



Newborn Screening and Beyond

Newborn Screening Update

Donald H. Chace

Pediatrix Analytical

Pittsburgh PA & Ft. Lauderdale, FL



The Beyond Department



What's **New** in **Newborn** Screening?

- 1990: First “research” results in filter paper blood spot by MS/MS (Duke)
- 1992: First lab using MS/MS in routine screening (Neo Gen Screening)
- 1996: Routine Postmortem Screening (Screening Saves Lives)
- 1998: First State Pilot Screening Program (North Carolina)
- 2000: First State Screening Programs (New England, North Carolina)
- 2008: All States either performing, mandating or planning MS - NBS

Newborn Screening by MS/MS has grown up (18 years) – Thanks to Parents Support



Where is the Focus?

Current Issues

- Achievements
 - ACMG: Accepted and Being Implemented
 - Various Congressional Bills Signed
- Uniform Panel
 - Requires a “single approach, method”
 - Is this realistic?
 - Does it discourage expansion?
- Harmonization
 - More realistic, achievable
 - Shared Data (should be a tool for harmonization)





Panel Expansion

Tandem MS Based Assays

- 17-OH Progesterone for CAH
 - MS/MS analysis with other steroids to reduce false results.
 - Challenging assay (one of the most difficult in clinical chemistry)
 - 2nd Tier test being implemented in some labs
 - 1st Tier being improved
- Succinylacetone for Tyrosinemia Type I
 - 2nd Tier being implemented in some labs
 - 1st Tier being improved
- Lysosomal Storage Diseases
 - 1st Tier in New York for 1 disease
 - Research in expanding to 4-5 LSD's



The only new “screen” is LSD (most work is focused on improving existing tests)



Parents Perspective

- Possible Parent View:
 - All children should be screened for greatest number of diseases..?
- Possible Bureaucratic View:
 - What diseases? How much does it cost? Who will pay? Who will do the tests?
- Possible Public Health View:
 - What is benefit of screening? Is it treatable? Educational resources? How can it be implemented? What is method? Is it doable?
- My view:
 - Sort out which genetic diseases are most important from a screening perspective. It may be just one or two.
 - Develop a cost-effective method to screen these two by adding related diseases that can be screening simultaneously
 - Achieve another “expanded panel” and key diseases that is easier to “sell” to all groups
 - Reason why some rare diseases are screened by MS/MS (broad panel)



Newborn Screening

Genetic Diseases

- Newborn Screening is based in the fundamental concept of detecting congenital (genetic based, inborn error of metabolism) diseases.
- Screening Methods (non-DNA based) detect the expression of a metabolic disease
 - The “crime scene evidence” so to speak.
 - *Blood at the crime scene doesn't always mean a murder*
 - An abnormal result doesn't always mean a metabolic disease
 - *Blood at a crime scene does indicate that someone got hurt*
 - An abnormal result either indicates a collection problem, lab problem or a metabolic aberration due to diet, environment etc.



Metabolism

Traffic Analogy 1

- Inherited Disease teach metabolic specialists and scientist a great deal about integrated metabolism.
- Using a Traffic Model for Metabolism
 - Consider the roads as the enzyme pathways with each intersection product of an enzyme.
 - Getting from Point A to B to C as in a car is like a process of metabolism where say Tyrosine ends up as a neurotransmitter Dopamine (several steps on the way.
 - Imagine how your child with a metabolic disease may fit into this analogy...





Metabolism

Traffic Analogy 2

- Think of a highway – getting from home to downtown...
- In the middle of the day – no traffic – getting from A to B is easy.
- At rush hour, traffic backs up, certain products may accumulate – but always temporarily
 - Think of diet, just after eating, think of iv nutrition in preemies where we control what goes in?
- Measurement – Detect traffic jams based on road video, helicopters etc (this is like screening)
- A measurement at rush hour will show a back up.

Ever think of why they don't like to collect blood shortly after a meal?



Metabolism

Traffic Analogy 3

- Metabolic Disease

- The Parent

- Your highway has one lane closed

- But traffic gets through and it is likely other roads have compensated for highway problems over time... maybe use breakdown lane – alternate routes or commute...



DETOUR

- The Affected Child

- His/Her highway closed or only breakdown lane open.
 - Alternate routes are only route of A to B.
 - Traffic builds up.

- Solution is Diet, attempt to repair road, find alternate routes

- From a NBS perspective

- It is easier to detect a complete road closure so to speak.
 - What about traffic backs up due to heavy use or accidents....

A Focus for Metabolism that is partially genetic, partially environment



Beyond NBS

Nutrition

- Premature Infants
 - Give intravenous mixture of essential amino acids, fatty acids etc.
 - What is administered is controlled by physician (not infant).
 - Baby can't “burp” up excess food or eat more based on needs.
- High False Positive results from Preemies...
 - Why? Too much protein and/or poor sample collection
 - We may be “creating a metabolic disease state in preemies due to very high protein
 - They develop liver disease (some fatty liver) like a inherited disease
 - In fact, some very high AA levels raise isovaleric acid (IVA) and Propionic Acid.



False Positives

Are they False?

- Screening –
 - A perfect lab (no lab errors) would still have a moderate abnormal result rate due to
 - Sample collection (from preemies, collected sample from iv line)
 - High hematocrit
 - Heterozygote (carrier) and stress
 - Vitamin deficiency of infant and/or mom
 - Often a reason for high C3 levels and false positives.
 - Other diseases present create abnormal metabolism
 - (enough to be just above the cutoff).
- Much of the future work in Metabolic Screening
 - Newborn Screening is just a portion of this.



Treatments Monitoring

- Future is understanding complex relationships.
- Developing screening techniques to sort out inherited diseases, nutritional issues, environment, age, infection etc.
- Improved treatment of existing inherited disorders – but also improve general health of everyone
- Obesity Research
 - Abnormal Metabolism – look like VLCAD
 - Diet, Exercise all affect metabolism
 - Can this help both IEM and “normal” individuals? Can we tailor diet to metabolism... can we alter metabolism via diet?

Future is exciting – so much more to learn....



Screening Save Lives

Including our own

- The work in newborn screening and metabolism is going to expand into other area from
 - Premature Infants
 - Pregnant Moms
 - Children
 - Adolescents
 - Normal Adults
 - Senior Citizens
 - Hospitalized Patients
 - Clinical Trials
 - Drugs and Treatment strategies

You efforts will improve
not only your child's life
– but also
yours and mine.



Questions?