The Great Plains Laboratory, Inc.

William Shaw, Ph.D., Director | 11813 West 77th Street, Lenexa, KS 66214 | (913) 341-8949 | Fax (913) 341-6207

Requisition #:	777543	***Physician:***	JULIA CASSETTA
Patient Name:	Robert Stehlin	***Date of Collection:***	02/12/2020
Patient Age:	56	***Time of Collection:***	07:00 AM
Patient Sex:	M	***Print Date:***	02/20/2020

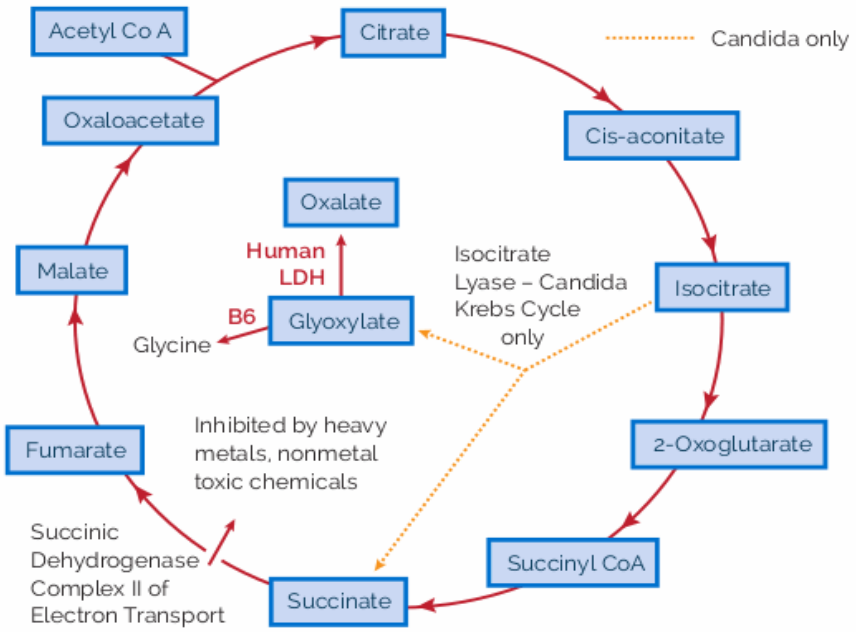
Organic Acids Test - Nutritional and Metabolic Profile

Metabolic Markers in Urine	Reference Range *(mmol/mol creatinine)*		Patient Value	Reference Population - Males Age 13 and Over
Intestinal Microbial Overgrowth				
Yeast and Fungal Markers				
1 Citramalic	0.11 - 2.0		1.3	1.3
2 5-Hydroxymethyl-2-furoic *(Aspergillus)*	≤ 18	H	73	73
3 3-Oxoglutaric	≤ 0.11		0	0.00
4 Furan-2,5-dicarboxylic *(Aspergillus)*	≤ 13	H	64	64
5 Furancarbonylglycine *(Aspergillus)*	≤ 2.3		0.11	0.11
6 Tartaric *(Aspergillus)*	≤ 5.3	H	15	15
7 Arabinose	≤ 20	H	56	56
8 Carboxycitric	≤ 20	H	21	21
9 Tricarballylic *(Fusarium)*	≤ 0.58	H	0.66	0.66
Bacterial Markers				
10 Hippuric	≤ 241	H	1,190	1190
11 2-Hydroxyphenylacetic	0.03 - 0.47		0.32	0.32
12 4-Hydroxybenzoic	≤ 0.73		0.62	0.62
13 4-Hydroxyhippuric	≤ 14		13	13
14 DHPPA (Beneficial Bacteria)	≤ 0.23	H	0.44	0.44
Clostridia Bacterial Markers				
15 4-Hydroxyphenylacetic *(C. difficile, C. stricklandii, C. lituseburense & others)*	≤ 18		11	11
16 HPHPA *(C. sporogenes, C. caloritolerans, C. botulinum & others)*	≤ 102	H	162	162
17 4-Cresol *(C. difficile)*	≤ 39		36	36
18 3-Indoleacetic *(C. stricklandii, C. lituseburense, C. subterminale & others)*	≤ 6.8		0.99	0.99

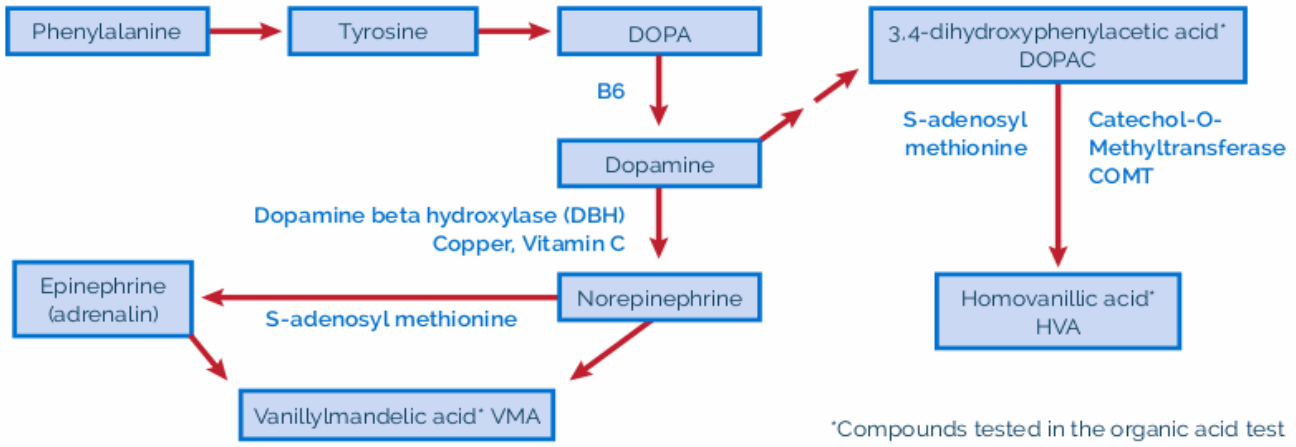
Testing performed by The Great Plains Laboratory, Inc., Lenexa, Kansas. The Great Plains Laboratory has developed and determined the performance characteristics of this test. This test has not been evaluated by the U.S. FDA; the FDA does not currently regulate such testing.

The Great Plains Laboratory, Inc.

Human Krebs Cycle showing Candida Krebs Cycle variant that causes excess Oxalate via Glyoxylate



Major pathways in the synthesis and breakdown of **catecholamine neurotransmitters** in the absence of microbial inhibitors



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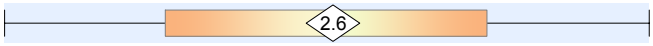
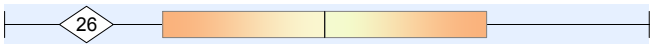
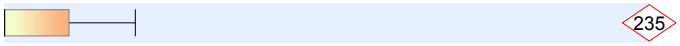
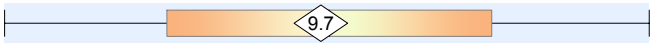
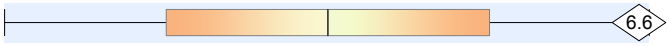
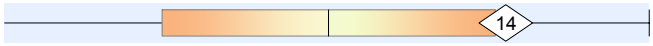
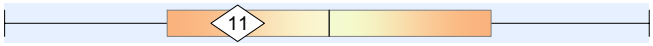
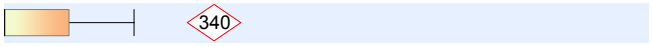
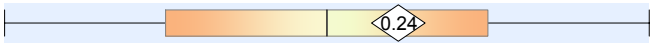
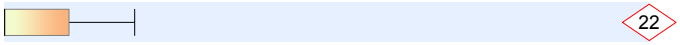
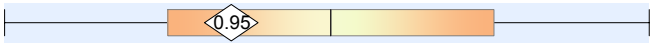
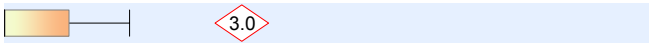
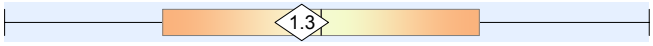
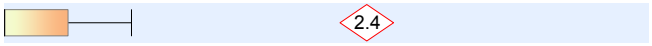
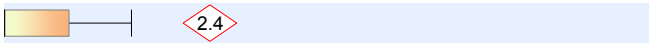
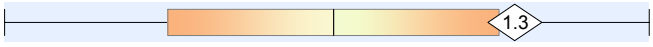
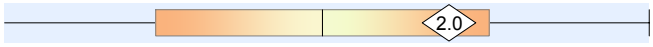
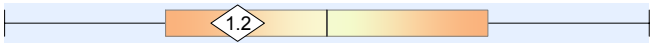
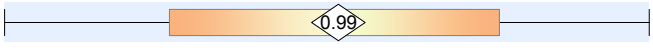
Requisition #:	777543	*Physician:*	JULIA CASSETTA
Patient Name:	Robert Stehlin	*Date of Collection:*	02/12/2020

Metabolic Markers in Urine	Reference Range *(mmol/mol creatinine)*	Patient Value	Reference Population - Males Age 13 and Over
Oxalate Metabolites			
19 Glyceric	0.21 - 4.9	2.6	
20 Glycolic	18 - 81	26	
21 Oxalic	8.9 - 67	H 235	
Glycolytic Cycle Metabolites			
22 Lactic	0.74 - 19	9.7	
23 Pyruvic	0.28 - 6.7	6.6	
Mitochondrial Markers - Krebs Cycle Metabolites			
24 Succinic	≤ 5.3	3.1	
25 Fumaric	≤ 0.49	0.28	
26 Malic	≤ 1.1	0.83	
27 2-Oxoglutaric	≤ 18	14	
28 Aconitic	4.1 - 23	11	
29 Citric	2.2 - 260	H 340	
Mitochondrial Markers - Amino Acid Metabolites			
30 3-Methylglutaric	0.02 - 0.38	0.24	
31 3-Hydroxyglutaric	≤ 4.6	H 22	
32 3-Methylglutaconic	0.38 - 2.0	0.95	
Neurotransmitter Metabolites			
Phenylalanine and Tyrosine Metabolites			
33 Homovanillic (HVA) *(dopamine)*	0.39 - 2.2	H 3.0	
34 Vanillylmandelic (VMA) *(norepinephrine, epinephrine)*	0.53 - 2.2	1.3	
35 HVA / VMA Ratio	0.32 - 1.4	H 2.4	
36 Dihydroxyphenylacetic (DOPAC) *(dopamine)*	0.27 - 1.9	H 2.4	
37 HVA/ DOPAC Ratio	0.17 - 1.6	1.3	
Tryptophan Metabolites			
38 5-Hydroxyindoleacetic (5-HIAA) *(serotonin)*	≤ 2.9	2.0	
39 Quinolinic	0.52 - 2.4	1.2	
40 Kynurenic	0.12 - 1.8	0.99	

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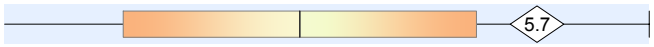
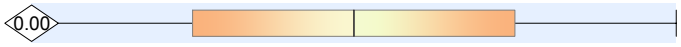
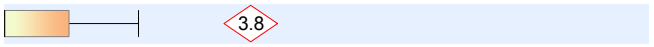
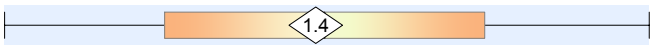
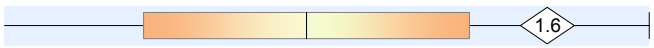
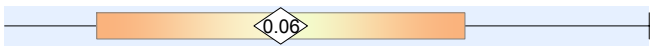
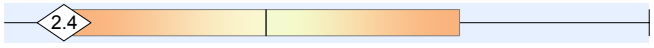
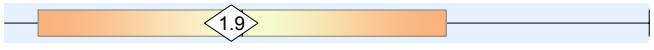
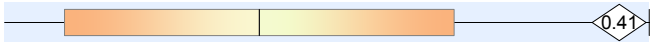
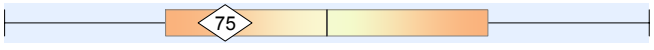
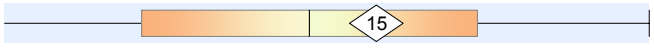
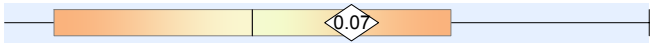
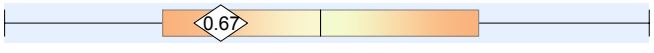
Patient Name:	Robert Stehlin	***Date of Collection:***	02/12/2020

Metabolic Markers in Urine	Reference Range *(mmol/mol creatinine)*	Patient Value	Reference Population - Males Age 13 and Over
Pyrimidine Metabolites - Folate Metabolism			
41 Uracil	≤ 6.9	5.7	
42 Thymine	≤ 0.36	0.17	
Ketone and Fatty Acid Oxidation			
43 3-Hydroxybutyric	≤ 1.9	1.3	
44 Acetoacetic	≤ 10	0	
45 Ethylmalonic	0.13 - 2.7	H 3.8	
46 Methylsuccinic	≤ 2.3	H 4.4	
47 Adipic	≤ 2.9	1.4	
48 Suberic	≤ 1.9	1.6	
49 Sebacic	≤ 0.14	0.06	
Nutritional Markers			
Vitamin B12			
50 Methylmalonic ✱	≤ 2.3	0.56	
Vitamin B6			
51 Pyridoxic (B6)	≤ 26	2.4	
Vitamin B5			
52 Pantothenic (B5)	≤ 5.4	1.9	
Vitamin B2 (Riboflavin)			
53 Glutaric ✱	≤ 0.43	0.41	
Vitamin C			
54 Ascorbic	10 - 200	75	
Vitamin Q10 (CoQ10)			
55 3-Hydroxy-3-methylglutaric ✱	≤ 26	15	
Glutathione Precursor and Chelating Agent			
56 N-Acetylcysteine (NAC)	≤ 0.13	0.07	
Biotin (Vitamin H)			
57 Methylcitric ✱	0.15 - 1.7	0.67	

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

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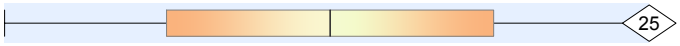
Requisition #:	777543	***Physician:***	JULIA CASSETTA
Patient Name:	Robert Stehlin	***Date of Collection:***	02/12/2020

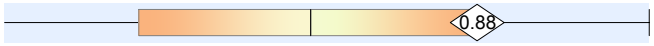
Metabolic Markers in Urine	Reference Range *(mmol/mol creatinine)*	Patient Value	Reference Population - Males Age 13 and Over

Indicators of Detoxification

Glutathione

58	Pyroglutamic ✱	5.7 - 25		25	

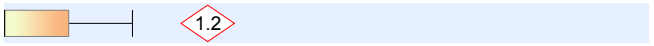
Methylation, Toxic exposure

59	2-Hydroxybutyric ✱✱	≤ 1.2		0.88	

Ammonia Excess

60	Orotic	≤ 0.46		0.14	

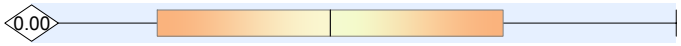
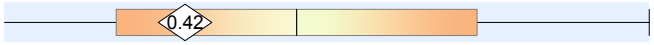
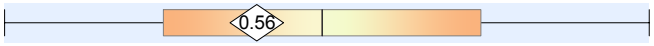
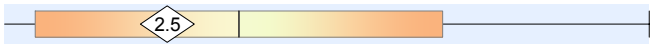
Aspartame, salicylates, or GI bacteria

61	2-Hydroxyhippuric	≤ 0.86	H	1.2	

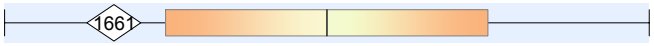
✱ ***A high value for this marker may indicate a Glutathione deficiency.***

✱✱ ***High values may indicate methylation defects and/or toxic exposures.***

Amino Acid Metabolites

62	2-Hydroxyisovaleric	≤ 0.41		0	
63	2-Oxoisovaleric	≤ 1.5		0.42	
64	3-Methyl-2-oxovaleric	≤ 0.56		0.48	
65	2-Hydroxyisocaproic	≤ 0.39		0.04	
66	2-Oxoisocaproic	≤ 0.34		0.08	
67	2-Oxo-4-methiolbutyric	≤ 0.14		0.03	
68	Mandelic	≤ 0.09		0	
69	Phenyllactic	≤ 0.10		0.02	
70	Phenylpyruvic	0.02 - 1.4		0.56	
71	Homogentisic	≤ 0.23		0.02	
72	4-Hydroxyphenyllactic	≤ 0.62		0.30	
73	N-Acetylaspartic	≤ 2.5		1.1	
74	Malonic	≤ 9.9		2.5	
75	4-Hydroxybutyric	≤ 4.3		1.1	

Mineral Metabolism

76	Phosphoric	1,000 - 4,900		1,661	

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Patient Name:	Robert Stehlin	***Date of Collection:***	02/12/2020

Indicator of Fluid Intake

77	*Creatinine	134	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.

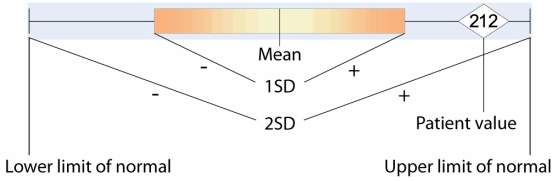
The first graph will occur when the value of the patient is within the reference (normal) range, defined as the mean plus or minus two standard deviations.

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.

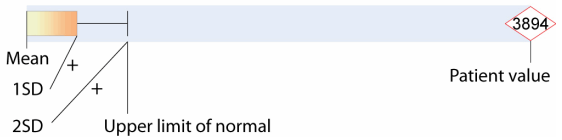
Example of Value Within Reference Range

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	

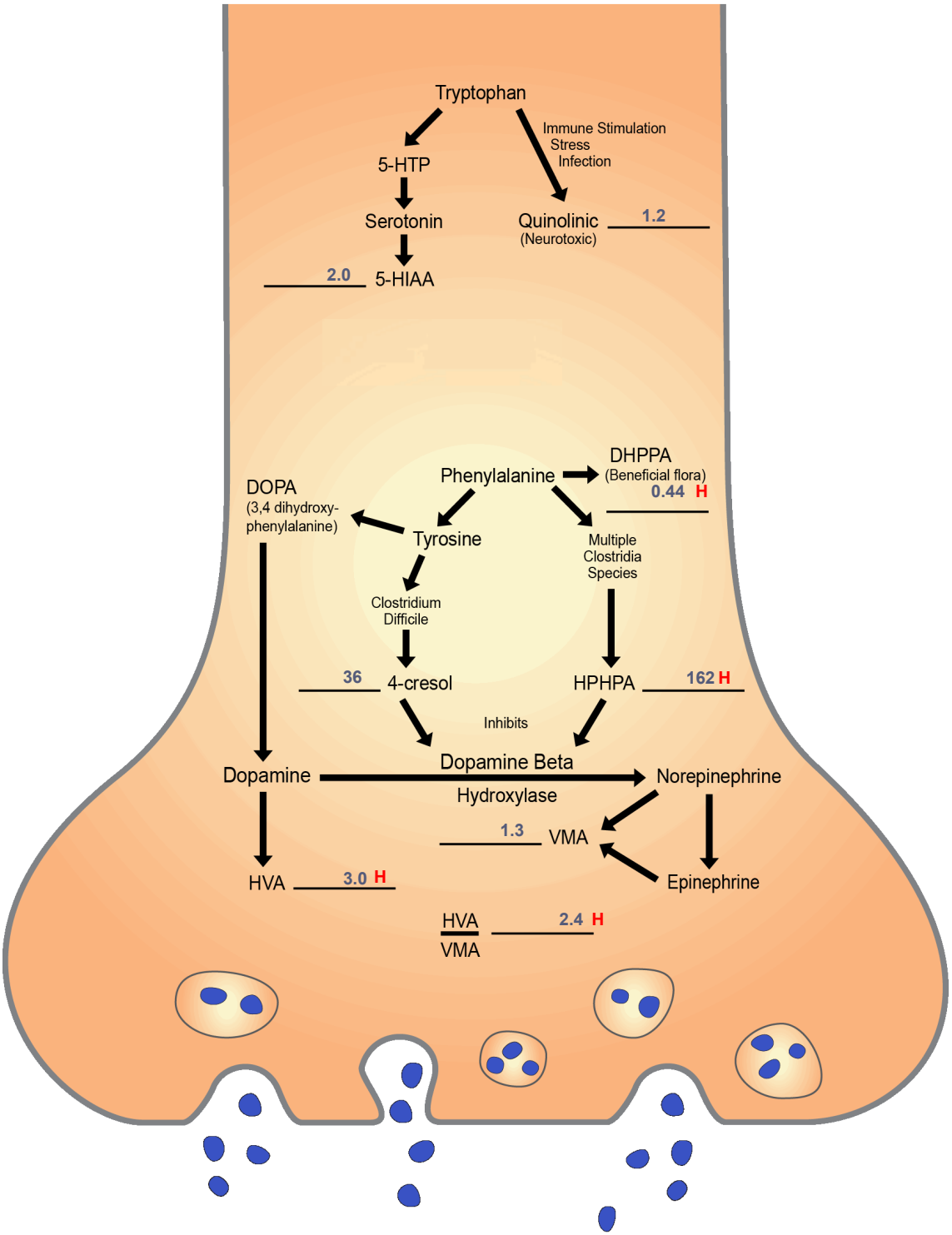


Example of Elevated Value

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 (1-8) Elevations of one or more metabolites indicate a yeast/fungal overgrowth of the gastrointestinal (GI) tract. Prescription or natural (botanical) anti-fungals, along with supplementation of high potency multi-strain probiotics, may reduce yeast/fungal levels.

High 5-hydroxymethyl-2-furoic acid (2), furan-2,5-dicarboxylic acid (4), or furancarbonylglycine (5). High 5-hydroxymethyl-2-furoic acid, furan-2,5-dicarboxylic acid, and furancarbonylglycine have been reported to be byproducts of fungi such as Aspergillus species. Tartaric acid and oxalic acid have also been reported as fungal byproducts. Values of these compounds in urine decreased after antifungal treatment so high values may indicate fungal colonization of the gastrointestinal tract. Individuals with high values may want to followup with The Great Plains Laboratory urine Mycotoxin test.

High tricarballylic acid (propane-1,2,3-tricarboxylic acid) (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. Confirmation of Fusarium species can be done by the urine Mycotoxin test of The Great Plains Laboratory.

High hippuric acid (10) 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 DHPPA (3,4 dihydroxyphenylpropionic acid) (14) indicates excessive intake of chlorogenic acid, a common substance found 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. Harmless or beneficial bacteria such as Lactobacilli, Bifidobacteria, and E. coli mediate the breakdown of chlorogenic acid to 3,4-dihydroxyphenylpropionic acid (DHPPA), and high values may indicate increased amounts of these species in the GI tract. In addition, one *Clostridia* species, *C. orbiscindens*, can convert the flavanoids luteolin and eriodictyol, occurring only in a relatively small food group that includes parsley, thyme, celery, and sweet red pepper to 3,4-dihydroxyphenylpropionic acid. The quantity of *Clostridia orbiscindens* in the GI tract is negligible (approximately 0.1% of the total bacteria) compared to the predominant flora of *Lactobacilli, Bifidobacteria,* and *E. coli*. Consequently, this marker is essentially useless as a general *Clostridia* marker but may be a good indicator of the presence of beneficial flora.

High HPHPA (3-(3-hydroxyphenyl)-3-hydroxypropionic acid) (16) is an abnormal phenylalanine metabolite produced when byproducts of *Clostridium* bacteria combine with human metabolites. High concentrations of this compound cause abnormal behavior by inhibiting metabolism of dopamine to epinephrine, resulting in high levels of the dopamine metabolite homovanillic acid (HVA) in the urine and insufficient epinephrine/norepinephrine in the body. It is associated with behavioral, gastrointestinal, and neuropsychiatric symptoms including tic disorders, depression, autism, schizophrenia, aggression, seizures, anorexia, obsessive compulsive disorder, and hyperactivity. Neuropsychiatric effects are more common when values exceed 500 mmol/mol creatinine.

The *Clostridia* species that cause the greatest quantities of urinary HPHPA are *C. sporogenes, C. caloritolerans,* and *C. botulinum*. Additionally, *C. mangenoti, C. ghoni, C. bifermentans, C. caproicum, and C. sordellii* are also capable of causing elevated urinary levels of HPHPA.

HPHPA precursors are not produced by *C.perfringens* -types A-F*, C.tetani, C.subterminale C.capitovale, C.septicum, C.difficile, C.histolyticum,* or *C.tertium.*

C. botulinum would appear to be an unlikely source unless clinical symptoms of botulism are present. The botulinum toxin can cause a severe flaccid paralytic <http://en.wikipedia.org/wiki/Flaccid_paralysis> disease in humans and animals and is the most potent toxin known to humankind, with a lethal dose of less than 1 µg in humans. Symptoms of botulism include weakness, impaired vision, fatigue, and impaired speech. This may then be followed by weakness of the arms, chest muscles and legs. Surprisingly, symptoms may sometimes be mild and the severity of symptoms appears to be modulated by the amount of beneficial flora in the intestinal tract. In food borne botulism, symptoms generally begin 18 to 36 hours after eating contaminated food, but they can occur as early as 6 hours or as late as 10 days. *C. caloritolerans* is so named because it can survive at the boiling point for 8 hours. Its extreme resistance to heat may allow common food borne transmission. *C. sporogenes* is the name given to strains of *Clostridium botulinum* that do not produce botulinum <http://en.wikipedia.org/wiki/Botulinum> neurotoxins. *C. sporogenes* differs from C. botulinum by a single gene. C. sporogenes is ubiquitous in nature and is commonly found in the flora of humans. *C. sordellii* can be pathogenic and has been implicated in fatal toxic shock syndrome among women of child bearing age.

Treatment with Metronidazole or Vancomycin is close to 100% effective at killing parent organisms but not their spores. At least three months of probiotic therapy is recommended after antimicrobial treatment due to spore formation by *Clostridia* species. *Clostridia* overgrowth can sometimes be controlled by supplementation with *Corebiotic*, *Lactobacillus rhamnosus GG* (Culturelle) or *Saccharomyces boulardii.* Phenalalanine or tyrosine supplements should be avoided because of the possibility of conversion to HPHPA or other toxic byproducts.

High oxalic (21) with or without elevated glyceric (19) or glycolic acids (20) 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. In addition, oxalate deposits in the breast have been associated with breast cancer.

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>.

People with abnormally high markers characteristic of the genetic diseases should do the following:
1. Avoid spinach, soy, nuts, and berries for one month.
2. If *Candida* is present, treat *Candida* for at least one month.
3. Repeat the organic acid test having abstained 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.

High citric acid (29) may be due to increased intake of foods containing citric acid or as a result of intestinal yeast that either produce citric acid or perhaps inhibit the human citric acid cycle.

High 3-hydroxyglutaric (31) is a metabolite associated with the genetic disease glutaric aciduria type I, which is due to a deficiency of glutaryl CoA dehydrogenase, an enzyme involved in the breakdown of lysine, hydroxylysine, and tryptophan. Other organic acids elevated include glutaric and glutaconic. 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 have developed bleeding in the brain or eyes that may be mistaken for the effects of child abuse . This abnormality should be confirmed by additional testing of enzyme deficiencies and/ or DNA at a major pediatric medical genetics center (Morton et al. Glutaric aciduria type I: a common cause of encephalopathy and spastic paralysis in the Amish of Lancaster County, Pennsylvania. American J. Med. Genetics 41: 89-95, 1991). Elevated values may also be found in hepatic carnitine palmitoyltransferase I deficiency, short-chain acyl dehydrogenase deficiency (SCAD), and ketosis. Mitochondrial dysfunction induced by glutaric acid metabolites causes astrocytes to adopt a proliferative phenotype, which may underlie neuronal loss, white matter abnormalities and macrocephalia. Values in glutaric aciduria type I range from 60-3000 mmol/mol creatinine. Values higher than normal but less than 60 mmol/mol creatinine may be due to mild glutaric acidemia type I or to the other causes indicated above. Treatment of this disorder includes special diets low in lysine and supplementation with carnitine or acetyl-L-carnitine.

High HVA (33) High HVA is usually associated with Clostridia colonization or excess fusaric acid from fungus of the gastrointestinal tract and/or deficiencies of dopamine-beta-hydroxylase (DBH) activity due to single nucleotide polymorphisms (SNPs) or genetic deletions that code for enzymes with low activity. The Great Plains Laboratory now offers a test for the activity of the DBH enzyme on blood serum. The genetic deficiencies of DBH can be treated with the drug Droxidopa (L-*threo*-dihydroxyphenylserine). Droxidopa has the ability to cross the blood brain barrier and be converted to norepinephrine by an alternate biochemical pathway that bypasses the DBH genetic block. Individuals with genetic deficiencies of DBH may have orthostatic hypertension and hypoglycemia and may be more susceptible to attention deficit disorder, Alzheimer's disease, and Parkinson's disease, depression, and bipolar depression. The severity of ADHD symptoms is related to decreased DBH enzyme activity. Cocaine abusers with low-activity DBH SNPs have increased sensitivity to cocaine-induced paranoia and euphoria. The drugs disulfiram and Etamicastat inhibit DBH and the inhibition of alcohol, drug, and gambling addictions by disulfiram may be mediated by DBH inhibition.

If HVA is elevated and VMA is normal and the patient has elevated Clostridia markers, avoid supplementation with L-DOPA, phenylalanine or tyrosine until *Clostridia* is treated. 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 can result from the intake of L-DOPA, dopamine, phenylalanine, or tyrosine. Elevated HVA may also result from ingestion of aspartame (Nutrasweet®), salicylates (aspirin), and dietary salicylates. For more information about salicylates in foods go to <http://www.feingold.org/salicylate.php>. Elevated HVA may also result from toxic metal exposure (including lead, aluminum, manganese,arsenic, and mercury), presumably due to DBH inhibition. Heavy metal testing (blood or hair) might be useful to determine if such exposure is significant.

If values are more than double the upper limit of normal, toxoplasmosis and tumors such as neuroblastoma, or other catecholamine-secreting tumors should be ruled out. 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.

Vanillylmandelic acid (VMA) levels (34) below the mean indicate low production and/or decreased metabolism of the neurotransmitters norepinephrine and epinephrine. Vanillylmandelic acid is a metabolite of the neurotransmitters norepinephrine and epinephrine. Low production of VMA can be due to decreased intake or absorption of norepinephrine's and epinephrine's precursor amino acids such as phenylalanine and/or tyrosine, decreased quantities of cofactors needed for biosynthesis of norepinephrine and epinephrine such as tetrahydrobiopterin and vitamin B6 coenzyme or decreased amounts of cofactors such as S-adenosylmethionine (Sam-e) needed to convert norepinephrine and epinephrine to VMA. In addition, a number of genetic variations such as single nucleotide polymorphisms (SNPs) or mutations in MAO or COMT genes can cause reduced production of VMA. Such SNPs are available on **The Great Plains DNA methylation pathway test** which can be performed on a cheek swab. VMA values below the mean but which are much lower than HVA values are usually due to impairment of dopamine beta hydroxylase due to Clostridia metabolites, the mold metabolite fusaric acid, pharmaceuticals such as disulfiram, or food additives like aspartame or deficiencies of cofactors such as vitamin C or copper. Values may be decreased in patients on monoamine oxidase (MAO) inhibitors. Another cause for a low VMA value is a genetic variation (single nucleotide polymorphism or SNP) of the DBH enzyme. This DBH test is now available at The Great Plains Laboratory on blood serum. Patients with low VMA due to Clostridia metabolites or genetic DBH deficiency should not be supplemented with phenylalanine, tyrosine, or L-DOPA.

High HVA/VMA ratio (35) the HVA/VMA ratio reflects the balance between dopamine and norepinephrine/epinephrine production by catecholamine producing neurons in the central nervous system, sympathetic nervous system, and adrenal gland. The most common reason for an elevation of the HVA/VMA ratio is a decreased conversion of dopamine to norepinephrine. The enzyme responsible for this conversion, dopamine beta-hydroxylase (DBH), is copper and vitamin C dependent so an elevated ratio could be due to deficiencies of these cofactors. **The most common reason** for this elevated ratio is inhibition of this enzyme by Clostridia byproducts including HPHPA, 4-cresol, or 4-hydroxyphenylacetic acid. Other causes of an increased ratio include inhibition of DBH by the mold metabolite fusaric acid, pharmaceuticals such as disulfiram, or food additives like aspartame. Another cause for an elevated ratio is a genetic variation (single nucleotide polymorphism or SNP) of the DBH enzyme. Alternatively, the activity of the DBH enzyme can be measured on blood serum. Individuals with low DBH activity can be treated with the drug Droxidopa™, which provides adequate norepinephrine by an alternate biochemical pathway. This DBH test on blood serum is now available at The Great Plains Laboratory. High ratios are common in a large number of neuropsychiatric diseases regardless of the reason for DBH deficiency.

High 3,4-dihydroxyphenylacetic acid (DOPAC) (36) 3,4-dihydroxyphenylacetic acid (DOPAC) is an intermediate in the metabolism of dopamine. Values may be elevated due to increased intake of amino acid precursors of DOPAC such as phenylalanine, tyrosine, or DOPA. Values may be elevated due to factors that inhibit dopamine beta hydroxylase (DBH) like Clostridia metabolites, the mold metabolite fusaric acid, pharmaceuticals such as disulfiram, or food additives like aspartame, or to deficiencies of the DBH enzyme due to copper deficiency, vitamin C deficiency, or malic acid deficiency. Single nucleotide polymorphisms (SNPs) of DBH or catechol-O-methyltransferase (COMT) that result in reduced enzyme activities also result in increased amounts of DOPAC. SNPs of COMT are available on **The Great Plains Laboratory DNA methylation pathway test** which can be performed on a cheek swab. Deficiencies of S-adenosylmethionine (S-ame) also are associated with high amounts of DOPAC. DOPAC may also be increased when bananas are ingested the day before urine collection.

High ethylmalonic, methylsuccinic, adipic, suberic, or sebacic acids (45,46,47,48,49) 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 may be beneficial.

Pyridoxic acid (B6) levels below the mean (51) may be associated with less than optimum health conditions (low intake, malabsorption, or dysbiosis). Supplementation with B6 or a multivitamin may be beneficial.

Pantothenic acid (B5) levels below the mean (52) may be associated with less than optimum health conditions. Supplementation with B5 or a multivitamin may be beneficial.

Ascorbic acid (vitamin C) levels below the mean (54) may indicate a less than optimum level of the antioxidant vitamin C. Individuals who consume large amounts of vitamin C can still have low values if the sample is taken 12 or more hours after intake. Supplementation with buffered vitamin C taken 2 or 3 times a day is suggested.

High 2-hydroxyhippuric acid (61) may result from ingestion of aspartame (Nutrasweet®), salicylates (aspirin), dietary salicylates, or from GI bacteria converting tyrosine or phenylalanine to salicylic acid. For more information about salicylates in foods go to <http://www.feingold.org/salicylate.php>. 2-Hydroxyhippuric acid is a conjugate of hydroxybenzoic acid (salicylic acid) and glycine. Very high 2-hydroxyhippuric also inhibits dopamine beta-hydroxylase resulting in elevated HVA, decreased VMA, and elevated HVA/VMA ratio.

High quality nutritional supplements can be purchased through your practitioner or at New Beginnings Nutritionals, www.NBNUS.com <http://www.NBNUS.com> , or call 877-575-2467.

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.