SHORT AND LONG OF NEWBORN SCREENING

The New England Experience in Follow-Up for Out-of-Range Markers for Glutaric Aciduria-II

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UMASS MEDICAL SCHOOL
Commonwealth Medicine
Applied Knowledge in Public Service

Glutaric Aciduria- Type II

- Multiple Acyl-CoA Dehydrogenase Deficiency (MADD)
- Electron transfer flavoprotein enzymes (ETFA, ETFB, or ETFDH).
- Long , Medium & Short-Chain Acyl-CoA, Isovaleryl CoA and Glutaryl CoA dehyrodogenases

Clinical Presentation: GA-II

Severe / Neonatal

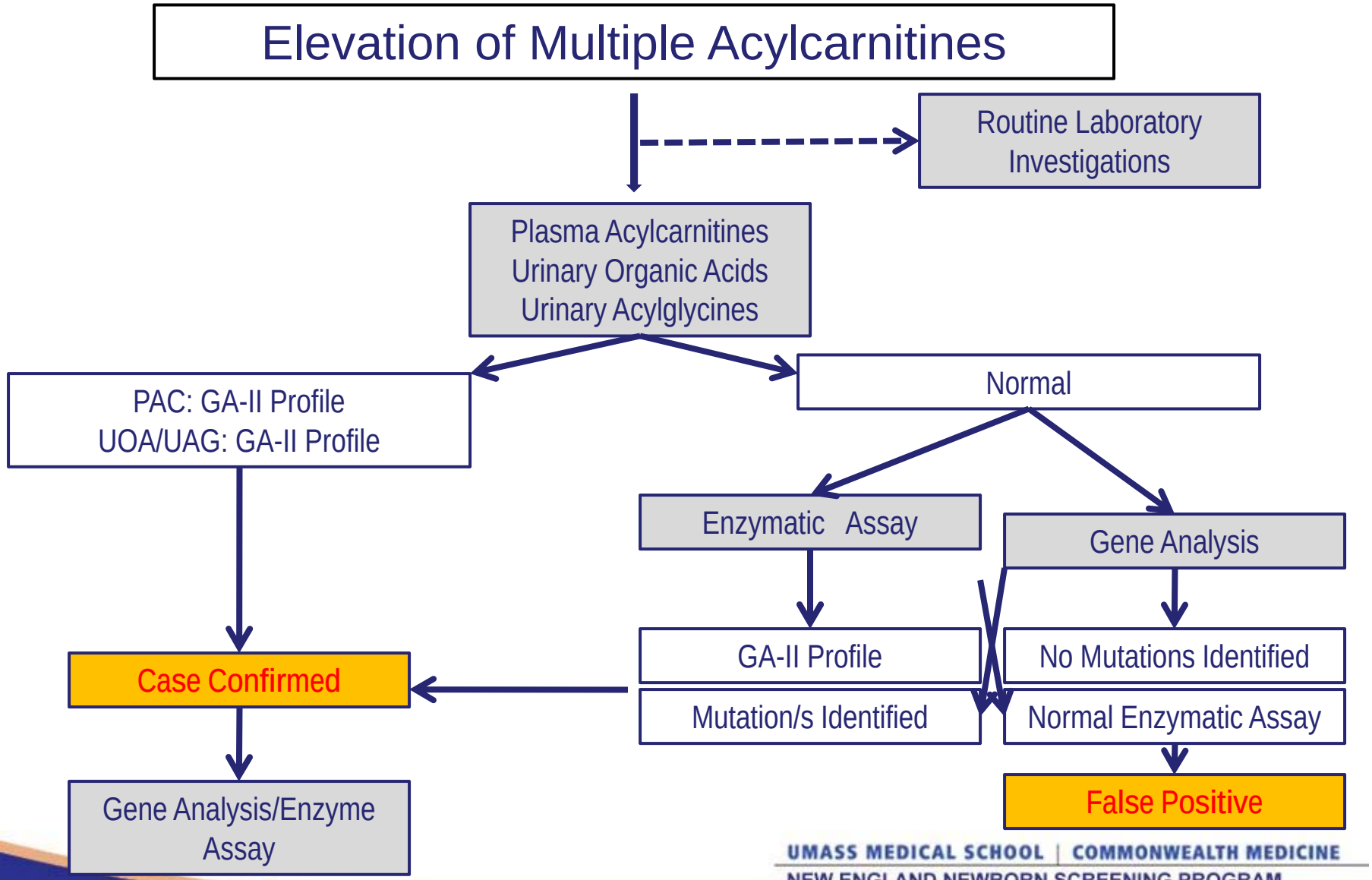
- Congenital Anomalies
- Hypotonia
- Hepatomegaly
- Sweaty Feet Odor
- Metabolic Acidosis
- Hypoglycemia
- Liver Dysfunction
- Death

Mild / Late

- Myopathy
- Exercise Induced Muscle Pain
- Metabolic Crises

Individuals with disorder are most susceptible during periods of increased metabolic requirements (illness) and decreased glucose intake (fasting, vomiting)

FOLLOW-UP ALGORITHM



GA-II Profile on Newborn Screening

- Elevation of Multiple Acylcarnitines (≥ 2)

- C4
- C5
- C8
- C5DC
- C12, C14, C14:1

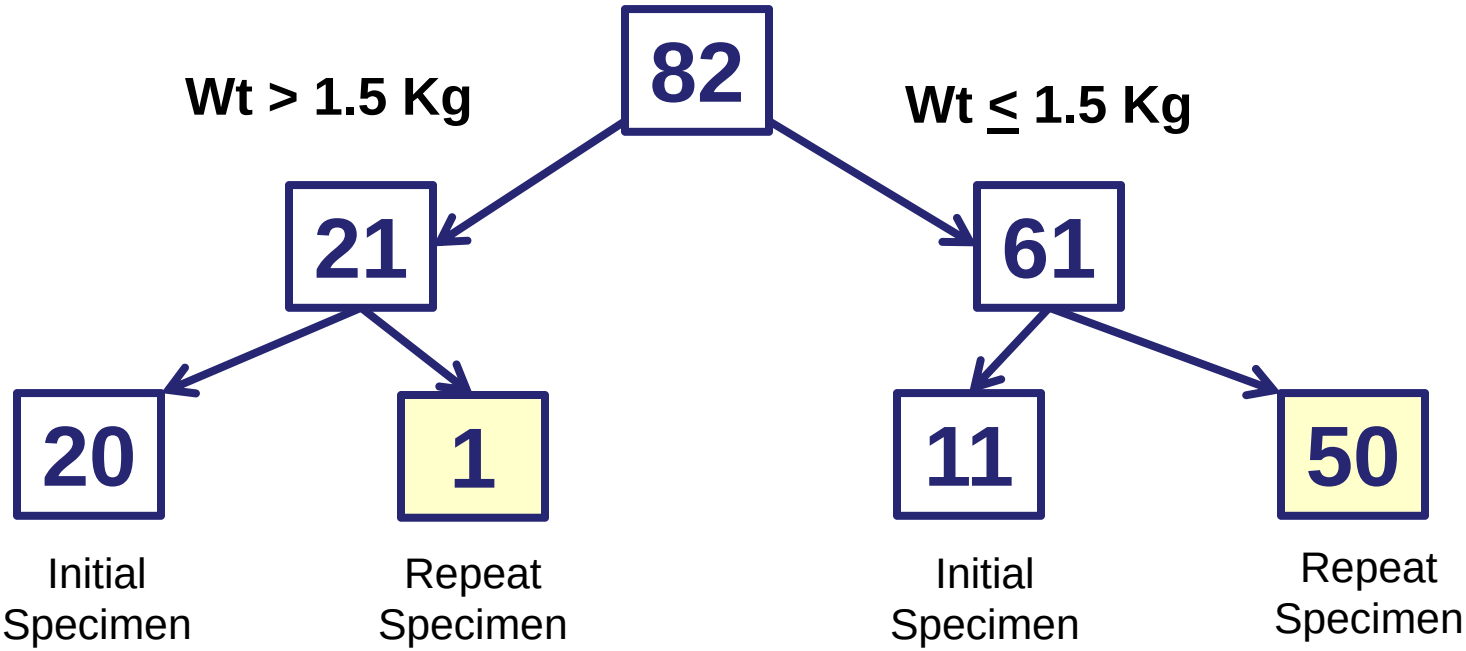
- Profile not consistent with another Fatty Acid Oxidation Defect.

- MCAD: C8 & C5DC
- VLCAD: C12, C14, C14:1 (C14:1 >C14)

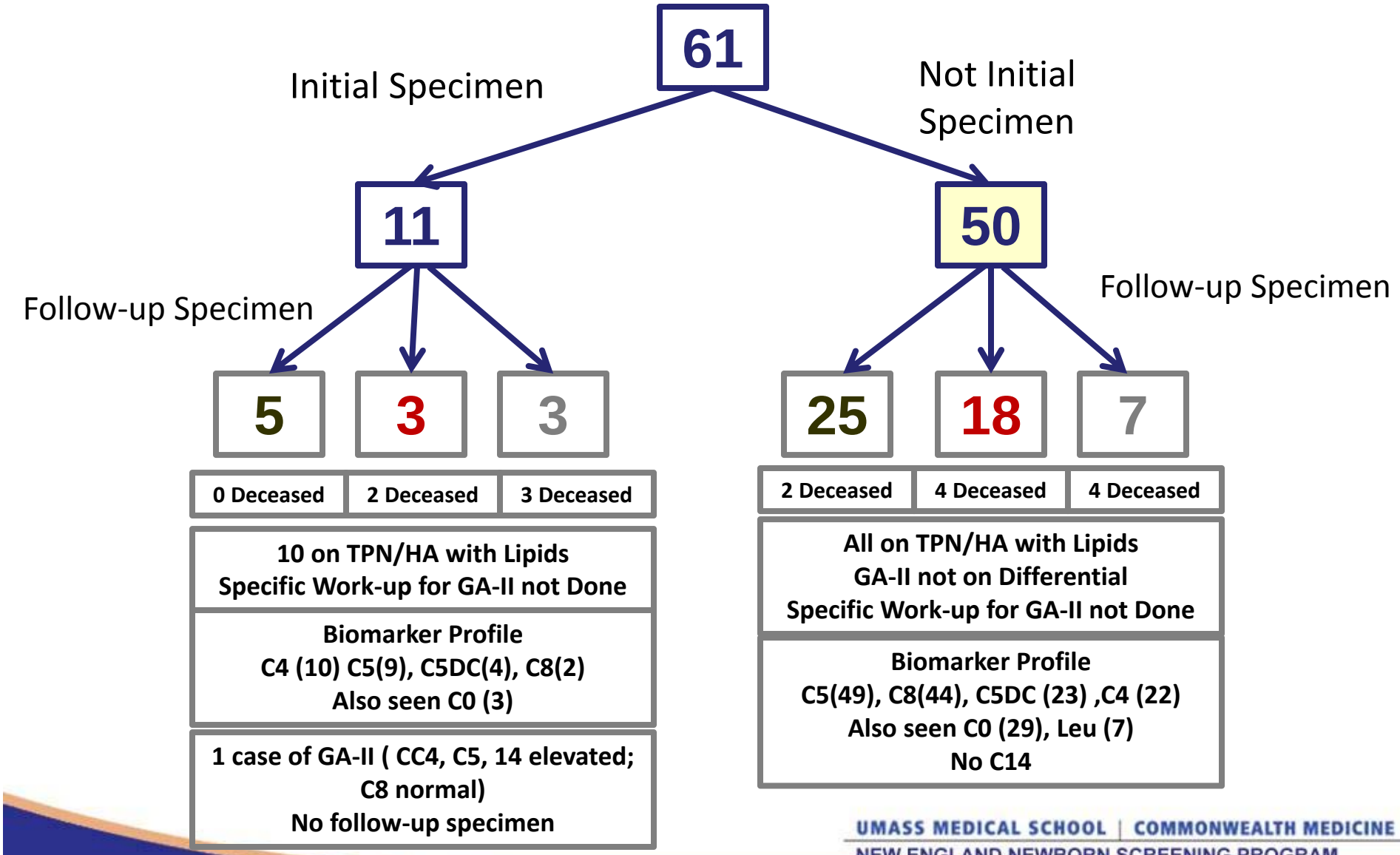
Neonates with Elevations of Multiple Acylcarnitines

(in screening specimens collected within 30 days of life)

February 1999-Dec 2012 (MA, ME, NH, RI, VT)
1.5 Million Neonates

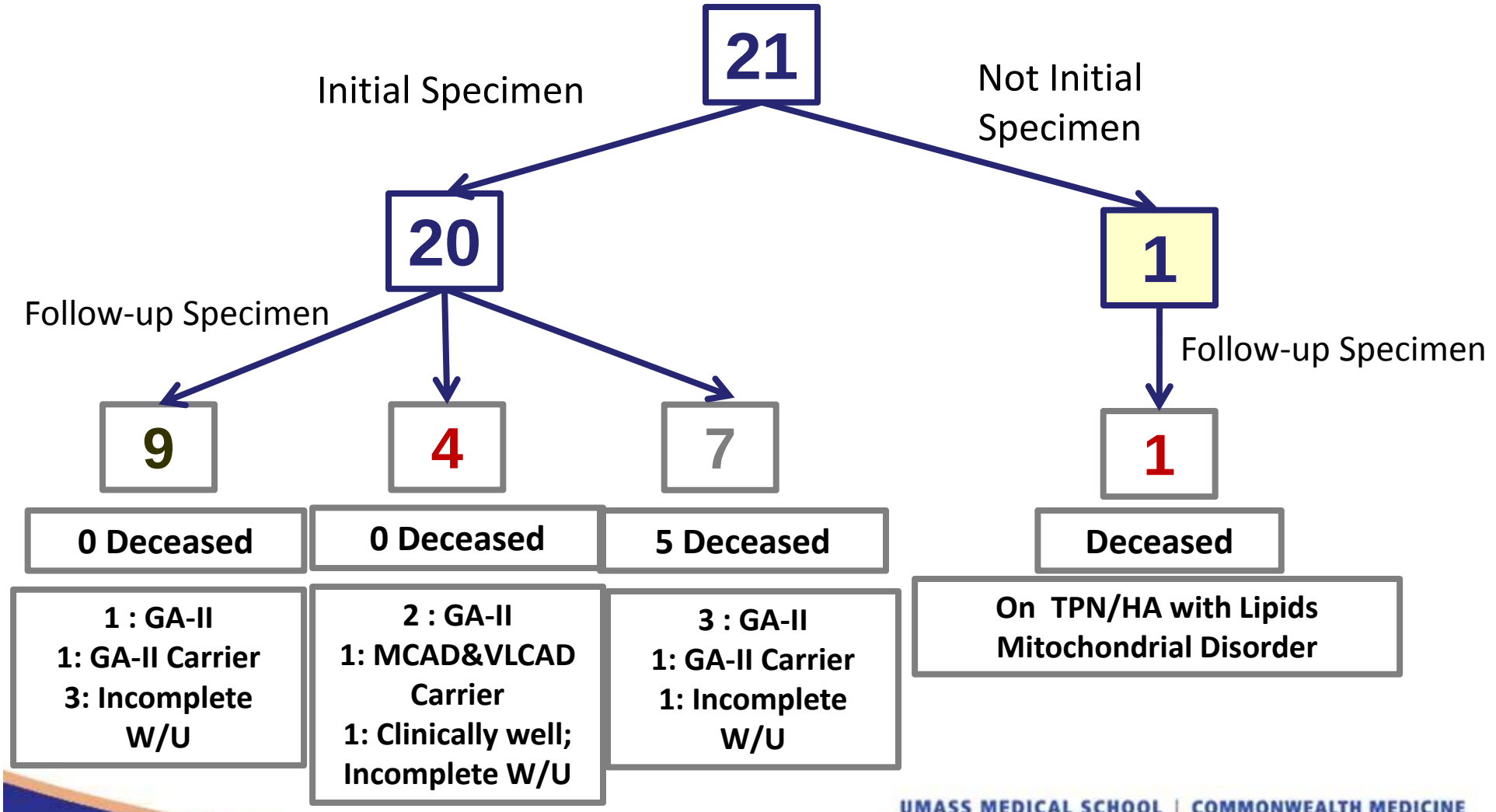


Very Low Birth Weight (< 1.5 Kgs) Neonates with Elevations of Multiple Acylcarnitines



Neonates (> 1.5 Kgs) with Elevations of Multiple Acylcarnitines

(in screening specimens collected within 30 days of life)



Multiple Acylcarnitine Profiles (Neonates > 1.5 Kgs ; Initial Specimen OOR)

C0		C2		C3		C4		C5		C5OH		C8		C5DC		C14:1		C14		C16	
5.1	**-4.4**	3.0	**-6.0**	0.1	**-7.3**	**4.6**	**7.7**	**5.3**	**10.7**	0.0	**-3.0**	0.1	1.3	**0.9**	**7.7**	0.2	1.0	0.8	**3.8**	**11.8**	**3.9**
8.7	**-2.8**	...	**...**	0.4	**-4.0**	**2.6**	**6.0**	**6.9**	**11.5**	0.1	-2.3	0.4	**5.8**	0.2	**3.8**	**1.3**	**5.6**	**4.0**	**9.0**	**10.3**	**3.6**
7.8	**-3.1**	4.6	**-4.7**	0.1	**-8.1**	**3.3**	**6.7**	**6.7**	**11.4**	0.0	**-3.9**	0.2	2.1	**0.5**	**6.2**	0.4	2.3	**1.5**	**5.9**	8.6	**3.0**
5.2	**-4.3**	3.1	**-5.9**	0.1	**-8.9**	**3.2**	**6.6**	**3.3**	**9.3**	0.0	**-3.9**	0.2	**2.7**	**0.6**	**6.7**	0.5	**3.0**	**2.0**	**6.8**	6.9	2.4
17.9	-0.7	28.9	0.7	2.1	0.6	0.9	**2.9**	0.3	1.9	0.1	0.5	**0.6**	**7.1**	0.2	**3.7**	**2.5**	**7.3**	**2.3**	**7.2**	5.7	1.8
37.8	1.5	37.0	1.5	2.2	0.6	**13.3**	**10.7**	**2.3**	**8.1**	0.1	0.7	**3.5**	**13.3**	**0.4**	**6.0**	**3.3**	**7.9**	**5.5**	**10.1**	**13.3**	**4.3**
52.0	2.4	...	**...**	2.1	0.5	**3.1**	**6.5**	0.9	**5.2**	0.1	0.2	**1.6**	**10.4**	**0.3**	**4.8**	**4.8**	**8.9**	**6.6**	**10.7**	**13.3**	**4.3**
23.4	0.1	30.0	0.9	2.2	0.7	1.0	**3.4**	0.4	2.3	0.1	0.2	0.3	**5.0**	**0.2**	**4.5**	**0.9**	**4.7**	0.8	**3.7**	5.7	1.8
21.5	-0.2	39.6	1.7	1.5	-0.4	0.4	0.5	0.1	-0.5	0.1	0.0	0.3	**4.3**	0.1	2.4	0.7	**3.8**	**1.0**	**4.7**	6.8	2.3
25.6	**2.9**	21.5	-0.1	2.2	0.7	**2.5**	**5.9**	**2.8**	**8.7**	0.1	0.7	**1.6**	**10.5**	**0.3**	**5.3**	**1.4**	**5.7**	**2.2**	**7.2**	6.0	2.0
41.5	1.7	32.9	1.1	2.4	0.9	1.4	**4.3**	0.4	**2.8**	0.2	1.3	**1.9**	**11.1**	**0.3**	**4.9**	**1.5**	**5.9**	**1.6**	**6.1**	5.9	1.9
25.0	0.3	38.0	1.6	2.6	1.1	1.2	**3.7**	0.4	**2.7**	0.1	0.0	0.4	**5.9**	**0.2**	**4.2**	1.1	**5.2**	**0.9**	**4.3**	6.7	2.3
24.8	0.4	33.7	1.2	1.5	-0.4	0.4	0.7	0.3	1.3	0.1	-0.3	**0.6**	**6.9**	0.1	**2.8**	**1.0**	**4.8**	**0.6**	**3.0**	4.8	1.3
61.6	**2.9**	59.9	**2.9**	**10.1**	**4.7**	2.5	**5.9**	0.6	**4.1**	0.3	**2.6**	0.1	1.3	0.1	1.1	0.4	2.3	**0.8**	**3.9**	**11.0**	**3.7**
25.5	0.3	25.3	0.3	4.7	**2.7**	**2.0**	**5.2**	0.9	**5.3**	0.2	0.9	**0.9**	**8.3**	**0.4**	**5.5**	**0.7**	**4.1**	0.8	**3.7**	5.0	1.4
100.0	**4.3**	51.6	2.5	9.9	**4.7**	**2.4**	**5.8**	**3.2**	**9.2**	0.4	**3.7**	0.3	**4.8**	0.1	1.5	0.2	0.2	0.2	-1.1	2.1	-1.1
48.0	2.2	44.0	2.0	2.2	0.7	0.7	2.5	**1.3**	**6.4**	0.2	1.8	**0.6**	**7.0**	**0.2**	**4.5**	0.3	2.0	0.3	1.1	2.6	-0.5
126.0	**5.0**	116.9	**4.9**	**17.7**	**6.2**	**2.1**	**5.5**	**1.7**	**7.2**	0.4	**3.6**	0.3	**4.3**	0.1	1.1	0.5	**3.0**	**1.0**	**4.7**	**12.7**	**4.2**
26.5	**-4.3**	38.4	1.6	2.2	0.6	0.8	**2.6**	0.3	2.0	0.2	1.4	0.4	**5.6**	**0.3**	**5.2**	**0.9**	**4.5**	**1.2**	**5.1**	8.5	**3.0**
48.2	2.2	58.8	**2.9**	**14.3**	**85.6**	**1.9**	**5.2**	**1.2**	**6.2**	0.2	2.3	0.1	1.8	0.1	1.1	0.3	2.0	0.4	1.8	5.2	1.6
48.0	2.2	63.7	**3.1**	4.5	**2.6**	0.6	1.9	0.4	2.3	0.2	1.8	**0.8**	**8.0**	**0.3**	**5.0**	**0.9**	**4.5**	**1.2**	**5.2**	7.9	**2.8**

(Neonates > 1.5 Kgs; Initial Specimen OOR)

Outcome	Repeat Screen	[C4xC5xC8xC14]/ [C0xC3]	Z Score
GA-II	…	**4.051**	**15.62**
GA-II	…	**9.291**	**16.71**
GA-II	…	**8.062**	**16.52**
GA-II	…	**12.132**	**17.06**
GA-II	Abnormal	**0.010**	**7.72**
GA-II	Abnormal	**7.209**	**16.38**
GA-II	Normal	**0.260**	**12.03**
GA-II Carrier	…	0.002	5.51
GA-II Carrier	Normal	0.000	3.77
Incomplete Work-W/U	Normal	**0.429**	**12.69**
Incomplete Work-W/U	Normal	**0.018**	**8.51**
Incomplete Work-W/U	Normal	0.003	**6.11**
Incomplete Work-W/U	Normal	0.001	4.68
Incomplete Work-W/U	Normal	0.000	2.94
Incomplete Work-W/U	Normal	**0.010**	**7.76**
FP	…	0.000	**3.63**
FP	…	0.002	5.54
FP	…	0.000	3.76
FP	Normal	0.002	5.69
FP	Normal	0.000	2.65
MCAD & VLCAD Carrier	Abnormal	0.001	4.70

Glutaric Aciduria- II Confirmed Cases 4/7 Deceased

- Prenatal Findings:

  IUGR, Oligohydamnios (1/4)

- Congenital Anomalies (3/4)

  Renal cysts (2/3), Cystic lesions in brain (1/3)

  Cleft palate (1/3)

- Initial Clinical Presentation (Birth-DOL 2)

  Hypotonia (3/4), Respiratory Distress at Birth (1/4)

  Change in Mental Status / Seizures (2/4)

  Cardiac Arrest (1/4)

Glutaric Aciduria- II Confirmed Cases

- Laboratory Findings:

  Hypoglycemia, Acidosis (4/4)

  Hyperammonemia (1/4)

- Diagnostic Testing:

  GA-II Profile on UOA, PAG and PAC(4/4)

  Enzymatic assay (Performed on 1)

  DNA Studies (Performed on 1)

- Deceased: On DOL 3 (3/4), DOL 7 (1/4)

Case 5

- Clinically Asymptomatic
- NBS DOL 2: Screen positive for GA-II
- Repeat Screen DOL 7: Markers in range.
- Diagnostic testing (In 1st month):

UOA: EMA only

UAG: Hexanoyl & Butryl.

Enzymatic activity: Mild increase in C4 (SCAD)

? SCAD

Case 5: Clinical Course

- 7 months (GI Illness)

  Lost babbling, Hypotonia, Hypoglycemia

- 1 year: Food aversion

  Hypoglycemic Episodes, G-Tube

- 1-1/2 Year (During Illness)

  Biochemical studies c/w GA-II

  DNA & Repeat Enzymatic Studies: GA-II

- Current (Age 11 years):

  Height & Weight 50th%ile; Cognitively intact

  G-Tube feeding at night, Mild hypotonia,

  Difficulty with sustained activities

Case 6

- DOL 2: Pale, Tachypnea. Anemia (h/o intrauterine bleed), Mild hypoglycemia that resolved with IV dextrose.
- NBS DOL 2: Screen positive for GA-II (as was repeat screen)
- Diagnostic Testing: GA-II Confirmed
- Current (Age 5 years)

  Mild hypotonia. Cognitively intact.

  G-Tube feeding at night

  Metabolic decompensations when ill.

  Persistent elevations of LFT's

Case 7

- NBS DOL 3: Screen positive for GA-II
- Evaluated in ER: Asymptomatic, but glucose 30 mg/dl. LFT's slightly high.
- Diagnostic Testing:

  Urine: C/W GA-II, PAC: ? VLCAD

  DNA: 1110C>G / 250G>A in ETFDH gene

  Enzyme Test: Pending

Conclusions

- Severe form not likely to benefit from Screening
- Mild forms may have normal repeat screens or atypical biochemical profiles
- Enzymatic/Molecular studies should be completed; even if initial biochemical tests are normal, especially in neonates with a positive screen on initial specimen when not on TPN/ lipids .
- C14 (& other long chain acylcarnitine species) are typically not seen as part of multiple acylcarnitine elevations due to TPN/lipids

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