKU mild hyperphenylalaninemia; pterin defects; transient hyperphenylalaninemia.

Condition Description: In PKU the phenylalanine from ingested protein cannot be metabolized to tyrosine because of deficient liver phenylalanine hydroxylase (PAH). This causes elevated phenylalanine. Pterin defects result from deficiency of tetrahydrobiopterin (BH4), the cofactor for PAH and other hydroxylases. This produces not only increased phenylalanine but also neurotransmitter deficiencies.

YOU SHOULD TAKE THE FOLLOWING ACTIONS IMMEDIATELY:

- Contact family immediately to inform them of the newborn screening result.
- Consult with pediatric metabolic specialist.
- Evaluate the newborn and refer as appropriate.
- Initiate confirmatory/diagnostic tests in consultation with metabolic specialist.
- Provide the family with basic information about PKU and dietary management.
- Report findings to newborn screening program.

Diagnostic Evaluation: Plasma amino acid analysis which shows increased phenylalanine without increased tyrosine (increased phenylalanine:tyrosine ratio). Urine pterin analysis and red blood cell DHPR assay will identify pterin defects. Consider PAH mutation testing.

Clinical Considerations: Asymptomatic in the neonate. If untreated PKU will cause irreversible mental retardation, hyperactivity, autistic-like features, and seizures. Treatment will usually prevent these symptoms. Pterin defects cause early severe neurologic disease (developmental delay/seizures) and require specific therapy.

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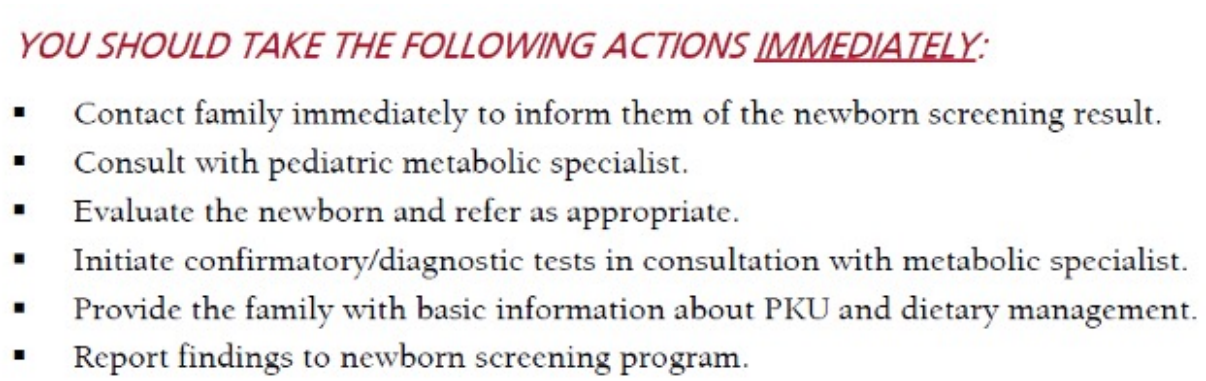

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Best Practices for Contacting Parents

- Ideally call parents and bring them in that day or the following morning
- Avoid calling on Friday if the patient won't be seen till Monday, in that case we call the family on Sunday afternoon with the appointment for the following day
- HAVE ESTABLISHED PROTOCOLS

Establishing Protocols and Communication Channels

- Having established protocols and communication channels in place will speed initiation of appropriate treatment
  - Communication between primary care and specialist when needed
  - Performing follow-up diagnostic tests to confirm NBS finding
  - Discussion with parents/caregivers
  - Developing a treatment plan
  - Initiation of treatment when appropriate

Tips for Talking to Parents

- Result of NBS are elevated and we need to see the patient to repeat testing
- Try not to discuss the specific disorder over the phone; the doctor will explain the disorder when they see the parents in the office
- The screen is not a diagnosis, the physicians need to see the baby

Advice to Physicians from a Parent

Video link: https://vimeo.com/657131808/f3da43942e

Clinical Pearls

- NBS matters
- NBS can change lives
- Preliminary results are preliminary. NBS has its limitations
- Best practices for responding to NBS results need to be be established, including contacting and talking with parents and other health care specialists
- Importance of having management sheets available to determine next steps for all NBS conditions