Organic Acid Disorders
(aka Organic Acidemias)

These metabolic disorders cause a buildup of toxic organic acid intermediates due to the body's inability to breakdown certain amino acids and odd-chain organic acids. The enzyme deficiencies are farther down the pathways of amino acid metabolism, so there is not a buildup of amino acids but rather their intermediate organic acid states. Organic acid disorders are autosomal recessive. Most of these disorders have severe forms that present in the first week of life and constitute a neonatal emergency. Infants are usually well at birth, but develop poor feeding, irritability, lethargy, vomiting, metabolic acidosis, ketosis, or coma.

Late onset and milder variant forms of organic acidemias may present with an acute decomposition brought on by an intercurrent illness similar to those described above, or with failure to thrive, hypotonia, mental retardation and a history of bouts of vomiting, protein intolerance, acidosis, and/or hypoglycemia. While these patients typically have "milder" disease, the neurological damage may be just as severe as those presenting earlier. Newborn screening may be very beneficial to these infants as the initial crisis may be prevented.

As of July 1st, 2005, the Missouri Newborn Screening Program has been screening every newborn for several organic acid disorders using tandem mass spectrometry. The disorders are typically named after the organic acid marker that becomes elevated in that disorder or the deficient enzyme. Due to the lengthy names of the disorders, acronyms are most commonly used. Some organic acid disorders share the same marker analytes and therefore cannot be differentiated in the newborn screening test. Specific confirmatory testing is done to confirm that a disorder is present and identify the specific enzyme deficiency.

The list of organic acid disorders that we screen for are:

- 2-Methyl-3-hydroxybutyric aciduria (2M3HBA)
- 2-Methylbutyryl-CoA dehydrogenase deficiency (2MBG, SBCAD)
- 3-Hydroxy 3-methylglutaric aciduria (HMG, 3-Hydrox 3-methylglutaryl-CoA lyase)
- 3-Methylcrotonyl-CoA carboxylase deficiency (3-MCC)
- 3-Methylglutaconic aciduria (3MGA, Type I hydratase deficiency)
- Beta ketothiolase (BKT, mitochondrial acetoacetyl-CoA thiolase, short-chain ketoacyl thiolase)
- Glutaric acidemia type I (GA-1, glutaryl-CoA dehydrogenase)
- Isobutyryl-CoA dehydrogenase deficiency (IBG)
- Isovaleric acidemia (IVA, Isovaleryl-CoA dehydrogenase)
- Malonic acidemia (MAL, malonyl-CoA decarboxylase)
- Methylmalonic acidemia (CBL A,B; vitamin B12 disorders)
- Methylmalonic acidemia (CBL C,D)
- Methylmalonic acidemia (MUT, methylmalonyl-CoA mutase)
- Multiple carboxylase deficiency (MCD, holocarboxylase synthetase)
- Propionic acidemia (PROP, propionyl-CoA carboxylase)

Prevalence: 1: 25,000 (This is the projected, combined prevalence of all the organic acid disorders).

Analytes Measured: The list of organic acid markers and ratio of markers that we monitor in each dried blood spot sample for these disorders are:

Disorder	Marker	Abnormal Range
PROP, MUT, Cbl A,B and Cbl C,D	C3	> 6.0 umol/L
	C3/C2	> 0.20
	C3/C16	> 3.0
MA	C3DC	> 0.30 umol/L
IBG	C4	1.30 umol/L
	C4/C3	> 0.75
	C4/C2	> 0.05
IVA and 2MBG	C5	> 0.70 umol/L
	C5/C3	> 0.70
	C5/C2	> 0.05
3MCC, HMG, 3MGA, MCD, BKT, and 2M3HBA	C5OH	> 0.65 umol/L
	C5OH/C8	> 12.0
	C5OH/C0	> 0.026
GA-I	C5DC	> 0.32 umol/L
	C5DC/C5OH	> 2.0
	C5DC/C8	> 4.0

Reported Abnormal Ranges may change slightly with reagent kit lot changes.

Feeding Effect: Protein feeding is helpful in detecting the condition as it challenges the metabolic pathways involved and causes the identifying markers to elevate above the normal cutoff levels allowing detection of the disorder. The optimum collection time for the newborn screening sample is between 24 and 48 hours after birth, and sufficient protein feeding has taken place by then. This includes TPN feeding, which contains amino acids.

Timing Effect: The recommended sample collection time is between 24 and 48 hours after birth. If the sample is collected before 24 hours of age, then a second screening sample is required after 24 hours of age.

We have special sample collection guidelines for premature, sick, low birth-weight, and NICU infants in regards to minimizing interferences from factors causing false positives in that population; while at the same time upholding prompt identification of true disorders (see NICU guidelines on this web-site).

Confirmation: Screening results that indicate a low risk for an organic acid disorder require only a repeat newborn screening test. This means that only a slight elevation of one of the markers was detected on the initial screening test, and that specific diagnostic testing does not appear necessary. Our cutoffs are set low enough so that some normal infants (sometimes carriers of the disorder) will be flagged for retesting. If, however, the infant is sick or displays signs of metabolic

distress, the physician may wish to conduct diagnostic testing instead of, or in addition to the repeat screen.

Screening results that indicate a moderate to high risk for an organic acid disorder are considered "presumptive positive" and are immediately phoned and faxed to the physician of record. The doctor is then referred to our contracted genetic referral centers for expert advice on the disorder in question and is informed on what confirmatory diagnostic testing should be done to rule out the disorder, and what precautionary measures should be taken until the confirmatory results are completed.

Treatment: Patients with organic acid disorders are treated with a low-protein diet, and in some cases, supplementation with carnitine and/or vitamins. Infants with suspected organic acidemias should in most, if not all, cases be transferred to a major medical center as quickly as possible. The investigations and management are very complicated. Death or permanent neurological deficits can occur rapidly in untreated cases. Early identification and treatment of patients with an organic acid disorder can prevent recurring episodes of metabolic crises.

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