The Great Plains Laboratory, Inc.

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Requisition #:	315030	*Physician:*	
Patient Name:	Jonathan Barnett	*Date of Collection:*	9/18/2013
Patient Age:	57	*Time of Collection:*	07:00 AM
Patient Sex:	M	*Print Date:*	09/25/2013

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	H	2.3	2.3
2	5-Hydroxymethyl-2-furoic	≤ 18	H	26	26
3	3-Oxoglutaric	≤ 0.11	H	0.13	0.13
4	Furan-2,5-dicarboxylic	≤ 13	H	19	19
5	Furancarbonylglycine	≤ 2.3		2.2	2.2
6	Tartaric	≤ 5.3		1.5	1.5
7	Arabinose	≤ 20	H	88	88
8	Carboxycitric	≤ 20		5.0	5.0
9	Tricarballylic	≤ 0.58		0.44	0.44
Malabsorption and Bacterial Markers					
10	2-Hydroxyphenylacetic	0.03 - 0.47		0.44	0.44
11	4-Hydroxyphenylacetic	≤ 18	H	23	23
12	4-Hydroxybenzoic	0.01 - 0.73	H	1.0	1.0
13	4-Hydroxyhippuric	≤ 14		14	14
14	Hippuric	≤ 241	H	279	279
15	3-Indoleacetic	≤ 6.8		1.6	1.6
16	Succinic	≤ 5.3	H	7.9	7.9
17	HPHPA *(other pathogenic clostridia species)*	≤ 102		95	95
18	4-Cresol (C. difficile)	≤ 39		11	11
19	DHPPA (Beneficial Bacteria)	≤ 0.23		0.11	0.11

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.

C# 018283

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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	H	5.1	5.1
21	Glycolic	18 - 81		34	34
22	Oxalic	8.9 - 67	H	286	286
Glycolytic Cycle Metabolites					
23	Lactic	0.74 - 19		8.1	8.1
24	Pyruvic	0.28 - 6.7		1.5	1.5
25	2-Hydroxybutyric	≤ 1.2		0.59	0.59
Krebs Cycle Metabolites					
26	Succinic	≤ 5.3	H	7.9	7.9
27	Fumaric	≤ 0.49		0.24	0.24
28	Malic	≤ 1.1		0.75	0.75
29	2-Oxoglutaric	≤ 18		7.7	7.7
30	Aconitic	4.1 - 23		18	18
31	Citric	2.2 - 260		199	199
Neurotransmitter Metabolites					
32	Homovanillic (HVA) *(dopamine)*	0.39 - 2.2		2.0	2.0
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		0.84	0.84
36	Quinolinic	0.52 - 2.4	H	6.4	6.4
37	Kynurenic	0.12 - 1.8		1.4	1.4
38	Quinolinic / 5-HIAA Ratio	≤ 2.5	H	7.6	7.6
Pyrimidine Metabolites - Folate Metabolism					
39	Uracil	≤ 6.9		3.2	3.2
40	Thymine	≤ 0.36		0.11	0.11

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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		0.78	0.78
42	Acetoacetic	≤ 10		1.0	1.0
43	4-Hydroxybutyric	≤ 4.3		2.0	2.0
44	Ethylmalonic	0.13 - 2.7		2.3	2.3
45	Methylsuccinic	≤ 2.3	H	2.9	2.9
46	Adipic	≤ 2.9	H	4.1	4.1
47	Suberic	≤ 1.9	H	5.2	5.2
48	Sebacic	≤ 0.14	H	0.24	0.24
Nutritional Markers					
Vitamin B12					
49	Methylmalonic ✱	≤ 2.3		1.0	1.0
Vitamin B6					
50	Pyridoxic (B6)	≤ 26		6.7	6.7
Vitamin B5					
51	Pantothenic (B5)	≤ 5.4	H	17	17
Vitamin B2 (Riboflavin)					
52	Glutaric ✱	≤ 0.43	H	0.65	0.65
Vitamin C					
53	Ascorbic	10 - 200	L	7.9	7.9
Vitamin Q10 (CoQ10)					
54	3-Hydroxy-3-methylglutaric ✱	≤ 26		15	15
Glutathione Precursor and Chelating Agent					
55	N-Acetylcysteine (NAC)	≤ 0.13		0.04	0.04
Biotin (Vitamin H)					
56	Methylcitric ✱	0.15 - 1.7	H	2.4	2.4

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

Biotin!

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Metabolic Markers in Urine		Reference Range (mmol/mol creatinine)		Patient	Reference Population - Males Age 13 and Over
Indicators of Detoxification					
Glutathione					
57	Pyroglutamic *	5.7 - 25		25	25
Ammonia Excess					
58	Orotic	≤ 0.46		0.33	0.33
59	2-Hydroxyhippuric	≤ 0.86		0.43	0.43
Amino Acid Metabolites					
60	2-Hydroxyisovaleric	≤ 0.41		0	0.00
61	2-Oxoisovaleric	≤ 1.5		0	0.00
62	3-Methyl-2-oxovaleric	≤ 0.56		0.33	0.33
63	2-Hydroxyisocaproic	≤ 0.39		0.05	0.05
64	2-Oxoisocaproic	≤ 0.34		0	0.00
65	2-Oxo-4-methiolbutyric	≤ 0.14		0.05	0.05
66	Mandelic	≤ 0.09	H	0.20	0.20
67	Phenyllactic	≤ 0.10		0.02	0.02
68	Phenylpyruvic	0.02 - 1.4		0.88	0.88
69	Homogentisic	≤ 0.23		0.02	0.02
70	4-Hydroxyphenyllactic	≤ 0.62		0.56	0.56
71	N-Acetylaspartic	≤ 2.5		1.3	1.3
72	Malonic	≤ 9.9		0	0.00
73	3-Methylglutaric	0.02 - 0.38		0.35	0.35
74	3-Hydroxyglutaric	≤ 4.6		0.28	0.28
75	3-Methylglutaconic	0.38 - 2.0		1.5	1.5
Bone Metabolites					
76	Phosphoric	1 000 - 4 900		2 147	2147

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

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Indicator of Fluid Intake

77	*Creatinine	114	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).

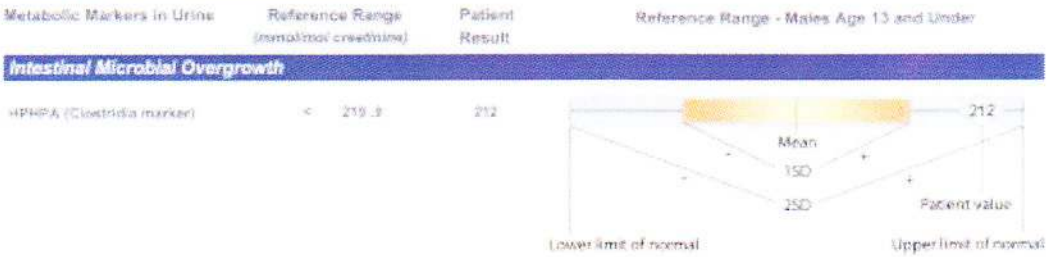
There are two types of graphical representations of patient values found in the new report format of both the standard Organic Acids Test and the Microbial Organic Acids Test.

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.

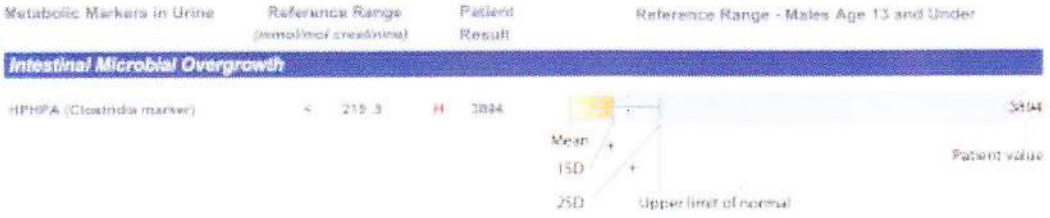
The second graph will occur when the value of the patient exceeds the upper limit of normal. In such cases, the graphical reference range is "shrunk" so that the degree of abnormality can be appreciated at a glance. In this case, the lower limits of normal are not shown, only the upper limit of normal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



Example of Elevated Value



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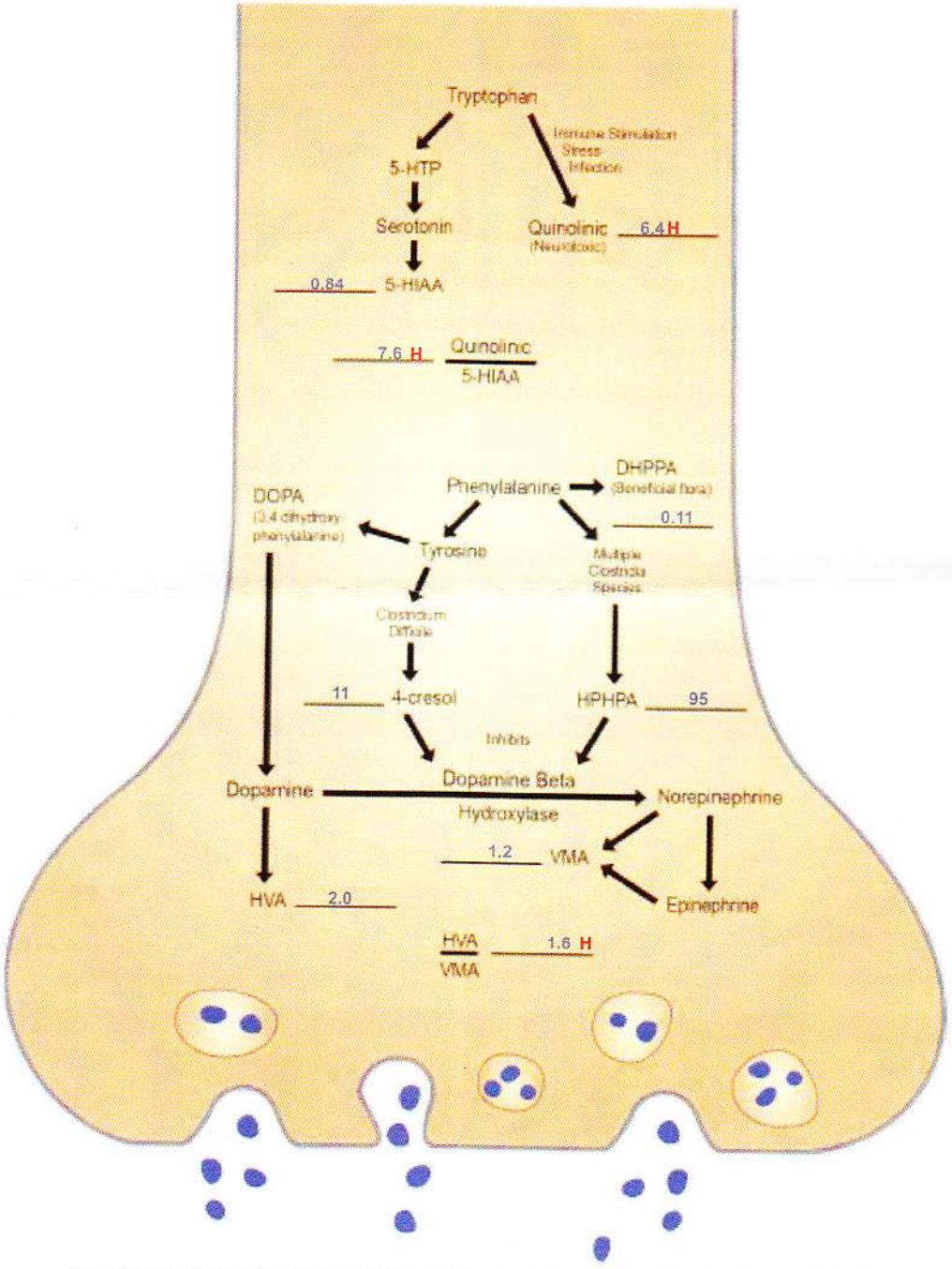
Neurotransmitter Metabolism Markers



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.

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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 4-hydroxyphenylacetic acid (Marker 11) is a tyrosine product of GI bacteria that is associated with bacterial overgrowth and small bowel disease (Chalmers et al, Clin Chem 25:1791,1979). Elevated values may also indicate celiac disease. Suggest supplementation with 20-30 billion cells per day of probiotics and evaluation for celiac disease.

High 4-hydroxybenzoic acid and/or 4-hydroxyhippuric acid (Markers 12,13) may be due to bacterial overgrowth of the GI tract, intake of fruits such as blueberries rich in polyphenols (anthocyanins, flavonols, and hydroxycinnamates), or may be from paraben additive exposure. Parabens are 4-hydroxybenzoic acid alkyl esters with antimicrobial properties. 4-Hydroxybenzoic acid may be excreted as its glycine conjugate 4-hydroxyhippuric acid. High levels of these paraben metabolites in urine (>10 mmol /mol creatinine) may result from excessive exposure to parabens. Parabens are common preservatives allowed in foods, drugs, cosmetics and toiletries, but they also have a long history of use in a variety of pharmaceutical products for injection, inhalation, oral, topical, rectal or vaginal administration. Some individuals experience skin reactions as most parabens are readily and completely absorbed through the skin and the GI tract. Parabens have been considered safe because of their low toxicity profile and their long history of safe use; however, recent studies challenge this view. In 1998, Routledge *et.al.*, (Toxicol.Appl.Pharmacol. **153**,12-19), reported parabens having estrogenic activity *in vitro*. A number of *in vivo* studies have further elucidated potential endocrine disruption by parabens affecting reproduction or promote tumor growth. Parabens have been found at high levels in breast cancer biopsies, although a definitive relationship with breast cancer has not been demonstrated. Parabens may contribute to mitochondrial failure by uncoupling oxidative phosphorylation and depleting cellular ATP. 4-Hydroxyhippuric acid has been found to be an inhibitor of Ca2+-ATPase in end-stage renal failure. Eliminate all sources of parabens. To accelerate paraben excretion, use sauna therapy, the Hubbard detoxification protocol employing niacin supplementation, or glutathione supplementation (oral, intravenous, transdermal, or precursors such as N-acetyl cysteine [NAC]).

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 succinic acid (Markers 16, 26) may indicate a relative deficiency of riboflavin and/or coenzyme Q10 (cofactors for succinic dehydrogenase in the Krebs cycle). Supplementation with a minimum of 20 mg riboflavin (which could be provided through a high quality multivitamin) and/or 50 mg/day of coenzyme Q10 is recommended. Clinical observation suggests that succinic acid levels also decrease after treatment for GI dysbiosis.

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High oxalic with or without elevated glyceric or glycolic acids (Markers 20,21,22) may be associated with the genetic hyperoxalurias, autism, women with vulvar pain, fibromyalgia, and may also be due to high vitamin C intake. However, kidney stone formation from oxalic acid was not correlated with vitamin C intake in a very large study. Besides being present in varying concentrations in most vegetables and fruits, oxalates, the mineral conjugate base forms of oxalic acid, are also byproducts of molds such as *Aspergillus* and *Penicillium* and probably *Candida*. If yeast or fungal markers are elevated, antifungal therapy may reduce excess oxalates. High oxalates may cause anemia that is difficult to treat, skin ulcers, muscles pains, and heart abnormalities. Elevated oxalic acid is also the result of anti-freeze (ethylene glycol) poisoning. Oxalic acid is a toxic metabolite of trichloroacetic acid and other environmental pollutants. In addition, decomposing vitamin C may form oxalates during transport or storage.

Elevated oxalate values with a concomitant increase in glycolic acid may indicate genetic hyperoxaluria (type I), whereas increased glyceric acid may indicate a genetic hyperoxaluria (type II). Elevated oxalic acid with normal levels of glyceric or glycolic metabolites rules out a genetic cause for high oxalate. However, elevated oxalates may be due to a new genetic disorder, hyperoxaluria type III.

Regardless of its source, high oxalic acid may contribute to kidney stones and may also reduce ionized calcium. Oxalic acid absorption from the GI tract may be reduced by calcium citrate supplementation before meals. Vitamin B6, arginine, vitamin E, chondroitin sulfate, taurine, selenium, omega-3 fatty acids and/or N-acetyl glucosamine supplements may also reduce oxalates and/or their toxicity. Excessive fats in the diet may cause elevated oxalate if fatty acids are poorly absorbed because of bile salt deficiency. Unabsorbed free fatty acids bind calcium to form insoluble soaps, reducing calcium's ability to bind oxalate and increase its absorption. If taurine is low in a plasma amino acid profile, supplementation with taurine (1000 mg/day) may help stimulate bile salt production (taurocholic acid), leading to better fatty acid absorption and diminished oxalate absorption.

High levels of oxalates are common in autism. Malabsorption of fat and intestinal *Candida* overgrowth are probably the major causes for elevated oxalates in this disorder. Even individuals with elevated glyceric or glycolic acids may not have a genetic disease. To rule out genetic diseases in those people with abnormally high markers characteristic of the genetic diseases, do the following steps: (1) Follow the nutritional steps indicated in this interpretation for one month; (2) If *Candida* is present, treat *Candida* for at least one month; (3) Repeat the organic acid test after abstaining from vitamin C supplements for 48 hours; (4) If the biochemical markers characteristic of genetic oxalate disorders are still elevated in the repeat test, consider DNA tests for the most common mutations of oxalate metabolism. DNA testing for type I hyperoxaluria is available from the Mayo Clinic, Rochester, MN as test #89915 "*AGXT* Gene, Full Gene Analysis" and, for the p.Gly170Arg mutation only, as # 83643 "Alanine:Glyoxylate Aminotransferase [*AGXT*] Mutation Analysis [G170R], Blood"). Another option to confirm the genetic disease is a plasma oxalate test, also available from the Mayo Clinic (Phone 507.266.5700). Plasma oxalate values greater than 50 micromol/L are consistent with genetic oxalate diseases and may serve as an alternate confirmation test.

Bone tends to be the major repository of excess oxalate in patients with primary hyperoxaluria. Bone oxalate levels are negligible in healthy subjects. Oxalate deposition in the skeleton tends to increase bone resorption and decrease osteoblast activity.

Oxalates may also be deposited in the kidneys, joints, eyes, muscles, blood vessels, brain, and heart and may contribute to muscle pain in fibromyalgia. Oxalate crystal formation in the eyes may be a source of severe eye pain in individuals with autism who may exhibit eye-poking behaviors. High oxalates in the GI tract also may significantly reduce absorption of essential minerals such as calcium, magnesium, zinc, and others.

A low oxalate diet may also be particularly useful in the reduction of body oxalates even if dysbiosis of GI flora is the major source of oxalates. Foods especially high in oxalates include spinach, beets, chocolate, soy, peanuts, wheat bran, tea, cashews, pecans, almonds, berries, and many others. A complete list of high oxalate foods is available online at <http://www.greatplainslaboratory.com/home/eng/oxalates.asp>.

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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, 4-Cresol, or other elevations of metabolites 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.

5-hydroxyindoleacetic acid (5-HIAA) levels below the mean (Marker 35) may indicate lower production of the neurotransmitter serotonin. 5-hydroxy-indoleacetic acid is a metabolite of serotonin. Low values have been correlated with symptoms of depression. Supplementation with the precursor 5-HTP (5-hydroxytryptophan) at 50-300 mg/day may be beneficial. Supplementation with tryptophan itself may form the neurotoxic metabolite quinolinic acid, however, 5-HTP is not metabolized to quinolinic acid. Excessive tryptophan supplementation has been associated with eosinophilia myalgia syndrome.

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 quinolinic acid / 5-HIAA ratio (Marker 38) indicates an imbalance of these organic acids and may be a sign of neural excitotoxicity. Quinolinic acid is an excitotoxic stimulant of certain brain cells that have NMDA-type receptors. Overstimulated nerve cells may die. 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. However, quinolinic acid is derived from the amino acid tryptophan and is an important intermediate that the body uses to make the essential nutritional cofactor nicotinamide adenine dinucleotide (NAD), which can also be derived from niacin (B3).

An elevated ratio is not specific for a particular medical condition and is commonly associated with excessive inflammation due to recurrent infections. If quinolinic acid is not elevated, low 5-HIAA from serotonin may be the source of the imbalance. Supplementation with 5-HTP may increase serotonin levels, but 5-HTP is not metabolized to quinolinic acid. Immune overstimulation, excess adrenal production of cortisol due to stress, or high exposure to phthalates may also increase the quinolinic acid/5-HIAA acid ratio.

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.

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.

Pyridoxic acid (B6) levels below the mean (Marker 50) may be associated with less than optimum health conditions (low intake, malabsorption, or dysbiosis). Supplementation with B6 (20 - 50 mg/day) or a multivitamin 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.

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.

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Ascorbic acid (vitamin C) levels below the mean (Marker 53) may indicate a less than optimum level of the antioxidant vitamin C. Suggested supplementation is 1000 mg/day of buffered vitamin C, divided into 2-3 doses.

High methylcitric acid (Marker 56) is commonly due to biotin deficiency. Biotin is an essential B vitamin. Biotin deficiency may be due to malabsorption, excessive intake of raw egg white, dietary deficiency, or dysbiosis. Methylcitric values greater than 100 mmol/mol creatinine may be due to inborn errors of metabolism involving biotin-dependent enzymes and may require biotin supplementation at very high doses. Methylcitric values of 12-100 mmol/mol creatinine may be due to biotin deficiency. A high quality multivitamin with a minimum of 300 mcg biotin per day is recommended.

High mandelic acid (Marker 66) usually results from exposure to styrene. Mandelic acid in urine samples of people exposed to styrene ranges from less than 4 to 2200 mmol/mol creatinine. Mandelic acid is the major metabolite of styrene. Styrene (vinylbenzene) is used as an intermediate in plastic synthesis. Values less than 5 mg/L are due to normal metabolism of phenylalanine or tyrosine. High concentrations of styrene cause central nervous system depression, nausea, headache, fatigue, and liver damage. When exposed to 100 ppm of styrene in air, mandelic acid in urine was found to average 1700 mmol/mol creatinine. Mandelic acid is also a metabolite of ethylbenzene, and some antispasmodic and vasodilator drugs. High values of mandelic acid also occur in phenylketonuria (PKU). Normal values of phenyllactic and phenylpyruvic acids may rule out PKU; a mild or heterozygous form of PKU might be present. Measuring serum phenylalanine will rule out PKU. Other causes may be increased dietary phenylalanine or phenylalanine supplements. Normal phenyllactic and phenylpyruvic acids indicate that styrene or drug exposure is more likely than PKU as a cause of these abnormalities. Dopamine metabolism is a target for the neurotoxic effects of some monocyclic aromatic hydrocarbons and their metabolites. Reduce exposure by eliminating plastic and styrofoam containers for cooking, reheating, eating or drinking (especially warm or hot) food or beverages. Replace these containers with glass, paper, or stainless steel whenever possible. Elimination of styrene can be accelerated by sauna treatment, reduced glutathione supplementation (oral, intravenous, transdermal, precursors such as N-acetyl cysteine [NAC]). Ascorbic acid deficiency may also be related to this abnormality since ascorbic acid is a cofactor for phenylalanine hydroxylase. Supplementation with ascorbic acid (vitamin C) at 1000 mg/day or more may be beneficial.

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.