Navigating Newborn Screening

Where We Are, What's on the Horizon

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UMKC

BEST CHILDREN'S HOSPITALS

Learning Outcomes

- **Describe the rationale for universal newborn screening**
- **List the types of disorders on universal newborn screening panels**
- **Outline the steps required for working up an abnormal newborn screen**

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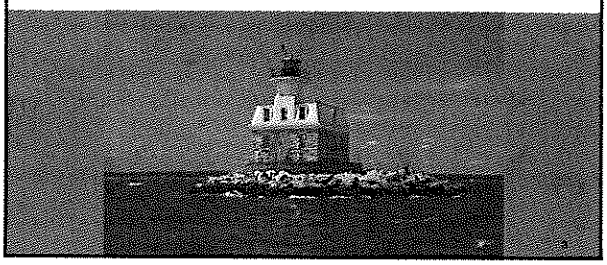
How We Got Here



What is the rationale for universal newborn screening?

a) To determine whether screening tests are effective
b) To determine how many infants per year are born with inherited diseases
c) To diagnose infants and initiate treatment before they become ill
d) To identify infants who are carriers of genetic disorders

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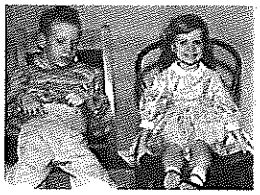
A Brief History of NBS: PKU

- Diagnosis prior to idea of NBS
  - Workup of ID
  - Workup of neuro symptoms
  - Workup because older sibling had PKU



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Universal NBS for PKU

- Diagnose before symptomatic
- Early initiation of treatment
- Need a screening test
- Need everyone to be screened
- Some states start NBS for PKU in 1963

Dr. Robert Guthrie

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Early 2000s: Expansion of NBS

- HRSA Maternal and Child Health Bureau
- ACMG commissioned to assemble an expert panel
- Identify conditions that should be screened
- Creation of the Recommended Uniform Screening Panel (RUSP)

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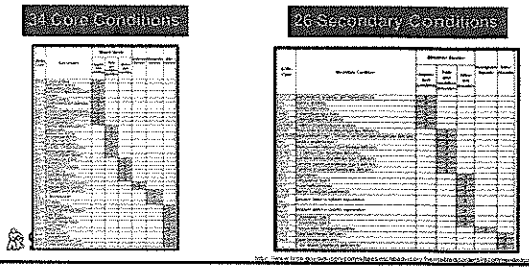
Recommended Uniform Screening Panel



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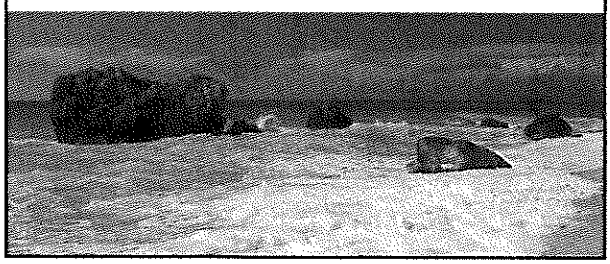
Where We Are



Kansas and Missouri screen for cystic fibrosis.

a) True

b) False

TRUE

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Kansas and Missouri screen for Fragile X Syndrome.

a) True

b) False **FALSE**

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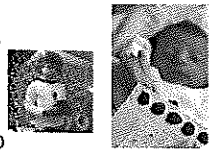
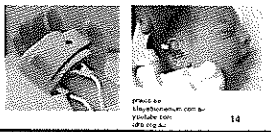
Types of Conditions



- Endocrine
- Hemoglobinopathies
- Cystic Fibrosis
- Inborn errors of metabolism
- SCID
- CCHD
- Congenital hearing loss



73% of RUSP Core
92% RUSP 2°

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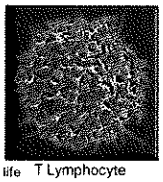
Severe Combined Immunodeficiency

- Impairment of T and B lymphocytes
- Newborns with SCID healthy-appearing at birth
  - Autosomal recessive or X-linked
- If unrecognized and untreated
  - Frequent viral, bacterial, and fungal infections
  - If unrecognized and untreated, death in first two years of life
- Bone marrow transplant can treat most patients



T Lymphocyte

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Severe Combined Immunodeficiency

- Contact Immunology – flow cytometry
- Contact family same day
  - No live virus vaccines for infant or contacts
  - Avoid sick contacts
  - Practice good handwashing
- See infant within 2 days – no waiting room, wear PPE

David Vetter

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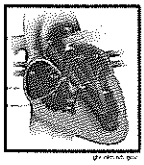
Critical Congenital Heart Defects

- Best at detecting cyanotic heart disease
  - Decreased pulmonary blood flow
  - Mixed blood flow
- Estimated 50% of cases missed
  - Mostly acyanotic lesions



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Mahle WT et al. *Pediatrics* 2009

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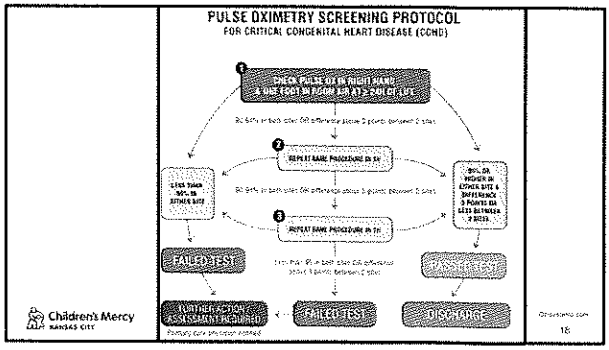

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Inborn Errors of Metabolism

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Categories of IEM

Disorder Type	Prototype
Fatty acid oxidation defects	Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency
Organic acidemias	Methylmalonic acidemia (MMA)
Amino acid disorders	Phenylketonuria (PKU)
Urea cycle defects*	Citrullinemia
Lysosomal Storage Disorders	Pompe disease
Other	Biotinidase deficiency Galactosemia (GALT deficiency)

*OTC deficiency is not on newborn screen except in CA and CT

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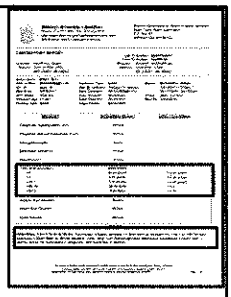
Notification

- State contacts PCP
- Notification of referral center
  - Kansas – Lab **does not** notify
  - Missouri – Lab **does** notify
    - Exception: SCID – PCP **must** contact Immunology at treatment center
- Contacting treatment center recommended



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Contact us!

Meghan Strenk Randi Hanson
Certified Genetic Counselors

- Fax us the screen
- Talk with our friendly genetic counselors
- Counselors will confer with metabolic physician
- Counselors will call you back with recommendations

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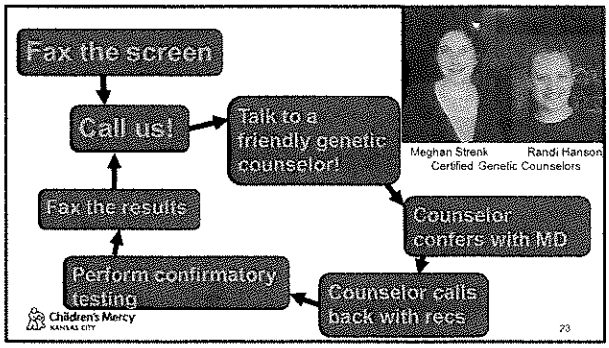

Fatty Acid Oxidation Disorders

- Risk of decompensation with fasting or illness
- Hypoglycemia, lethargy, low ketones
- Long-chain disorders – can have cardiac, muscle complications
- MCAD – liver failure

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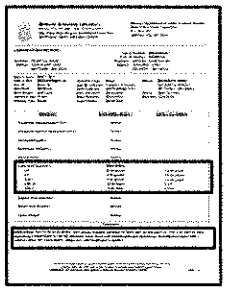
Case - MCAD

- Fatty acid oxidation disorder
- Make sure baby is well
- Avoid fasting: feed every 3 hrs ATC
- Minimum workup:
  - Plasma acylcarnitine profile
  - Urine organic acids
  - Urine acylglycines



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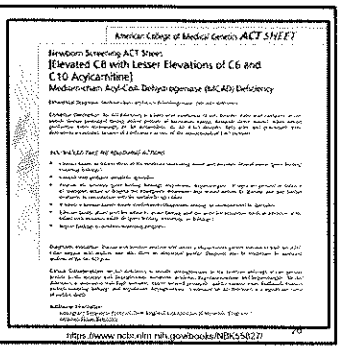
ACT SHEET

- ACMG
- Actions to take
- Diagnostic evaluation
- Clinical considerations
- Additional resources



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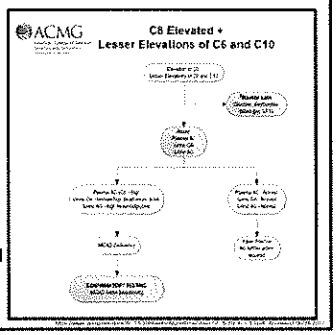
https://www.ncbi.nlm.nih.gov/books/NBK558227

Algorithm

- Analyte(s) flagged
- Confirmatory labs
- Interpretation of results
- Next steps
- Helps to insure ordering appropriate tests



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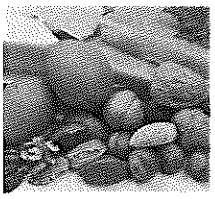
Amino Acid Disorders

- PKU
- Homocystinuria
- Maple syrup urine disease
- Tyrosinemia
- Two urea cycle disorders: Citrullinemia, ASA



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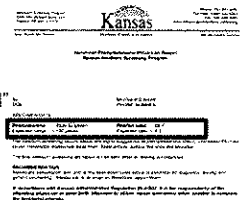
Case - PKU

- Premature infant
- Initial screen < 24 hours: "normal"
- 2nd screen at DOL 6: abnormal!
- ACMG Practice Guideline
  - Initiate treatment in first week
  - Achieve treatment levels by two weeks



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Vockley et al *Genet Med*

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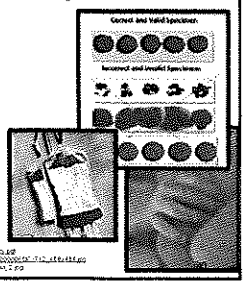
Appropriate Reasons to Repeat NBS

- Reasons states ask for a repeat:
  - Appropriate protocol for condition
  - Unsatisfactory sample
  - Screen performed too early (<24 hrs)
  - Infant too young for test (LSDs)
  - History of transfusion (Hb, GALT)
  - "Low risk" result for certain conditions



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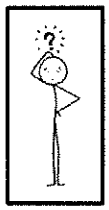
Risks of Repeating Screen on a Referral



- Delay of diagnosis
- Delay of treatment
- Missed diagnosis
- One analyte = multiple conditions
  - Additional tests to differentiate
- Repeat NBS = entire screen

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Disorders Screened with Enzyme Assays

- Lysosomal storage disorders
  - Fabry
  - Gaucher
  - Hurler
  - Krabbe
  - Pompe

- Galactosemia
  - GALT deficiency
- Biotinidase deficiency

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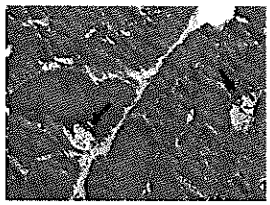
GSD II – Pompe Disease

- 1:40,000 in US
- Deficiency of acid α-glucosidase
- Lysosomal glycogen accumulation
  - Myopathy, cardiomyopathy
  - Respiratory muscle weakness
- Spectrum of disease
- Enzyme replacement therapy
  - Early treatment = better outcome



https://commons.wikimedia.org/wiki/File:Pompe_vacuoles.jpg Jensflorian, H&E

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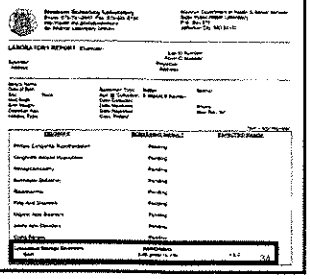
Case - GSD II

- Full-term male infant
- Screen reported DOL 5
- PCP and family contacted
- Specialized testing
  - GAA enzyme assay, molecular testing
  - Echo and EKG required



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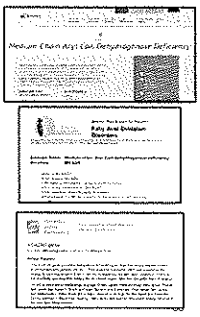
Educational Materials



- Baby's First Test
  - Conditions by State
  - Links to State NBS Brochures
- STAR-G
- Genetics Home Reference

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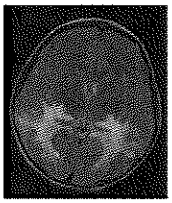
What's on the Horizon

Addition of RUSP Conditions

- Kansas working on SCID
  - MPSI (Hurler) most likely next in line

- X-linked ALD



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Conditions with New Treatments

- Spinal muscular atrophy
  - Nusinersen approved in **December 2016**
  - Missouri first state to have law passed **June 2017**
  - NBS test piloted in Taiwan – Chien et al. *J. Pediatr* **2017**

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- Duschenne MD – Eteplirsen
  - Exon 51 deletion
- MPS II – idursulfase
- MPS IVA – elosufase alfa
- MPS VI – galsulfase
- Wolman – sebelipase alfa

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End Diagnostic Odyssey?

- Fragile X Syndrome
  - Average 3 yrs at diagnosis
- Late diagnosis
  - "Odyssey"
  - Delay of interventions
  - Lost opportunity for prenatal/preconception diagnosis

Children's Mercy KANSAS CITY Bailey DB Jr et al. *Pediatrics* 2017

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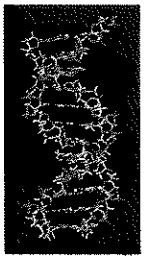
Expansion of DNA Testing?

- NSIGHT Study – Genome as NBS tool
- Instruments, people, training =

- Doesn't predict function
- Ethical issues
  - Loss of future autonomy for infant
  - Carrier status
  - Adult onset conditions



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Summary

- **Newborn screening allows for prompt identification and treatment of presymptomatic infants**
- **Workup algorithms and disorder-specific information sheets are available**
- **Newborn screening panels will continue to increase in size and scope with time**

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Acknowledgements

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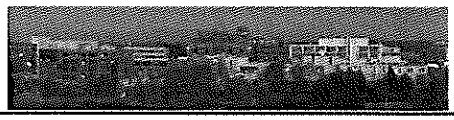
Kansas Department of Health and Environment NBS Lab
Patients and Families



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Resources/References

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