2007 Newborn Screening Standards in Georgia
(specifically methylmalonic acidemia)

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Newborn screening standards for genetic diseases have expanded from 11 tests to 28
## Disorders

### Old standards
1. PKU (1/100,000)
2. CAH (1/19,000 in GA)
3. Hypothyroidism (1/4,000)
4. Galactosemia (1/40,000 in GA)
5. MSUD (130,000)
6. Tyrosinemia (1/400,000)
7. Homocystinuria (1/350,000)
8. Biotinidase deficiency (1/60,000)
9. MCAD
10. Sickle cell diseases (1,300 in GA)

### New Standards-Jan 2007
1. 3-methylcrotonyl CoA carboxylase deficiency (1/50,000)
2. MMA (2 types) (1/50,000-100,000)
3. Argininosuccinic acidemia (1/70,000)
4. Beta ketothiolase deficiency (?)
5. Trifunctional Protein Deficiency
6. Carnitine uptake defect (1/40,000)
7. Citrullinemia (1/200,000)
8. CF (1/3,200 caucasions)
9. Glutaric acidemia type 1 (<100 cases)
10. 3-OH 3-CH Glutaric aciduria (“rare”)
11. Biotinidase deficiency
12. Multiple carboxylase Deficiency (1/87,000)
13. Homocystinuria
14. Proprionic acidemia (1/100,000)
15. Isovaleric acidemia (1/50,000)
16. MCHAD (and LCHAD and VLCHAD) (<1/69,000)
17. Tyrosinemia
18. Sickle Cell diseases (3)
19. PKU
20. MSUD
21. Galactosemia
22. Hypothyroidism
23. CAH
24. Tyrosinemia

[www.health.state.ga.us/programs/nsmscd/](http://www.health.state.ga.us/programs/nsmscd/)
Basics of MMA pathology

- Organic acid BC aciduria
- Mutations in mitochondrial methylmalonyl CoA mutase
  - Several subtypes of mutations
- Enzyme requires B12
  - Dz may respond to B12 admin.
- Methylmalonate accumulates in blood, urine, & CSF
- hyperammonemia
- FTT. Poor feeding- weight loss- neuro sx: brain edema-hypotonia, seizures, resp distress, hypothermia, coma, death in a few days

Figure 1. Computed tomogram taken at 3 years of age revealed marked brain atrophy and low-density areas in the bilateral putamen.
MMA affects quality of life

- Neonatal onset variant: sx start shortly after birth
  - Mental retardation, epilepsy, dystonia
  - Lesions in globus pallidus
  - Massive accum. of MMA causes bioenergetic stroke d/t inhibition of mitochondrial respiration.
  - Renal tubule dysfunction
  - Hypertrophic cardiomyopathy
  - Pancreatitis

Figure 2. The brain is small. Macroscopic horizontal section reveals the shrinkage of cerebral white matter and light brown changes with petechiae in the bilateral caudate nuclei and putaminae.
MMA affects quality of life, cont.

- Late onset- more variable
  - Intermittent ataxia
  - FTT: Selective refusal of protein-rich foods, recurrent vomiting, Dev delay
  - Ketonuria
  - Neutropenia
  - May appear normal b/t attacks
  - Varying degrees of organ pathology of neonatal form.

4 YO s/p severe met. acidosis

13 YO p/w dystonia at age 4
There is an asymptomatic period

- Typically full term babies, nl pregnancies
- Neonatal forms: onset usually hrs-wks after birth
  - Initial symptom free interval
  - Catabolic stress/ febrile illnesses $\rightarrow$ proteolysis $\rightarrow$ methylmalonic acid accum. $\rightarrow$ metabolic acidosis $\rightarrow$ increased energy requirement $=$ hypoglycemia $+$ inhibition of urea cycle $+$ bone marrow suppression $+$ glycine degrad. $\rightarrow$ symptoms $\rightarrow$
    - Ketoacidosis $=$ lethargy, vomiting
    - Hypoglycemia $=$ lethargy $+$ eventually a fatty liver
    - Neutropenia
    - Hyperammononemia $=$ lethargy
    - Hyperglycinemia
- “later” onset forms present 2º to decompensation
Method of detection

- Blood collected from newborn via heel stick @ 48-72 h
- Blood placed on filter paper
- Mailed to central public health facility in Decatur on same day or sent by courier
Method of detection, cont.

• Expanded newborn screening accomplished by MS/MS
• One specimen = >20 tests in 5 min.
• Cost: 10-15 $
• Results are reported same day if +, or within 3 days if -
Incidence of MMA

• Estimated 1/50,000 to 1/100,000
• But.........
Here’s Some Data:

<table>
<thead>
<tr>
<th>MMA per 100,000</th>
<th>Incidence</th>
<th># of false positives</th>
<th>Cost of false positives</th>
<th>Discount if detected early</th>
<th>Discount if detected late</th>
<th>difference</th>
<th>Cost savings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>50</td>
<td>$50,000</td>
<td>$51,489</td>
<td>$8,938</td>
<td>$42,551</td>
<td>$85,102</td>
<td></td>
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</tbody>
</table>

*This numbers were extrapolated from a study by Kaiser Permanente HMO Metabolic Clinic. Represents >200 children with IEMs, 8 had MMA.
## More Data from Same Study

<table>
<thead>
<tr>
<th></th>
<th>MMA detected early</th>
<th>MMA detected late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life expectancy</td>
<td>65</td>
<td>45</td>
</tr>
<tr>
<td>Total QALY</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td>Cost of inpatient stay</td>
<td>4,000</td>
<td>8,000</td>
</tr>
<tr>
<td>% of pts under 5 yrs with 5+ HDs</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>“” for pts over 5 yrs</td>
<td>3%</td>
<td>9%</td>
</tr>
</tbody>
</table>
Treatment

- 1st diagnose
- Varies depending on mutation type, stage of disease at detection, and organ system involvement
  - Infantile/non-B12 responsive type presents week + after birth w/ acidotic, hyperammononemic crisis
    - Need stabilization
    - May need dialysis
    - May die despite aggressive measure
Treatment

- Sometimes treatment can be effective.
  - If stabilization achieved
    - Dietary tx: low protein, high cal., propriogenic AA restriction, branched chain deficient formula
    - B12 injection (if B12 responsive variant)
    - Antibiotics to reduce gut flora production of propionate
    - Consider liver transplantation

Courtesy of www.myspecialdiet.com

$ 10,000/yr

$ 2,500/yr
MMA has many features common to other Organic Acidemias

- Ketoacidotic crises are common to all
- Lethargy
- Jaundice
- +/- hepatosplenomegaly
- Poor feeding
- FTT
- Would anything other than IEM be in the differential?
- What does that mean?
It’s Important to Consider!

1. Incremental cost effectiveness in quality of life year gained in screened vs. unscreened
2. The oldest patients tested via MS/MS are ~ 10 yrs old
3. Cost of testing for MMA (or any individual test) is nominal since 20+ other tests are included in the cost (and some of these are decidedly cost effective.)
4. There need to be larger scale/ longer term analyses.
5. Cost of screening per QALY:
   - IEM’s- $736 - $11,419
   - Prostate Ca- $ 23,100
   - Breast Ca $5,815 - $ 232,000
   - DM retinopathy- $ 49,760
Example of early detection

• The Monaco family
  – Oldest 2 boys not diseased
  – Stephen, age 9, diagnosed after crisis at age 3
  – Caroline, age 5, diagnosed in utero
My Recommendation

- Literature supports
- I recommend to support screening based on support by literature, lack of opposition in current literature, and real life stories of survivors
References

9. CDC Laboratory Standards. Available at: http://www.cdc.gov/labstandards/nsqap_links.html
Can I answer any questions for you?