

Improving health outcomes through Newborn screening



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BC Society of Lab Science

Newborn Screening

- Newborn screening is a blood test performed routinely on all babies after birth
- Purpose: to identify those who will have one of several rare disorders, for whom early treatment is expected to improve health outcomes



Outline

- Blood collection...a critical step in the process
- History of newborn screening
- What to test? What are the criteria? How are decisions made?
- Recent advances and the current test panel
- Informing Parents: The parents right to know

Newborn Screening (NBS)

- Blood dot cards are collected prior to discharge from hospital
- Each year ~45,000 babies are born in over ~40 birthing hospitals across the province and Yukon



The “heel prick test”



FAQ's for blood collectors...

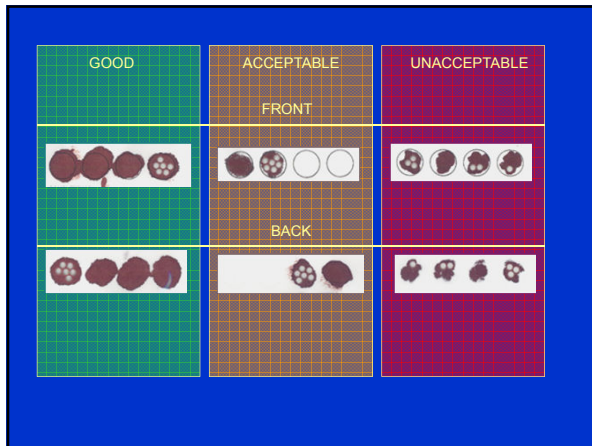
- Q: What if the blood flow from the heel is slow?
- A: The newborn screening tests can be completed on 2 well-saturated blood spots.
- When spots are not fully saturated, the tests are not accurate. The sample is rejected and repeat collection is required



Good spot!!



Bad spots!! = NSQ!



Why do we request 4 blood spots?

- The remainder of the spots are used for any repeat testing to follow up on abnormal results.
- The most important thing to remember: completely fill each circle before moving on to the next...!!!
- If you are only able to get 2 fully saturated blood spots, do not poke the baby again

Newborn screening was initially justified for a single disorder..

- 1964: Phenylketonuria (PKU)
- 1979: Hypothyroidism
- 1985: Galactosemia
- 2003: Introduction of tandem mass spectrometry: Medium Chain acyl-CoA dehydrogenase deficiency (MCAD)
- 2007: further expansion of tandem mass spec panel (LCHAD, Glutaric aciduria type I)
- As of Nov 2010, 22 disorders now on the test panel

*Newborn Screening criteria
#1: Incidence*

- The condition is relatively common in the population being screened
- Congenital hypothyroidism (CH)
 - Incidence 1/3,500 births
 - ~12 cases detected each year in BC

*Criteria #2: The condition is a serious health problem
Criteria #3: Early treatment...better health outcome*

- Congenital hypothyroidism:
 - Without screening, affected children have severe intellectual disability and growth retardation
 - With newborn screening and early treatment with thyroxin, excellent intellectual outcome and normal growth



How about PKU?



↑ Phenylalanine

Neurotoxicity



•Most early treated PKU children have normal intelligence

Criteria #4: A reliable, cost effective screening test is available

- In newborn screening, test performance is focused on positive predictive value (PPV)
- PPV: The probability that a person with a positive test result actually has the disease

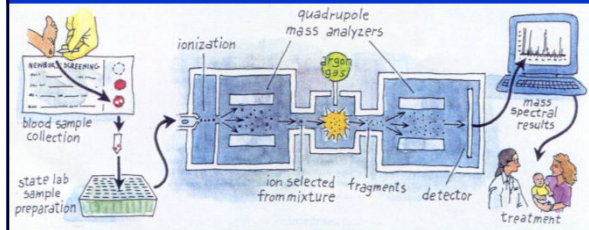
- Hypothyroidism – TSH: PPV ~ 25%
- PKU – Phenylalanine / Tyrosine: PPV ~90%

New technologies.....

- **Liquid chromatography / dual mass spectrometry (LC/MS/MS) commonly known as “tandem mass spectrometry” (TMS)**



MS/MS Technology

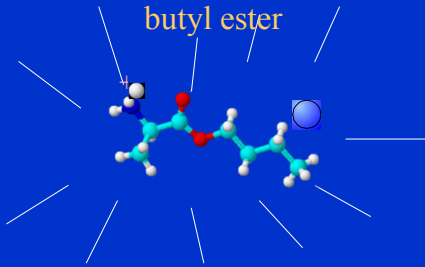


Alanine, butyl ester



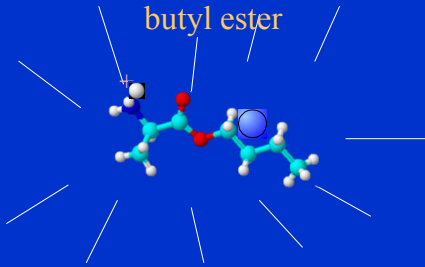
MW 148

MS Fragmentation eg. Alanine
butyl ester



MW 148

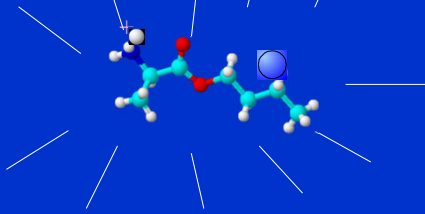
MS Fragmentation eg. Alanine
butyl ester



MW 148

MS Fragmentation eg. Alanine

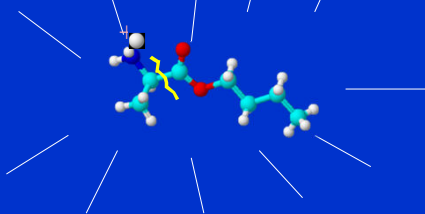
butyl ester



MW 148

MS Fragmentation eg. Alanine

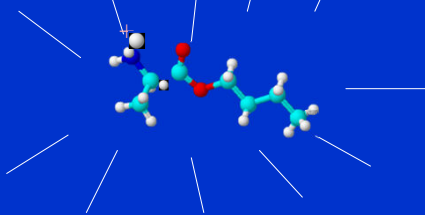
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MW 148

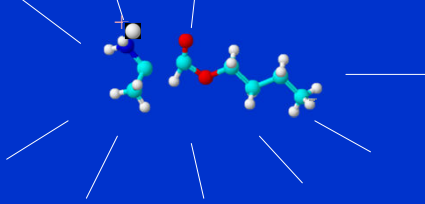
MS Fragmentation eg. Alanine

butyl ester



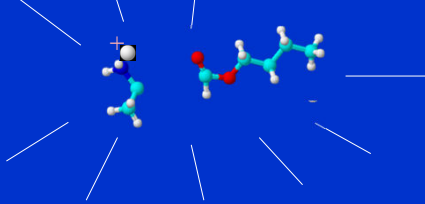
MS Fragmentation eg. Alanine

butyl ester



MS Fragmentation eg. Alanine

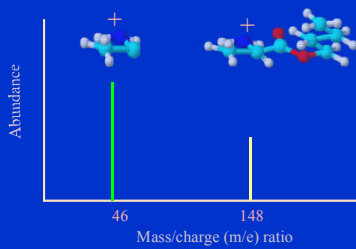
butyl ester



MW 46

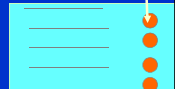
MW 102

Mass Spectrum of Alanine Butyl Ester



Tandem Mass spectrometry (TMS)

- Can simultaneously detect several treatable metabolic disorders
- Rapid throughput
- Analytical sensitivity: > 50 analytes measured on a single 'punch' from a conventional blood dot card

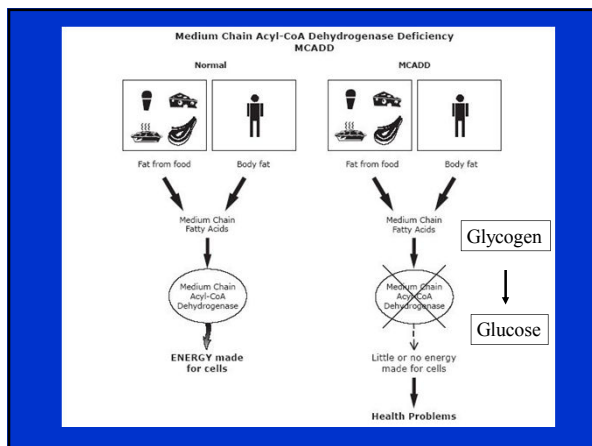


Acylcamitine profile

Patient AR	Apr-03	Cutoff
Carotene	29.48	
C2	35.68	
C3:1	0.00	
C3	2.21	
C4	1.81	
C5:1	0.01	
iso-C5	0.23	
C4 OH	0.17	
C5 OH	0.14	0.38
C6:1	1.33	0.21
C6:2	1.74	0.20
C6:3	1.74	0.08
C7:1	1.34	0.09
C7:2	1.34	0.18
C8	0.09	0.15
C4DC	0.09	0.09
C12:1	0.10	0.19
C12	0.17	0.53
C9 DC	0.02	
C12:1 OH	0.02	
C12 OH	0.02	
C14:2	0.03	
C14:1	0.18	
C14	0.23	
C9 DC	0.05	
C14:1 OH	0.03	
C14 OH	0.03	
C18	3.37	
C18:1 OH	0.05	
C18 OH	0.03	
C18:2	0.03	
C18:1	1.46	
C18	0.87	
C18:2 OH	0.01	
C18:1 OH	0.02	
C18 DC	0.02	
C18:1 DC	0.02	
Total C	77.85	
Fraction	0.62	
C3 / C2	0.06	
C3 / C16	0.06	

MCAD +ve screen

	umol / L	
	Result	Cutoff
<i>Primary</i>		
C8	11	< 0.38
<i>Secondary</i>		
C8 : C10	8.4	< 0.3



Medium chain acyl-CoA dehydrogenase deficiency: Lets call it “MCADD”!

- Incidence: 1 / 15,000 (3 cases / year)
- Natural history:
 - Episodes of drowsiness and low blood sugar
 - 25% present with sudden unexpected death
 - Triggers: intercurrent illness with fasting stress

MCAD: Diagnosis, treatment and outcome

- Treatment: avoidance of fasting and supportive care during inter-current illness
- Outcome: mortality reduced from 25% to <2%

MCAD neonatal screening in B.C.

- Outcome: all BC NBS-detected children with MCAD clinically well
- No deaths or acute life-threatening episodes

• REF: Horvath G....Vallance H. Newborn screening for MCAD: experience of first 3 years in BC. Can J of Pub Health 2008

The potential of tandem mass spectrometry

PKU Tyrosinemia Maple syrup urine disease
Glutaric aciduria Isoleucic acidemia CPTI and II
Propionic acidemia Carnitine uptake disorder Homocystinuria
SCAD 3-Methylcrotonyl-CoA Carboxylase Deficiency
VLCAD
HMGCoA lyase LCHAD
MCAD Ketothiolase
 Citrullinemia
Methylmalonic acidemia



Systematic evidence review: Does the disorder meet NBS criteria?

- Incidence justify screening?
- Good understanding of natural history and spectrum of disorder?
- Significant health problem?
- Does early detection improve health outcome?
- Does Health benefit outweighs any harm of screening?
- Adequate test performance?

Potential harms of detecting mild / benign variants



Potential harms: Labeling, stigmatization, "sick child syndrome", unnecessary investigation and treatment



Delay in Symptomatic Diagnosis of Cystic fibrosis

- There has been no improvement in the interval between onset of symptoms and diagnosis of CF for last 25 years
- Diagnosis ~2 years after onset of symptoms
 - Failure to thrive
 - Recurrent chest infections

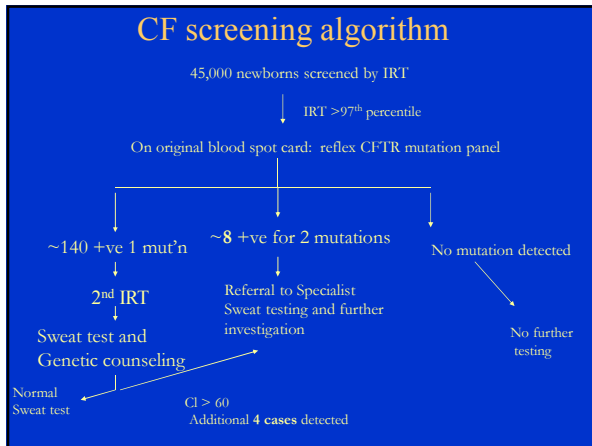
Complications in Symptomatic Diagnosis

- At time of diagnosis: kids are “skinny and short”
 - ~1/2 < 5th percentile for weight
 - ~1/3 < 5th percentile for height
 - 15% serious lung infection

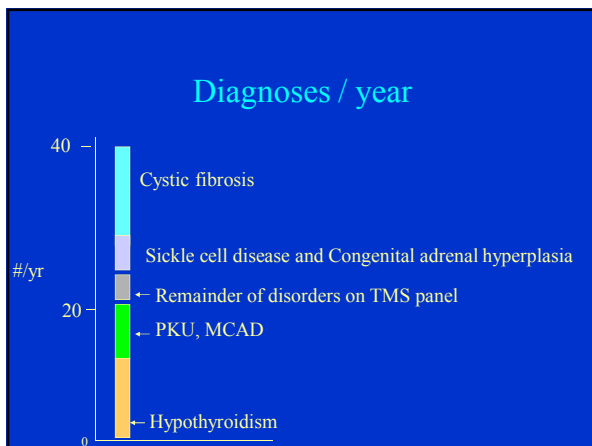
– (Steinrath M, Vallance HD, Davidson AGF Delays in diagnosing CF. Can Family Phys 2008;54:877-83)

The evidence for Cystic Fibrosis Newborn Screening

- 2 randomized clinical trials: USA and UK
- Results demonstrated that newborn screening
 - Improves growth (height and weight)
 - Reduces mortality
 - Improves pulmonary function and reduced infection rates



- ### CF carrier detection
- Detection of CF carriers is seen as a potential harm of newborn screening
 - Good communication and education is key to mitigating harm
 - Resources in place to counsel parents and other family members
 - Nurse clinician available to counsel parents
 - Dept of medical Genetics takes referrals



What happens to the blood spot cards after testing is complete?

- NBS blood spot cards are stored for 10 years
- Kept for clinical purposes:
 - Investigation of unexplained illness or death of a child
 - Test development for new disorders or test improvement
- Secondary uses:
 - Public health research (anonymized cards / Clinical research ethics board approval)



“A Simple blood test could save your baby’s life...”

- Why is my Baby screened?
- Which disorders are included in the screen?
- What does it mean if my baby screens positive?
- Will screening find anything else?
- What happens to the card when the testing is complete?
- What if I leave hospital early?

Parents’ right to know.....

- Why should parents be informed about newborn screening?
 - 1. Must respect parents right to know about their baby’s medical care
 - 2. Prior knowledge of the test prepares parents if their newborn has a positive screen
 - 3. Alerts parents that a 2nd card needed if initial card collected < 24h
 - 4. Parent surveys indicate a desire to know what happens to the blood spot card after testing is complete
- Parent Information Sheet
 - available in several languages
- Website: www.newbornscreeningbc.ca

What are we doing to help with education?

- New initiative to encourage Health care professionals to give the Parent information sheet to pregnant patients during a 3rd trimester visit

What can you do to help?

- Do you know how to access the Parent information sheets if parents have questions?

Thank you!

- To all of you who answer parents questions, who organize, collect and send us those newborn screening cards...thank you!



Any questions out there?