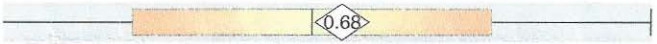
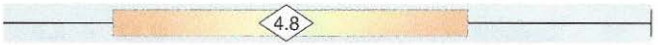
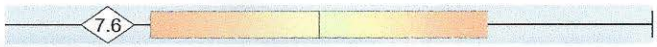
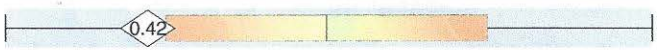
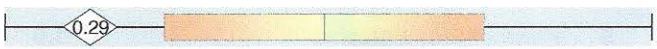
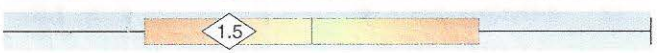
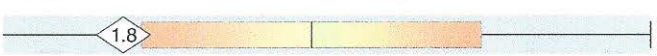
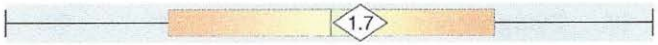
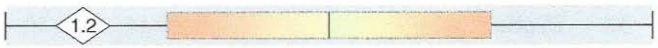
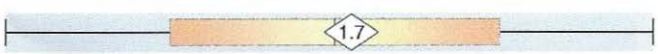
Organic Acids Test - Nutritional and Metabolic Profile

	Metabolic Markers in Urine	Reference Range (mmol/mol creatinine)		Patient	Reference Population - Females Age 13 and Over
Intestinal Microbial Overgrowth					
Yeast and Fungal Markers					
1	Citramalic	≤ 3.6		1.4	
2	5-Hydroxymethyl-2-furoic	≤ 14	H	20	
3	3-Oxoglutaric	≤ 0.33		0.13	
4	Furan-2,5-dicarboxylic	≤ 16	H	29	
5	Furancarbonylglycine	≤ 1.9		0.07	
6	Tartaric	≤ 4.5	H	31	
7	Arabinose	≤ 29	H	124	
8	Carboxycitric	≤ 29	H	64	
9	Tricarballylic	≤ 0.44	H	0.89	
Malabsorption and Bacterial Markers					
10	2-Hydroxyphenylacetic	0.06 - 0.66	H	1.1	
11	4-Hydroxyphenylacetic	≤ 19	H	26	
12	4-Hydroxybenzoic	≤ 1.3		0.68	
13	4-Hydroxyhippuric	0.79 - 17	H	22	
14	Hippuric	≤ 613		500	
15	3-Indoleacetic	≤ 11		4.8	
16	Succinic	≤ 9.3	H	11	
17	HPHPA (Clostridia Marker)	≤ 208		167	
18	4-Cresol (C. difficile)	≤ 75		0.62	
19	DHPPA (Beneficial Bacteria)	≤ 0.38		0.29	

Metabolic Markers in Urine		Reference Range (mmol/mol creatinine)		Patient	Reference Population - Females Age 13 and Over
Oxalate Metabolites					
20	Glyceric	0.77 - 7.0		5.8	
21	Glycolic	16 - 117		40	
22	Oxalic	6.8 - 101		89	
Glycolytic Cycle Metabolites					
23	Lactic	≤ 48		7.6	
24	Pyruvic	≤ 9.1		4.4	
25	2-Hydroxybutyric	0.03 - 1.8		0.42	
Krebs Cycle Metabolites					
26	Succinic	≤ 9.3	H	11	
27	Fumaric	≤ 0.94	H	1.4	
28	Malic	0.06 - 1.8		0.29	
29	2-Oxoglutaric	≤ 35		11	
30	Aconitic	6.8 - 28	H	36	
31	Citric	≤ 507	H	1 040	
Neurotransmitter Metabolites					
32	Homovanillic (HVA) *(dopamine)*	0.80 - 3.6	H	7.0	
33	Vanillylmandelic (VMA) *(norepinephrine, epinephrine)*	0.46 - 3.7		2.9	
34	HVA / VMA Ratio	0.16 - 1.8	H	2.4	
35	5-Hydroxyindoleacetic (5-HIAA) *(serotonin)*	≤ 4.3		1.5	
36	Quinolinic	0.85 - 3.9	H	6.8	
37	Kynurenic	0.17 - 2.2		1.7	
38	Quinolinic / 5-HIAA Ratio	0.42 - 2.0	H	4.7	
Pyrimidine Metabolites - Folate Metabolism					
39	Uracil	≤ 9.7		1.8	
40	Thymine	≤ 0.56		0.15	

Ketone and Fatty Acid Oxidation

41	3-Hydroxybutyric	≤ 3.1		1.7	
42	Acetoacetic	≤ 10		1.2	
43	4-Hydroxybutyric	≤ 4.8		2.0	
44	Ethylmalonic	0.44 - 2.8		1.7	
45	Methylsuccinic	0.10 - 2.2		2.0	
46	Adipic	0.04 - 3.8		1.5	
47	Suberic	0.18 - 2.2	H	4.6	
48	Sebacic	≤ 0.24	H	0.36	

Nutritional Markers

Vitamin B12

49	Methylmalonic *	≤ 2.3		2.0	

Vitamin B6

50	Pyridoxic (B6)	≤ 34	H	47	

Vitamin B5

51	Pantothenic (B5)	≤ 10		6.1	

Vitamin B2 (Riboflavin)

52	Glutaric *	0.04 - 0.36	H	2.4	

Vitamin C

53	Ascorbic	10 - 200	L	2.1	

Vitamin Q10 (CoQ10)

54	3-Hydroxy-3-methylglutaric *	0.17 - 39		32	

Glutathione Precursor and Chelating Agent

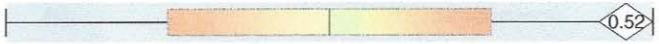
55	N-Acetylcysteine (NAC)	≤ 0.28		0.12	

Biotin (Vitamin H)

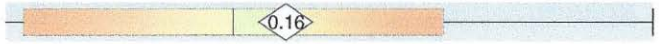
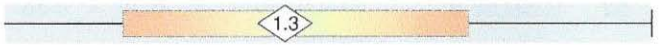
56	Methylcitric *	0.19 - 2.7		1.6	

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

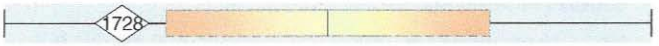
Indicators of Detoxification

57	Pyroglutamic	10 - 33		20		
58	Orotic	0.06 - 0.54		0.52		
59	2-Hydroxyhippuric	≤ 1.3		1.3		

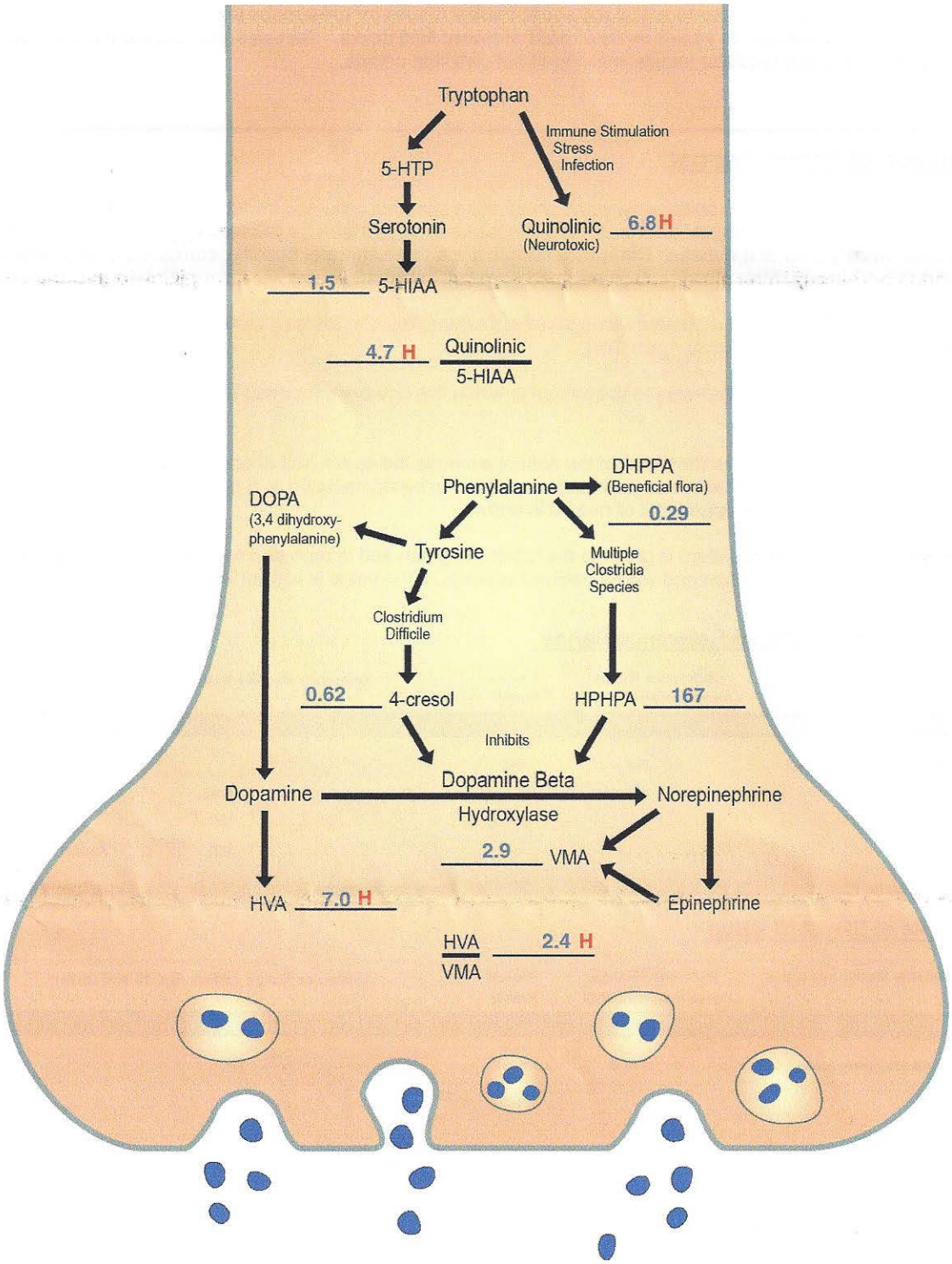
Amino Acid Metabolites

60	2-Hydroxyisovaleric	≤ 0.42		0.08		
61	2-Oxoisovaleric	≤ 2.1		0.59		
62	3-Methyl-2-oxovaleric	≤ 0.87		0.41		
63	2-Hydroxyisocaproic	≤ 0.48		0.04		
64	2-Oxoisocaproic	≤ 0.37		0.16		
65	2-Oxo-4-methiolbutyric	≤ 0.16		0.13		
66	Mandelic	≤ 0.21	H	0.34		
67	Phenyllactic	≤ 0.20	H	0.31		
68	Phenylpyruvic	0.20 - 1.9		0.66		
69	Homogentisic	≤ 0.36		0.13		
70	4-Hydroxyphenyllactic	≤ 0.80	H	1.1		
71	N-Acetylaspartic	≤ 3.0		1.3		
72	Malonic	≤ 9.7		1.8		
73	3-Methylglutaric	≤ 0.76	H	0.79		
74	3-Hydroxyglutaric	≤ 6.2		2.1		
75	3-Methylglutaconic	≤ 4.5		2.4		

Bone Metabolites

76	Phosphoric	1 000 - 5 000		1 728		

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 tricarballylic acid (*propane-1,2,3-tricarboxylic acid) *(Marker 9) could be caused by the intake of corn or corn-based food contaminated with fumonisins, a group of mycotoxins produced primarily by *F. verticillioides*, and other related species. Tricarballylic acid is released from fumonisins during passage through the gastrointestinal tract. Tricarballylic acid is an inhibitor of the enzyme aconitase and therefore interferes with the Krebs cycle. The main symptoms of aconitase deficiency are myopathy and exercise intolerance. It may also act as a magnesium chelator. Tricarballylic acid is also metabolite of a component of a substance in modified corn starch, octenylsuccinic acid, found in a number of infant formulas such as Nutramigen, Vivonex, and Pregestimil. In addition, tricarballylic acid is a byproduct of beet sugar and maple sugar refining and might appear after ingestion of these sugars. Tricarballylic acid is also released from fumonisins upon certain food processing conditions. Clinical syndromes due to the intact mycotoxin are rare and characterized by abdominal pain and diarrhea. A specific role for fumonisins in the development of neural tube defects was suggested after the appearance of a cluster of such defects in Texas associated with consumption of corn from the heavily fumonisin-contaminated 1989 corn crop. More recent studies have shown that fumonisin B1 inhibits folate metabolism in cultured cells.

High 2-hydroxyphenylacetic acid (Marker 10) is associated with intestinal bacteria overgrowth and with the genetic disease.

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 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.

High fumaric acid (Marker 27) may be due to impaired Krebs cycle function, defect of the enzyme fumarase or a defect in mitochondrial function. Recommendations for supporting mitochondrial function include supplementation with coenzyme Q-10 (300-600 mg), NAD (25-50mg), L-carnitine or acetyl-L-carnitine (1000-2000 mg), riboflavin (40-80 mg), nicotinamide (40-80 mg), biotin (4-8 mg), and vitamin E (200-400 IU's) per day. All of these supplements are known to benefit mitochondrial dysfunction.

High aconitic and citric acids (Markers 30, 31) may be due to increased intake of citric acid-containing foods, or as a result of intestinal yeast that either produce citric acid or perhaps inhibit the human citric acid cycle. Increased citric acid may also indicate depletion of glutathione, which is required for the enzyme aconitase to metabolize both aconitic and citric acids. If pyroglutamic acid is also high, consider supplements of reduced glutathione, n-acetyl cysteine (NAC), or lipoic acid.

High HVA (Marker 32) may result from toxic metal exposure (including lead, aluminum, manganese, and mercury), presumably due to increased release of dopamine from neurons. Heavy metal testing (blood or hair) might be useful to determine if such exposure is significant. Homovanillic acid (HVA), a dopamine metabolite, is often elevated due to stress-induced catecholamine output from the adrenal gland which depletes vitamin C. Supplementation with vitamin C (ascorbate) may be helpful in such cases. Elevated HVA may also result from the intake of L-DOPA, dopamine, phenylalanine, or tyrosine. If values are more than double the upper limit of normal, the possibility of catecholamine-secreting tumors can be ruled out by 24-hour VMA and/or HVA testing in urine. Even in this subgroup, the incidence of tumors is extremely rare. High HVA may be associated with *Clostridia*. If HVA is elevated and VMA is normal, avoid supplementation with phenylalanine or tyrosine until *Clostridia* is treated.

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.

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.

High pyridoxic acid (Marker 50) indicates high recent intake of vitamin B6. Pyridoxic acid is a major metabolite of vitamin B6. Because some individuals may require very high doses of vitamin B6, high values do not necessarily indicate the need to reduce vitamin B6 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.

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 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.

High phenyllactic acid (Marker 67) may indicate increased intake of dietary phenylalanine, or heterozygous (carrier state) or homozygous for the genetic disease phenylketonuria (PKU). Values observed in clinically diagnosed PKU typically exceed 200 mmol/mol creatinine. Phenyllactic acid is a metabolite of phenylalanine.

High 4-hydroxyphenyllactic acid (Marker 70) is associated with tyrosinemia, which can be due to immature development of enzymes in infants or to genetic deficiencies. Even a mild case would have levels at least of 100 mmol/mol creatinine. Values between the upper limit of normal and 100 mmol creatinine may be due to the heterozygous genetic carrier state, or mild disease or unknown physiological conditions.

High 3-methylglutaric and/or high 3-methylglutaconic acids (Markers 73,75) may be due to reduced capacity to metabolize the amino acid leucine. This abnormality is found in the genetic disease methylglutaconic aciduria and in mitochondrial disorders in which there are severe deficiencies of the respiratory complexes (Complex I, NADH ubiquinone oxidoreductase and complex IV, cytochrome c oxidase.). Small elevations may be due to impairment of mitochondrial function and may respond to the recommended supplements below. Typical results found in genetic defects are above 10 mmol/mol creatinine. A few non-genetic conditions including pregnancy and kidney failure may also produce elevation of these organic acids in urine. Confirmation of the genetic disease requires enzymes and/or DNA testing. Multiple genetic defects can cause the biochemical abnormality. Confirmation of mitochondrial disorder usually requires tissue biopsy for mitochondria testing. Symptoms differ within different types of genetic disorders, but in severe cases may include speech delay, delayed development of both mental and motor skills (psychomotor delay), metabolic acidosis, abnormal muscle tone (dystonia), and spasms and weakness affecting the arms and legs (spastic quadriparesis). Recommendations include supplementation with coenzyme Q-10 (300-600 mg), NAD 25-50mg, L-carnitine and acetyl-L-carnitine (1000-2000 mg), riboflavin (40-80 mg), nicotinamide (40-80 mg), biotin (4-8 mg), and vitamin E (200-400 IU's) per day.

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.

The nutritional recommendations in this test are not approved by the US FDA. Supplement recommendations are not intended to treat, cure, or prevent any disease and do not take the place of medical advice or treatment from a healthcare professional.

Certain uses of the compounds arabinose, citramalic, tartaric, 3-oxoglutaric, carboxycitric, 3,4-dihydroxyphenylpropionic acid, and 3-(3-hydroxyphenyl)-3-hydroxypropionic acid in their application to autism in the Organic Acid Test and Microbial Organic Acid Test are protected by USA patent 5,686,311 granted to The Great Plains Laboratory, Inc., November 11, 1997.