The Great Plains Laboratory, Inc.

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Requisition #:	303497	*Physician:*	
Patient Name:	Jonathan Barnett	*Date of Collection:*	6/5/2013
Patient Age:	56	*Time of Collection:*	06:30 AM
Patient Sex:	M	*Print Date:*	06/12/2013

Organic Acids Test - Nutritional and Metabolic Profile

	Metabolic Markers in Urine	Reference Range (mmol/mol creatinine)		Patient	Reference Population - Males Age 13 and Over
Intestinal Microbial Overgrowth					
Yeast and Fungal Markers					
1	Citramalic	0.11 - 2.0		0.80	0.80
2	5-Hydroxymethyl-2-furoic	≤ 18		4.7	4.7
3	3-Oxoglutaric	≤ 0.11		0	0.00
4	Furan-2,5-dicarboxylic	≤ 13		11	11
5	Furancarbonylglycine	≤ 2.3		0.31	0.31
6	Tartaric	≤ 5.3	H	5.4	5.4
7	Arabinose	≤ 20	H	81	81
8	Carboxycitric	≤ 20		5.2	5.2
9	Tricarballylic	≤ 0.58		0	0.00
Malabsorption and Bacterial Markers					
10	2-Hydroxyphenylacetic	0.03 - 0.47		0.22	0.22
11	4-Hydroxyphenylacetic	≤ 18		18	18
12	4-Hydroxybenzoic	0.01 - 0.73		0.64	0.64
13	4-Hydroxyhippuric	≤ 14		6.7	6.7
14	Hippuric	≤ 241	H	739	739
15	3-Indoleacetic	≤ 6.8		0.86	0.86
16	Succinic	≤ 5.3		3.7	3.7
17	HPHPA (Clostridia Marker)	≤ 102	H	160	160
18	4-Cresol (C. difficile)	≤ 39		7.7	7.7
19	DHPPA (Beneficial Bacteria)	≤ 0.23		0.14	0.14

Testing performed by The Great Plains Laboratory, Inc., Lenexa, Kansas. The Great Plains Laboratory has developed and determined the performance characteristics of this test. This test has not been evaluated by the U.S. FDA; the FDA does not currently regulate such testing.

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Metabolic Markers in Urine		Reference Range (mmol/mol creatinine)		Patient	Reference Population - Males Age 13 and Over
Oxalate Metabolites					
20	Glyceric	0.21 - 4.9		1.8	1.8
21	Glycolic	18 - 81		79	79
22	Oxalic	8.9 - 67		59	59
Glycolytic Cycle Metabolites					
23	Lactic	0.74 - 19		12	12
24	Pyruvic	0.28 - 6.7		3.3	3.3
25	2-Hydroxybutyric	≤ 1.2		0.77	0.77
Krebs Cycle Metabolites					
26	Succinic	≤ 5.3		3.7	3.7
27	Fumaric	≤ 0.49		0.29	0.29
28	Malic	≤ 1.1		0	0.00
29	2-Oxoglutaric	≤ 18		17	17
30	Aconitic	4.1 - 23		18	18
31	Citric	2.2 - 260		240	240
Neurotransmitter Metabolites					
32	Homovanillic (HVA) *(dopamine)*	0.39 - 2.2		1.9	1.9
33	Vanillylmandelic (VMA) *(norepinephrine, epinephrine)*	0.53 - 2.2		1.2	1.2
34	HVA / VMA Ratio	0.32 - 1.4	H	1.6	1.6
35	5-Hydroxyindoleacetic (5-HIAA) *(serotonin)*	≤ 2.9	H	27	27
36	Quinolinic	0.52 - 2.4	H	3.8	3.8
37	Kynurenic	0.12 - 1.8	H	1.9	1.9
38	Quinolinic / 5-HIAA Ratio	≤ 2.5		0.14	0.14
Pyrimidine Metabolites - Folate Metabolism					
39	Uracil	≤ 6.9		2.5	2.5
40	Thymine	≤ 0.36		0	0.00

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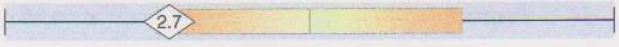
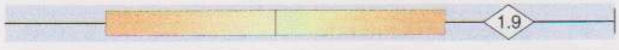
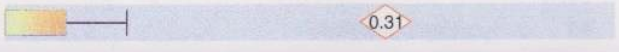
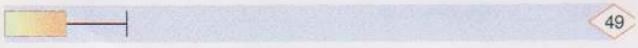
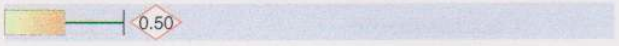
Metabolic Markers in Urine		Reference Range (mmol/mol creatinine)		Patient	Reference Population - Males Age 13 and Over
Ketone and Fatty Acid Oxidation					
41	3-Hydroxybutyric	≤ 1.9		1.5	
42	Acetoacetic	≤ 10		2.7	
43	4-Hydroxybutyric	≤ 4.3		2.8	
44	Ethylmalonic	0.13 - 2.7		2.1	
45	Methylsuccinic	≤ 2.3		1.9	
46	Adipic	≤ 2.9	H	3.3	
47	Suberic	≤ 1.9	H	6.4	
48	Sebacic	≤ 0.14	H	0.31	
Nutritional Markers					
Vitamin B12					
49	Methylmalonic *	≤ 2.3		1.6	
Vitamin B6					
50	Pyridoxic (B6)	≤ 26		12	
Vitamin B5					
51	Pantothenic (B5)	≤ 5.4	H	49	
Vitamin B2 (Riboflavin)					
52	Glutaric *	≤ 0.43	H	0.50	
Vitamin C					
53	Ascorbic	10 - 200		199	
Vitamin Q10 (CoQ10)					
54	3-Hydroxy-3-methylglutaric *	≤ 26		15	
Glutathione Precursor and Chelating Agent					
55	N-Acetylcysteine (NAC)	≤ 0.13		0	
Biotin (Vitamin H)					
56	Methylcitric *	0.15 - 1.7		1.4	

* *A high value for this marker may indicate a deficiency of this vitamin.*

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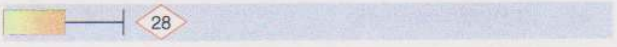
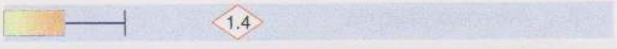
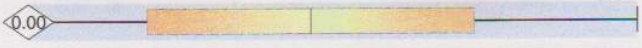
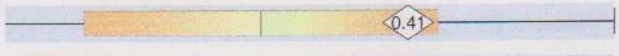
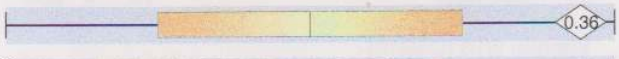
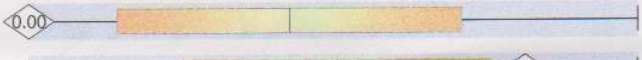
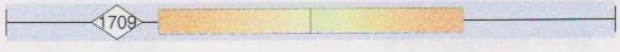
Metabolic Markers in Urine		Reference Range (mmol/mol creatinine)		Patient	Reference Population - Males Age 13 and Over
Indicators of Detoxification					
57	Pyroglutamic	5.7 - 25	H	28	
58	Orotic	≤ 0.46		0.30	
59	2-Hydroxyhippuric	≤ 0.86	H	1.4	
Amino Acid Metabolites					
60	2-Hydroxyisovaleric	≤ 0.41		0	
61	2-Oxoisovaleric	≤ 1.5		0	
62	3-Methyl-2-oxovaleric	≤ 0.56		0	
63	2-Hydroxyisocaproic	≤ 0.39		0.05	
64	2-Oxoisocaproic	≤ 0.34		0	
65	2-Oxo-4-methiolbutyric	≤ 0.14		0.11	
66	Mandelic	≤ 0.09		0	
67	Phenyllactic	≤ 0.10		0	
68	Phenylpyruvic	0.02 - 1.4		1.3	
69	Homogentisic	≤ 0.23		0	
70	4-Hydroxyphenyllactic	≤ 0.62		0.41	
71	N-Acetylaspartic	≤ 2.5		0	
72	Malonic	≤ 9.9		3.5	
73	3-Methylglutaric	0.02 - 0.38		0.36	
74	3-Hydroxyglutaric	≤ 4.6		0	
75	3-Methylglutaconic	0.38 - 2.0		1.7	
Bone Metabolites					
76	Phosphoric	1 000 - 4 900		1 709	

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Indicator of Fluid Intake

77	*Creatinine	90	mg/dL	

*The creatinine test is performed to adjust metabolic marker results for differences in fluid intake. Urinary creatinine has limited diagnostic value due to variability as a result of recent fluid intake. Samples are rejected if creatinine is below 20 mg/dL unless the client requests results knowing of our rejection criteria.

Explanation of Report Format

The reference ranges for organic acids were established using samples collected from typical individuals of all ages with no known physiological or psychological disorders. The ranges were determined by calculating the mean and standard deviation (SD) and are defined as ± 2SD of the mean. Reference ranges are age and gender specific, consisting of Male Adult (≥13 years), Female Adult (≥13 years), Male Child (<13 years), and Female Child (<13 years).

There are two types of graphical representations of patient values found in the new report format of both the standard Organic Acids Test and the Microbial Organic Acids Test.

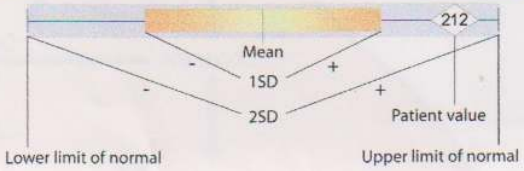
The first graph will occur when the value of the patient is within the reference (normal) range, defined as the mean plus or minus two standard deviations.

The second graph will occur when the value of the patient exceeds the upper limit of normal. In such cases, the graphical reference range is "shrunk" so that the degree of abnormality can be appreciated at a glance. In this case, the lower limits of normal are not shown, only the upper limit of normal is shown.

In both cases, the value of the patient is given to the left of the graph and is repeated on the graph inside a diamond. If the value is within the normal range, the diamond will be outlined in black. If the value is high or low, the diamond will be outlined in red.

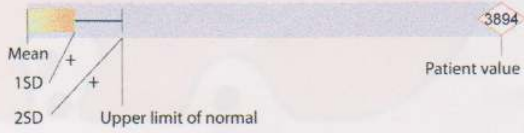
Example of Value Within Reference Range

Metabolic Markers in Urine	Reference Range (mmol/mol creatinine)	Patient Result	Reference Range - Males Age 13 and Under
Intestinal Microbial Overgrowth			
HPHPA (Clostridia marker)	< 219 .9	212	

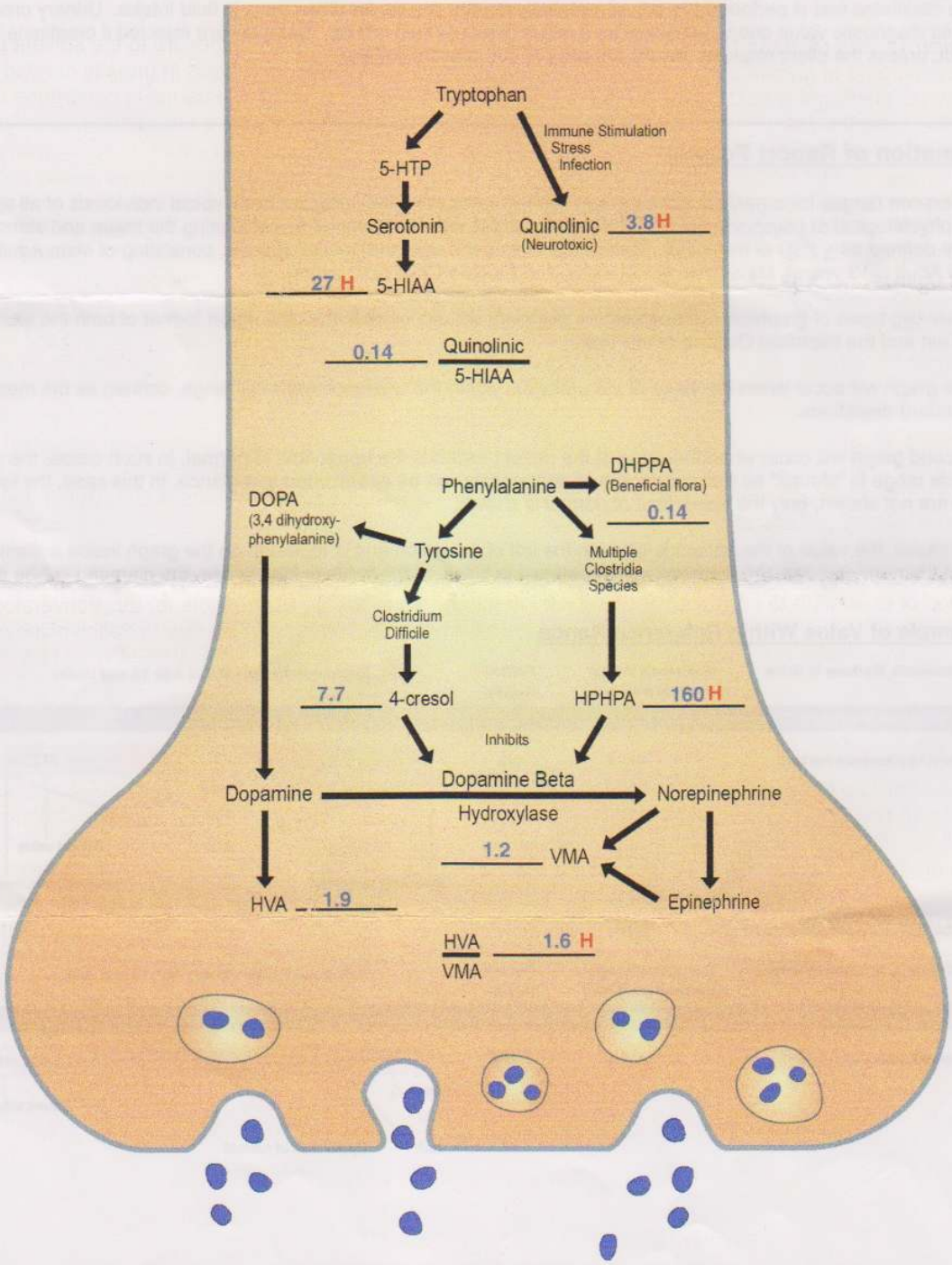


Example of Elevated Value

Metabolic Markers in Urine	Reference Range (mmol/mol creatinine)		Patient Result	Reference Range - Males Age 13 and Under
Intestinal Microbial Overgrowth				
HPHPA (Clostridia marker)	< 219 .9	H	3894	



Neurotransmitter Metabolism Markers



The diagram contains the patient's test results for neurotransmitter metabolites and shows their relationship with key biochemical pathways within the axon terminal of nerve cells. The effect of microbial byproducts on the blockage of the conversion of dopamine to norepinephrine is also indicated.

Interpretation

High yeast/fungal metabolites (Markers 1,2,3,4,5,6,7,8) indicate a yeast/fungal overgrowth of the gastrointestinal tract. Prescription or natural (botanical) anti-fungals, along with supplementation of high potency multi-strain probiotics (20-50 billion cfu's), may reduce yeast/fungal levels.

High hippuric acid (Marker 14) may derive from food, GI bacterial activity, or exposure to the solvent toluene. Hippuric acid is a conjugate of glycine and benzoic acid formed in the liver. Most hippuric acid in urine is derived from microbial breakdown of chlorogenic acid to benzoic acid. Chlorogenic acid is a common substance in beverages and in many fruits and vegetables, including apples, pears, tea, coffee, sunflower seeds, carrots, blueberries, cherries, potatoes, tomatoes, eggplant, sweet potatoes, and peaches. Benzoic acid is present in high amounts in cranberry juice and is a food preservative. The workplace is the most common source of toluene exposure, but toluene may be absorbed from outgassing of new carpets and other building materials, or absorbed during recreational abuse of solvents such as glue-sniffing. Because most hippuric acid in urine is from GI sources, this marker is a poor indicator of toluene exposure and is being replaced by other markers in occupational safety testing. Bacterial overgrowth can be treated with natural anti-bacterial agents and/or probiotics (30-50 billion cfu's) that include *Lactobacillus rhamnosus.*

High HPHPA (3-(3-hydroxyphenyl)-3-hydroxypropionic acid) (Marker 17) is associated with behavioral, GI, and/or neuropsychiatric effects. GI symptoms may include diarrhea or constipation. Neuropsychiatric effects are more common when values exceed 500 mmol/mol creatinine. HPHPA is an abnormal phenylalanine metabolite produced by GI bacteria of the *Clostridia* genus, including *C. sporogenes, C. botulinum, C. caloritolerans, C. mangenoti, C. ghoni, C. bifermentans, C. difficile, and C. sordelli.* Phenylalanine or tyrosine supplements should be avoided because of the possibility of conversion to HPHPA or other toxic byproducts. In most cases, *Clostridia* overgrowth can be controlled by probiotics supplementation, with 30 billion cfu's/day or more of *Lactobacillus rhamnosus GG* (Culturelle) and/or at least 2-6 billion cfu's/day of *Saccharomyces boulardii.*

High HVA/VMA ratio (Marker 34) The most common reason for an elevation of the HVA/VMA ratio is the decreased conversion of dopamine to norepinephrine and epinephrine. The enzyme responsible for this conversion, dopamine betahydroxylase, is copper and vitamin C dependent, so an elevated ratio could be due to deficiencies of these cofactors. Another common factor is inhibition of this enzyme by *Clostridia* byproducts. A high HPHPA would be consistent with the latter explanation.

VMA levels below the mean (Marker 33) may indicate lower production of the neurotransmitter norepinephrine or the hormone adrenaline, perhaps due to low dietary intake of the amino acid precursors phenylalanine or tyrosine. Vanylmandelic acid (VMA) is a metabolite of norepinephrine or adrenaline. Low VMA may also result from blocked conversion of dopamine to norepinephrine by *Clostridia* metabolites. Supplementation with phenylalanine or tyrosine may be beneficial. Enzyme cofactors magnesium, B6 (pyridoxine) or biopterin may also be deficient and respond to supplementation.

High 5-hydroxyindoleacetic acid (5-HIAA) (Marker 35) may occur in celiac or tropical sprue, carcinoid tumors, or from ingestion of foods high in serotonin, such as avocado, banana, tomato, plum, walnut, pineapple or eggplant. Elevated values may also result from supplementing with tryptophan itself or 5-hydroxy-tryptophan (5-HTP); if this is the case, a high value does not necessarily indicate the need to reduce or eliminate supplementation. It is possible that excessive tryptophan intake can lead to overproduction of the neurotoxic and inflammatory metabolite quinolinic acid. (See quinolinic acid value and interpretation.)

High quinolinic acid (Marker 36) may be a sign of inflammation and/or neural excitotoxicity. Quinolinic acid is derived from the amino acid tryptophan and is neurotoxic at high levels. As an excitotoxic stimulant of certain brain cells that have NMDA-type receptors, high quinolinic acid may cause nerve cell death with continuous stimulation. Brain toxicity due to quinolinic acid has been implicated in Alzheimer's disease, autism, Huntington's disease, stroke, dementia of old age, depression, HIV-associated dementia, and schizophrenia. High levels of quinolinic acid may inhibit heart contractions, cause lipid peroxidation in the brain, and increase apoptosis (programmed cell death) of astrocytes in human brain. The level of quinolinic acid is also highly correlated with the degree of arthritis impairment.

Quinolinic acid is also a metal chelator, and inhibits enzymes that allow the body to produce glucose when needed. Excessive immune stimulation and chronic inflammation, resulting in overproduction of cytokines like interferon, stimulates overproduction of quinolinic acid. However, quinolinic acid is an important intermediate in making the essential nutritional cofactor nicotinamide adenine dinucleotide (NAD), which is also derived from niacin (B3). Phthalates inhibit the conversion of quinolinic acid to NAD.

Treatment of excessive levels of quinolinic acid can be achieved by multiple approaches: reducing tryptophan supplements, preventing repeated infections and subsequent immune overstimulation by: supplementation with colostrum, transfer factor and probiotics; reducing the use of immune modulators like interferon that increase quinolinic acid production; or reducing the numbers of vaccines given at one time or increasing the interval between vaccinations. In addition, the drug deprenyl or the dietary supplements carnitine, melatonin, capsaicin, turmeric (curcumin) and garlic may reduce brain damage caused by quinolinic acid. Niacin (nicotinic acid) and niacinamide may also reduce quinolinic acid production by decreasing tryptophan shunting to the quinolinic acid pathway. Inositol hexaniacinate as an adult dose of 500-1000 mg does not cause niacin flush. A high quinolinic acid/ 5-hydroxyindoleacetic acid ratio would be indicative of immune overstimulation and/or phthalate toxicity.

High kynurenic acid (Marker 37) may result from vitamin B-6 (pyridoxine) deficiency, immune stimulation or ingestion of tryptophan supplements. The kynurenine pathway is the main path of tryptophan metabolism. Although kynurenic acid may be elevated in vitamin B-6 (pyridoxine) deficiency, excretion of pyridoxic acid itself, as the major metabolite of B-6, is a much better marker for deficiency. Kynurenine (KYN) is the central compound of the pathway which splits into two separate branches: to kynurenic acid and to quinolinic acid, the precursor of the coenzyme NAD. Endogenous kynurenic acid is an antagonist to the excitatory amino acid alpha 7-nicotinic acetylcholine and to N-methyl-D-aspartate (NMDA) receptors. In several studies, kynurenic acid has been protective against the neurotoxic effects of quinolinic acid, which is a specific agonist of NMDA receptors and a potent producer of free radicals. The pathogenesis of several neurodegenerative disorders has been demonstrated to involve imbalances in the kynurenine pathway, including Alzheimer's disease, Parkinson disease, multiple sclerosis, and amyotrophic laterosclerosis (ALS).

High ethylmalonic, methylsuccinic, adipic, suberic, or sebacic acids (Markers 44,45,46,47,48) may be due to fatty acid oxidation disorders, carnitine deficiency, fasting, or to increased intake of the medium-chain triglycerides found in coconut oil, MCT oil, and some infant formulas. The fatty acid oxidation defects are associated with hypoglycemia, apnea episodes, lethargy, and coma. [An acyl carnitine profile (Duke University Biochemical Genetics Laboratory, http://medgenetics.pediatrics.duke.edu) can rule out fatty acid oxidation defects.] Regardless of cause, supplementation with L-carnitine or acetyl-L-carnitine (500-1000 mg per day) may be beneficial.

High pantothenic acid (B5) (Marker 51) indicates high recent intake of pantothenic acid. Pantothenic acid is an essential B vitamin. Since some individuals may require very high doses of pantothenic acid, high values do not necessarily indicate the need to reduce pantothenic acid intake.

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High glutaric acid (Marker 52) can result from glutaric acidemias, fatty acid oxidation defects, riboflavin deficiency, ingestion of medium-chain triglycerides, metabolic effects of valproic acid (Depakene), and celiac disease. The genetic disorders are usually diagnosed in children but have occasionally been detected in adults. The probability of a genetic disease is higher when values exceed 10 mmol/mol creatinine but such diseases may also be present with lower urine values. DNA tests have been developed for the confirmation of both types of genetic disorders but may not be commercially available. This compound may be elevated in about 10% of children with autism. Regardless of the cause, supplementation with riboflavin (20-100 mg/day) and coenzyme Q-10 (50-100 mg/day) may be beneficial.

Glutaric acidemia type I is associated with elevations of 3-hydroxyglutaric and glutaconic acid. Normal values of 3-hydroxyglutaric acid greatly reduce but do not completely eliminate the possibility of glutaric acidemia type I. This disease has been associated with clinical symptoms ranging from near normal to encephalopathy, cerebral palsy, and other neurological abnormalities. Some individuals with glutaric acidemia type I have developed bleeding in the brain or eyes that may be mistaken for the effects of child abuse. Treatment of this disorder includes special diets low in lysine and carnitine supplementation.

Glutaric academia type II, also called acyl-CoA dehydrogenase deficiency, caused by a genetic defect in one of the mitochondrial electron transport proteins, is associated with dysmorphic features, seizures, hypoglycemia, and developmental delay. Glutaric acidemia II is commonly associated with elevations of 2-hydroxyglutaric acid as well as isovalerylglycine, hexanoylglycine, isobutyrylglycine, ethylmalonic acid, methylsuccinic acid, and adipic, suberic, and sebacic acids.

High or Low Pyroglutamic acid (Marker 57)

High pyroglutamic acid

Pyroglutamic acid is formed from intracellular gamma-glutamylcysteine conversion to pyroglutamic acid. This conversion is regulated by **intracellular** glutathione. When intracellular glutathione is low or there is a deficiency of glutathione synthetase, **greater** amounts of gamma-glutamylcysteine and pyroglutamic acid are formed. Intracellular glutathione deficiency and high pyroglutamic acid are commonly caused by moderate doses of acetaminophen (paracetamol), vigabatrin or antibiotics (flucloxacillin, netimicin). **High** pyroglutamic acid may also be caused by genetic deficiency of the enzyme oxoprolinase which breaks down pyroglutamic acid (5-oxoproline) and may also be associated with: urea cycle disorders; propionic acidemia; hawkinsinuria; Stevens-Johnson syndrome with severe burns; homocystinuria; prematurity; glycine deficiency; or infants on synthetic formulas. High pyroglutamic acid due to intracellular glutathione deficiency because of genetic deficiency or acetaminophen toxicity can be treated with the supplement N-acetyl cysteine (NAC). Administration of NAC is beneficial in preventing or mitigating hepatic injury caused by acetaminophen through stimulation of glutathione synthesis, enhancement of nontoxic routes of acetaminophen metabolism, detoxifying the toxic acetaminophen metabolite, and free radical scavenging. Individuals using acetaminophen on a regular basis may wish to take prophylactic doses of NAC with acetaminophen.

Low pyroglutamic acid

Other gamma-glutamyl amino acid conjugates (peptides) are formed from the condensation of **extracellular** glutathione with extracellular amino acids, forming gamma-glutamyl amino acid conjugates that are transferred into the cells, utilizing the cell membrane enzyme gamma-glutamyl transpeptidase. Once inside the cells, these gamma glutamyl conjugates may be converted to pyroglutamic acid. A low level of **extracellular** glutathione or a deficiency of gamma-glutamyl transpeptidase may result in a **deficiency** of pyroglutamic acid. Deficiency of the enzyme gammaglutamyl cyclotransferase may also cause deficiency of pyroglutamic acid.

Summary of both low and high pyroglutamic acid

An intracellular **deficiency of glutathione** raises pyroglutamic acid while extracellular **deficiency** of glutathione may **lower** pyroglutamic acid. Genetic disorders of glutathione metabolism and/or drug toxicity may result in pyroglutamic acid at concentrations of 1000 mmol/mol creatinine or higher. Even at therapeutic values, acetaminophen commonly elevates pyroglutamic acid to values 100 times the upper limit of normal due to depletion of intracellular glutathione.

Supplementation with reduced glutathione, N-acetyl L-cysteine, lipoic acid, and vitamin C (buffered) can raise glutathione levels. Selenium is essential to the antioxidant activity of glutathione; under most circumstances, adequate selenium supplementation can be obtained from a quality multivitamin. To prevent oxidative stress, antioxidants including vitamin C (1000 mg/day), vitamin E (400mg/day), beta-carotene, and grape seed extract, are recommended.

High 2-hydroxyhippuric acid (Marker 59) may result after ingestion of aspartame (Nutrasweet®) or salicylates (aspirin), or from GI bacteria converting tyrosine or phenylalanine to salicylic acid. 2-Hydroxyhippuric acid is a conjugate of hydroxybenzoic acid (salicylic acid) and glycine.

Low values for amino acid metabolites (Markers 60-75) indicate the absence of genetic disorders of amino acid metabolism. These markers are deamination (ammonia removed) byproducts that are very elevated only when a key enzyme has low activity; slight elevations may indicate a genetic variation or heterozygous condition which may be mitigated with diet or supplementation. Low values are not associated with inadequate protein intake and have not been proven to indicate specific amino acid deficiencies.