



The Great Plains Laboratory, Inc.

The following pages list the 74 metabolite markers of the Organic Acids Test. Included is the name of the metabolic marker, its clinical significance, and usual initial treatment.

INTESTINAL MICROBIAL OVERGROWTH

Yeast and Fungal Markers

Citramalic Acid	Elevated citramalic acid is produced mainly by <i>Saccharomyces</i> species or Propionibacteria overgrowth. High-potency, multi-strain probiotics may help rebalance GI flora.
5-Hydroxy-methyl-furoic Acid	A metabolite produced by <i>Aspergillus</i> and possibly other fungal species in the GI tract. Prescription or natural antifungals, along with high-potency, multi-strain probiotics, may reduce overgrowth levels.
3-Oxoglutaric Acid	Indicates a possible yeast overgrowth in the GI tract. High-potency, multi-strain probiotics may help rebalance GI flora.
Furan-2,5-dicarboxylic Acid	A metabolite produced by <i>Aspergillus</i> and possibly other fungal species in the GI tract. Prescription or natural antifungals, along with high-potency, multi-strain probiotics, may reduce overgrowth levels.
Furancarboxylglycine	A metabolite produced by <i>Aspergillus</i> and possibly other fungal species in the GI tract. Prescription or natural antifungals, along with high-potency, multi-strain probiotics, may reduce overgrowth.
Tartaric Acid	Produced by action of <i>Candida</i> hyaluronidase on the intercellular cement, hyaluronic acid. Oxidation of the hyaluronic acid breakdown by white blood cell hypochlorite produces tartaric acid and arabinose. Antifungal treatment and high-potency, multi-strain probiotics may help rebalance GI flora.
Arabinose	Produced by action of <i>Candida</i> hyaluronidase on the intercellular cement, hyaluronic acid. Oxidation of the hyaluronic acid breakdown by white blood cell hypochlorite produces tartaric acid and arabinose. Antifungal treatment and high-potency, multi-strain probiotics may help rebalance GI flora.
Carboxycitric Acid	Elevated yeast/fungal metabolites indicate overgrowth in the GI tract. Prescription or natural antifungals, along with high-potency, multi-strain probiotics, may reduce overgrowth.
Tricarballic Acid	A chemical byproduct released from fumonisins during passage through the gastrointestinal tract. Fumonisin are fungal toxins produced primarily by <i>F. verticillioides</i> . Elevated levels can be caused by the intake of corn or corn-based food contaminated with fumonisins.

Bacterial Markers

Hippuric Acid	A bacterial product of phenylalanine metabolism. Most hippuric acid in urine is derived from microbial breakdown of chlorogenic acid, a common substance found in beverages and in many fruits and vegetables. Higher levels indicate GI bacterial overgrowth that can be reduced with natural anti-bacterial agents and/or high-potency, multi-strain probiotics.
2-Hydroxyphenylacetic Acid	Elevated 2-hydroxyphenylacetic acid is associated with intestinal bacteria overgrowth. High-potency, multi-strain probiotics may help rebalance GI flora.
4-Hydroxybenzoic Acid	A marker for intestinal dysbiosis. Results may also show elevated values as a result of ingestion of foods such as jams and pie fillings containing paraben preservatives. The use of probiotics and the exclusion of paraben-containing foods is the first treatment consideration.
4-Hydroxyhippuric Acid	A glycine conjugate of 4-hydroxybenzoic acid, a metabolite of paraben preservatives. May be elevated after exposure to paraben antimicrobials in certain foods and cosmetics. Intake of fruits containing polyphenols rich in anthocyanins, flavonols, and hydroxycinnamates may increase this compound in the urine. Avoid exposure to parabens.
DHPPA (dihydroxyphenylpropionic acid)	DHPPA in urine indicates intake of chlorogenic acid, a common substance in beverages and many fruits and vegetables. Harmless or beneficial bacteria such as <i>Lactobacilli</i> , <i>Bifidobacteria</i> , and <i>E. coli</i> increase the breakdown of chlorogenic acid to DHPPA, so high values are mainly associated with increased amounts of these species in the GI tract.



Clostridia Bacterial Markers

4-Hydroxyphenylacetic Acid	A tyrosine metabolic product of certain Clostridia bacteria. Elevated levels are associated with Clostridia overgrowth, small intestinal bowel overgrowth (SIBO), or small bowel disease. May also indicate celiac disease.
HPPHA (3-(3-hydroxyphenyl)-3-hydroxypropionic acid)	An elevated value indicates an overgrowth of certain Clostridia bacteria in the GI tract including <i>C. sporogenes</i> , <i>C. caloritolerans</i> , and <i>C. botulinum</i> . This metabolite is commonly elevated in autism, psychiatric disorders, and GI disorders. This metabolite inhibits the enzyme dopamine-beta-hydroxylase, leading to a derangement of neurotransmitter balance.
4-Cresol	An elevated value indicates an overgrowth in the GI tract of <i>C. difficile</i> . This metabolite is commonly elevated in autism, psychiatric disorders, and GI disorders. This metabolite inhibits the enzyme, dopamine-beta-hydroxylase, leading to a derangement of neurotransmitter balance.
3-Indoleacetic Acid	3-Indoleacetic acid is a tryptophan byproduct of the following Clostridia species: <i>C. stricklandii</i> , <i>C. lituseburensis</i> , <i>C. subterminale</i> , and <i>C. putrefaciens</i> . Very high amounts of this metabolite derived from tryptophan may indicate a depletion of tryptophan needed for other physiological functions.

OXALATE METABOLITES

Glyceric Acid	Elevated in genetic hyperoxaluria type II. Normal values of glyceric acid rule out genetic causes of significant elevation of oxalic acid in urine.
Glycolic Acid	Very elevated in genetic hyperoxaluria type I. Normal values of glycolic acid rule out genetic causes of significant elevation of oxalic acid in urine. This genetic disease can be confirmed by DNA testing at the Mayo Clinic. Glycolic Acid is high in fruits and vegetables.
Oxalic Acid	Elevated oxalic acid may be associated with dysbiosis from <i>Aspergillus</i> , <i>Penicillium</i> , and possibly <i>Candida</i> , or from high doses of vitamin C. If yeast or fungal markers are elevated, antifungal therapy may reduce oxalates. Elevated oxalic acid may also result from anti-freeze (ethylene glycol) poisoning. Oxalic Acid may also be due to genetic mutations or SNPs in the oxalate pathway.

GLYCOLYTIC CYCLE METABOLITES

Lactic Acid	Elevated by a number of nonspecific influences, such as vigorous exercise, bacterial overgrowth of the GI tract, shock, poor perfusion, B-vitamin deficiency, mitochondrial dysfunction or damage, and anemia, among others. Tiglylglycine is a more specific indicator of mitochondrial dysfunction or damage. The possibility of an inborn error of metabolism increases when the lactic acid value exceeds 300 mmol/mol creatinine. There are many inborn errors of metabolism that are present with elevated lactic acid, including disorders of sugar metabolism, pyruvate dehydrogenase deficiency, and mitochondrial disorders.
Pyruvic Acid	Elevated by a number of non-specific factors, including vigorous exercise, bacterial overgrowth of the GI tract, shock, poor perfusion, B-vitamin deficiency, mitochondrial dysfunction or damage, and anemia, among others. High pyruvic acid indicates the possibility of an inborn error of metabolism when the value exceeds 100 mmol/mol creatinine.





MITOCHONDRIAL MARKERS - KREBS CYCLE METABOLITES	
Succinic Acid	Most commonly elevated due to a variety of metal and non-metal toxic chemical exposures. An elevated result may indicate a relative deficiency of riboflavin and/or coenzyme Q10. Also produced by bacterial degradation of unabsorbed glutamine supplement. Low levels may indicate the need for leucine/isoleucine supplementation. Suggest supplementation with riboflavin and/or coenzyme Q10.
Fumaric Acid	Increased urinary fumaric acid may be due to impaired Krebs cycle function, a defect in the enzyme fumarase, or in mitochondrial function. To support mitochondrial function, supplement with coenzyme Q10, nicotinamide adenine dinucleotide (NAD+), L-carnitine and acetyl-L-carnitine, riboflavin, nicotinamide, biotin, and vitamin E.
Malic Acid	Slightly elevated values usually indicate a higher need for nutrients such as niacin and coenzyme Q10. When malic acid is simultaneously elevated with citric, fumaric, and 2-ketoglutaric acids, a mitochondrial energy pathway dysfunction is strongly suggested.
2-Oxoglutaric Acid	Increased values in urine may be due to dietary vitamin deficiencies or the intake of 2-ketoglutaric acid as a supplement. The conversion of 2-oxoglutaric acid to succinyl-CoA requires coenzyme A (derived from pantothenic acid), flavin adenine dinucleotide (FAD) derived from riboflavin, and thiamine.
Aconitic Acid	Aconitase, the enzyme that metabolizes citric and aconitic acids, is dependent upon glutathione. Elevated in mitochondrial disorders (e.g. Complex I and Pierson Syndrome). Elevated aconitic acid may indicate an additional requirement for reduced glutathione.
Citric Acid	Elevations may be due to increased intake of citric acid-containing foods or result from intestinal yeast-producing citric acid, or perhaps inhibiting 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 values are low, consider supplements containing glutathione, or n-acetyl-cysteine.

MITOCHONDRIAL MARKERS - AMINO ACID METABOLITES	
3-Methylglutaric Acid 3-Methylglutaconic	Significant increase is due to a reduced ability to metabolize the amino acid, leucine. This abnormality is found in the genetic disease, methylglutaconic aciduria and in mitochondrial disorders. 3-Methylglutaconic acid may also be elevated. Supplementation with coenzyme Q10, niacin, L-carnitine and acetyl-L-carnitine, riboflavin, nicotinamide, biotin, and vitamin E may be useful.
3-Hydroxyglutaric	Marker of glutaryl CoA dehydrogenase deficiency. This enzyme is involved in the breakdown of lysine, hydroxylysine, and tryptophan, and is associated with the genetic disease, glutaric aciduria type 1. Elevated 3-hydroxyglutaric acid may occur in combination with glutaric and glutaconic acids. Symptoms of glutaryl CoA dehydrogenase deficiency are varied. Some individuals appear normal, while others display encephalopathy, autism, cerebral palsy, and additional neurological abnormalities. Treatment includes adherence to a diet low in lysine and supplementation with carnitine. Slight elevations may indicate mitochondrial dysfunction.

NEUROTRANSMITTER METABOLISM	
Phenylalanine and Tyrosine Metabolites	
HVA and VMA	HVA (homovanillic acid), a dopamine metabolite, and VMA (vanillylmandelic acid), a metabolite of epinephrine and norepinephrine, are often elevated due to stress increasing catecholamine output from the adrenal gland, or from lead toxicity. Elevated HVA may also result from the intake of L DOPA, dopamine, phenylalanine, or tyrosine, or due to <i>Clostridia</i> metabolites.
HVA/VMA Ratio	An elevated ratio is often the result of a decreased conversion of dopamine to norepinephrine by the enzyme, dopamine beta-hydroxylase. Inhibition of this enzyme is commonly caused by <i>Clostridia</i> by-products, including HPHPA, 4-cresol, and 4-hydroxyphenylacetic acid.

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Tryptophan Metabolites

5-Hydroxyindoleacetic Acid	Metabolite of the neurotransmitter, serotonin. Elevated values may result from supplementing tryptophan or 5 hydroxy tryptophan (5-HTP). Low values may indicate inadequate production of the neurotransmitter, serotonin. Often slightly elevated by ingestion of foods high in serotonin, such as avocado, banana, tomato, plum, walnut, pineapple, or eggplant. High values are found in carcinoid syndrome.
Quinolinic Acid	Increased values in urine may be caused by various factors such as chronic inflammation from microbial infections, central nervous system degeneration, excessive tryptophan supplementation, or even exposure to phthalates. Reduce excess quinolinic acid by eliminating tryptophan supplementation and also reduce exposure to infections and environmental pollutants. Brain damage induced by quinolinic acid can be mitigated by supplements containing acetyl L-carnitine, melatonin, B6, turmeric, and garlic.
Kynurenic Acid (KYNA)	The most common causes of elevated kynurenic acid are the use of tryptophan supplements and the presence of chronic infections. Very high urine values are found in genetic disorders involving kynureninase deficiency.
Quinolinic Acid / 5-HIAA Ratio	A high ratio indicates excessive inflammation due to recurrent infections, excessive tryptophan intake, immune overstimulation, excessive adrenal production of cortisol, or excessive exposure to phthalates.

PYRIMIDINE METABOLITES - FOLATE METABOLISM

Uracil	Because folic acid is involved as a methyl donor in the conversion of uracil to thymine, elevated uracil may indicate a defect in folic acid metabolism. Elevated uracil is found in about 10% of children with autism.
Thymine	Slightly elevated urinary thymine has no clinical significance. High values are associated with inflammatory diseases and cancer. Elevated pyrimidines and elevated thymine have been reported in dihydropyrimidine dehydrogenase deficiency, a rare genetic disease, which has been associated with seizures and autism.

KETONE AND FATTY ACID OXIDATION

3-Hydroxybutyric Acid Acetoacetic Acid	Ketones, such as 3-hydroxybutyric and acetoacetic acids, are the end-products of rapid or excessive fatty acid breakdown. Common causes of elevated ketones are prolonged fasting, protein malnutrition, high fat diet, vitamin B12 deficiency, severe GI <i>Candida</i> overgrowth, and pulmonary infections.
4-Hydroxybutyric Acid	A moderate urinary increase in 4-hydroxybutyric acid may be due to intake of dietary supplements containing 4-hydroxybutyric acid, also known as gamma-hydroxybutyric acid. Very high levels may indicate the genetic disorder involving succinic semialdehyde dehydrogenase deficiency.
Adipic Acid	Slightly elevated adipic acid may result from excessive ingestion of gelatin or other "junk" food containing adipic acid as an additive. Elevated adipic acid may also indicate an abnormality in fatty acid metabolism. Dietary supplements containing L-carnitine or L-acetyl-carnitine may be beneficial.
Suberic Acid Sebacic Acid Ethylmalonic Acid Methylsuccinic Acid	Increased urinary products of the omega fatty acid metabolism pathway may be due to carnitine deficiency, fasting, or increased intake of triglycerides from coconut oil, or some infant formulas. Very elevated values may indicate a genetic disorder. Fatty acid oxidation defects are associated with hypoglycemia and lethargy. Regardless of cause, intake of dietary supplements containing L-carnitine or acetyl-L-carnitine may improve clinical symptoms.






NUTRITIONAL MARKERS

Methylmalonic Acid (Vitamin B12)	Slightly elevated methylmalonic acid is commonly associated with vitamin B12 deficiency, or other factors such as pernicious anemia, GI bacterial metabolism, malabsorption, or gastroenteritis in very young infants. Very elevated values may indicate a genetic disorder.
Pyridoxic Acid (Vitamin B6)	A major metabolite of vitamin B6. High pyridoxic acid indicates high recent intake 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. Low values are associated with low B6 status, high oxalates, and/or low neurotransmitters.
Pantothenic Acid (Vitamin B5)	An essential vitamin (vitamin B5). High pantothenic acid indicates high recent intake of pantothenic acid. Since some individuals may require very high doses of pantothenic acid, high values do not necessarily indicate the need to reduce pantothenic acid intake.
Glutaric Acid (Vitamin B2)	Elevation indicates riboflavin deficiency (vitamin B2), a common factor in moderate urinary increases of glutaric acid. Other possible factors include fatty acid oxidation defects and metabolic effects of valproic acid (Depakene), or celiac disease. The probability of a genetic disease is higher with very high values. The use of dietary supplements containing riboflavin and coenzyme Q10 may improve clinical symptoms. This compound may be elevated in about 10% of children with autism.
Ascorbic Acid (Vitamin C)	Commonly elevated by supplementation. High values are usually of no concern, except in individuals with extremely high intake (>2000 mg/day), in whom ascorbic acid may be converted to oxalic acid, increasing the risk of kidney stones. It is unlikely that elevated vitamin C will contribute to kidney stone formation if oxalic acid is in the normal range.
3-Hydroxy-3-methylglutaric Acid (Coenzyme Q10)	The precursor of coenzyme Q10 and cholesterol. Slightly increased values may be caused by gastrointestinal yeast overgrowth. A moderate increase in urine HMG may also indicate decreased synthesis of coenzyme Q10. Certain cholesterol-lowering drugs may inhibit the synthesis pathway and result in high HMG values. Very elevated values may be caused by the genetic disorder, HMG aciduria.
N-Acetylcysteine Acid	A powerful antioxidant that increases the glutathione reserves in the body. Together with glutathione, acetylcysteine directly binds to toxic metabolites. Although acetylcysteine may be beneficial under certain conditions, excessive use of the supplement could be harmful.
Methylcitric Acid (Biotin (Vitamin H))	Elevation usually indicates a biotin deficiency (Vitamin H). Biotin deficiency may be due to malabsorption, excessive intake of raw egg white, dietary deficiency, or dysbiosis. Higher levels may indicate the presence of genetic disorders involving biotin-dependent enzymes and may require biotin supplementation at very high doses.

INDICATORS OF DETOXIFICATION

Glutathione

Pyroglutamic Acid	Pyroglutamic acid is a metabolite of glutathione. Glutathione serves as an antioxidant and is also conjugated to toxic compounds in the liver. Elevated values are most commonly caused by glutathione deficiency due to toxic exposure, such as acetaminophen toxicity. Elevated pyroglutamic acid may also result from a genetic disorder, metabolic effects of certain antibiotics, or intake of certain infant formulas. Supplementation with liposomal glutathione or N-acetyl-cysteine can raise glutathione levels. Selenium is essential to the antioxidant activity of glutathione; usually, adequate selenium can be obtained from a quality multivitamin.
2-Hydroxybutyric Acid	Elevated 2-hydroxybutyric acid is a byproduct of the breakdown of the sulfur amino acid metabolite, cystathionine, which may be formed in excess during oxidative stress or when toxic exposures increase the need for detoxification. When glutathione is depleted by excessive toxic exposure, pyroglutamic acid may also be elevated. May also be elevated due to certain genetic SNPs in the methylation pathway or deficiencies of methyl tetrahydrofolate, methyl B12, or betaine.

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Ammonia Excess

Orotic Acid	Elevations are most commonly associated with ammonia toxicity. Elevated ammonia may result from drug toxicity to the liver, viral liver infection, gastrointestinal bleeding, or inborn errors of ammonia metabolism. Confirmation of a genetic disorder requires testing plasma amino acids.
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Aspartame, Salicylates, or GI bacteria

2-Hydroxyhippuric Acid	A conjugate of the amino acids, glycine and hydroxybenzoic acid (salicylic acid). Intake of aspirin (salicylates) or the growth of salicylate-producing gastrointestinal bacteria may elevate levels. Also increased after the ingestion of the artificial sweetener, aspartame (NutraSweet).
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AMINO ACID METABOLITES

2-Hydroxyisovaleric Acid 2-Oxoisovaleric Acid 3-Methyl-2-oxovaleric Acid 2-Hydroxyisocaproic Acid 2-Oxoisocaproic Acid	A moderate increase of branched-chain amino acid metabolites in urine may result from lactic acidosis, episodic ketosis, or deficiencies of the vitamins, thiamine or lipoic acid. Elevated 2-hydroxyisocaproic acid in urine has also been linked to short bowel syndrome. A significant increase of branched-chain amino acid metabolites is associated with the genetic disorders, maple syrup urine disease (MSUD) and pyruvate dehydrogenase deficiency. Patients with slight to moderate elevations may use dietary supplements containing thiamine to improve clinical symptoms.
2-Oxo-4-methylbutyric Acid	Elevated in an inborn error of methionine metabolism. Confirmation of the genetic disorder requires testing of plasma amino acids.
Mandelic Acid	Increased by dietary phenylalanine or phenylalanine supplementation, but also due to exposure to styrene, a toxic environmental compound. Significant elevation is found in the genetic disorder, phenylketonuria (PKU). A plasma phenylalanine test will rule out PKU.
Phenyllactic Acid	A metabolite of phenylalanine. Elevated values indicate increased intake of dietary phenylalanine or the heterozygous carrier status (homozygosity) for the genetic disease, phenylketonuria (PKU). Values observed in clinically diagnosed PKU typically exceed 200 mmol/mol creatinine.
Phenylpyruvic Acid	Moderate elevations may result from intake of phenylalanine, from genetic carrier status for PKU, or from a deficiency in production of bipterin, a cofactor required for phenylalanine metabolism. Very high values are associated with the genetic disease, PKU.
Homogentisic Acid	Homogentisic acid is elevated in the genetic disorder, homogentisic aciduria (alkaptonuria). Slight increases may indicate the heterozygous genetic carrier state of the disease.
4-Hydroxyphenyllactic Acid	Increased values are commonly associated with tyrosinemias, which can result from immature development of enzyme synthesis in infants or genetic deficiencies. Slight increases may be due to increased tyrosine intake, bacterial gut metabolism, short bowel syndrome, or liver disease.
N-Acetylaspartic Acid	Elevated N-acetylaspartic acid is due to the genetic disorder, Carnavan's disease, a potentially fatal disease causing spongy degeneration of the brain.
Malonic Acid	Associated with the genetic disorders, malonyl-CoA decarboxylase deficiency and malonic aciduria with normal malonyl-CoA decarboxylase activity. Slightly elevated values in urine are unlikely to be clinically significant.

MINERAL METABOLITES

Phosphoric Acid	Phosphate urinary excretion is directly proportional to dietary intake. Processed foods high in phosphate include: sodas, candy, ice cream, chocolate, mayonnaise, frozen pizza, commercially baked goods, and meats. Excess phosphate is also associated with hyperparathyroidism, vitamin D-resistant rickets, immobilization following paraplegia or fracture due to bone resorption, vitamin D intoxication, blood lead levels above 1.5 ppm, renal tubular damage, familial hypophosphatemia, and metabolic acidosis. Low urinary phosphate is most common in low phosphate intake and in vitamin D deficiency.
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