Complications of Prematurity and Newborn Screening Test Performance

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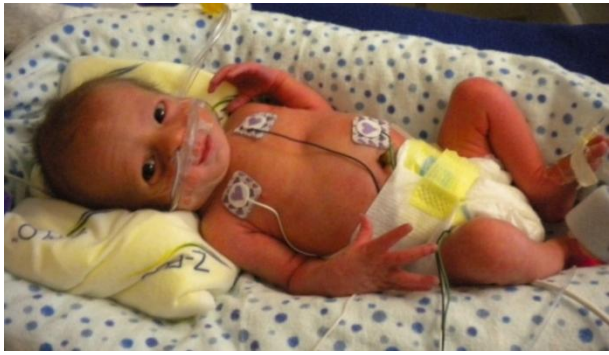
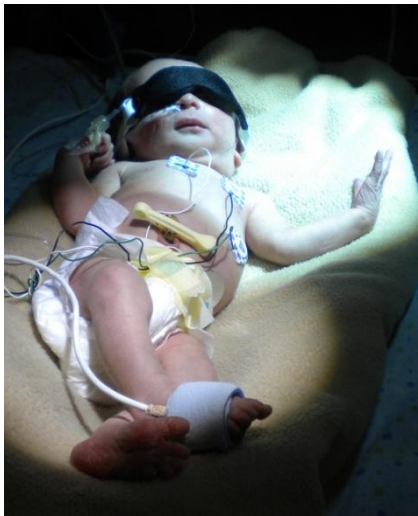
Preterm Birth



- Preterm Birth (gestation <37 weeks)
  - ~12% of infants in US are born preterm
  - 34 – 36 weeks: high numbers with short-term morbidities
  - <33 weeks: biggest impact on mortality and long term outcomes

- Premature infants are at increased risk for:
  - Respiratory distress
  - Jaundice
  - Sepsis
  - Developmental origins of adult disease



Newborn Screening and Preterm Birth

- Preterm and Low Birth Weight Infants have:
  - Higher false positive rates on NBS
  - Higher 17-OHP
  - Higher Amino Acids (generally)
  - Lower medium and long chain acylcarnitines (generally)
  - Lower TSH*

Gestational Age	CAH	MS/MS	Total
24-32 wk	8.9%	15.2%	22.9%
32-36 wk	4.3%	1.7%	6.8%
37-42 wk	0.2%	0.3%	1.5%

Data from Iowa: 2004-2009, 221,787 newborns

Why are levels different in premies?

- Fetal Stress/Sickness
  - Immature adrenal function
  - Immature kidney function
  - Higher levels of adrenocorticotropic hormone

- But…are all premies the same?
  - "Healthy" premies still have higher levels (of most analytes) compared to term babies but still lower than "sick" premies (Murphy *et al.*, 1983)

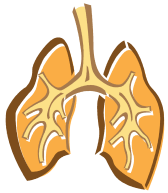
- Are all "sick" premies the same?
  - Not all "sick" premies have "abnormal" levels

Solutions…

- CLSI recommends screening preterm infants
  - At birth
  - 48-72 hours after birth
  - 28 days of life
- Gestational age/Birth weight cutoffs?
- Identify subsets of premature infants for additional screening?

Morbidities of Preterm Birth

Bronchopulmonary Dysplasia (BPD)
Respiratory Distress Syndrome (RDS)



Lung

Intraventricular Hemorrhage (IVH)

Brain

Retinopathy of Prematurity (ROP)

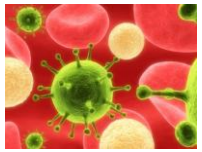
Ophthalmology

Prematurity Study (Dr. Jeff Murray)
762 infants born 22-36 weeks
NBS collected 24-72 hours after birth
No transfusion
Examined: 17-OHP, TSH, IRT, GALT, 13 amino acids and 36 acylcarnitines
Assessed false positive rate for each test

Patent Ductus Arteriosus (PDA)

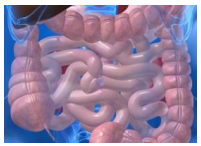
Cardiac

Sepsis



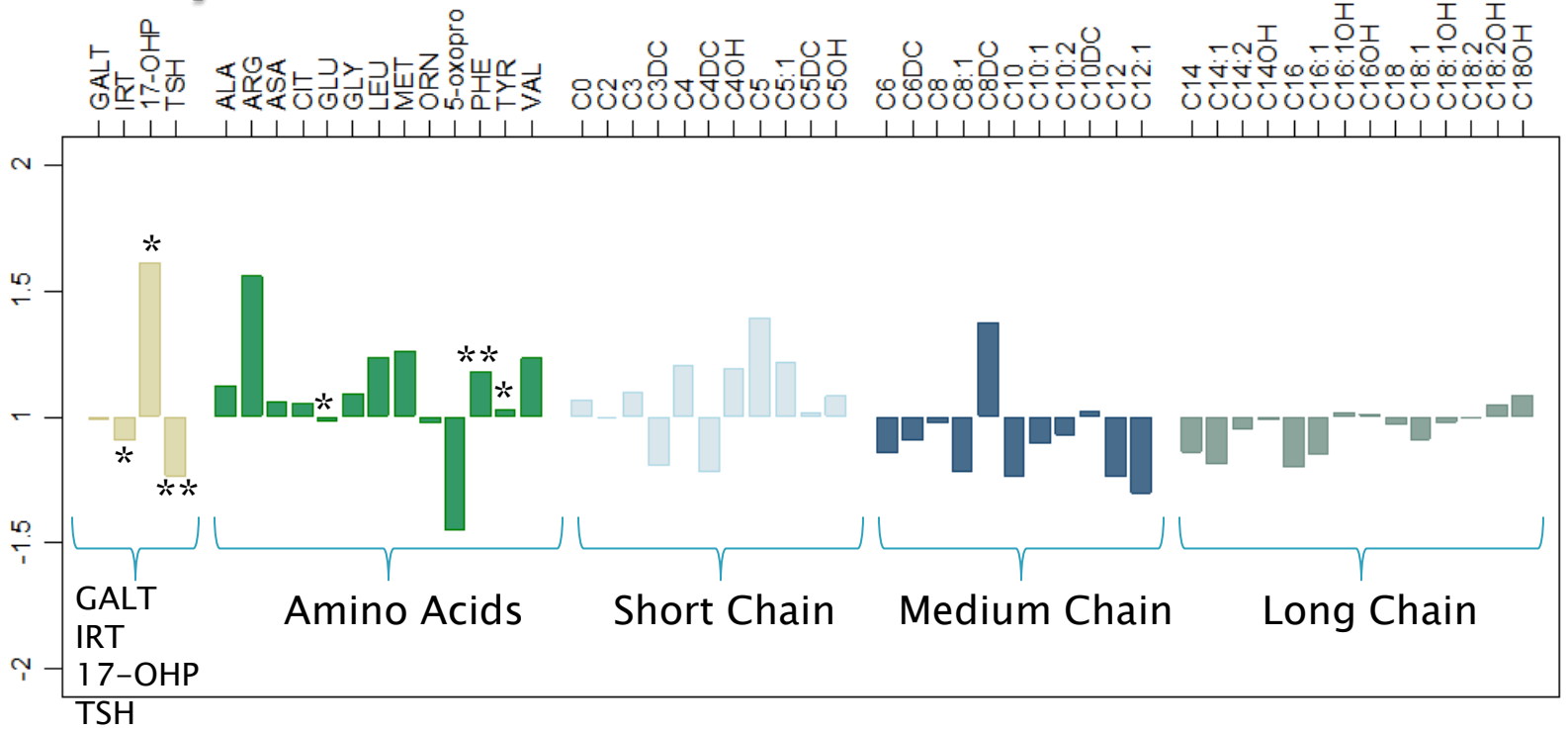
Infection

Necrotizing Enterocolitis (NEC)



Gastrointestinal

Respiratory Distress Syndrome (RDS)



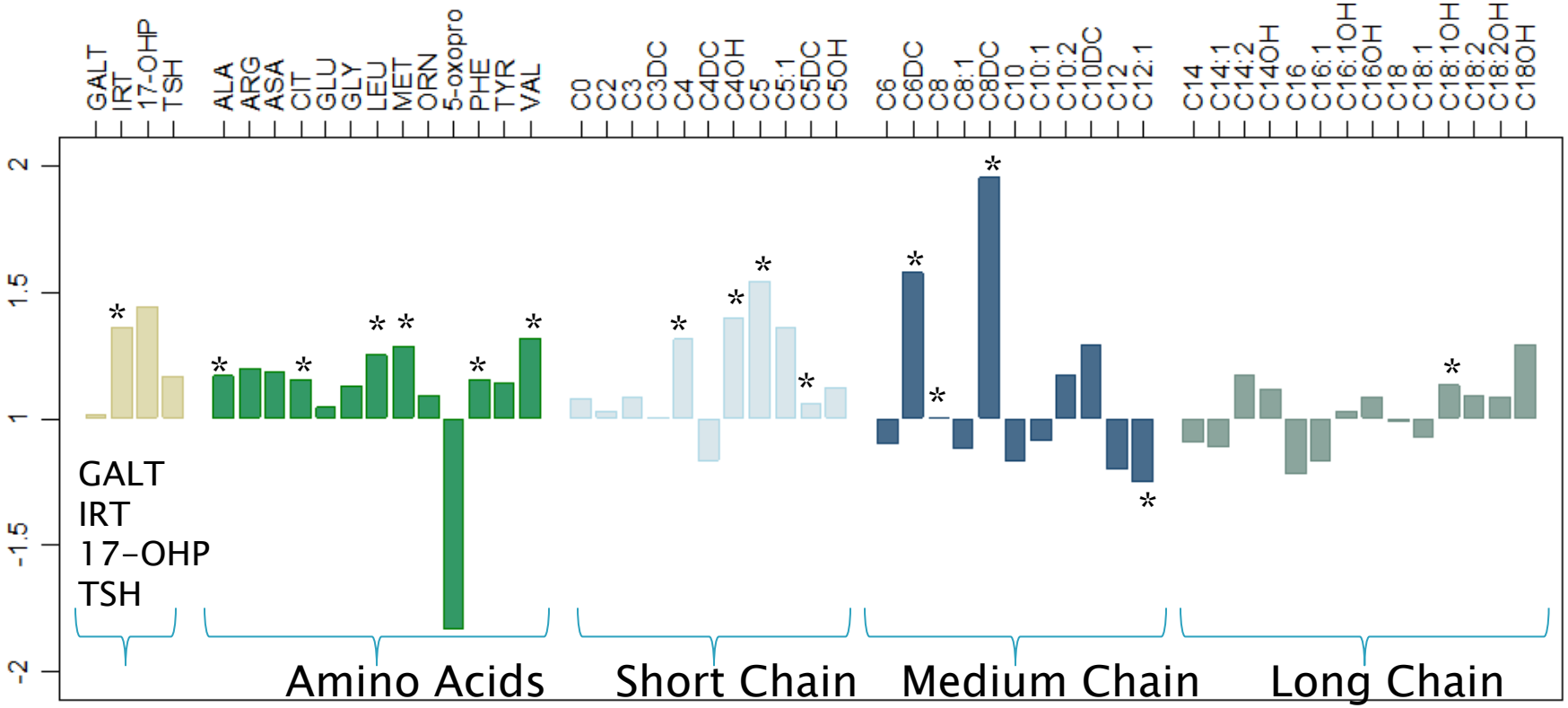
* P<0.05
** P<1x10^{-4}

RDS	False Positive CAH (n=64)	False Positive CH (n=4)	False Positive MS/MS (N=17)
No	6.3%	1.0%	1.6%
Yes	12.0%	0.8%	3.5%
p-value	**0.01**	1.0	0.21

RDS and TSH

- Thyroid stimulating hormone stimulates lung surfactant production
- Previous studies did not find an association with RDS and TSH (Romagnoli et al. 1982 and Tanaka et al. 2007)
- We observe a decrease in TSH in infants with RDS which is consistent with the hypothesis that preterm infants deficient in TSH are more likely to develop RDS

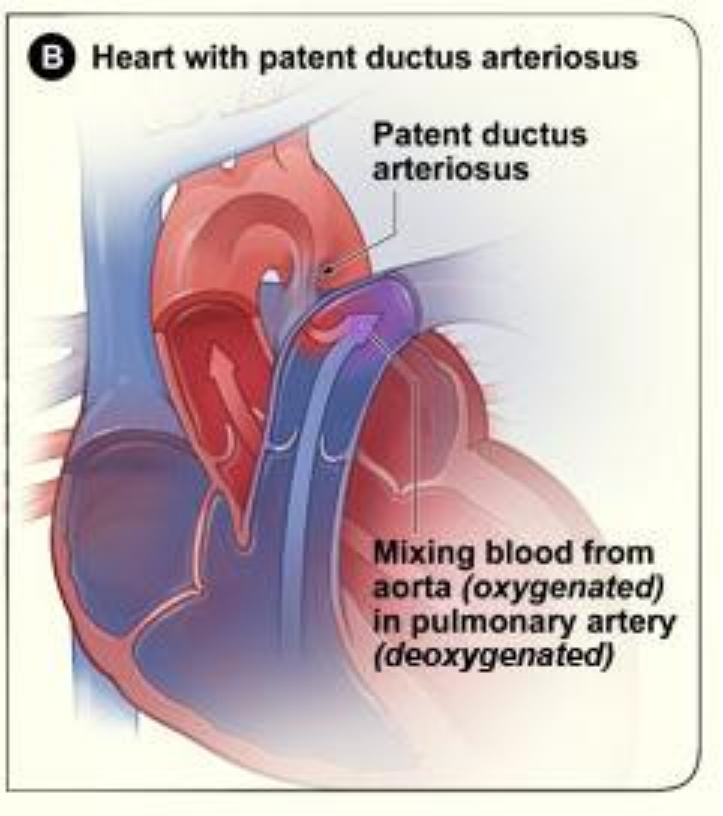
Patent Ductus Arteriosus (PDA)



* P<0.05
** P<1x10^{-4}

PDA	False Positive MS/MS (N=17)
No	2.2%
Yes	3.7%
p-value	0.35

Patent Ductus Arteriosus



http://www.nhlbi.nih.gov/health/health-topics/topics/pda/

PDA and Amino Acids

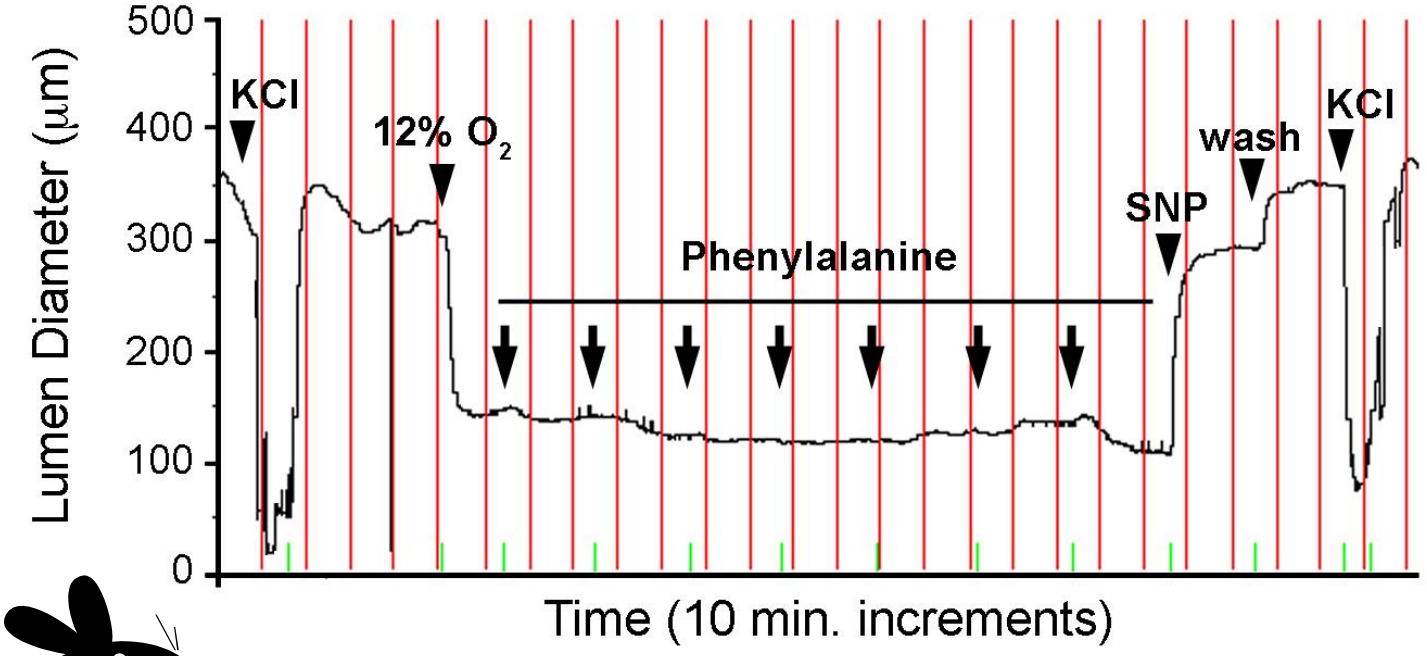
- Result of TPN?
- Metabolic patterns may be used to predict or inform on the etiology of a disease state
- Branch chained amino acids (LEU and VAL) associate with coronary artery disease (Huang *et al.*, 2011)
- Case report of a women with phenylketonuria (PKU) that had a term infant with a PDA

Testing Functionality

- Do these amino acids contribute to PDA pathophysiology?
- Isolated ductus arteriosus was examined term born mice by cannulated, pressurized vessel myography
- Vascular response to L-valine, L-methionine, L-phenylalanine and L-leucine under conditions that simulate newborn oxygen tension.

Results

- None of the amino acids elicited a response on the mouse ductus.



Conclusions

- Complications of prematurity do not seem to affect NBS test performance.
- There are distinct metabolic profiles identified for several complications including PDA and RDS.
- More studies in the mouse are underway to further examine functionality of these metabolites on PDA.

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