

Newborn Screening with Acylcarnitines

Lynette Shakespeare
Clinical Scientist

February 20th 2013

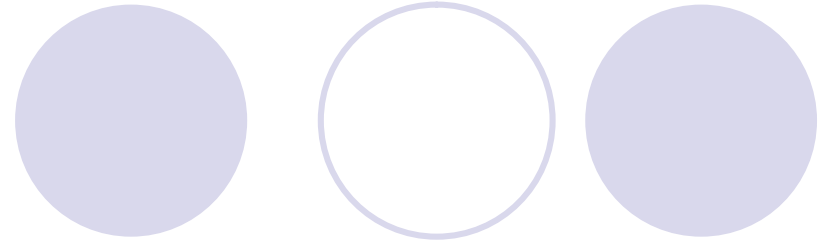


Newborn Screening in England

- Bloodspot sample at 5 days
- PKU
- Congenital Hypothyroidism
- Cystic Fibrosis
- Sickle Cell Disease
- MCADD
- Pilot - Expanded panel of 5 conditions

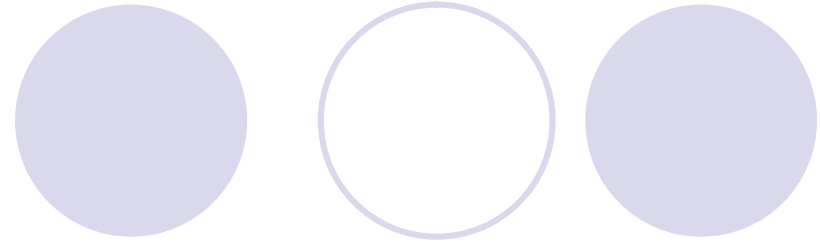
Expanded Panel

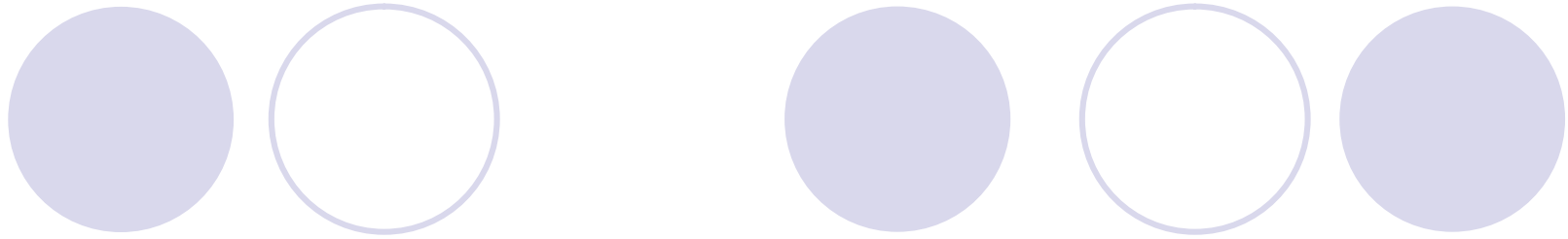
- IVA
- GA-1
- LCHADD
- MSUD
- Homocystinuria



Expanded Panel

- IVA
- GA-1
- LCHADD
- MSUD
- Homocystinuria





- Looking at healthy population
- Well babies, no clinical suspicions
- Not crisis samples

Screening Acylcarnitine Methodology

- 3mm punch from dried bloodspot
- Elute into methanolic internal standard
- Underivatized MRM for target analytes

Acylcarnitines by MRM for:

Condition	Primary analyte	Secondary analyte
MCADD	C8 (288→85)	C10 (316→85)
IVA	C5 (246→85)	
GA-1	C5DC (276→85)	
LCHADD	C16:OH (416→85)	

Screening cut-offs

- Maximise case detection
- Minimise false positives
- Cut-offs much higher than population normal values

Population and screening values

Analyte	Population mean	Screen cut-off	Metabolic lab ULN
C5	0.10	1.00	0.6
C5DC	0.11	0.70	0.1
C8	0.06	0.50* + ratio >1.0	0.3
C10	0.07	n/a	0.3
C16OH	0.01	0.15	0.05

* Local variation – all C8 >1.0 referred



Positive sample follow up

- Repunch in duplicate (underiv MRM)
- Elevated result refuted
 - Investigate cause of spurious elevation
- Elevated result confirmed
 - Full acylcarnitine scan (underiv)
 - Clinical referral – screening specialist nurse involvement

Diagnostic testing

Disorder	Diagnostic Testing
MCADD	ACCRN, OA, DNA (G985)
IVA	ACCRN, OA, benign mutation
GA1	ACCRN, OA, DNA if biochem normal/equiv
LCHADD	ACCRN, OA, DNA (G1528C), enzyme

Positive predictive values

Screen	PPV	Sensitivity
MCADD	80%*	
IVA	30%	100%
GA1	42%	100%
LCHADD	50%	100%

* 2005 value before ratio included in protocol

MCADD screening



- Screen pilot began 2004
- 6 centres covering 300,000 births
- Initially C8 and C0
- Now C8 and C10 – ratio involved in referral decision
- Full implementation in England from 2009



MCADD: what we've learnt

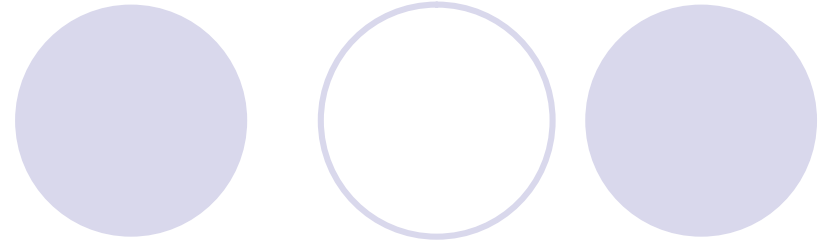
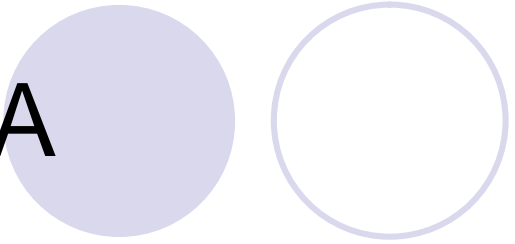
- Carriers
- MAD (GA2)
- 288 interference
- Early samples
- Asymptomatic patients
- Uncertain significance of screening-associated mutations

Expanded Panel



- Pilot began in July 2012
- 6 labs included
- Approx. 430,000 babies
- Runs until July 2013
- Anticipate 18-20 true positives
- Extension until March 2014 to allow evaluation to be completed
- Still a learning curve

IVA



- 4 referrals so far

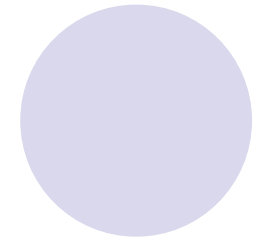
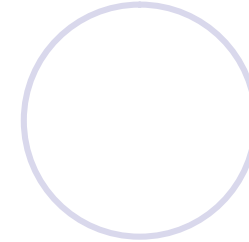
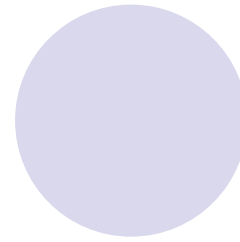
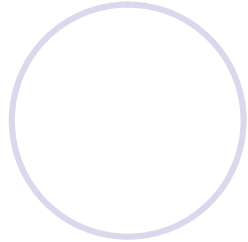
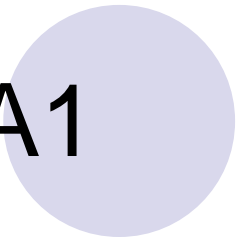
- Potential pitfalls:

- Antibiotics

- SBCAD

- GA2

GA1

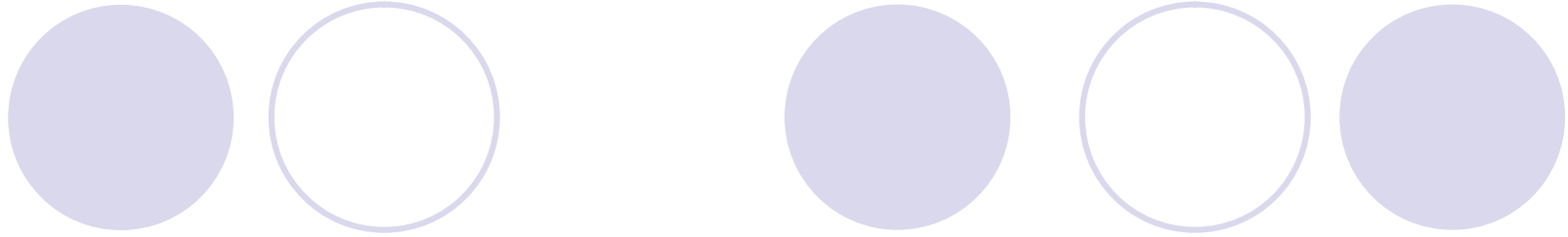


- No referrals so far
- C6-OH interference - confirm elevated level by derivatised scan

LCHADD



- 1 case so far – sib identified before screening
- Normal values on treatment
 - (Screen C16:OH 0.13 – cut-off at time was slightly higher)



- <http://www.expandedscreening.org/home/disorder-lchadd-video.asp>

The text is centered and surrounded by six light purple circles. Three circles are arranged in a horizontal row above the text, and three are arranged in a horizontal row below it. The circles are of varying opacities, with some being solid and others being hollow outlines.

Thank you for listening