

Newborn Screening With
Tandem Mass Spectrometry:

The Oregon and Northwest
Regional Newborn Screening
Programs

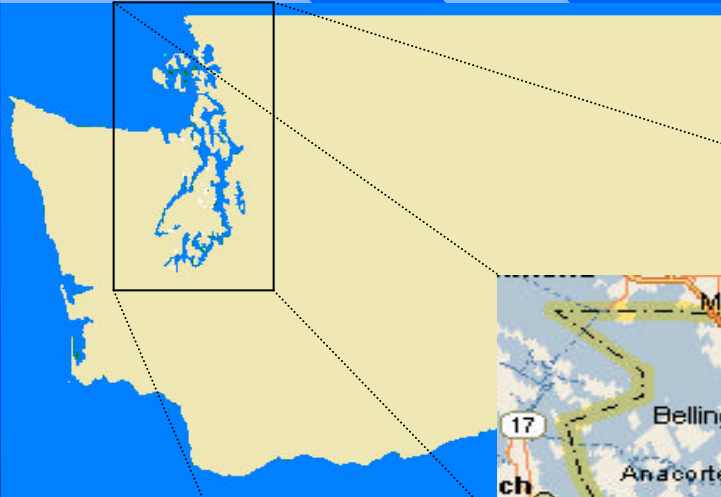
Oregon State Public Health Laboratory



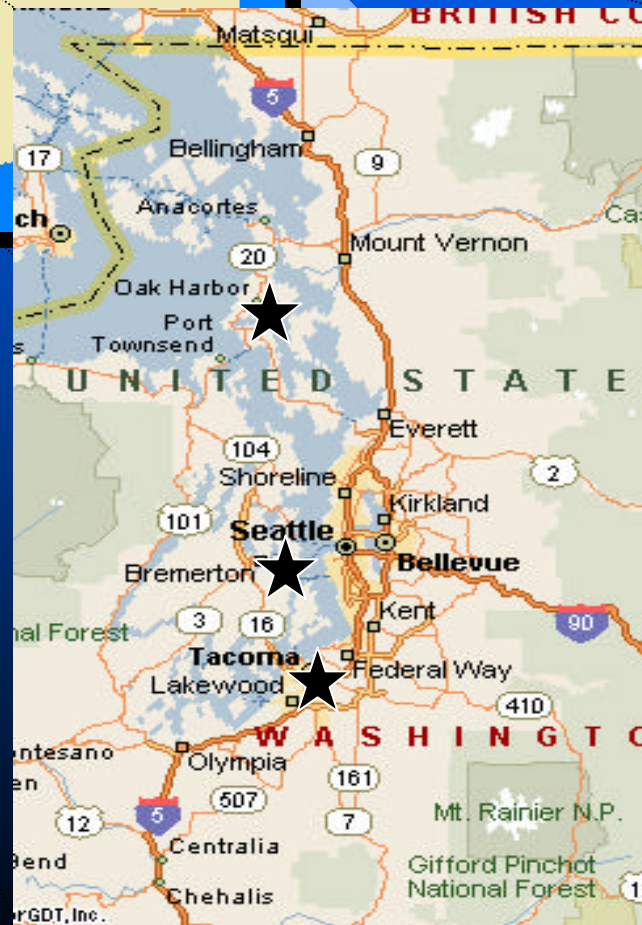
NW Regional States



NW Regional Military Bases



Washington



South Korea

NW Regional Birthing Centers



Initial Screening Panel



- Phenylketonuria (PKU)
- Congenital hypothyroidism (CH)
- Galactosemia
- Maple syrup urine disease (MSUD)
- Biotinidase
- Hemoglobinopathies
- Congenital adrenal hyperplasia (CAH)

Legislative

- House Bill 2268
- Introduced January 10, 2001
- Effective July 6, 2001
- Amended ORS 431.310
- Raised fee cap from \$16 to \$30 per NBS specimen
- Monies received to be used for expenses of the state public health laboratory

Rules

- Public hearing held July 22, 2002
- Amended the number of disorders screened for
- Modified the methods used
- Increased testing fee to cover additional testing costs

Implementation

- Disorders
- Analytes/Cutoffs
- Equipment
- Personnel/Training
- Education
- Follow-up
- Regional Timeline

MS/MS Expanded Screening

- Added 19 new disorders
- Increased test panel to 26 disorders
- PKU and MSUD converted from BIA

- Approx. 240,000 samples per year
- MS/MS run on all first and second screens received

Amino Acid Disorders

- Phenylketonuria (PKU)
- Maple Syrup Urine Disease (MSUD)
- Tyrosinemia (types I and II)
- Homocystinuria

Urea Cycle Disorders

- Citrullinemia
- Argininosuccinic aciduria (ASA)

Organic Acidemias

- Isovaleryl-CoA dehydrogenase deficiency (Isovaleric acidemia)
- 3-methylcrotonyl-CoA carboxylase deficiency (3-MCC)
- 3-methylglutaconyl-CoA hydratase deficiency
- 3-hydroxy-3-methylglutaryl-CoA lyase deficiency
- Propionic acidemia (PA)
- Methylmalonic acidemia (MMA)
- Glutaric aciduria, type I (glutaryl-CoA dehydrogenase deficiency) (GA-1)

Fatty Acid Oxidation Disorders

- Very long chain acyl-CoA dehydrogenase deficiency (VLCAD)
- Long chain L-3 hydroxyacyl-CoA dehydrogenase deficiency (LCHAD)
- Medium chain acyl-CoA dehydrogenase deficiency (MCAD)
- Short chain acyl-CoA dehydrogenase deficiency (SCAD)
- Glutaric aciduria, type II (multiple acyl-CoA dehydrogenase deficiency) (MAD)
- Carnitine acylcarnitine translocase deficiency (CT)
- Carnitine palmitoyl transferase II deficiency (CPT II)

Analytes

- Full scan
- PerkinElmer NeoGram AA/AC kit
- 37 analytes and ratios
 - 9 Amino acid
 - 24 Acylcarnitine
 - 4 Ratios: Phe/Tyr, Leu/Ala
C0/C16, C0/C18
- Cutoffs – continual evaluation and adjustments





Personnel/Training

■ Laboratory

- Two NBS employees
- PerkinElmer on and off-site training
- APHL MS/MS class
- Training of additional laboratory staff
- Testing rotation

■ Follow-up

- One new laboratory staff member
- OHSU medical consultants

Education

- Grand rounds
- CD summary article

CD Summary

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AN EPIDEMIOLOGY PUBLICATION OF THE OREGON DEPARTMENT OF HUMAN SERVICES

NEWBORN SCREENING — THIS BABY'S TAKING OFF

*"Strange is it, that our bloods, of colour,
weight and heat pour'd all together, would
quite confound distinction, yet stand off in
differences so mighty."¹*

DURING THE NEXT few weeks, the Oregon State Public Health Laboratory (OSPHL) will implement a major expansion of its newborn metabolic screening panel to bring the program in line with evolving national standards of practice.^{2,3} Currently, all Oregon infants are screened for six disorders: phenylketonuria (PKU), congenital hypothyroidism, galactosemia, biotinidase deficiency, maple syrup urine disease (MSUD) and hemoglobinopathies (e.g., sickle cell disease). By adopting a new technology—tandem mass spectrometry (MS/MS)—each child can

Program (currently OR, AK, ID, NV, HI, and three military bases), testing a total of 230,000 samples per year. To date, three million newborns have been screened and over 1,300 affected infants identified (see table). So far, we're unaware of any infant whose metabolic disorder was missed by the program.

TANDEM MASS SPECTROMETRY

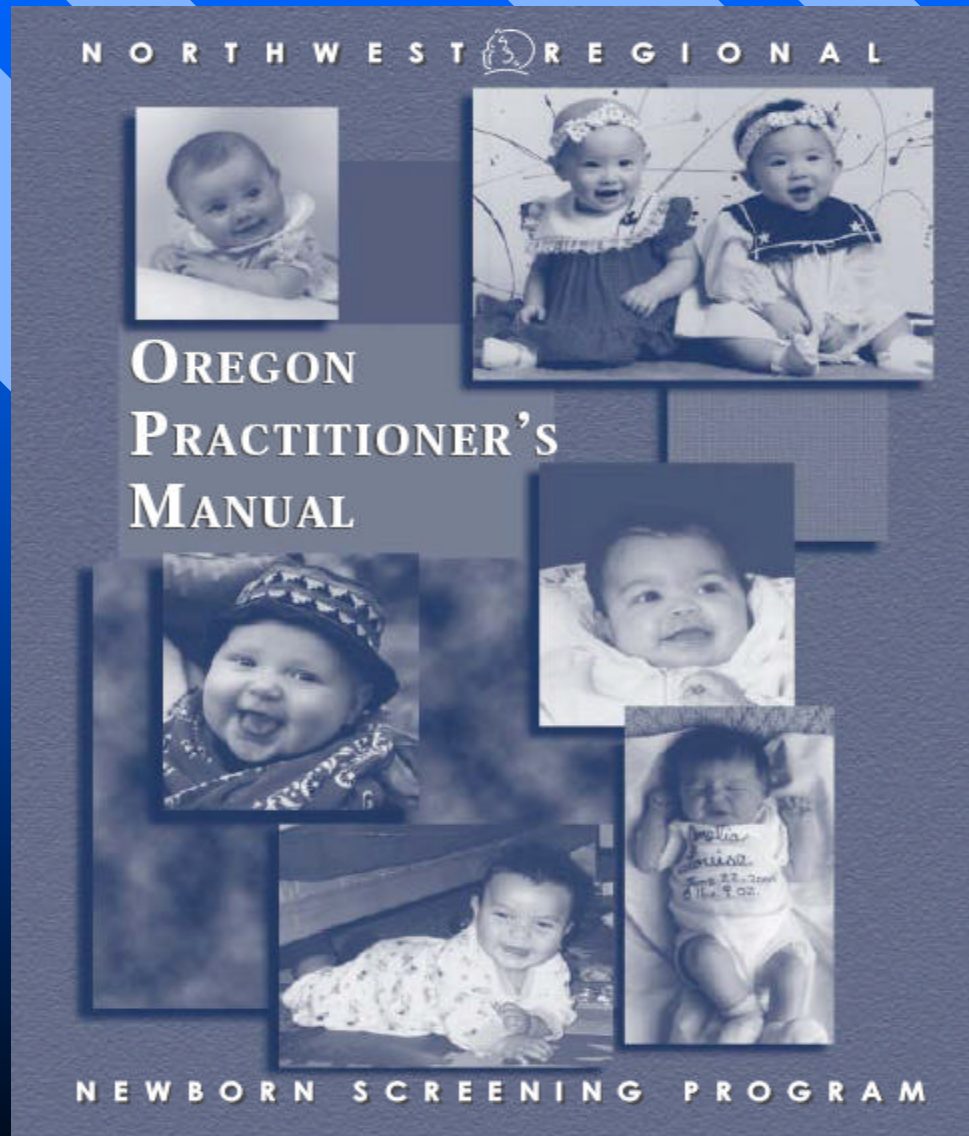
In 2001, the Oregon Legislative Assembly authorized the OSPHL to expand routine newborn screening tests to include disorders detectable by MS/MS. This will enable the laboratory to increase the number of metabolic disorders screened for from six to 26, including fatty, amino, and organic acid disorders, while also improving the detection of "current"

age. Postmortem testing of Oregon infants has documented several deaths due to MCADD that could have been prevented by neonatal screening and prompt treatment.

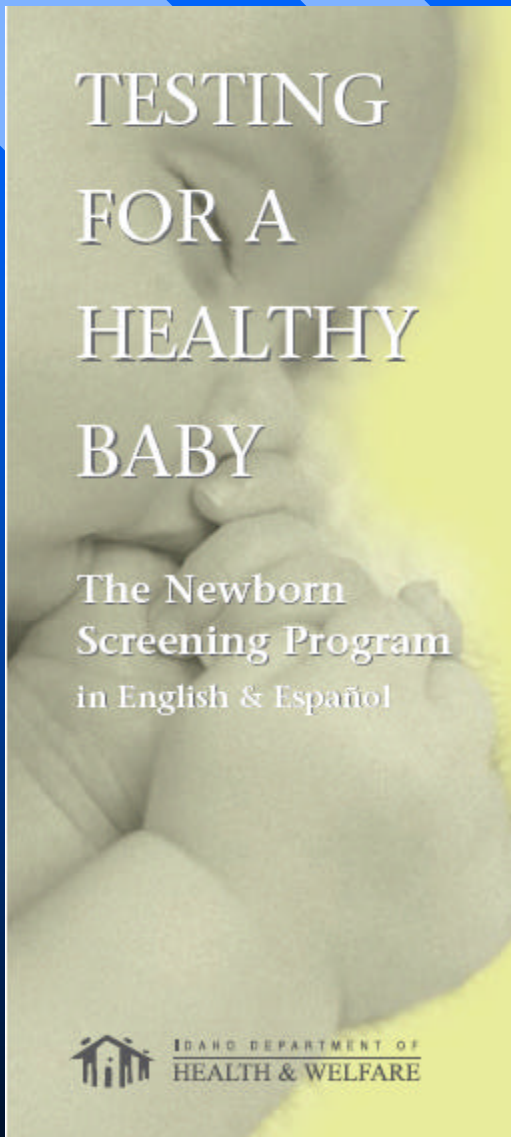
Amino acid disorders are characterized by the absence or reduced activity of enzymes necessary to metabolize certain amino acids. The build-up of these amino acids can cause severe developmental disability, seizures, microcephaly, cerebral palsy, hyperactivity, coma, and death. In addition to PKU and MSUD, infants will now be screened for tyrosinemia and homocystinuria.

Organic acid disorders result in the accumulation of these acids (e.g., propionic, methylmalonic) in blood and urine,

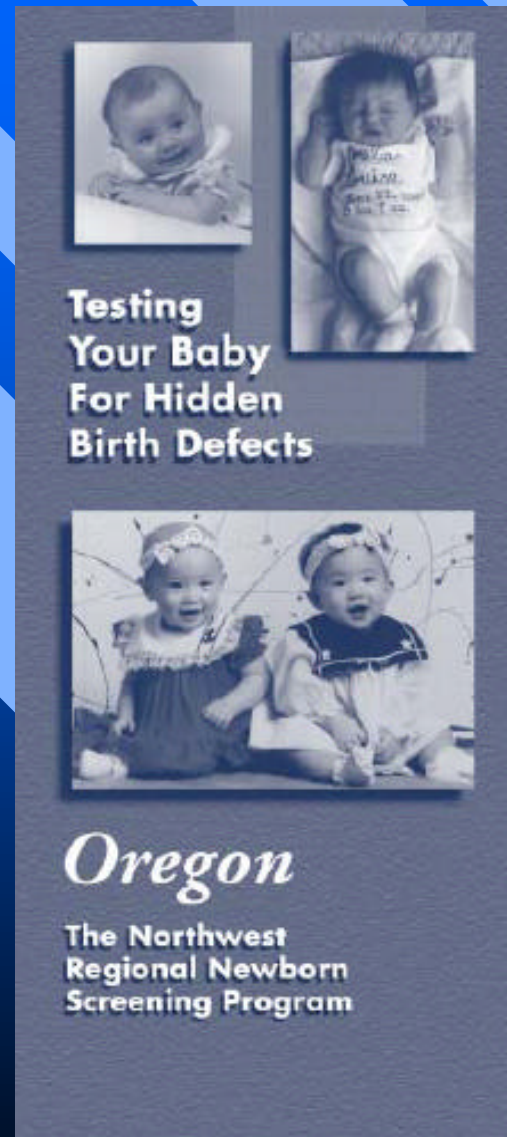
■ Practitioner's manual



■ Parent Brochures



Idaho



Oregon



Alaska

■ News coverage

Thursday, June 19, 2003
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INFANT HEALTH CARE: Newborn testing to expand

Mandate calls for screening for 19 additional disorders

By JOELLE BABULA
REVIEW-JOURNAL



Registered nurse Susan Brinker squeezes blood from the heel of 1-day-old McKayla Rose Williams on Wednesday at MountainView Hospital.

Photo by Clint Karlson.

effect next month will require the use of emerging technology to test newborns for an additional 19 birth disorders.

State officials hope new testing procedures will reduce incidents of death and severe mental retardation among Nevada newborns.

Currently, state law mandates that all newborns are tested within hours or days of birth for six disorders, including sickle cell disease and hypothyroidism.

A state mandate that takes



 **News Release**
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Nov. 13, 2002

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Newborn screening expands; babies are tested for 26 more conditions

Public Health Lab to expand newborn screening

A mother who appeared before an Oregon legislative committee last year had a compelling message: You can't save my baby, Nikki Hiatt told lawmakers, but you can save others in the future.

MS/MS Timeline

- Original target date: July 1, 2002
- Equipment installed in July 2002
- Validation studies: September 2002
- On-line: October 1, 2002

NW Regional MS/MS Expansion Timeline

2002

October

- Idaho
- Oregon

December

- WA military
- Guam
- Kwajalein

2003

April

- Saipan

July

- Nevada

September

- Hawaii

October

- Alaska

2004

January

- Korea

MS/MS Screening

October 2002 - April 2004

- 147,811 First screen specimens
- 120,416 Second screen specimens
- 268,227 Total

- Diagnosed cases: 53
- Representing 12 metabolic conditions

Identified Conditions

- Amino acid disorders
 - PKU/Hyperphenylalaninemia
- Urea cycle defects
 - Arginase deficiency
 - Argininosuccinic aciduria (ASA)
 - Citrullinemia

Identified Conditions

■ Organic acidemias

- 3-MCC
- GA-1
- MMA

■ Fatty acid oxidation disorders

- CPT 1
- Carnitine transport defect
- MCAD
- SCAD
- VLCAD

Identified Conditions

■ False negative LCHAD

- Four month old infant
- Two normal AC screens
- Samples sent to Mayo
- Review of spectra, procedures, analytes, and cutoffs
- Added 4 new analytes
(C14OH, C16:1, C18OH, C18:1OH)

NW Regional Cases Numbers per State

■ Hawaii	1
■ Alaska	2
■ Nevada	4
■ Washington	4
■ Idaho	17
■ Oregon	25

NW Regional Cases Numbers per Disorder

■ ASA	1	■ MCAD	15
■ Arginase Deficiency	2	■ 3-MCC	4
■ CPT 1	1	■ MMA	3
■ Carnitine Transport	2	■ PKU/Hyperphe	17
■ Citrullinemia	3	■ SCAD	1
■ GA-1	2	■ VLCAD	2

Frequency with PKU: 1/2,789
without PKU: 1/4,106

Second Screens

- 120,416 second specimens tested
- 4 disorders found
 - 1 Carnitine transport defect
 - 2 Arginase deficiency
 - 1 VLCAD
- 8% of cases found on second specimen

Second Screen Cutoffs

- First screen cutoffs used
- March 2004, re-evaluated and adjusted cutoffs for:
 - Citrulline (100 → 170 $\mu\text{mol/L}$)
 - Leucine (300 → 360)
 - C0/C16 (170 → 260)
 - C0/C18 (450 → 560)
- Others in process

Challenges

- Fee increase
- Internal procurement process
- Site preparation/equipment installation
- Education
- Follow-up
- Diagnostic workup
- Cutoff determinations

Oregon Website



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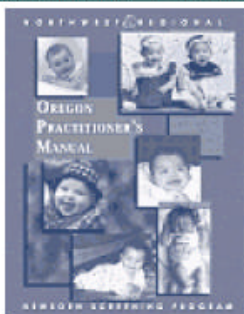
- [Newborn screening](#)
- [An overview](#)
- [Expanded screening](#)
- [Newborn screening kit request](#)
- [Practitioner's manual](#)
- [Disorders](#)

Newborn Screening

The Northwest Regional Newborn Screening Program conducts screening of all infants to prevent mental retardation and premature death in children through early detection and treatment of genetic disorders by:

- **Screening** for congenital hypothyroidism, galactosemia, phenylketonuria (PKU), biotinidase deficiency, maple syrup urine disease (MSUD), congenital adrenal hyperplasia (CAH), hemoglobinopathies (eg, sickle cell disease), selected amino acid disorders, urea cycle disorders, organic acidemias and fatty acid oxidation disorders.

Practitioner's Manual



Expanded Newborn Screening Disorders

The Northwest Regional Newborn Screening Program (NWRNSP) tests for these disorders using Tandem Mass Spectrometry (MS/MS). Newborn screening by Tandem Mass Spectrometry (MS/MS) is an effective tool to detect serious and life threatening metabolic disorders in newborns.

Below is the Northwest Regional Newborn Screening Program's list of expanded newborn screening disorders.

[Fact Sheets](#)

[Fact Sheets](#)

■ Disorder fact sheets

Urea Cycle Disorders [\(PDF\)](#)

- [Arginase Deficiency](#)
- [Argininosuccinate lyase deficiency \(ASA\)](#)
- [Citrullinemia](#)
 - [Classic Citrullinemia](#)
 - [Citrullinemia Type II](#)

Organic Acidemias [\(PDF\)](#)

- [Beta-Ketothiolase deficiency](#)
- [Glutaric aciduria, Type I](#) (glutaryl-CoA dehydrogenase deficiency)
- [HMG-CoA lyase deficiency](#) (3-hydroxy-3-methylglutaryl-CoA lyase deficiency)
- [Isobutyryl CoA dehydrogenase deficiency](#)
- [Isovaleryl-CoA dehydrogenase](#) deficiency (Isovaleric acidemia)
- [Malonic aciduria](#)
- [Maple Syrup Urine Disease](#)
- [Methylmalonic acidemia \(MMA\)](#)
 - [Methylmalonic aciduria, vitamin B-12 responsive](#)
 - [Methylmalonic aciduria, vitamin B-12 nonresponsive](#)
 - [Vitamin B12 metabolic defect with methylmalonicacidemia and homocystinuria](#)
- [Multiple carboxylase deficiency](#)

- [Propionic acidemia \(PA\)](#)
- [2-Methyl-3-hydroxybutyryl CoA dehydrogenase](#) deficiency
- [2-Methylbutyryl CoA dehydrogenase](#) deficiency
- [3-methylcrotonyl-CoA carboxylase](#) deficiency
- [3-methylglutaconyl-CoA hydratase](#) deficiency
 - [3-methylglutaconyl-CoA aciduria TYPE I](#)
 - [3-methylglutaconyl-CoA aciduria TYPE II](#)
 - [3-methylglutaconyl-CoA aciduria TYPEIII](#)
 - [3-methylglutaconyl-CoA aciduria TYPE IV](#)

Fatty Acid Oxidation Disorders [\(PDF\)](#)

- [Carnitine uptake/transporter defects](#)
 - [Carnitine-acylcarnitine translocase](#) deficiency
 - [Carnitine transporter](#) defect
 - [Carnitine palmitoyl transferase I](#) deficiency (CPT I)
 - [Carnitine palmitoyl transferase II](#) deficiency (CPT II)
- [Glutaric aciduria, Type II](#) (multiple acyl-CoA dehydrogenase deficiency (MADD))
- [Very long chain acyl-CoA](#) dehydrogenase deficiency (VLCADD)
- [Long chain L-3 hydroxyacyl-CoA](#) dehydrogenase deficiency (LCHADD)
- [Medium chain acyl-CoA](#) dehydrogenase deficiency (MCADD)
- [Short chain acyl-CoA](#) dehydrogenase deficiency (SCADD)

Disease Name:	MEDIUM CHAIN ACYL-CoA DEHYDROGENASE DEFICIENCY (ACADM DEFICIENCY; MCAD DEFICIENCY; MCADD DEFICIENCY)
Classification:	Fatty Acid Oxidation Disorder
Genetic Information:	Inheritance: Autosomal recessive Population Incidence: 1/15,000 Ethnic Incidence: Approximately 1/70 carrier rate; incidence higher in Northern Europeans and US Caucasians. Gene & Location: ACADM, 1p31 Common Mutation: 80% carry A985G; most are heterozygous for the A985G mutation and another private mutation.
OMIM #	#201450; *607008
Disease Information:	Symptom Onset: Typically 3-24 months, variable even within family member with identical gene mutations and can range from neonatal to adult. MCADD may account for about 3% of SIDS deaths. Symptoms: Episodes of hypoketotic hypoglycemia, encephalopathy, coma or SIDS triggered by a common illness and/or a period of fasting. In 18% of cases, sudden death is the initial presenting manifestation and up to 50% of patients die during their first episode. Survivors may have significant developmental disability, muscle weakness, failure to thrive and cerebral palsy. Physical Findings: No particular physical findings or dysmorphism. Treatment: Treatment is simple and effective: avoid fasting for more than 4 hrs as infant or 12 hours in older patients. It is imperative that glucose supplementation and hydration be provided during times of illness. A tangible clinical benefit of carnitine supplementation in patients with MCADD deficiency has not been proven, but several authors recommend oral supplementation with 100mg/kg/day to correct the observed secondary carnitine deficiency and to enhance the elimination of toxic metabolites. Natural History without treatment: Mortality rate of up to 50% when untreated. Metabolic episodes can cause developmental and physical delays from hypoglycemia and liver insult.

Oregon Website

www.
dhs.state.or.us/public health/
nbs/index.cfm