Clinical Significance of the Organic Acids Test

General Indicators of Gastrointestinal Dysbiosis	
Metabolic Marker	**Clinical Significance of Typical Abnormal Values and Usual Initial Treatment**
Citramalic Acid	Elevated citramalic acid is produced mainly by *Saccharomyces species* or Propionibacteria overgrowth. High-potency multi-strain probiotics may help rebalance GI flora.
5-Hydroxy-methyl-furoic Acid	A metabolite produced by *Aspergillus* 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 *Aspergillus* and possibly other fungal species in the GI tract. Prescription or natural antifungals, along with high potency multi-strain probiotics, may reduce overgrowth levels.
Furancarbonylglycine	A metabolite produced by *Aspergillus* 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 Candida hyaluronidase on the intercellular cement hyaluronic acid. Oxidation of the hyaluronic acid breakdown products produces tartaric acid and arabinose. Since grapes, grape juice, and dried grapes (raisins) contain tartaric acid, these foods must be avoided 24 hours prior to urine collection to avoid interference. Antifungal treatment and high-potency multi-strain probiotics may help rebalance GI flora.
Arabinose	Produced by action of Candida hyaluronidase on the intercellular cement hyaluronic acid. Oxidation of the hyaluronic acid breakdown products produces tartaric acid and arabinose. Since arabinose is also a major sugar in apples, grapes, and pears, these fruits and their products must be avoided 24 hours prior to urine collection to avoid interference. 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.
Tricarballylic Acid	A chemical by-product released from fumonisins during passage through the gastrointestinal tract. Fumonisins are fungal toxins produced primarily by *F. verticillioides*. Elevated levels can be caused by the intake of corn or corn-based food contaminated with fumonisins.
2-Hydroxyphenylacetic Acid	Elevated 2-hydroxyphenylacetic acid is associated with intestinal bacteria overgrowth. High-potency multi-strain probiotics may help rebalance GI flora.
4-Hydroxyphenylacetic Acid	A tyrosine metabolic product of GI bacteria. Elevated levels are associated with bacterial overgrowth or small bowel disease. May also indicate celiac disease.
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.
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.
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.

3-Indoleacetic Acid	A tryptophan metabolite that may be produced by GI bacteria or, rarely, it may be a marker for Hartnup's disease. Supplementation with tryptophan or 5-hydroxy-tryptophan (5HTP) may elevate levels, but a high value does not indicate the need to reduce or eliminate intake. Urine amino acid testing may confirm Hartnup's disease.
HPHPA (3-(3-hydroxyphenyl)-3-hydroxypropionic acid)	An abnormal phenylalanine metabolite produced by gastrointestinal bacteria of *Clostridia* species, including *sporogenes, botulinum, caloritolerans, mangenoti, ghoni, bifermentans, difficile, and sordellii.* Negative stool tests for *C.difficile* do not rule out the presence of other Clostridia species. This metabolite may is frequently associated with behavioral and neurological abnormalities that resolve after antimicrobial therapy. In many cases, *Clostridia* overgrowth can be controlled by supplementation with 30 billion cells per day of *Lactobacillus rhamnosus GG* (Culturelle) and/or 2-6 billion cfu's of *Saccharomyces boulardii.*
4-Cresol	Indicates a possible overgrowth of intestinal bacteria that are specific p-cresol producers including selected *Clostridia.* 4-Cresol is a phenolic product poorly metabolized in children with autism. High-potency multi-strain probiotics may help rebalance GI flora.
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 *Lactobacilli, Bifidobacteria*, and *E. coli* increase the breakdown of chlorogenic acid to DHPPA so high values are mainly associated with increased amounts of these species in the GI tract.
Oxalate Metabolism	
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	Elevated in genetic hyperoxaluria type I. Normal values of glycolic acid rule out genetic causes of significant elevation of oxalic acid in urine.
Oxalic Acid	Elevated oxalic acid may be associated with dysbiosis from *Aspergillus*, *Penicillium* and possibly *Candida*, 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.
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 as the lactic acid value exceeds 300 mmol/mol creatinine. There are many inborn errors of metabolism that present with elevated lactic acid, including disorders of sugar metabolism and pyruvate dehydrogenase deficiency.
Pyruvic Acid	Elevated by a number of nonspecific 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 increases as the value exceeds 100 mmol/mol creatinine.
2-Hydroxybutyric Acid	A ketone body produced as by-product of fatty acids oxidation for energy. High levels may occur in certain genetic disorders such as pyruvate dehydrogenase deficiency. Slightly elevated 2-hydroxybutyric acid in urine has little clinical significance.
Krebs Cycle Metabolites	
Succinic Acid	An elevated result may also indicate a relative deficiency of riboflavin and/or coenzyme Q10. Suggest supplementation with a minimum of 20 mg riboflavin and/or 50 mg per day of coenzyme Q10. Also produced by bacterial degradation of unabsorbed glutamine supplement. Low levels may indicate the need for leucine / isoleucine supplementation.
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 (300-600 mg), nicotinamide adenine dinucleotide (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) daily.
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), lipoic 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, n-acetyl cysteine, or lipoic acid.
Neurotransmitter Metabolism	
HVA and VMA	HVA (homovanillic acid), a dopamine metabolite, and VMA (vanilmandelic 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.
5-Hydroxyindoleacetic Acid	Metabolite of the neurotransmitter serotonin. Elevated values may result from supplementing tryptophan or 5-hydroxy-tryptophan (5HTP). High values of the neurotoxic tryptophan metabolite quinolinic acid may indicate neuroinflammation due to excessive production from tryptophan. In such cases, 5-HTP is a preferable supplement since it is not converted to quinolinic acid. Commonly 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; also reduce exposure to infections and environmental pollutants. Brain damage induced by quinolinic acid can be mitigated by the drug deprenyl and supplements containing L-carnitine, melatonin, turmeric, and garlic.
Kynurenic Acid (KYNA)	The most common causes of elevated kynurenic acid are the use of tryptophan supplements or the presence of chronic infections. Vitamin B6 deficiency may also elevate KYNA. Very high urine values are found in genetic disorders involving kynureninase deficiency.
Quinolinic Acid / Kynurenic Acid Ratio **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 Metabolism	
Uracil	Because folic acid is involved as a methyl donor in the conversion of uracil to thymine, elevated uracil may indicate a deficiency of folic acid or 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 Candida overgrowth, and pulmonary infections. Dietary supplements containing L-carnitine or acetyl-L-carnitine may be beneficial.
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 results 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 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	Slightly elevated methylmalonic acid is commonly associated with vitamin B12 deficiency, but other factors include pernicious anemia, GI bacterial metabolism, malabsorption, or gastroenteritis in very young infants. Very elevated values may indicate a genetic disorder.
Pyridoxic Acid	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.
Pantothenic Acid	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	Elevation indicates riboflavin deficiency (vitamin B2) is a common factor in moderate urinary increase 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	Commonly elevated by supplementation. High values are usually of no concern except in individuals with dysbiosis 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 when oxalic acid is in the normal range.
3-Hydroxy-3-methylglutaric Acid	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. A laboratory test to evaluate cholesterol levels and the use of dietary supplements containing CoQ10 is recommended.
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	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	
Pyroglutamic Acid	Pyroglutamic acid is a metabolite of glutathione. Glutathione serves as an antioxidant and also is conjugated to toxic compounds in the liver. Elevated values may be due to supplementation with glutathione or N-acetyl cysteine. Elevated pyroglutamic acid may also result from a genetic disorder, metabolic effects of certain antibiotics, or intake of certain infant formulas. Low values may indicate glutathione deficiency due to oxidative stress or chemical exposure. Supplementation with reduced glutathione, N-acetyl L-cysteine, lipoic acid, and vitamin C (buffered) can raise glutathione levels. Selenium is essential to the antioxidant activity of glutathione; usually, adequate selenium can be obtained from a quality multivitamin.
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.
2-Hydroxyhippuric Acid	A conjugate of the amino acid 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).

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) or pyruvate dehydrogenase deficiency. Patients with slight to moderate elevations may use dietary supplements containing thiamine to improve clinical symptoms.
2-Oxo-4-methiolbutyric 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 the 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 or 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 biopterin, a cofactor required for phenylalanine metabolism. Biopterin deficient patients may benefit from supplementation with the folate derivative folinic acid.
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 or malonic aciduria with normal malonyl-CoA decarboxylase activity. Slightly elevated values in urine are unlikely to be clinically significant.
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, NAD+, L-carnitine and acetyl-L-carnitine, riboflavin, nicotinamide, biotin, and vitamin E may be useful.
Bone Metabolism	
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 occurs in low intake and in vitamin D deficiency.