MOSAIC™
DIAGNOSTICS

ORGANIC ACIDS TEST (OAT)
PROVIDER SUPPORT GUIDE

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OAT
ORGANIC ACIDS TEST

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INTRODUCTION

What are Organic Acids

Organic acids are intermediates or end products of metabolic reactions that are excreted in urine and play essential roles in pathways related to energy production, detoxification, neurotransmitter synthesis, and amino acid breakdown. All organisms produce them, including specific ones from bacteria and fungi, allowing for additional insights into gut microbial activity.

When these metabolic pathways function efficiently, organic acids are processed and excreted at expected levels. However, when enzymatic function is impaired, nutrient cofactors are deficient, and/or inhibitors such as toxins or microbial byproducts are present, these pathways may become blocked, leading to abnormal accumulation of organic acids in the urine. Excess from organic acids that are specific to other organisms can also allude to overgrowth or infection from that organism.

How do they Apply to Integrative Health?

Clinically, the Organic Acids Test (OAT) offers valuable insight into a patient's biochemical pathways and microbiome. It provides practitioners with a comprehensive snapshot of multiple body systems in a single test, making it especially useful in cases involving complex or multisystem complaints. The test can help identify imbalances in energy metabolism, mitochondrial dysfunction, oxidative stress, detoxification, neurotransmitter metabolism, nutrient deficiencies, microbial overgrowth, and even, in rare instances, inborn errors of metabolism. In addition to its diagnostic utility, repeat testing can be used to monitor therapeutic progress, such as the effectiveness of orthomolecular interventions, antibiotics, or anti-fungal therapies.

The underlying mechanism of OAT interpretation relies on the understanding that organic acid accumulation and patterns often signal a disruption in normal metabolic flow. This disruption may stem from genetic enzyme defects, toxic exposures, poor dietary intake, or nutrient insufficiencies.

Organic acids are measured in urine and normalized to creatinine to account for differences in hydration status. Because urine reflects circulating metabolites over several hours, it provides a non-invasive and practical medium for evaluating systemic function. While dietary intake and supplement use near the time of collection can influence results, following test preparation instructions, including avoiding certain foods and supplements, helps improve validity and clinical interpretation.

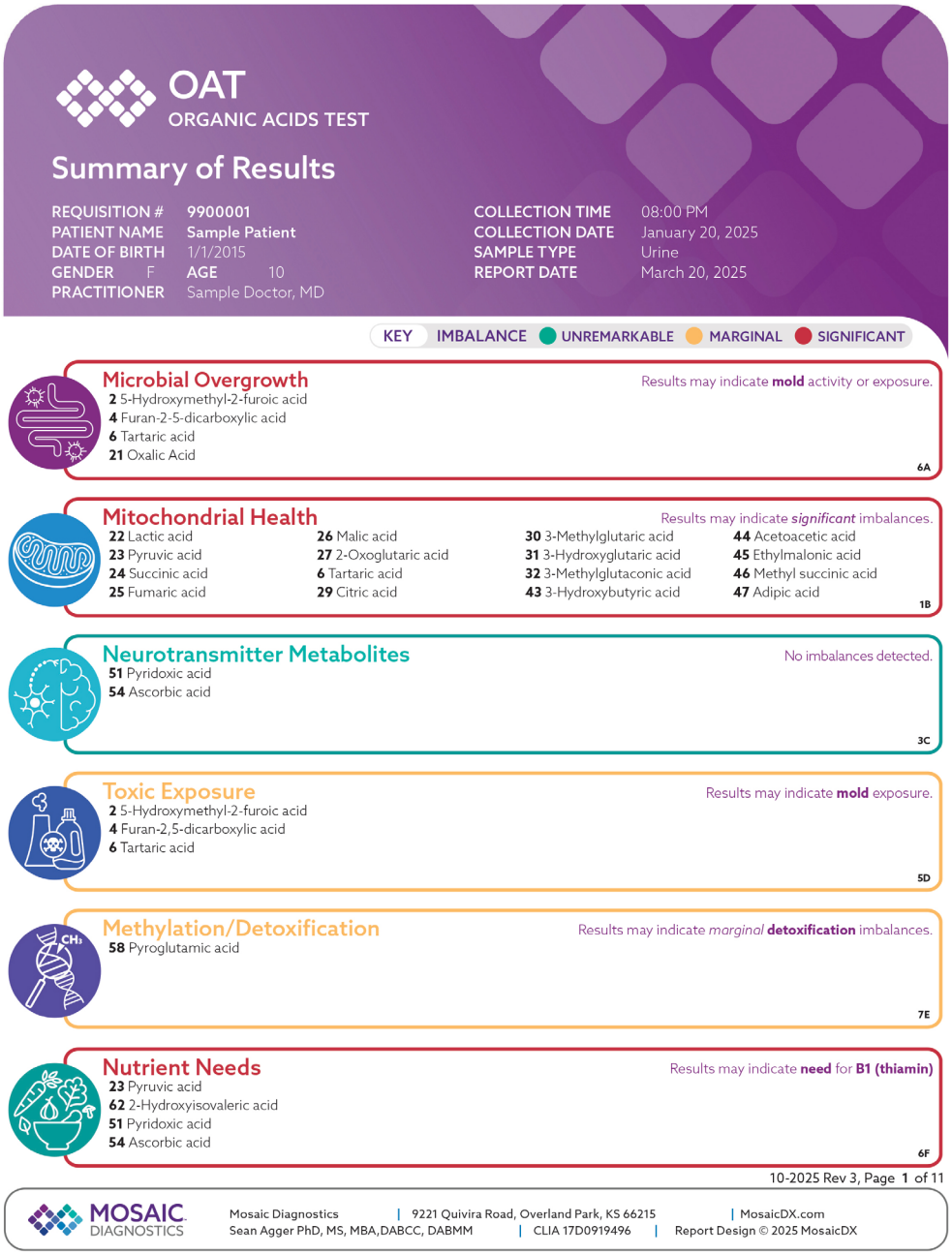
The Organic Acids Test (OAT) from Mosaic Diagnostics analyzes metabolic byproducts to provide a comprehensive snapshot of nutritional and metabolic health, supporting a functional and integrative approach to patient care. This also helps practitioners better understand each person's unique biochemistry to help optimize their health journey.

SUMMARY PAGE

The Summary of Results page was developed to give clinicians a streamlined high-level overview of Organic acids Test (OAT) findings. The summary organizes abnormal organic acids into six key **clinical categories**, allowing practitioners to quickly identify patterns and prioritize areas of concern.

Each category is assessed and results **color-coded** to reflect the level of imbalance (green = **unremarkable**, yellow = **marginal**, red = **significant**), allowing clinicians to quickly prioritize areas of concern.

Category-specific icons are also introduced and carried through the interpretation section, to indicate the category(s) associated with each organic acid.



OAT
ORGANIC ACIDS TEST

Summary of Results

REQUISITION # 9900001
PATIENT NAME Sample Patient
DATE OF BIRTH 1/1/2015
GENDER F AGE 10
PRACTITIONER Sample Doctor, MD

COLLECTION TIME 08:00 PM
COLLECTION DATE January 20, 2025
SAMPLE TYPE Urine
REPORT DATE March 20, 2025

KEY IMBALANCE UNREMARKABLE MARGINAL SIGNIFICANT

Microbial Overgrowth — Results may indicate **mold** activity or exposure.
2 5-Hydroxymethyl-2-furoic acid
4 Furan-2-5-dicarboxylic acid
6 Tartaric acid
21 Oxalic Acid
6A

Mitochondrial Health — Results may indicate *significant* imbalances.
22 Lactic acid
23 Pyruvic acid
24 Succinic acid
25 Fumaric acid
26 Malic acid
27 2-Oxoglutaric acid
6 Tartaric acid
29 Citric acid
30 3-Methylglutaric acid
31 3-Hydroxyglutaric acid
32 3-Methylglutaconic acid
43 3-Hydroxybutyric acid
44 Acetoacetic acid
45 Ethylmalonic acid
46 Methyl succinic acid
47 Adipic acid
1B

Neurotransmitter Metabolites — No imbalances detected.
51 Pyridoxic acid
54 Ascorbic acid
3C

Toxic Exposure — Results may indicate **mold** exposure.
2 5-Hydroxymethyl-2-furoic acid
4 Furan-2,5-dicarboxylic acid
6 Tartaric acid
5D

Methylation/Detoxification — Results may indicate *marginal* **detoxification** imbalances.
58 Pyroglutamic acid
7E

Nutrient Needs — Results may indicate **need** for **B1 (thiamin)**
23 Pyruvic acid
62 2-Hydroxyisovaleric acid
51 Pyridoxic acid
54 Ascorbic acid
6F

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KEY CLINICAL CATEGORIES

Allowing for easier visualization and interpretation of results quickly. Each flagged analyte is grouped within a category based on its clinical relevance, with accompanying comments that explain the significance of the findings.

These **six clinical insight categories** include:

Microbial Overgrowth

Markers of fungal yeast and mold, bacteria, and Clostridia species, and their metabolic byproducts.

Toxic Exposure

Organic acids associated with environmental toxins and toxicants, oxidative stress, and glutathione depletion.

Mitochondrial Health

Intermediates of glucose, fatty acid, and amino acid metabolism involved in energy production.

Methylation/Detoxification

Metabolites reflecting methyl group cycling, glutathione status, and nutrients involved in both methylation and detoxification.

Neurotransmitter Metabolites

Dopamine, serotonin, and norepinephrine/epinephrine pathway metabolites, providing insights into neurotransmitter imbalances.

Nutritional Needs

Direct and indirect biomarkers reflecting the functional demand for B-vitamins, antioxidants, and other key micronutrients.

This categorization system gives practitioners a clear, functional snapshot of metabolic imbalances, supporting efficient clinical decision-making and individualized patient care. It also coincides with the grouping of the interpretations in the next section, connecting how they influence the **six categories of clinical insight**, and summary page.

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EXPLANATION OF INTERPRETATIONS FORMAT

These interpretations are based on an extensive review of biochemical and scientific literature. These interpretations expand on the information provided on the OAT report. Each is structured in the following way:

(6) Tartaric acid

Tartaric acid is a naturally occurring dicarboxylic acid associated with the activity of Aspergillus, Penicillium, and to a lesser extent, Candida and Saccharomyces.[127 128 129] Elevated levels may indicate fungal dysbiosis.[130] It can also inhibit the Krebs cycle by disrupting malic acid utilization, potentially impacting mitochondrial function.[131] Additionally, dietary sources such as grapes, red wine, tamarind, and certain food additives may contribute to elevated levels.[132 133 134]

The icons indicate the clinically relevant categories associated with Tartaric Acid. The expanded interpretations below provide information related to each category.

Microbial Overgrowth (Mold and/or Yeast)

Elevated levels of tartaric acid are associated with mold and potentially yeast as it is known to be produced by Aspergillus and Penicillium and possibly Candida and Saccharomyces.[10,39,40,41,42] Tartaric acid can also encourage growth of yeast.[41]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Mitochondrial Health

Tartaric acid is an analog of malic acid and may inhibit this part of the Citric Acid Cycle.[42] Evaluate **Fumaric acid** (25) and **Malic acid** (26) abnormalities for further insights if this is suspected.

Toxic Exposure

If tartaric acid is thought to be coming from mold, it is important to evaluate the presence of mycotoxins. **Mycotoxins**, which are toxic byproducts of mold (e.g., Aspergillus), pose significant health risks.[19,20] Identifying specific mycotoxins can aid effective remediation and address mold-related health concerns.[19,21] Regardless of source, tartaric acid can act as a muscle toxin in very high concentrations, inhibiting **malic acid** production and potentially causing adverse effects such as paralysis. These toxic effects are very rare and are usually associated with extremely elevated levels.[46]

Refer to the Mold/Mycotoxin Exposure Table for corresponding metabolites and patterns.

Additional Insights

Dietary: Elevated urinary tartaric acid levels can result from dietary intake of tartaric-rich foods, especially grapes and red wine, as well as tamarind and hawthorn.[43,44] It is also used as a food additive for its antioxidant properties and tart flavor and can be found in candies (especially lime and grape flavors), mustards, jams, fruit juices, ice creams, and leavening agents (e.g., cream of tartar).[43,45]

Low Values There is no known clinical significance for low values.

Helpful Reference Tables

The following tables are useful references and support the interpretations.

Microbial Overgrowth Tables

These subsequent tables highlight metabolites linked to specific microbial organisms and may support clinical interpretation by revealing patterns suggestive of overgrowth. Findings should be interpreted in context with the clinical presentation to support identification of potential microbial involvement.

TABLE 1: FUNGAL OVERGROWTH

Fungus	Associated OAT Metabolite	
Mold (*Aspergillus, Penicillium, Cladosporium*)	Citramalic acid (1) 5-Hydroxymethyl-2-furoic acid (2) Furan-2,5-dicarboxylic acid (4) Furancarbonylglycine (5) Tartaric acid (6)	Oxalic acid (21) Fumaric acid (25) Malic acid (26) Citric acid (29)
Candida	Tartaric acid (6) Arabinose (7) Oxalic acid (21)	Glutaric acid (53) Methylcitric (Biotin) (57) Orotic acid (60)
Saccharomyces spp.	Tartaric acid (6) Glycolic acid (20) Oxalic acid (21)	Lactic acid (22) Succinic acid (24)
Various Yeast	3-Oxoglutaric acid (3) Carboxycitric acid (8) Glyceric acid (19)	Glycolic acid (20) 2-Oxoglutaric acid (27)

TABLE 2: BACTERIAL OVERGROWTH

Bacteria	Associated OAT Metabolite	
Firmicutes phylum	Tricarballylic acid (9)	
Clostridiales and *Faecalibacterium prausnitzii*	Hippuric acid (10)	
Various Bacteria	2-Hydroxyphenylacetic acid (11)	5HIAA (38) Quinolinic acid (39)

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Bifidobacterium, Clostridium, Escherichia coli, and *Eubacterium*	4-Hydroxybenzoic acid (12)	4-Hydroxyhippuric acid (13)
Bifidobacteria, E. coli, or *Lactobacilli*	DHPPA (14)	
Various *Clostridium spp.*	4-Hydroxyphenylacetic acid (15) HPHPA (16) 4 Cresol (17) 3-Indoleacetic acid (18)	HVA (33) VMA (low) (34) HVA/VMA ratio (35) DOPAC (36) Phenyllactic acid (69)
Acetobacter and *Gluconobacter*	Glyceric acid (19)	
Acetobacter, Escherichia, or *Rhodococcus*	Glycolic acid (20)	
Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia, Enterococcus faecalis, Streptococcus group B, Bacillus	Lactic acid (22)	
Prevotellaceae, Veillonellaceae	Succinic acid (24)	
Gram-negative bacteria	Malic acid (26)	
Corynebacterium glutamicum	2-Oxoglutaric acid (27)	
Butyrate-producing bacteria	Ethylmalonic acid (45)	
Propionic acid producing bacteria	Methylmalonic acid (50)	
B. fragilis and P. copri, Bifidobacterium longum, Collinsella aerofaciens and H. Pylori, and *arious Firmicutes*	Pyridoxic acid (51)	
Lactobacillus plantarum	Pantothenic acid (52)	
Bifidobacterium longum, Lactobacillus spp.	Methylcitric acid (Biotin) (57)	

Bacteroidetes spp. and *thermophilic lactic acid producing bacteria*	Pyroglutamic acid (58)
Escherichia coli	Orotic acid (60)
Pseudomonas, Bacillus, Azospirillum, Salmonella, Achromobacter, Vibrio, Yersinia, and *Mycobacteria*	2-Hydroxyhippuric acid (61)
Lactic acid producing bacteria, and Clostridium species	2-Hydroxyisocaproic acid (65)
Bifidobacteria, Lactobacillus, and *Clostridium spp.*	4-Hydroxyphenyllactic acid (72)
Clostridium aminobutyricum, Pseudomonas spp	4-Hydroxybutyric acid (75)

Toxic Exposure Tables

The following tables highlight metabolites linked to specific toxic exposures (mycotoxins, toxicants, and heavy metals) and can support clinical interpretation by revealing patterns suggestive of exposure. Findings should be interpreted in context with the clinical presentation and the patient's history.

TABLE 3: MOLD/MYCOTOXINS EXPOSURE

Exposure Category	Mold and Mycotoxin Association	Associated OAT Metabolite
Mold and Mycotoxins *(Aspergillus, Penicillium, Fusarium, Cladosporium)*	*Aspergillus* spp	Citrimalic acid (1) Furancarbonylglycine (5) Fumaric acid (25) Citric acid (29)
	Aspergillus, Cladosporium *spp*	5-Hydroxymethyl-2-furoic acid (2)
	Aspergillus, Fusarium spp	Tricarballylic acid (9)
	Aspergillus, Penicillium spp	Furan-2,5-dicarboxylic acid (4) Tartaric acid (6) Oxalic acid (21) Malic acid (26)
	Aflatoxins and other Mycotoxins	Succinic acid (24)
	OTA, Fusaric acid (Fusarium)	HVA (33)
	Fusaric acid	VMA (Low) (34) HVA/VMA (35) DOPAC (36)
	Various Mycotoxins	Pyroglutamic acid (58) 2-hydroxybutyric acid (59)

*Of note this does not rule out mold or mycotoxin exposure, rather it serves as clues to potentially identify involvement.

TABLE 4: TOXICANT EXPOSURE

Exposure Category	Toxicant	Associated OAT Metabolite
Industrial Solvents / VOCs / Parabens	Polyethylene furanoate (PEF)	Furan-2,5-dicarboxylic acid (4)
	Toluene	Hippuric acid (6)
	Parabens	4-Hydroxybenzoic acid (12) 4-Hydroxyhippuric acid (13)
	Ethylene glycol, polyglycolate, trichloroacetic acid	Glycolic acid (20)
	Ethylene glycol, ethylene oxide	Oxalic acid (21)
	Polychlorinated Biphenyls (PCBs)	HVA/DOPAC ratio- Low (37)
	Styrene, benzene, acrylonitrile, 1-bromopropane, 1,3 butadiene, ethylene oxide, vinyl chloride	Pyroglutamic acid (58)
	Styrene and ethylbenzene	Mandelic acid (68)
Pesticides	Glyphosate, Organophosphate	4-Hydroxyphenylacetic acid (15) HPHPA (16) 4-Cresol (17) 3-Indoleacetic acid (18)
	Numerous	HVA (33) DOPAC (36)
Other	Ingredients in various industrial application	Sebacic acid (49)
	Acrylamide	5HIAA (38)
	Phthalates	Quinolinic acid (39)
	Organic solvents and pollutants	2-Hydroxyhippuric acid (61)
	Acrolein	Malonic acid (74)
	GHB	4-Hydroxybutyric acid (75)
General Toxicant Exposure		Succinic acid (24) Pyroglutamic acid (58) 2-Hydroxybutyric acid (59)

*Note: this does not rule out exposure, rather it serves as clues to potentially identify toxicant involvement.

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TABLE 5: HEAVY METAL EXPOSURE

Exposure Category	Associated OAT Metabolite	Additional Details
Heavy Metals/ Elements	Lactic acid (22)	Antimony, cadmium, and mercury
	Pyruvic acid (23)	Antimony, cadmium, and mercury
	Succinic acid (24)	Aluminum, Cadmium, and other heavy metals
	Fumaric acid (25)	Aluminum, cadmium, gallium, mercury, silver, and zinc
	Malic acid (26)	Arsenic and cadmium
	Aconitic acid (28)	Aluminum, arsenic, and fluoride
	Citric acid (29)	Aluminum, arsenic, cadmium, mercury, and tin
	HVA (33)	Aluminum, arsenic, lead, manganese, and mercury
	VMA (Low) (34)	Aluminum, lead, manganese, and mercury
	HVA/VMA (35)	Aluminum and manganese
	DOPAC (36)	Aluminum, arsenic, lead, manganese, and mercury
	Pyroglutamic acid (58)	Various Heavy Metals
	2-Hydroxybutyric acid (59)	Various Heavy Metals
	Phosphoric acid (76)	Lead and uranium

*Of note this does not rule out exposure, rather it serves as clues to potentially identify heavy metal involvement.

TABLE 6: NUTRIENT–MARKER REFERENCE TABLE

The following table highlights metabolites linked to specific nutrients and may support clinical interpretation by revealing patterns suggestive of insufficiencies.

Nutrient/Category	Relevant OAT Marker(s)	Interpretation
B1 (Thiamin)	• Glycolytic markers (22)-(23) • 2-Oxoglutaric acid (27) • 2-Hydroxyhippuric acid (61) • BCKA Metabolites (62)-(66)	Required for pyruvate dehydrogenase; elevation: impaired carbohydrate metabolism, potential thiamin need, or mitochondrial stress.
B2 (Riboflavin)	• Pyruvic acid (23) • Succinic acid (24), 2-Oxoglutaric acid (27) • HVA (33), VMA (34), DOPAC (36), HVA/DOPAC (36) • Tryptophan metabolites (38)-(40) • Folate metabolites (41),(42) • Ketone and Fatty Acid markers (45)-(49) • Glutaric acid (53) • Indicators of Detoxification (59),(60) • Amino Acid metabolites(62)-(66) (68)-(77)	Needed for acyl-CoA dehydrogenase and glycolate oxidase; elevations in Krebs or fatty acid markers may reflect B2 need.
B3 (Niacin)	• Glyceric acid (19) • Glycolytic markers (22),(23) • Malic acid (26), 2-Oxoglutaric acid (27) • VMA (33), HVA/VMA (35) • Quinolinic acid (39), Kynurenic acid (40) • 3-Hydroxybutyric acid (43), acetoacetic acid (44) • 2-Hydroxybutyric acid (59) • Amino acid metabolites (62)-(66), (75)	Niacin is required for NAD^+/$NADP^+$ production; abnormal tryptophan metabolites or Krebs cycle imbalances may indicate B3 insufficiency or inflammation-driven demand.
B5 (Pantothenic Acid)	• Hippuric acid (10) • Pyruvic acid (23) • 2-Oxoglutaric acid (27) • Pantothenic acid (52) • BCKA metabolites (62)-(66)	Pantothenic acid is a precursor to CoA; elevations in Krebs or fatty acid markers may suggest impaired energy metabolism and B5 need.

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B6 (Pyridoxine)	• 2-Hydroxyphenylacetic acid (11) • Oxalate metabolites (20)-(21) • HVA (33), VMA (34), DOPAC (36) • Tryptophan metabolites (38)-(40) • Pyrimidine metabolites (41),(42) • Pyridoxic acid (51) • Indicators of Detoxification (58),(59) • 2-Hydroxyisocaproic (65), 2-Oxo-4-methiolbutyric acids (67)	Cofactor for transamination and neurotransmitter synthesis; elevations in oxalates and neurotransmitter markers may indicate a functional B6 deficiency. Influential in methylation and energy production.
B7 (Biotin)	• Methylmalonic acid (50) • Methylcitric acid (57)	Cofactor for carboxylase enzymes; elevations in methylmalonic or methylcitric acids may reflect biotin deficiency or dysbiosis-related interference.
B9 (Folate)	• HVA/DOPAC (37) • Pyrimidine metabolites (41)-(42) • 2-Hydroxybutyric acid (59) • Amino Acid metabolites (68)-(70)	Essential for methylation and nucleotide synthesis; abnormalities in folate metabolites or 2-hydroxybutyric acid may suggest B9 deficiency or MTHFR-related need.
B12 (Cobalamin)	• Succinic acid (L) (24) • HVA/DOPAC (37) • Pyrimidine Metabolites (41)-(42) • Methylmalonic acid (50) • Methylcitric acid (57) • Indicators of Detoxification (59),(60)	Abnormal = functional or genetic B12 deficiency.
Vitamin C	• Aconitic acid (28) • HVA (33), VMA (34), HVA/VMA (35), DOPAC (36) • Ascorbic acid (54) • Amino Acid Metabolites (68)-(70)	Excess can potentially raise oxalates; deficiency may impact immunity and antioxidant defenses.
CoQ10 (Ubiquinone)	• 4-hydroxybenzoic acid (12) • Lactic acid (22) • Succinic acid (24) • 3-Hydroxy-3-Methylglutaric acid (CoQ10) (55)	Essential for the electron transport chain; low CoQ10 may impair mitochondrial function.

Calcium	• Tricarballylic acid (9) • Oxalic acid (21) • 2-Oxoglutaric acid (27) • Citric acid (29) • HVA/DOPAC ratio (37)	Can be depleted by tricarballylic or oxalic acids, while an insufficiency can influence enzymatic function in mitochondrial function. Excess can impair neurotransmitter metabolism.
Magnesium	• Tricarballylic acid (9) • Oxalic acid (21) • Pyruvic acid (23) • Citric Acid Cycle metabolites (26),(27),(29) • HVA (33), VMA (34), DOPAC (36), HVA/DOPAC (37) • 5-HIAA (38) • Ketone and Fatty Acid markers (47),(48) • Indicators of Detoxification (58),(60) • Amino Acid metabolites (62)-(65)	Needed for ATP-dependent enzymes; deficiency can impair oxalate, Krebs, and ketone metabolism. Also necessary for proper catecholamine metabolism.
Zinc	• Tricarballylic acid (9) • Lactic acid (22) • 2-Oxoglutaric acid (27) • 5-HIAA (38) • Ascorbic acid (54) • Orotic acid (60)	Cofactor for kynureninase; deficiency may shift tryptophan pathway toward quinolinic, zinc can inhibit (27) as well as support reactions.
Iron	• Oxalic acid (21) • Lactic acid (22) • Mitochondrial – Citric Acid Cycle markers (24),(25),(26),(28),(29) • HVA (33), VMA (34), DOPAC (36), HVA/DOPAC (37) • Quinolinic acid (39) • Ascorbic acid (54) • Amino Acid metabolites (68)-(70)	Cofactor in mitochondrial SOD and metabolism of oxalate precursors.
Glutathione	• Glycolic acid (20) • Aconitic acid (28), Citric acid (29)	Markers of oxidative stress, methylation support; elevation: glutathione depletion or detox strain.

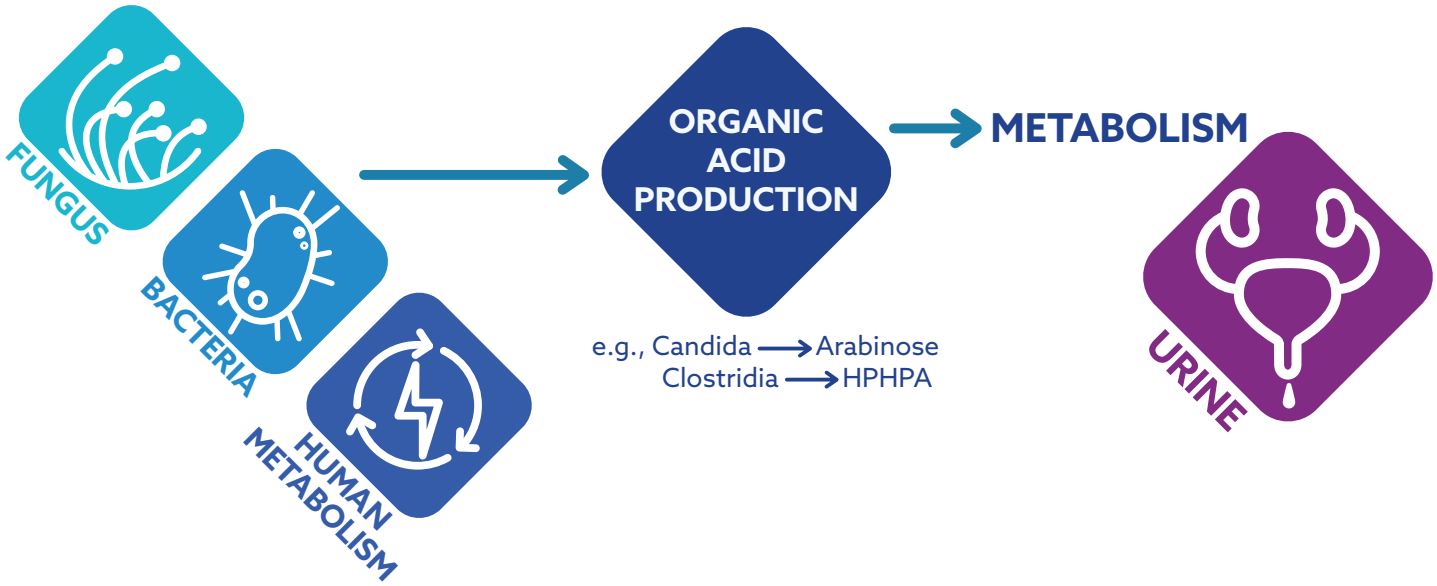
Glycine	• Hippuric acid (10), 4-Hydroxyhippuric acid (13) • Pyroglutamic acid (58)	Building block of glutathione; elevated pyroglutamic acid could indicate glycine deficiency.
Carnitine	• Ketone and Fatty Acid Oxidation markers (45)-(49)	Needed for FA transport into mitochondria; elevations suggest carnitine need or mitochondrial block.
Phenylalanine/ Tyrosine	• 2-Hydroxyphenylacetic acid (11) • HVA (33), VMA (34), DOPAC (36), Mandelic (68), Phenyllactic acid (69), Phenylpyruvic acid (70)	Involved in the synthesis of dopamine, norepinephrine, and epinephrine.
Tryptophan	• 5-Hydroxyindoleacetic acid (5-HIAA) (38), Quinolinic acid (39), Kynurenic acid (40)	Precursor to these neurotransmitters has the potential to go down kynuernic pathway vs serotonin.
Lipoic Acid	• Pyruvic acid (23) • 2-Oxoglutaric acid (27)	Coenzyme in pyruvate and α-KG dehydrogenase; need suspected if elevations + oxidative stress markers.

INTERPRETATIONS

Intestinal Microbial Overgrowth

FIGURE 1

In additional to organic acids being biproducts of human metabolic pathways, various microorganisms, including bacteria and fungi, can metabolize certain substrates into organic acids through metabolic process such as fermentative and oxidative pathways. Once absorbed, these metabolic byproducts enter circulation and are transported to the liver, where partial metabolism may occur, and then eliminated via renal filtration and excreted in the urine. Measurement of these urinary organic acids can provide an indirect biomarker profile of microbial overgrowth or dysbiosis.



YEAST AND FUNGAL MARKERS

(1) Citramalic acid

Citramalic acid, produced by microorganisms such as *Aspergillus niger* and some bacteria, can be a marker of dysbiosis and fungal overgrowth, and may be linked to mold exposure.[1-4] Elevated levels may impair energy production by disrupting the Citric Acid Cycle and are influenced by dietary intake of foods like apples, tomatoes, and wine.[5-9]

Microbial Overgrowth (Mold)

Citramalic acid may originate from fungi such as *Aspergillus niger*.[1,5,10] While certain bacteria, including Rhodospirillum rubrum, Chloroflexus aurantiacus, and Alcaligenes xylosoxydans can also produce this metabolite, these organisms are not found in the human microbiome.[11-15] Although Aspergillus is not a typical resident in the human GI Tract, it can be ingested, and there is potential to overgrow.[16-18] Additionally, studies have identified citramalic acid as a marker of dysbiosis and an indicator of fungal overgrowth.[3,4]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Mitochondrial Health

Citramalic acid is an analog of **malic acid**, with an additional CH3 group, and as an analog, it has the potential to inhibit **malic acid** utilization in the Citric Acid Cycle. This interference could potentially cause elevations in **malic acid** (26) while depleting oxalacetic acid, stressing the Citric Acid Cycle activity and impairing energy production.[10]

Toxic Exposure

If citramalic acid is thought to be coming from mold, it is important to evaluate the presence of mycotoxins. **Mycotoxins**, which are toxic byproducts of mold (e.g. *Aspergillus*), pose significant health risks.[19, 20] Identifying specific mycotoxins can aid effective remediation and address mold-related health concerns.[19, 21]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Additional Insights

Dietary: Citramalic acid levels can also be influenced by dietary intake of ripe fruits such as apples, pitaya, tomatoes, and sugar beets, as well as **wine**.[6-9]

Low Values There is no known clinical significance for low values.

2 5-Hydroxymethyl-2-furoic acid

5-Hydroxymethyl-2-furoic acid (HMFA) is a normal human urinary metabolite in minor amounts, but has also been identified as both *Aspergillus* and *Cladosporium* byproducts, linking it to **mold** exposure.[22,23] It is found to have antimicrobial activity, particularly on bacteria (*Staphylococcus aureus* and *Bacillus subtilis*), which could impact the microbiome. Additionally, HMFA can form during cooking processes such as "browning" food or the breakdown process of certain sugars, negatively impacting human health, even from food.[24,25,26]

Microbial Overgrowth (Mold)

Both *Aspergillus* and *Cladosporium* species, along with other molds such as *Gibberella fujikuroi*, *Helminthosporium maydis*, and *Pyricularia grisea* have all demonstrated production of this metabolite.[22,23]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Toxic Exposure

If HMFA is thought to be coming from mold, it is important to evaluate the presence of mycotoxins. **Mycotoxins**, which are toxic byproducts of mold like *Aspergillus* and *Cladosporium*, pose significant health risks.[19, 20] Identifying specific mycotoxins can aid effective remediation and address mold-related health concerns.[21]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Additional Insights

Dietary: Foods rich in HMFA, such as **coffee**, **beer**, **fruit juices**, **dried fruit** (**especially plums** and **grapes**), **bread**, **honey**, and **breakfast cereals**, can contribute to increased HMFA levels in urine.[25-28] Of note is HMFA's tendency to quickly degrade once exposed to additional heating methods, or aeration.[29]

Low Values There is no known clinical significance for low values.

3 3-Oxoglutaric acid

3-Oxoglutaric acid is a short-chain keto acid and a simple carboxylic acid. It is a microbial metabolite of **yeast** and is also an analog of 2-oxoglutarate (also known as alpha-ketoglutaric acid) from the Citric Acid Cycle, playing a potential role in **mitochondrial health**.[4]

Microbial Overgrowth (Mold)

Elevated levels of 3-oxoglutaric acid may indicate **yeast overgrowth**, or other **dysbiotic gut flora**, however, evidence linking this marker to dysbiosis is still limited.[4,10]

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Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Mitochondrial Health

3-oxoglutaric acid is an analog of 2-oxoglutarate (also known as alpha-ketoglutaric acid), an intermediate in the Citric Acid Cycle. This analog can potentially interfere with the alpha-ketoglutaric dehydrogenase complex, which converts 2-oxoglutarate to succinyl CoA, thereby influencing mitochondrial activity and potentially causing elevations in **2-oxoglutaric acid** (27).[10]

Additional Insights

Low Values There is no known clinical significance for low values.

(4) Furan-2,5-dicarboxylic acid

Furan-2,5-dicarboxylic acid (FDCA) is a dicarboxylic acid produced from hydroxymethylfurfural (HMF). Various microorganisms, including **molds** such as *Aspergillus* and *Penicillium*, can metabolize HMF into FDCA. FDCA can be generated by certain foods and beverages and is also a byproduct of polyethylene furanoate (PEF) polymer found in **plastics**.[28,30-33]

Microbial Overgrowth (Mold)

Elevated levels of FDCA in urine may suggest *Aspergillus* exposure or activity.[31,34] Other organisms such as **soil-based bacteria** (e.g. *Cupriavidus basilensis* and *Raoultella ornithinolytica*) and other fungi such as ***Penicillium*** *spp*. and *Pleurotus ostreatus* (oyster mushroom), have also been known to produce FDCA.[31,35]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Toxic Exposure

If FDCA is thought to be coming from mold, it is important to evaluate the presence of mycotoxins. **Mycotoxins**, which are toxic chemical byproducts produced by certain types of mold, such as *Aspergillus* and *Pennicillium*, pose significant health risks.[19,20] Identifying specific mycotoxins can aid effective remediation and address mold-related health concerns.[19,21] Additionally, FDCA is used as a monomer with **ethylene glycol** to produce polyethylene furanoate **(PEF)** in plastics, which can also potentially contaminate foods.[33,36] There are other toxicants found in PEF containing plastics, and while FDCA itself is not yet assessed, frequent exposure to plastics may warrant a TOXDetect order.

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Additional Insights

Dietary: FDCA has been shown to be from food sources containing furans, such as coffee, alcoholic beverages, preserved foods, and baked goods.[28,32,37]

Low Values There is no known clinical significance for low values.

5 Furancarbonylglycine

Furancarbonylglycine, also known as 2-furoylglycine, is a furan-derived acyl glycine that may be linked to the fungus *Aspergillus*, serving as a marker for **mold** exposure or overgrowth. Additionally, dietary intake of high-temperature processed foods and beverages, such as coffee, can influence their levels. [34,38]

Microbial Overgrowth (Mold)

Furancarbonylglycine, a urinary metabolite associated with the fungus *Aspergillus* may indicate fungal exposure or overgrowth when elevated. In one study, antifungal treatment lowered levels of furancarbonylglycine (along with **5-hydroxy-methyl-2-furoic acid** (2), **furan-2,5-dicarboxylic acid** (4)), further suggesting its potential role as a marker for fungal dysbiosis.[34]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Toxic Exposure

If Furancarbonylglycine is thought to be coming from mold, it is important to evaluate the presence of mycotoxins. **Mycotoxins**, which are toxic byproducts of mold (e.g. *Aspergillus*), pose significant health risks.[19,20] Identifying specific mycotoxins can aid effective remediation and address mold-related health concerns.[19,21]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Additional Insights

Dietary: Intake of foods processed at high temperatures, such as coffee, can increase levels of this furan derivative.[38]

Low Values There is no known clinical significance for low values.

6 Tartaric Acid

Tartaric acid is a naturally occurring dicarboxylic acid associated with the activity of *Aspergillus*, *Penicillium*, and to a lesser extent, *Candida* and *Saccharomyces*.[39-41] Elevated levels may indicate **fungal** dysbiosis. It can also inhibit the Citric Acid Cycle by disrupting malic acid utilization, potentially impacting mitochondrial function. Additionally, dietary sources such as grapes, red wine, tamarind, and certain food additives may contribute to elevated levels.[43-45]

Microbial Overgrowth (Mold and/or Yeast)

Elevated levels of tartaric acid are associated with mold and potentially yeast, as it is known to be produced by *Aspergillus* and *Penicillium* and possibly *Candida* and *Saccharomyces*.[10,39-42] Tartaric acid can also encourage the growth of yeast.[41]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Mitochondrial Health

Tartaric acid is an analog of malic acid and may inhibit this part of the Citric Acid Cycle. Evaluate **Fumaric acid** (25) and **Malic acid** (26) abnormalities for further insights if this is suspected.[42]

Toxic Exposure

If tartaric acid is thought to be coming from mold, it is important to evaluate the presence of mycotoxins. **Mycotoxins**, which are toxic byproducts of mold (e.g. *Aspergillus*), pose significant health risks.[19,20] Identifying specific mycotoxins can aid effective remediation and address mold-related health concerns.[19,21] Regardless of source, tartaric acid can act as a muscle toxin in very high concentrations, inhibiting **malic acid** production and potentially causing adverse effects such as paralysis.[46] These toxic effects are very rare and are usually associated with extremely elevated levels.[46]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Additional Insights

Dietary: Elevated urinary tartaric acid levels can result from dietary intake of tartaric-rich foods, especially grapes and red wine, as well as tamarind and hawthorn.[43,44] It is also used as a food additive for its antioxidant properties and tart flavor and can be found in candies (especially lime and grape flavors), mustards, jams, fruit juices, ice creams, and leavening agents (e.g., cream of tartar).[43,45]

Low Values There is no known clinical significance for low values.

(7) Arabinose

Arabinose is an aldopentose sugar that can be metabolized by various organisms through pathways involving conversion into intermediates of the pentose phosphate pathway. It has been studied as a marker for intestinal **yeast** overgrowth and shown clinically to respond to antifungal therapies. [4,10] Arabinose is also a naturally occurring sugar compound found in numerous plants, such as beets and grains.[41,48]

Microbial Overgrowth(Yeast)

Elevated levels of L-arabinose suggest a potential yeast overgrowth such as Candida spp. or other dysbiotic gut flora.[4,10] Case studies, including individuals with autism, have shown reductions in arabinose levels and symptom improvement following antifungal therapy, supporting its potential role in clinically significant fungal overgrowth.[4,10]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Additional Insights

Dietary: Arabinose elevations can also originate from dietary sources. It is naturally found in the cell wall of plants (e.g. grains, beets, plant gums) or may be derived from the breakdown of hemicellulose and pectins found in numerous fruits and vegetables.[48,49]

Low Values There is no known clinical significance for low values.

8 Carboxycitric Acid

Carboxycitric acid is used to evaluate intestinal microbial overgrowth, particularly with **yeast**. While evidence supporting its role as a marker for Microbial Overgrowthis still developing, levels may provide insights into fungal activity.[10,50]

Microbial Overgrowth(Yeast)

Elevated carboxycitric acid levels in urine may indicate intestinal fungal overgrowth.[50] Studies suggest that these levels can decrease following antifungal therapy, which highlights the potential association with yeast and fungal dysbiosis, however data is still limited.[4,10]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Additional Insights

Low Values There is no known clinical significance for low values.

9 Tricarballylic Acid

Tricarballylic acid is often associated with the fumonisin class of mycotoxins produced mainly by various Fusarium species and Aspergillus section Nigri (black aspergilli).[51-53] These mold exposures can come from indoor environments and contaminated dietary sources such as numerous grain products.[53,54] This metabolite may also be produced from certain bacteria.[50] Tricarballylic acid has been shown to bind to various minerals, influencing nutritional needs.[51]

Microbial Overgrowth(Mold or Bacteria)

Exposure to fumonisins, a mycotoxin class produced by various Fusarium species and Aspergillus section Nigri found in contaminated foods, releases tricarballylic acid during breakdown in the gastrointestinal tract.[53,54] Certain gut bacteria, such as species from the Firmicutes phylum, can also produce tricarballylic acid during their metabolic processes.[50,51]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Toxic Exposure

Fumonisins, mycotoxins linked to *Fusarium* and *Aspergillus* contamination, are major sources of tricarballylic acid.[52,54] *Fusarium* is a mold that has been found in water-damaged buildings as well as food sources such as grains and grain products.[53-55] Elevated levels of tricarballylic acid in urine may indicate mycotoxin exposure, suggesting the need for further assessment, such as urine mycotoxin testing.

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Nutritional Needs

Tricarballylic acid has the ability to bind divalent ions, like **magnesium**, **calcium**, and **zinc**, potentially contributing to mineral imbalances.[51]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Additional Insights

Low Values There is no known clinical significance for low values.

BACTERIAL MARKERS

10 Hippuric acid

Hippuric acid is a conjugate of glycine and benzoic acid, and may be influenced by gut bacteria, diet, and environmental exposures. It can be produced during the breakdown of benzene-type aromatic compounds from either microbial activity in the gut, exposure to toluene, or naturally produced in the liver from dietary intake of polyphenol-rich foods. Low levels can indicate poor microbial activity, glycine or B5 insufficiencies, and have also been associated with numerous chronic conditions.[56-62] In rare cases, extreme elevations may be linked to genetic metabolic disorders.[62,63]

Microbial Overgrowth (non-specific Bacteria)

Hippuric acid can be the result of gut bacterial metabolism of phenylalanine, or from their metabolism of polyphenol-rich compounds that generate benzoic acid. [64] Microbial Overgrowths in the gut may influence hippuric acid levels, with elevated levels potentially indicating an overgrowth of certain bacteria, such as those from the order Clostridiales and the species Faecalibacterium prausnitzii, possibly due to their enhanced ability to metabolize polyphenols.[64,65]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Toxic Exposure

Elevated hippuric acid can be indicative of exposure to toluene.[66] Toluene is a solvent used

in paints, dyes, fingernail polish, and gasoline, all of which can emit into the air, leading to exposures.[67-70] Toluene metabolism produces benzoic acid via hydroxylation and P450 enzymes, leading to increased hippuric acid levels.[71]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Nutritional Needs

Theoretically, elevated hippuric acid levels may induce glycine depletion, as glycine is required for its production.

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

In rare instances, extremely elevated hippuric acid can be associated with certain genetic disorders including Phenylketonuria (PKU), hydroxymethylglutaryl-CoA lyase deficiency, tyrosinemia 1, Maple Syrup Urine Disease (MSUD), and propionic acidemia.[72,73]

Corresponding markers to the aforementioned genetic diseases include: **2-Hydroxyphenylacetic acid** (11), **3-Indoleacetic acid** (18), **2-Hydorxyisovaleric acid** (62), **Mandelic acid** (68), **Phenylactic acid** (69), or **Phenylpyruvic acid** (70) for PKU. **3-Hydroxyglutaric acid** (31), elevations for hydroxymethylglutaryl-CoA lyase deficiency, **2-Hydroxyphenylacetic acid** (11), **4-Hydroxyphenylacetic acid** (15), **2-Hydroxyisovaleric acid (62)** and **4-Hydroxyphenyllactic acid** (72) for tyrosinemia. **2-Hydroxyisovaleric acid** (62), **2-Oxoisovaleric acid** (63), **3-Methyl-2-oxovaleric acid** (64), **2-Hydroxyisocaproic acid** (65), or **2-Oxoisocaproic acid** (66) for MSUD, or **Methylmalonic acid** (50), **Methylcitric acid** (57), **Pyroglutamic acid** (58), **2-Hydroxybutryic acid** (59), and **2-Hydroxyisovaleric acid** (62) for propionic acidemia.

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary: Foods such as potatoes, apples, pears, blueberries, black currants, blackberries, and beverages like certain juices, coffee, and tea all have specific polyphenols (e.g. chlorogenic acids and epicatechins) that can be broken down into benzoic acid from gut bacteria and then conjugated with glycine in the liver to form hippuric acid.[74,75] Benzoic acid is also naturally present in certain foods, such as dairy products and strawberries, and can also be used as a preservative (e.g. sodium benzoate) due to its antimicrobial properties.[58,64,76]

Other markers associated with intake of polyphenol-rich food include: **4-Hydroxybenzoic acid** (12), **4-Hydroxyhippuric acid** (13), **DHPPA (3,4-dihydroxyphenylpropionic acid)** (14), and **Hydroxyphenylacetic acid** (15).

Low Values

Microbial Overgrowth: Low levels have also been associated with dysbiosis and may be

significant when evaluating for shifts in the microbiome.[61]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Nutritional Needs: Since glycine conjugates with benzoic acid to form hippuric acid, low levels may be due to inadequate glycine, which would impact production.[62] Additionally, Vitamin B5 itself plays a role by facilitating benzoic acid's conversion into hippuric acid; therefore, if hippuric acid is low, B5 insufficiency may be an influence.[62]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Associated Conditions: Very low hippuric acid may be used in evaluating renal clearance and hepatic function. Low levels have also been associated with high blood pressure, atherosclerosis, obesity, diabetes, autism, schizophrenia, and depression.[56-60]

(11) 2- Hydroxyphenylacetic acid

2-Hydroxyphenylacetic acid is a metabolite of phenylalanine and plays a role in microbial and metabolic processes.[77] It is associated with microbial activity in the gut, phenylalanine utilization for neurotransmitter production, and certain genetic and dietary influences.[77-79]

Microbial Overgrowth(non-specific Bacteria

2-Hydroxyphenylacetic acid is mainly discussed in the literature as a microbial metabolite that can indicate bacterial overgrowth or dysbiosis in the gastrointestinal tract.[77] Various bacteria may produce this compound as part of the breakdown of phenolic containing compounds, although non-specific with current literature.[56] Additionally, *Caenorhabditis elegans*, which is a nematode, and *Penicillium chrysogenum* have been shown to produce it, but evidence is limited.[80-82]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Neurotransmitter Metabolites

2-Hydroxyphenylacetic acid can be a byproduct of phenylalanine metabolism and may reflect altered phenylalanine hydroxylase function or biopterin pathway disruptions tied to neurotransmitter metabolism.[78]

Evaluate **Homovanillic acid (HVA)** (33), **Vanillylmandelic acid (VMA)** (34), **Dihydroxyphenylacetic acid (DOPAC)** (36) and **5-Hydroxyindoleacetic acid (5-HIAA)** (38) abnormalities for further insights.

Nutritional Needs

Decreased vitamin B6 can impair tetrapyrrole biosynthesis, leading to potentially reduced biopterin synthesis, influencing phenylalanine's conversion to dopamine.[83]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

Genetics

In rare instances, very elevated levels of 2-hydroxyphenylacetic acid are associated with Phenylketonuria (PKU), a genetic disorder caused by a deficiency of the enzyme phenylalanine hydroxylase. This condition results in the accumulation of phenylalanine and its metabolites, including **Hippuric acid** (10), **2-Hydorxyisovaleric acid** (62), **Mandelic acid** (68), **Phenyllactic acid** (69), **Phenylpyruvic acid** (70).[79]

Tyrosinemia, a group of rare disorders affecting tyrosine metabolism, can also result in extreme elevations due to impaired enzymatic breakdown of tyrosine and its derivatives. Additional markers associated with this disease include **Hippuric acid** (10), **4-Hydroxyphenylacetic acid** (15), **2-Hydroxyisovaleric acid** (62), and **4-Hydroxphenyllactic acid** (72).[84]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional insights

Dietary Sources: 2-Hydroxyphenylacetic acid is a metabolite produced when certain foods are consumed, such as blueberries, strawberries, apricots, tomatoes, chanterelle mushrooms, and grapes .[77]

Medications/Supplement Influences: Taking certain botanicals such as chaste tree (Vitex trifolia), parsley, oregano, and lemon verbena may increase 2-hydroxyphenylacetic acid levels due to their metabolism.[77]

Associated Conditions: 2-hydroxyphenylacetic acid has also been linked to specific conditions, including chronic constipation and atopic dermatitis.[85,86]

Low Values There is no known clinical significance for low values.

(12) 4- Hydroxybenzoic acid

4-Hydroxybenzoic acid (4-HBA) is an organic compound that can be formed through the bacterial metabolism of dietary polyphenols or certain amino acids.[87] Natural elevations may also be linked to dietary polyphenol intake and can potentially support CoQ10 synthesis.[88,89] However, exposure to endocrine-disrupting preservatives, known as parabens, has been shown to elevate 4-HBA.[90]

Microbial Overgrowth(non-specific Bacteria

4-HBA can serve as a marker of gut microbiota activity. Elevated urinary levels may indicate intestinal dysbiosis or bacterial overgrowth. Certain bacterial genera, such as *Clostridium*, *Eubacterium*, *Escherichia*, and *Bifidobacterium*, are involved in metabolizing dietary polyphenols and amino acids into 4-HBA, contributing to its increased production.[87]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Toxic Exposure

Parabens, commonly used as preservatives in personal care products, pharmaceuticals, and packaged foods, are absorbed through the skin or GI tract and metabolized into 4-HBA, increasing urinary levels.[91] Recent studies link parabens to health concerns, including endocrine disruption, particularly with regard to estrogenic activity.[90,92]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Nutritional Needs

4-HBA has been shown to support Coenzyme Q10 (CoQ10) biosynthesis.[89]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

Additional Insights

Dietary: Dietary intake of polyphenol-rich foods such as green tea, coconut, garlic, some berries, soybeans, and almonds can naturally elevate 4-HBA levels.[88,93-95]

Other markers associated with intake of polyphenol rich food include **Hippuric acid** (10), **4-Hydroxyhippuric acid** (13), **DHPPA (3,4 dihydroxyphenylpropionic acid)** (14), and **Hydroxyphenylacetic acid** (15).

Medications/Supplement Influences: Supplements that contain botanicals with higher amounts of rosmarinic acid (e.g. oregano, rosemary, mint, lemon balm, holy basil) can metabolize into 4-Hydroxyhippuric acid.[94,95]

Associated Conditions: 4-HBA has been associated with various conditions, including celiac disease, cystic fibrosis, short bowel syndrome, and unclassified enteritis.[96]

Low Values There is no known clinical significance for low values.

(13) 4-Hydroxyhippuric acid

4-Hydroxyhippuric acid is a urinary metabolite formed by the conjugation of glycine with **4-hydroxybenzoic acid** (12), a compound produced from microbial metabolism of dietary polyphenols, amino acids, or parabens. Elevated levels may stem from gastrointestinal bacterial overgrowth, high intake of polyphenol-rich foods, or paraben exposure from personal care products, pharmaceuticals, and packaged foods.[88,90] In the case of a low value, in theory, if 4-hydroxybenzoic acid (12) is elevated, and 4-hydroxyhippuric acid is low, it could be an indication of glycine insufficiency.[97]

Microbial Overgrowth(non-specific Bacteria

Bacterial overgrowth in the GI tract can lead to increased metabolism of dietary compounds, resulting in elevated levels of 4-hydroxyhippuric acid.[87] Microbial species such as

Bifidobacterium, Clostridium, Escherichia coli, and Eubacterium have all been found to metabolize polyphenols and amino acids like tyrosine and phenylalanine into 4-hydroxybenzoic acid, which is subsequently conjugated to form 4-hydroxyhippuric acid.[87]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Toxic Exposure

Parabens, commonly used as preservatives in personal care products, pharmaceuticals, and packaged foods, are absorbed through the skin or GI tract and metabolized into **4-hydroxybenzoic acid** (12), which is then conjugated to form 4-hydroxyhippuric acid. Recent studies link parabens to health concerns, including endocrine disruption, particularly with regard to estrogenic activity.[90,92]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Additional Insights

Dietary: Dietary intake of polyphenol-rich foods such as green tea, coconut, garlic, some berries, soybeans, and almonds can naturally elevate 4-Hydroxyhippuric acid levels.88,93

Other markers associated with intake of polyphenol-rich food include **Hippuric acid** (12), **4-Hydroxybenzoic acid** (12), **DHPPA (3,4 dihydroxyphenylpropionic acid)** (14), and **Hydroxyphenylacetic acid** (15).

Medications/Supplement Influences: Supplements that contain botanicals with higher amounts of rosmarinic acid (e.g. oregano, rosemary, mint, lemon balm, holy basil) can metabolize into 4-Hydroxyhippuric acid.[94,95]

Low Values Theoretically, if **4-hydroxybenzoic acid** (12) is elevated, and **4-hydroxyhippuric acid** is low, it could be an indication of **glycine** insufficiency, since 4-hydroxyhippuric acid conjugates with glycine to form it.[97]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

(14) 3,4 dihydroxyphenylpropionic acid (DHPPA)

3,4-Dihydroxyphenylpropionic acid (DHPPA), also known as dihydrocaffeic acid, is a metabolite produced by gut microbiota through the breakdown of certain dietary polyphenols.[98] DHPPA is primarily associated with *Lactobacilli*, *Bifidobacteria*, *E. coli*, and some *Clostridium* species, often identified as commensal.[98-100] Elevated levels may indicate a polyphenol-rich diet or an abundance of these flora, while low levels suggest insufficient polyphenols or potentially reduced beneficial bacteria.[101]

Microbial Overgrowth(Beneficial Bacteria)

Elevated DHPPA levels may indicate bacterial growth, particularly from the genera of *Lactobacilli* or *Bifidobacteria*, or species *E. coli*, which metabolize the polyphenol chlorogenic acid into DHPPA.[98-100,102] Clostridium orbiscindens can also contribute to elevations by converting flavonoids like luteolin and quercetin into DHPPA, but this species is generally identified as commensal.[102-104]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Additional Insights

Dietary Intake: A diet rich in chlorogenic acid can significantly elevate DHPPA levels. Beverages such as coffee and wine, fruits like apples, pears, peaches, blueberries, cherries, eggplants, and tomatoes, leafy greens like collard greens, and other foods such as chicory, beets, sweet and white potatoes, carrots, asparagus, olives, peas, sunflower seeds, mustard, and rosemary, are all abundant in chlorogenic acid.[99,105] Consuming these foods increases the availability of substrates for bacterial metabolism, resulting in higher urinary DHPPA levels.[99,105] Probiotic-rich foods may also influence levels.

Medications/Supplement Influences: Theoretically, probiotics containing Lactobacilli or Bifidobacteria may influence elevations.

Benefits: DHPPA elevations have been shown to directly inhibit pro-inflammatory cytokines.[106] It has also been shown to have other potential health benefits including reducing oxidative stress and having cardio and neuroprotective properties.[107]

Low Values Reduced DHPPA may indicate insufficient dietary intake of polyphenol-rich foods or a depletion of beneficial gut bacteria.[101] Factors such as dysbiosis, antibiotic use, or health conditions affecting the microbiome may limit the breakdown of chlorogenic acid into DHPPA.[108]

Other markers associated with intake of polyphenol rich foods include **Hippuric acid** (10), **4-Hydroxybenzoic acid** (12), **4-Hydroxyhippuric acid** (13), and **Hydroxyphenylacetic acid** (15).

CLOSTRIDIA BACTERIAL MARKERS

(15) 4-Hydroxyphenylacetic acid

4-Hydroxyphenylacetic acid (4-HPAA) is a microbial metabolite derived from the bacterial transamination of tyrosine and polyphenols.[109] Dysbiosis is often associated with *Clostridia* species, which may influence neurotransmitter balance.[110,111] Elevations have also been observed in gastrointestinal disorders such as SIBO and may be affected by polyphenol consumption.[112,113]

Microbial Overgrowth(Clostridia Bacteria)

Elevated 4-HPAA levels are often associated with anaerobic bacterial overgrowth, particularly *Clostridia spp.* including *C. difficile*, *C. stricklandii*, *C. lituseburense*, *C. subterminale*, *C. putrefaciens*, and *C. propionicum*.[114-116] Overgrowth can result from gut microbiota disruptions due to antibiotic use, glyphosate or organophosphate exposure, or similar factors.[117,118] Other potential bacterial contributors include *Acinetobacter*, *Klebsiella*, *Pseudomonas*, and *Proteus*, however evidence is limited for these genera. Of note, it is common for only one *Clostridia* metabolite to be elevated and still be significant.[119]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Neurotransmitter Metabolites

Theoretical and anecdotal evidence shows that phenylalanine and tyrosine related metabolites from *Clostridia spp.* may inhibit the conversion of dopamine to norepinephrine through blocking the dopamine beta hydroxylase (DBH) enzyme.[120-123] *C. difficile* has the ability to decarboxylate 4-HPAA to produce **4-cresol** (17), and this *clostridia* metabolite has been shown to directly influence the DBH enzyme.[110,111]

When this occurs, a pattern of elevated **Homovanillic acid (HVA)** (33), low **Vanillylmandelic acid (VMA)** (34), and elevated **HVA/VMA ratio** (35) may be observed.

Toxic Exposure

Pesticides like glyphosate and organophosphates can disrupt the microbiome by reducing beneficial bacteria, creating conditions that favor pathogenic dysbiosis. These chemicals have been shown to promote *Clostridia* overgrowth.[117, 118]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Genetics

Though rare, certain metabolic conditions, such as tyrosinemia, are associated with extreme elevations. Other markers associated with tyrosinemia include **Hippuric acid** (10), **2-Hydroxyphenylacetic acid** (11), **2-Hydroxyisovaleric acid** (62), and **4-Hydroxyphenyllactic acid** (72).[19]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary: High levels of 4-HPAA may result from a diet rich in polyphenols, commonly found in fruits, vegetables, tea, coffee, wine, and whole grains.[113] Gut microbes metabolize these compounds into 4-HPAA, which can then become elevated even in the absence of dysbiosis.[113]

Other markers associated with intake of polyphenol-rich foods include: **Hippuric acid** (10), **4-Hydroxybenzoic acid** (12), **4-Hydroxyhippuric acid** (13), **and DHPPA (3,4 dihydroxyphenylpropionic acid)** (14).

Associated Conditions: Elevated levels of 4-HPAA have been associated with conditions such as small intestinal bacterial overgrowth (SIBO), Giardia lamblia infections, celiac disease, cystic fibrosis, and post-surgical changes like ileal resection.[112,124]

Low Values There is no known clinical significance for low values.

(16) HPHPA (3-(3-Hydroxyphenyl)-3-hydroxypropanoic acid)

HPHPA (3-(3-Hydroxyphenyl)-3-hydroxypropionic acid) is produced by various *Clostridia* bacteria through the metabolism of phenylalanine and may disrupt catecholamine metabolism and signaling.[99,115] Elevated HPHPA levels are linked to numerous behavioral, gastrointestinal, and neuropsychiatric conditions.[99]

Microbial Overgrowth(Clostridia Bacteria)

Evidence suggest HPHPA may be produced by various *Clostridia* bacteria including *C. sporogenes*, *C. botulinum*, *C. chlortoluron's*, *C. mangenoti*, *C. ghoni*, *C. bifermentans*, *C. sordellii*, and occasionally *C. difficile* via the metabolism of phenylalanine.[99,115,125] Phenylpropionic or m-tyrosine, both of which can break down to HPHPA, have been shown to be neurotoxic and metabotoxic, and may disrupt catecholamine signaling or amino acid transport.[99,126,127] Additionally, through beta-oxidation, HPHPA can be converted into hydroxybenzoic acid, and its glycine conjugate, hydroxyhippuric acid, meaning elevated levels of **4-Hydroxybenzoic acid** (12), and **4-hydroxyhippuric acid** (13) may also provide insights .Of note, it is common for only one *Clostridia* metabolite to be elevated and still be significant.[126]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Neurotransmitter Metabolites

It has been theorized that HPHPA's phenolic structure may disrupt catecholamine metabolism by inhibiting the conversion of dopamine to norepinephrine/epinephrine. Clinical observations have shown when HPHPA is elevated, urinary dopamine metabolites (Homovanillic acid (HVA) (33)) become higher, and norepinephrine/epinephrine metabolites (**Vanillylmandelic acid (VMA)** (34)) are reduced, creating an elevated **HVA/VMA ratio** (35).[120]

Toxic Exposure

Pesticides like glyphosate and organophosphates can disrupt the microbiome by reducing beneficial bacteria, creating conditions that favor pathogenic dysbiosis. These chemicals have been shown to promote *Clostridia* overgrowth.[117,118]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Additional Insights

Associated Conditions: Elevated levels of HPHPA are associated with a range of behavioral, gastrointestinal, and neuropsychiatric symptoms, including conditions such as autism, schizophrenia, ADHD, tic disorders, obsessive-compulsive disorder, chronic fatigue syndrome, and anorexia.[99,126,128]

Low Values There is no known clinical significance for low values.

(17) 4-Cresol

4-Cresol is primarily produced by *Clostridium difficile* and related bacteria through the metabolism of tyrosine.[116] It is a significant marker of gut dysbiosis and can inhibit dopamine beta-hydroxylase (DBH), leading to elevated dopamine and toxic byproducts.[116,123] It is linked with environmental toxicants such as toluene, creosote-treated wood, and pesticides, as well as attributed to more severe symptoms in autistic children.[129-133] It has also been associated with cardiovascular, metabolic, and renal diseases.[134]

Microbial Overgrowth(Clostridia Bacteria)

4-Cresol is primarily produced by *C. difficile* and *C. scatologenes*, with *C. difficile* being the most common source.[116] Other bacterial families, such as *Coriobacteriaceae*, *Lactobacillus*, and *Enterobacteriaceae* also could produce 4-cresol with certain substrates, but to a much lesser degree.[135-137] Elevated levels often indicate gut dysbiosis, potentially caused by interventions or exposures that disrupt the microbiome.[138] Moreover, 4-cresol has demonstrated antimicrobial properties that can potentially further dysbiosis.[116]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Neurotransmitter Metabolites

4-cresol has been shown to inhibit the dopamine beta hydroxylase enzyme (DBH), reducing the conversion of dopamine to norepinephrine.[111,123] 4-cresol can form covalent bonds with DBH, leading to elevated dopamine levels. An excessive increase in dopamine can result in unstable dopamine quinones, toxic dopamine adducts that disrupt the brain's mitochondrial energy production, and oxygen superoxide, all of which can cause significant damage to the brain.[120]

Inhibition of DBH can cause the pattern of elevated **Homovanillic acid (HVA)** (33) and

3,4-dihydroxyphenylacetic acid (DOPAC) (36), along with low **Vanillylmandelic acid (VMA)** (34) and elevated **HVA/VMA ratio** (35).

Toxic Exposure

Pesticides like glyphosate and organophosphates have been shown to promote *Clostridia* overgrowth.[117,118] To a much lesser degree, 4-cresol can also be produced from the metabolism of toluene, menthofuran (from peppermint and pennyroyal essential oils), and creosote, a wood preservative containing polycyclic aromatic hydrocarbons (PAHs) and phenolic compounds.[129-132] Another organic acid that can be a metabolite of **Toluene is Hippuric acid** (10).

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Additional Insights

Associated Conditions: Urinary levels of 4-cresol have been found to be significantly higher in autistic children compared to controls and are associated with greater clinical severity.[133,139] This metabolite has also been associated with cardiovascular, metabolic, and renal diseases.[134,140,141]

Low Values There is no known clinical significance for low values.

(18) 3-Indoleacetic acid

3-Indoleacetic acid (IAA) is a metabolite of tryptophan that is produced primarily through the indolic pathway. It is often linked to *Clostridia*, though other bacteria and yeast may also contribute.[142] While IAA has been associated with systemic inflammation, increased virulence of fungus, and various conditions, including autism, cardiovascular disease, kidney dysfunction, and psychological disorders, it has also been shown to exhibit certain beneficial properties.[143-146]

Microbial Overgrowth(Clostridia Bacteria)

IAA is mainly produced by intestinal bacteria through tryptophan breakdown with elevated levels being linked to *C. stricklandii*, *C. lituseburense*, *C. subterminale*, and *C. putrefaciens*.[142] Other bacteria like *Escherichia*, *Bacteroides*, *Lactobacillus*, and *Pseudomonas*, as well as other fungi such as *Saccharomyces cerevisiae* and *Candida tropicalis*, may also produce IAA.[144,147] Moreover, IAA has been shown to induce filamentation, and promote biofilm formation in fungus.[144,148]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Toxic Exposure

Pesticides like glyphosate and organophosphates have been shown to promote Clostridia overgrowth.[117,118]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Genetics

Extreme IAA levels are linked to Hartnup's Disease, a rare genetic disorder that impairs the renal and intestinal transport of neutral amino acids (e.g. tryptophan), causing elevated urinary amino acids and IAA.[149] Symptoms include skin rashes, ataxia, psychosis, and rashes resembling pellagra.[150] IAA may also be elevated in phenylketonuria (PKU).[151] Other associated metabolites of PKU include **Hippuric acid** (10), **2-Hydroxyphenylacetic acid** (11), **2-Hydorxyisovaleric acid** (62), **Mandelic acid** (68), **Phenyllactic acid** (69), **Phenylpyruvic acid** (70).

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Associated Conditions: Elevated IAA levels have been linked to systemic inflammation, autism, cardiovascular disease, kidney dysfunction, and psychological disorders like anxiety and depression.[143,146,152]

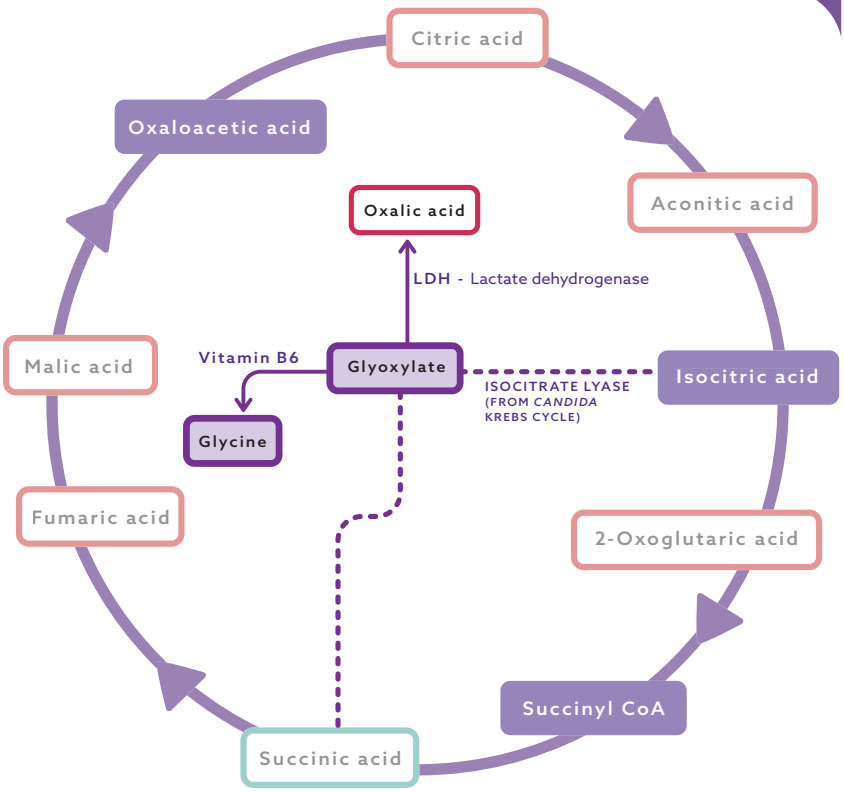
Benefits: The IAA metabolite has been shown to reduce oxidative stress, scavenge free radicals, lower pro-inflammatory cytokine production, and support intestinal homeostasis and mucosal immunity via activation of the aryl hydrocarbon receptor (AhR) pathway.[145]

Low Values There is no known clinical significance for low values.

OXALATE METABOLITES

Figure 2:

This figure explains how oxalic acid elevations can result from both direct and indirect microbial metabolism. Molds such as *Aspergillus niger* and *Penicillium spp.* are capable of direct oxalate production as part of their primary metabolic processes. In contrast, yeasts, including *Candida*, generate glyoxylate through the glyoxylate cycle, wherein isocitrate is cleaved by isocitrate lyase to yield glyoxylate. This intermediate can subsequently be converted in the liver to oxalic acid via lactate dehydrogenase (LDH)–mediated reactions. Glyoxylate can also be converted to glycine with the support of B6.



19 Glyceric Acid

Elevated glyceric acid can result from Microbial Overgrowths, nutrient deficiencies, diet, or genetic mutations. Elevated glyceric acid from fungal or microbial overgrowth, may be through the glyoxylate pathway, where excess glyoxylate is converted to glyceric acid or from direct production.[153-155] Insufficiencies in vitamin B3 or tryptophan, which are cofactors for glyoxylate reductase/hydroxypyruvate reductase (GRHPR), the enzyme regulating this pathway, may also contribute to increased levels.[153,156] Additionally, high fructose intake, glycerol metabolism, and various genetic conditions can also lead to excess glyceric acid.[157-160]

Microbial Overgrowth(Fungal and Bacteria)

Elevated glyceric acid, may result from overgrowth from fungi or other organisms.[153] It is theorized that elevated glyceric acid may stem from the intestinal microbes' glyoxalate pathway, where excess glyoxylate can convert to glyceric acid.[153,154] Other microbes shown to produce glyceric acid directly, include *Acetobacter* and *Gluconobacter*.[155]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Nutritional Needs

The enzyme glyoxylate reductase/hydroxypyruvate reductase (GRHPR) utilizes reduced forms of NAD as cofactors, requiring either **Vitamin B3** (Niacin) or **tryptophan** for its production.[156,161,162]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Primary Hyperoxaluria Type 2 (PH2) is linked to mutations in the *GRHPR* gene, which causes a deficiency of the enzyme GRHPR.[163] The lack of GRHPR prevents glyoxylates conversion to glycolate, leading to an excess amount of glyceric acid and **Oxalic acid** (21).[157]

D-glyceric aciduria is another genetic disorder associated with elevated glyceric acid and is caused by the deficiency of glycerate 2-kinase, though this disease is not well studied at this time.[164]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary: High fructose or fat intake can metabolize into glyceric acid.[158] Metabolism of glycerol containing foods or beverages can form intermediate glyceric acid, before reacting with aldehyde dehydrogenase to generate glyceraldehyde.[165]

Associated Conditions: Elevated glyceric acid has been shown to induce pancreatic islet cell damage, inducing glucose intolerance.[158] It has also been associated with rheumatoid arthritis, schizophrenia, and bipolar disorder, though the mechanism has yet to be explained.[159,160]

Low Values There is no known clinical significance for low values.

(20) Glycolic Acid

Glycolic acid is a small alpha-hydroxy acid involved in various metabolic pathways. Increased levels have been attributed to several different causes including overgrowth of bacteria and fungi, exposures to certain toxicants such as ethylene glycol (antifreeze), polyglycolate (PGA), and trichloroacetic acid, reduced B6 and glutathione levels, the use of supplemental collagen or skincare products, and certain rare genetic diseases.[153,166-171] Regardless of the source, elevated levels in urine have been associated with oxidative stress.[169]

Microbial Overgrowth (Fungal and Bacteria)

Elevated glycolic acid, may result from overgrowth of **fungi or other organisms**.[153] It is theorized that elevated glyceric acid may stem from the intestinal microbes' glyoxalate pathway, where excess glyoxylate can convert to glycolic acid.[153,172] Other microbes shown to produce glycolic acid directly, include *Acetobacter*, *Escherichia*, *Cryptococcus*, *Rhodococcus*, and *Saccharomyces*.[155,167]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Toxic Exposure

Ethylene glycol, found in anti-freeze, can be metabolized into glycolic acid, as well as **Oxalic acid** (21), **Lactic acid** (22), and **Pyruvic acid** (23).[166]

In addition, glycolic acid can be used as a component for creating polyglycolate (PGA), which is a synthetic polymer used in sutures and implantable medical devices.[167,173] It can also be a metabolite of trichloroacetic acid exposures from certain metals, plastics, or dermatological agents to treat warts, dermal peeling or tattoo removal.[174] **Oxalic acid** (21) is also a metabolite of exposure and may help with evaluation.[174]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Nutritional Needs

The enzyme alanine:glyoxylate aminotransferase (AGT), which prevents excess glycolic acid buildup, is B6-dependent.[168]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

Moreover, oxidative stress depletes glutathione (GSH), which normally helps convert glycolic acid into less harmful compounds. When GSH is low, glycolic acid is diverted to oxalate

production, increasing oxalic acid levels. Evaluate **Pyroglutamic acid (58)** for further clarification if GSH could be a factor.[169]

Genetics

Primary Hyperoxaluria Type 1 (PH1) is caused by mutations in the AGXT gene, leading to a defect in the liver specific enzyme AGT.[171] This enzyme impairs the ability to break down oxalates, increasing levels of glycolic and **Oxalic acids** (21).[171,175]

Furthermore, glycolic aciduria, another genetic condition linked to type 1 primary hyperoxaluria, can result from HAO1 gene mutations affecting glycolate oxidase or D-glycerate dehydrogenase, disrupting glycolic acid metabolism.[176]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Medications/Supplement Influences: Supplemental collagen can contribute significantly to urinary glycolic acid due to hydroxyproline metabolism.[170] Dermal applications that use glycolic acid, such as certain facial regimens or chemical peels, may increase output of glycolic acid in the urine.[177]

Associated Conditions: Lipid peroxidation and protein glycation produce glyoxal, which is metabolized into glycolic acid.[56] Elevated levels may indicate increased oxidative stress.[178]

Low Values There is no known clinical significance for low values.

(21) Oxalic Acid

Oxalates, the anionic form of oxalic acid, are naturally occurring compounds that can form crystalline structures when combined with a cation (e.g. calcium, lead, etc.).[179] Various organisms such as plants and fungi produce them for structure, defense, and function, but they are also a normal part of human metabolism.[180,181] Molds and yeasts can produce oxalates directly and indirectly, respectively, while beneficial bacteria such as *Oxalobacter formigenes* help break them down.[180,182] Additionally, exposure to certain toxicants such as ethylene oxide, ethylene glycol, and trichloroacetic acid can increase levels in the urine. When consumed from oxalate containing plants (e.g. spinach, soy, beets, tea. etc.), soluble and unbound oxalates are either absorbed in the colon or bind to minerals like calcium and form insoluble compounds in the intestinal lumen, followed by excretion in feces.[183,184] Oxalates' ability to bind essential minerals may contribute to deficiencies, while factors like vitamin B6 insufficiency, fat malabsorption, high-oxalate food consumption, collagen supplementation, and certain medications can further impact oxalate excretion.[170,179,185,186] Regardless of source, in humans, excessive oxalates can potentially cause systemic problems and have been associated with numerous health conditions involving pain and inflammation.[187-194]

Microbial Overgrowth (Fungal and Bacteria)

Oxalic acid can be elevated due to indirect or direct production from various organisms.[180,182] Mold, particularly *Aspergillus niger* and *Penicillium spp*, have been shown to produce oxalates directly, while certain yeast such as Candida spp and Saccharomyces spp, produce glyoxylate via the glyoxylate pathway, which is then processed into either oxalates, glycine, glycerate (19) and glycolate (20).[40,172,180,181,195-197]

Certain beneficial bacteria, including *Oxalobacter formigenes*, *Lactobacillus plantarum*, *L. acidophilus*, *L. fermentum*, *L. gastricus*, *Bifidobacterium breve*, and *B. longum*, are known to be oxalotrophic, meaning they metabolize oxalates as a source of carbon and electrons.[180]

An imbalance in beneficial gut bacteria can disrupt oxalate breakdown, leading to increased absorption from the gut and excess oxalates being filtered through urine instead of excreted in stool.[180]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Toxic Exposure

Ethylene oxide, or its hydrolyzed form ethylene glycol, can both metabolize to oxalic acid.[198] These toxicants can be found in various plastics, cosmetics, the food industry, stain removers, and antifreeze.[198] Additionally, trichloroacetic acid exposures through metals, plastics, or dermatological agent to treat warts, dermal peeling or tattoo removal, can contribute to oxalic acid in the urine. **Glycolic acid** (20) can also be a metabolite generated from both ethylene glycol and trichloroacetic acid exposures and may help with interpretation.[166,174] If mold is a suspected source of oxalates, mycotoxin exposure may also need to be considered.[174]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Nutritional Needs

High amounts of oxalates may contribute to mineral deficiencies due to their high affinity for certain minerals like **calcium**, **magnesium**, and **iron**.[179]

Insufficiencies in **Vitamin B6 (pyridoxine)** can cause glyoxylate to favor the oxalate pathway instead of glycine, so elevations in oxalic acid may be related to low B6.[185]

Refer to the Nutrient-Marker Reference Table for the corresponding organic acids associated with those nutrients.

Additionally, elevated urinary oxalate levels may be influenced by fat malabsorption, as unabsorbed fats bind calcium, increasing soluble oxalate absorption.[186] Fat malabsorption can influence the status of fat-soluble vitamins, including **Vitamins A**, **D**, **E**, and **K**. **Phosphoric acid** (76) can be influenced by Vitamin D levels, and may help support running a serum Vitamin D, 25-Hydroxy.[199]

Genetics

Rare genetic hyperoxalurias, types I and II can both causes elevated urinary oxalic acid.[175]

Type 1 is usually associated with elevated **Glycolic acid** (20), while type II is associated with elevated **Glyceric acid** (19).[175]

Aside from type I and II hyperoxalurias, other genetic SNPs have been shown to influence calcium oxalate formations. The **UMOD gene** codes for uromodulin, which inhibits calcium crystals in the urine.[200] A SNP in this gene may increase oxalate formation risk and potentially be worsened by a SPP1 variant. [200] The **calcium-sensing receptor (CaSR) gene** codes for a receptor that senses extracellular calcium levels in the kidneys and has been shown to promote calcium oxalate crystal adhesion.[201] The **SLC26A4 gene** provides instructions for making pendrin, which transports negative particles across cell membranes and influences mineral properties, and may consequently increase calcium oxalate formation, particularly in the vestibular system.[202]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary: Elevations can be caused by consumption of high oxalate foods including spinach and other various greens, soy, beets, sweet potato, variety of berries, cocoa, black tea, nuts (especially almonds), tea, and various grains.[183,203] This is not an exhaustive list, but it should be noted, oxalate abundance in food has biological variation including cultivation practices, time of harvest, and growing conditions, as well as cooking methods and amount consumed.[204]

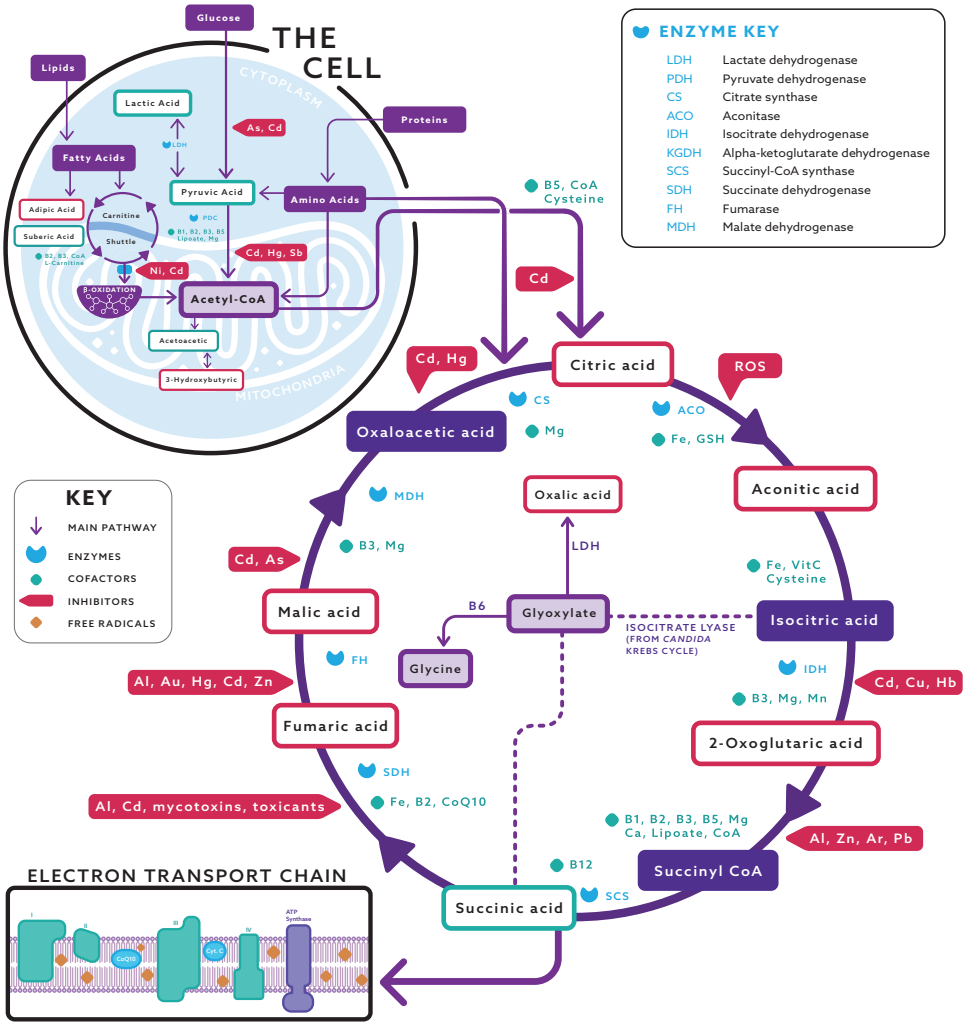
Medication/ Supplement Influences: Supplemental collagen can contribute to elevated urinary oxalic acid and **glycolic acid** (20) due to hydroxyproline metabolism. Although studies on high doses of vitamin C (>500–1500 mg/day) contributing to oxalic acid are conflicting, ascorbate's conversion to oxalate can be upregulated in the presence of high copper.[179,205-208] Associated markers for **Vitamin C** (54) as well as **HVA/VMA ratio** (35), which is influenced by copper, may provide additional insights.[170]

Associated Conditions: High oxalate levels have been linked to numerous conditions involving orthopedic, urogenital, cardiovascular, ocular, neuromuscular, skeletal, dental, pulmonary, neurological, endocrine, and gastrointestinal systems.[187-194]

Low Values There is no known clinical significance for low values.

MITOCHONDRIAL METABOLITES

Figure 3:



This diagram presents key markers involved in glycolysis, fatty acid oxidation, and mitochondrial energy production, as depicted in the metabolic pathway diagram. Glucose is metabolized through glycolysis to pyruvic acid, which may convert to lactic acid or enter the mitochondria as acetyl-CoA to fuel the citric acid (Krebs) cycle. Fatty acids, shuttled into mitochondria via carnitine, are also oxidized to generate acetyl-CoA, supporting further energy production. As the cycle progresses through intermediates, such as aconitic, 2-oxoglutaric, succinic, fumaric, and malic acids, electrons are transferred to the electron transport chain (ETC), driving ATP synthesis.

The diagram also maps how organic acid levels can reflect underlying enzymatic function, highlighting areas of dysfunction and their potential causes. Inhibitors like heavy metals or mycotoxins, and deficiencies in cofactors such as vitamins and minerals, can impair key enzymes involved in these pathways. Metabolites shown in red and green, represent measured organic acids in the report, and are dynamic based on abnormal or normal values, respectively.

GLYCOLYTIC CYCLE METABOLITES

(22) Lactic acid

Lactic acid is primarily produced in the cytoplasm when mitochondrial oxidative phosphorylation is impaired, causing a shift toward anaerobic glycolysis. Elevations can indicate mitochondrial dysfunction, especially when seen with other mitochondrial metabolites.[209] It may also be produced by various microbes—including *E. coli*, *Streptococcus*, and *Saccharomyces*—suggesting possible dysbiosis.[209,210] Environmental toxins like cadmium, mercury, and mycotoxins can impair enzymes such as pyruvate dehydrogenase or lactate dehydrogenase, further contributing to lactic acid buildup.[211-219] Nutrient insufficiencies in CoQ10, zinc, iron, or B vitamins may also drive elevations by impairing energy metabolism or increasing anaerobic glycolysis.[223-229] In rare cases, genetic mitochondrial disorders or certain medications may be involved, while elevated levels are also associated with hypoxia, diabetes, and other chronic conditions.[209,220-222]

Microbial Overgrowth

Lactic acid can be produced by many different microbial organisms including *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Enterococcus faecalis*, *Streptococcus group B*, *Bacillus*, *Saccharomyces cerevisiae*, *Rhizopus spp.*, and more.[209,210]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Mitochondrial Health

Elevations, especially in the presence of other mitochondrial metabolite elevations can indicate issues with overall mitochondrial health and energy production.

For more insight into mitochondrial health, reference the other **mitochondrial markers** (22)-(32) and **fatty acid oxidation markers** (45)-(49).

Toxic Exposure

Cadmium, mercury, and antimony can impact enzymes such as pyruvate dehydrogenase (PDH), pyruvate carboxylase and lactate dehydrogenase (LDH).[211-218] These heavy metals can interfere with enzyme function in several ways, typically by binding to thiol (sulfhydryl) groups in proteins or disrupting the enzymes' normal cofactors, leading to altered activity. Mycotoxins can induce hypoxia through various mechanisms which can increase lactic acid levels.[219]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Nutritional Needs

Without sufficient **CoQ10**, the electron transport chain cannot function appropriately and may increase lactic acid levels.[223] **Zinc** deficiency can also lead to increased lactate dehydrogenase activity promoting the conversion of pyruvate to lactate. Insufficient zinc also disrupts mitochondrial function leading to an increased reliance on anaerobic glycolysis and therefore

increasing lactic acid levels.[224,225] With low **iron** levels or in an anemic state, tissue hypoxia may be induced and can increase lactic acid levels.[224,225] Lactic acidosis may be caused by **B1** (thiamine) deficiency.[227] When **B3** levels are low, NAD+ levels decrease, leading to an impaired conversion of pyruvate to lactate by lactate dehydrogenase, thereby increasing lactic acid formation.[228,229]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Some rare metabolic disorders may cause increased incidence of lactic acidosis due to defects in enzymes involved in carbohydrate metabolism and/or mitochondrial function. These disorders may include, among others, pyruvate dehydrogenase or pyruvate carboxylase deficiency, fumarase deficiency, or defects in the electron transport chain.[230-232]

For additional insight into rare mitochondrial disorders, reference **pyruvic acid** (23), **succinic acid** (24), and **fumaric acid** (25).

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Medication/Supplement Interactions: In some cases, a few medications may increase lactate levels, such as metformin (especially in those with renal impairment), aspirin, and nucleoside reverse transcriptase inhibitors (NRTIs) used in HIV treatment.[220,221]

Associated Conditions: Lactic acid buildup may result in cases of tissue hypoxia or hypoperfusion, such as with intense activity or exercise, with low iron levels or in an anemic state, in sleep-related breathing disorders such as sleep apnea, or with pulmonary or cardiac dysfunction.[209,226,233,234] Increased lactic acid levels may occur with insulin or blood sugar dysregulations such as hyperglycemia or in the case of diabetes mellitus. This occurs due to high glucose levels increasing the rate of glycolysis and subsequent levels of pyruvate and lactate. Hyperglycemia may also impair the oxidation of lactate, leading to its accumulation.[235] Lactic acid levels can be elevated in conditions like liver disease, alcohol dependence, seizure disorders, and severe infections due to impaired lactate clearance, increased lactate production, and metabolic disruptions.[222]

Low Values There is no known clinical significance for low values.

23 Pyruvic acid

Pyruvic acid is produced during glycolysis and, depending on oxygen availability, is either converted into acetyl-CoA in the mitochondria or lactic acid under anaerobic conditions.[236] Elevated pyruvate levels can indicate mitochondrial dysfunction or be associated with prolonged fasting, exercise, or certain toxic exposures (e.g., cadmium, mercury, antimony).[211-217,237,238] Nutrient deficiencies in vitamins B1, B2, B3, B5, and magnesium can also lead to increased pyruvate levels.[237-239] In rare genetic disorders, pyruvate accumulation may occur. Additional factors such as liver damage, alcoholism, and certain diets may also contribute to elevated pyruvate.[240-245]

Mitochondrial Health

Elevations, especially in the presence of other mitochondrial metabolite elevations, can indicate issues with overall mitochondrial health and energy production.

Pyruvate levels also may increase through the Cahill cycle during prolonged fasting and exercise. In the liver, alanine derived from muscle is converted to pyruvate, which is then used to produce glucose via gluconeogenesis. This process helps maintain blood glucose levels when glycogen stores are low and supports energy production during physical activity, elevating pyruvate levels in the process.[237,238]

For more insight into mitochondrial health, reference the other **mitochondrial markers** 22-32 and **fatty acid oxidation markers** 45-49.

Toxic Exposure

Cadmium, mercury, and antimony can impact enzymes such as pyruvate dehydrogenase (PDH) and pyruvate carboxylase.[211-217] These heavy metals can interfere with enzyme function in several ways, typically by binding to thiol (sulfhydryl) groups in proteins or disrupting the enzymes' normal cofactors, leading to altered activity.

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Nutritional Needs

The conversion of pyruvic acid to acetyl-CoA by the pyruvate dehydrogenase complex (PDC) requires several essential cofactors **vitamin B1** (Thiamine pyrophosphate), **B2** (FAD), **B3** (NAD+), **B5** (coenzyme A), **lipoic acid** and **magnesium**. Deficiencies of these nutrients can cause an elevation of pyruvic acid.[237-239]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Several rare metabolic disorders, including pyruvate dehydrogenase deficiency and disorders

of sugar metabolism, can cause pyruvate accumulation due to defects in enzymes that normally convert pyruvate to other metabolites (e.g., acetyl-CoA, oxaloacetate). The common clinical feature is lactic acidosis, with symptoms ranging from developmental delays to muscle weakness and neurological issues. Proper diagnosis typically involves biochemical assays and genetic testing to identify the specific enzyme deficiencies or genetic mutations involved.[240,246]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary Influences: Pyruvic elevations can be caused by consuming a high-fat, low-carbohydrate diet or high-sucrose diet.[244,245]

Associated Conditions: Pyruvic acid levels may be elevated in conditions associated with liver damage or alcoholism.[241-243]

Low Values There is no known clinical significance for low values

CITRIC ACID CYCLE METABOLITES

24 Succinic acid

Succinic acid plays a key role in the Citric Acid Cycle and the electron transport chain, where it is oxidized to fumarate (fumaric acid) via succinate dehydrogenase (SDH), also known as mitochondrial Complex II. SDH is the only enzyme that participates in both the Citric Acid Cycle and the Electron Transport Chain (ETC), giving insights into both pathways.[247] Elevated levels can indicate mitochondrial dysfunction, Microbial Overgrowth, or toxic exposures, such as heavy metals or certain fungicides.[248-258] Deficiencies in nutrients such as iron, riboflavin (B2), and CoQ10 can also contribute to increased succinic acid levels.[259-262] Low succinic acid levels are possible in rare metabolic disorders such as SSADH deficiency, and in theory could be reflective of impaired glycolysis, fatty acid oxidation, or vitamin B12 deficiency, all of which could reduce acetyl-CoA or succinyl-CoA availability for the citric acid cycle though evidence in the scientific literature is limited.[263-266]

Microbial Overgrowth

Imbalances in the gut microbiota are linked to higher levels of succinic acid, with conditions like inflammatory bowel disease and obesity showing increased levels due to shifts in succinate-producing and consuming bacteria. Dysbiosis, marked by an overgrowth of succinate-producing bacteria such as *Prevotellaceae* and *Veillonellaceae*, is associated with higher circulating succinate levels. Elevated succinate levels are also observed in animal models of intestinal inflammation and in patients with severe systemic inflammatory response

syndrome (SIRS), suggesting that gastrointestinal dysbiosis plays a role in various pathological conditions.[251-254] Fungi also produce succinic acid mainly through the Citric Acid Cycle, with anaerobic conditions or respiratory chain inhibition prompting the use of the reductive Citric Acid Cycle. Fungi like *Penicillium simplicissimum* and *Aspergillus saccharolyticus* produce succinate via fumarate reductase. *Saccharomyces cerevisiae* also produces succinic acid through both branches of the TCA cycle during anaerobic fermentation, with the reductive branch being the primary pathway.[267-270]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Mitochondrial Health

Elevated succinic acid may indicate impaired activity of succinate dehydrogenase (SDH), a key enzyme that links the Citric Acid Cycle and electron transport chain (ETC) at Complex II.[248-250] This disruption can create a bottleneck in electron flow, leading to reduced ATP production and increased oxidative stress.[271,272] Succinate accumulation also reflects shifts in the mitochondrial redox state and can signal broader dysfunction in mitochondrial energy metabolism.[273,274] Elevations, especially in the presence of other mitochondrial metabolite elevations can indicate issues with overall mitochondrial health and energy production.

For more insight into mitochondrial health, reference the other **mitochondrial markers** (22)-(32) and **fatty acid oxidation markers** (45)-(49).

Toxic Exposures

The succinate dehydrogenase enzyme is particularly vulnerable to toxic exposures that inhibit its function and can therefore increase succinic acid levels. Aluminum has been found to reduce the activity and expression of succinate dehydrogenase. Cadmium impairs enzymatic function by disrupting the electron transport chain, particularly at complexes II and III, while also promoting the production of reactive oxygen species (ROS).[255,256] A class of fungicides known as succinate dehydrogenase inhibitors (SDHIs) includes boscalid and fluxapyroxad among others and are used widely in agriculture and inhibit succinate dehydrogenase activity which may increase succinic acid levels.[257,258] Various mycotoxins, particularly Aflatoxin B1 (AFB1), has been demonstrated to inhibit succinate cytochrome c reductase, a part of the succinate dehydrogenase complex and potentially leading to an increased level of succinic acid as well as compromised mitochondrial function.[275]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Nutritional Needs

Succinate dehydrogenase contains three iron-sulfur clusters, making iron essential for proper electron transfer during the conversion of succinic acid to fumaric acid. In iron-deficient states, succinic acid may increase.[259,260] FAD, which is synthesized by **vitamin B2** (riboflavin), supports the activity of succinate dehydrogenase. In riboflavin deficiency, succinate dehydrogenase activity decreases, and succinic acid levels increase.[261] **CoQ10** accepts electrons from succinate dehydrogenase, enabling the electron transport chain to continue and prevents the buildup of

succinate. Research shows that CoQ10 can also protect succinate dehydrogenase activity from being inhibited by L-malate.[262]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Rare causes of elevated succinic acid include mitochondrial mutations, which can result from changes in nuclear or mitochondrial DNA affecting mitochondrial proteins, such as in Kearns-Sayre syndrome.[276]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Medication/ Supplement Interactions: Succinic acid is a byproduct of gamma-aminobutyric acid (GABA), and supplementation, as well as derivatives such as gabapentin, may increase levels.[277,278]

Associated Conditions: Lipopolysaccharides (LPS) increase succinic acid levels by triggering a metabolic shift in macrophages, boosting glycolysis and glutamine-dependent anaplerosis, which stabilizes HIF-1α and promotes inflammation.[279,280] Under hypoxic conditions, succinate dehydrogenase activity is reversed, leading to the production of succinic acid, which is transported to oxygen-rich tissues.[281] Elevated succinic acid levels are also found in autism spectrum disorder (ASD), linked to mitochondrial dysfunction and metabolic disturbances. Additionally, changes in the gut microbiome in ASD may contribute to increased succinic acid production and metabolism.[282,283]

Low Values

Mitochondrial Health: Theoretically, impaired glycolysis or fatty acid oxidation could lead to less acetyl-CoA entering the citric acid cycle and therefore, decreasing intermediate levels.[264,265]

For more insight into mitochondrial health, reference the other **mitochondrial markers** (22)-(32).

Nutrient Needs: Vitamin B12 is crucial for the enzyme methylmalonyl-CoA mutase, which converts methylmalonyl-CoA to succinyl-CoA. When vitamin B12 is deficient, methylmalonyl-CoA mutase activity is impaired, causing an accumulation of methylmalonic acid and a decrease in succinyl-CoA production. As succinyl-CoA is a precursor to succinic acid in the Citric Acid Cycle, this deficiency could possibly lead to lower succinic acid levels.[266]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

Genetics: In the rare disorder known as Succinic semialdehyde dehydrogenase (SSADH) deficiency, the enzyme SSADH, which is involved in the breakdown of GABA to succinic acid

via the intermediate succinic semialdehyde, is absent, and GABA is alternatively converted to GHB while succinic acid levels fall. For additional insights, refer to **4-hydroxybutyric acid** (75).[263]

Associated Conditions: Succinic acid levels are lower in individuals with attention-deficit/hyperactivity disorder (ADHD), possibly in part due to the impact of antibiotics and stimulant medications on GI microbiota and short-chain fatty acid (SCFA) production. Age also influences SCFA profiles, with children showing different patterns from adults. Disruptions in the microbiota-gut-brain axis, influenced by diet, medication, and antibiotic use, may contribute to these lower succinic acid levels and the psychiatric symptoms in ADHD.[284]

(25) Fumaric acid

Fumaric acid is a key intermediate in the Citric Acid Cycle, produced from succinic acid by succinate dehydrogenase (SDH) and then converted to malic acid by the enzyme fumarase.[285] Elevated fumaric acid levels may indicate mitochondrial dysfunction, toxic exposure (e.g., to metals such as aluminum, mercury, and cadmium), or metabolic changes in immune cells.[286-288] Iron is essential for the proper function of fumarase and succinate dehydrogenase, and deficiencies can lead to elevated fumaric acid.[259,260,289] Fumaric acid and its derivatives have therapeutic potential, particularly in treating neurodegenerative diseases due to their antioxidant and anti-inflammatory properties.[288,290,291] Low fumaric acid levels, in theory, may result from impaired glycolysis, fatty acid oxidation, or toxic exposures that inhibit key enzymes in the Citric Acid Cycle.[255-258,264,265,275]

Microbial Overgrowth

Fumaric acid is a metabolite of *Aspergillus*.[285]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Mitochondrial Health

Elevations, especially in the presence of other mitochondrial metabolite elevations, can indicate issues with overall mitochondrial health and energy production.

For more insight into mitochondrial health, reference the other **mitochondrial markers** (22)-(32) and **fatty acid oxidation markers** (45)-(49).

Toxic Exposure

Some metals inhibit fumarase activity, especially by way of interfering with iron metabolism or targeting the iron-sulfur clusters of the enzyme, leading to inactivation or downregulation. Metals that impact fumarase include aluminum, gallium, silver, mercury, cadmium, and zinc, which can all lead to elevated levels of fumaric acid.[286,287] Fumaric acid is also a metabolite of *Aspergillus*.[285]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Nutritional Needs

Iron is important in the proper functioning of iron-sulfur cluster-containing enzymes such as fumarase.[289] Low iron levels can impair the enzymatic function of fumarase and lead to elevated levels of fumaric acid. However, succinate dehydrogenase also contains three iron-sulfur clusters, making iron essential for proper electron transfer during the conversion of succinic acid to fumaric acid.[259,260]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

Additional Insights

Benefits: When immune cells are activated, they undergo metabolic changes, including increased glycolysis and glutaminolysis, which lead to fumaric acid accumulation and epigenetic reprogramming, key to trained immunity.[288] Fumarase can translocate to the nucleus in response to DNA damage, potentially acting as a tumor suppressor and contributing to elevated fumaric acid levels.[290] Additionally, fumaric acid esters activate the Nrf2 pathway, reducing oxidative stress and neuroinflammation, with potential therapeutic benefits.[291]

Low Values

Mitochondrial Health: Theoretically, impaired glycolysis or fatty acid oxidation could lead to less acetyl-CoA entering the citric acid cycle and therefore, decreasing intermediate levels.[264,265]

For more insight into mitochondrial health, reference the other **mitochondrial markers** (22)-(32).

Toxic Exposure: The succinate dehydrogenase enzyme is particularly vulnerable to certain toxic exposures that inhibit its function and can therefore potentially lower fumaric acid levels, though this is theoretical. Aluminum has been found to reduce the activity and expression of succinate dehydrogenase. Cadmium impairs enzymatic function by disrupting the electron transport chain, particularly at complexes II and III, while also promoting the production of reactive oxygen species (ROS).[255,256] A class of fungicides known as succinate dehydrogenase inhibitors (SDHIs) includes boscalid and fluxapyroxad among others and are used widely in agriculture and inhibit succinate dehydrogenase activity, which may decrease fumaric acid levels.[257,258] Various mycotoxins, particularly, Aflatoxin B1 (AFB1) has been demonstrated to inhibit succinate cytochrome c reductase, a part of the succinate dehydrogenase complex and potentially leading to an increased level of succinic acid as well as compromised mitochondrial function.[275]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

(26) Malic acid

Malic acid is an important metabolite in the Citric Acid Cycle, helping with energy production by transferring reducing equivalents in aerobic conditions and assisting glycolysis in anaerobic conditions.[292] Elevated malic acid levels can result from Microbial Overgrowth, mitochondrial dysfunction, or toxic exposures such as arsenic and cadmium, which inhibit malate dehydrogenase.[10,292-297] Nutrient deficiencies, particularly in vitamin B3, which is essential for malate dehydrogenase function, can also lead to increased malic acid levels.[298,299] Malic acid is found in foods such as apples and wines and is sometimes used in supplements or medications.[292,300,301] Low levels, in theory, could result from impaired metabolism, magnesium deficiency, or certain heavy metals that inhibit key enzymes in the Citric Acid Cycle.[264,265,286,287,302,303]

Microbial Overgrowth

LPS from Gram-negative bacteria promotes the growth of organic acid-producing bacteria, influencing metabolism and byproducts. Overgrowth increases malic acid production via MleR-regulated pathways, enhancing acid tolerance and further stimulating malic acid synthesis.[293,294] Fungi such as *Aspergillus* and *Penicillium* can also produce malic acid.[292,295] Additionally, **citramalic acid** (1) from fungus has the potential to inhibit malic acid utilization in the Citric Acid Cycle, causing interference leading to elevations in malic acid.[10]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Mitochondrial Health

Elevations, especially in the presence of other mitochondrial metabolite elevations, can indicate issues with overall mitochondrial health and energy production.

For more insight into mitochondrial health, reference the other **mitochondrial markers** (22)-(32) and **fatty acid oxidation markers** (45)-(49).

Toxic Exposure

Arsenic and cadmium can both inhibit malate dehydrogenase activity, disrupting the citric acid cycle and electron transport chain, leading to increased malic acid levels.[296,297] Mycotoxins from Aspergillus and Penicillium have also been shown to influence malic acid levels.[292,295]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Nutritional Needs

NAD^+, derived from **Vitamin B3**, is the main cofactor for the enzyme malate dehydrogenase, serving as an electron acceptor in the conversion of malate to oxaloacetate. The enzymatic function is highly dependent on the presence of NAD^+, as it enables the transfer of electrons during the catalytic reaction.[298,299] Without adequate B3, malic acid levels may increase.

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

Additional Insights

Dietary Influences: Malic acid is a tart-tasting organic acid in some wines and foods such as apples, especially contributing to the sourness of green apples.[292]

Medication/ Supplement Interactions: Malic acid can be used in medications such as almotriptan malate for migraines or supplements such as Super Malic used in fibromyalgia.[300,301]

Associated Conditions: Oxidative stress can also increase malic acid levels as part of a broad metabolic response and the associated mitochondrial dysfunction.[304]

Low Values

Mitochondrial Health: Theoretically, impaired glycolysis or fatty acid oxidation could lead to less acetyl-CoA entering the citric acid cycle and therefore, decreasing intermediate levels.[264,265]

For more insight into mitochondrial health, reference the other **mitochondrial markers** (22)-(32).

Toxic Exposure: Some metals inhibit the fumarase activity, especially by way of interfering with **iron** metabolism or targeting the iron-sulfur clusters of the enzyme, leading to inactivation or downregulation. Metals that impact fumarase include aluminum, gallium, silver, mercury, and zinc, which can all lead to decreased levels of malic acid.[286,287] Although cadmium can inhibit both malate dehydrogenase and fumarase, it has a stronger effect on inhibiting fumarase, which could conceptually reduce malic acid levels.[303]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Nutritional Needs: Magnesium can boost the activity of MDH by stabilizing the enzyme's structure and playing a role in the catalytic process, hypothetically decreasing malic acid levels.[302]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

Associated conditions: Some studies have shown that only tissue malate is depleted after intense physical activity, while other crucial metabolites from the Citric Acid Cycle required for energy production remain unaffected. As a result, a malic acid deficiency has been proposed as a primary cause of physical exhaustion.[292]

(27) 2-Oxoglutaric acid

2-Oxoglutaric acid, produced from isocitrate by isocitrate dehydrogenase in the Citric Acid Cycle, is crucial for energy production.[305] Elevated levels of 2-oxoglutaric acid can indicate mitochondrial dysfunction, microbial overgrowth, or nutrient deficiencies, particularly in vitamins B1, B2, B3, B5, and magnesium, which are essential for its metabolism.[305-308] Rare genetic disorders, such as fumarase deficiency, may also cause increased levels.[305] 2-Oxoglutaric acid plays a key role in nitrogen scavenging, protein synthesis, and collagen production, and is essential for bone tissue formation.[305] Low levels, in theory, may result from manganese deficiency, impaired glycolysis, or fatty acid oxidation.[264,265,309]

Microbial Health

Some evidence has been found supporting 2-oxoglutaric acid production by some bacteria (*Corynebacterium glutamicum*) and yeasts.[305,306]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Mitochondrial Health

Elevations, especially in the presence of other mitochondrial metabolite elevations, can indicate issues with overall mitochondrial health and energy production.

For more insight into mitochondrial health, reference the other **mitochondrial markers** (22)-(32) and **fatty acid oxidation markers** (45)-(49).

Nutritional Needs

Vitamins **B1** (thiamine, precursor of TPP), **B2** (riboflavin, precursor of FAD), **B3** (niacin, precursor of NAD+), **B5** (pantothenic acid, a component of CoA), and **calcium** are essential for alpha-ketoglutarate dehydrogenase function.[307] **Lipoic acid** supports the enzyme's oxidative decarboxylation of 2-oxoglutaric acid, while **magnesium** stabilizes the enzyme complex and aids TPP binding. Deficiencies in these nutrients may elevate 2-oxoglutaric acid levels.[307,308,310] Additionally, elevated **zinc** levels may inhibit alpha-ketoglutarate dehydrogenase, further increasing 2-oxoglutaric acid levels.[311]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

2-oxoglutaric elevations may be linked to fumarase deficiency and 2-ketoglutarate dehydrogenase complex deficiency, both of which are rare inherited metabolic disorders.[305]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Medication/ Supplement Interactions: Supplemental alpha-ketoglutarate may also increase values.[305]

Associated Conditions: Both liver and kidney dysfunction or diseases may alter the activity of alpha-ketoglutarate dehydrogenase, leading to increased levels of 2-oxoglutaric acid.[312] Alpha-ketoglutarate dehydrogenase is sensitive to downregulation in the presence of reactive oxygen species (ROS) and under oxidative stress.[313] Conditions with elevated glutamate levels, such as cerebral ischemia, may lead to increased production of 2-oxoglutaric acid, serving as an alternative energy source for the Citric Acid Cycle during energy-deprived states.[314]

Benefits: 2-oxoglutaric acid acts as a nitrogen scavenger and a precursor to glutamate and glutamine, enhancing protein synthesis and inhibiting degradation in muscles. It supports bone tissue formation and is essential for collagen production by aiding proline hydroxylation. Additionally, it promotes the differentiation of regulatory T-cells.[305]

Low Values

Mitochondrial Health: Impaired glycolysis or fatty acid oxidation could hypothetically lead to less acetyl-CoA entering the citric acid cycle and therefore, decreasing intermediate levels.[264,265]

For more insight into mitochondrial health, reference the other **mitochondrial markers** (22)-(32).

Nutritional Needs: Manganese has been shown to inhibit the activity of glutamate dehydrogenase (GDH), the enzyme responsible for converting glutamate into 2-oxoglutaric acid, potentially leading to decreased levels.[309]

(28) Aconitic acid

Aconitic acid is formed as an intermediate between citrate and isocitrate, where the enzyme aconitase catalyzes the conversion of citrate to aconitic acid and then aconitic acid to isocitrate.[315] The enzyme requires variable cofactors, including an iron-sulfur cluster, for its activity and is sensitive to oxidative and nitrative stress, which can lead to elevated aconitic acid levels in the step from aconitic acid to isocitric acid.[316,317] Elevated aconitic acid can indicate mitochondrial dysfunction, toxic exposures (such as arsenic, aluminum, or fluoride), or nutrient deficiencies, particularly in iron.[316-322] Glutathione can protect aconitase from stress-induced inhibition, and iron deficiency can impair its function, leading to increased aconitic acid levels.[316,317] Impaired glycolysis or fatty acid oxidation theoretically could result in decrease aconitic acid levels due to reduced acetyl-CoA availability in the citric acid cycle, though evidence is limited.[264,265]

Mitochondrial Health

Elevations, especially in the presence of other mitochondrial metabolite elevations, can indicate issues with overall mitochondrial health and energy production.

For more insight into mitochondrial health, reference the other **mitochondrial markers** (22)-(32) and **fatty acid oxidation markers** (45)-(49).

Toxic Exposure

Toxic exposures, such as arsenic, aluminum, and tin, can inhibit aconitase activity and lead to an increase in aconitic acid levels.[318-320] High intake of fluoride may also cause increased aconitic acid levels.[321]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Methylation/Detoxification

Aconitase is particularly susceptible to stress and may become inhibited under conditions of oxidative and nitrative stress, leading to increased aconitic acid levels. **Glutathione** can modulate the inactivity and protect the enzymatic activity.[317]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with glutathione.

Nutritional Needs

Aconitase enzymatic function is dependent on **iron**. In iron-deficient states, the enzyme's activity is reduced and may lead to elevated levels of aconitic acid.[145] Aconitase also requires **glutathione** to support its enzymatic activity by maintaining the redox state of the Fe-S cluster, along with **vitamin C** to preserve enzymatic activity and cysteine to contribute to the formation and maintenance of the Fe-S cluster.[317,322]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients and glutathione.

Additional Insights

Low Values: Theoretically, impaired glycolysis or fatty acid oxidation could lead to less acetyl-CoA entering the citric acid cycle and therefore, decreasing intermediate levels.[264,265]

For more insight into mitochondrial health, reference the other **mitochondrial markers** (22)-(32).

29 Citric acid

Citric acid is a key component of the Citric Acid Cycle, formed from acetyl-CoA and oxaloacetate by the enzyme citrate synthase. The enzyme aconitase, which requires iron for activity, converts citric acid to isocitrate, and its function is essential for proper citric acid metabolism.[315,316] Elevated citric acid levels can indicate microbial overgrowth, mitochondrial dysfunction, or toxic exposure to substances such as arsenic or aluminum.[318-321,323-325] Nutrient deficiencies, particularly in iron, can reduce aconitase activity, leading to increased citric acid levels, while oxidative stress can also inhibit the enzyme.[316] Low citric acid levels may result from conditions such as hypokalemia, impaired metabolism, or iron overload, and can increase the risk of oxalate stone formation due to greater free calcium availability.[265,326-329]

Microbial Health

Many fungi, such as *Aspergillus spp*, and yeasts, produce citric acid, meaning overgrowths in the microbiome may lead to an increased value.[323]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Mitochondrial Health

Elevations, especially in the presence of other mitochondrial metabolite elevations, can indicate issues with overall mitochondrial health and energy production.

For more insight into mitochondrial health, reference the other **mitochondrial markers** 22-32 and **fatty acid oxidation markers** 45-49.

Toxic Exposure

Toxic exposures, such as cadmium, mercury, arsenic, aluminum and tin, can inhibit aconitase activity and lead to an increase in citric acid levels.[318-320,324,325] Though data is limited, studies suggest high intake of fluoride may also cause increased citric acid levels. Additionally, if suspicious of *Aspergillus*, may need to consider mycotoxins.[321]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Nutritional Needs

Aconitase requires iron to convert citric acid to aconitic acid. In iron deficient states, the enzyme's activity is reduced and may lead to elevated levels of citric acid.[316] Aconitase may become inhibited under conditions of oxidative and nitrative stress leading to increased citric acid levels. Glutathione can modulate inactivity and protect enzymatic activity.[317]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient and glutathione.

Additional Insights

Dietary Influences: Citrus fruits such as lemons, oranges, and limes contain citric acid, which may be reflected in the value.[330] Citrate is commonly added to foods and products as a flavor additive and preservative. Diet sodas are a significant source of citrate, while other sources may include dietary supplements, processed foods, and skincare products or cosmetics.[331-334] Given its antibacterial properties, citric acid may be used in cleaning products.[335]

Associated Conditions: Aconitase enzymatic activity is highly sensitive to oxidative stress, leading to its downregulation or inhibition and subsequent increase in citric acid levels.[336]

Low Values

Mitochondrial Health: Impaired glycolysis or fatty acid oxidation could lead to less acetyl-CoA entering the citric acid cycle and, therefore, decreasing citric acid levels.[265]

For more insight into mitochondrial health, reference the other **mitochondrial markers** (22)-(32).

Nutritional Needs: **Magnesium** is required for citrate synthase as this enzyme requires magnesium to facilitate the binding of substrates and subsequent catalytic reactions, including the condensation of acetyl CoA and oxaloacetic to form citrate.[337]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

Associated Conditions: Hypokalemia can result in low levels of citric acid due to intracellular acidosis and decreased tubular pH, leading to increased citrate uptake and metabolism.[326] **Iron** overload can reduce citric acid levels by increasing aconitase activity and promoting the formation of iron-citrate complexes, which disrupt citrate metabolism and availability.[327] Low citric acid levels result in more free **calcium** availability and decreased inhibition of crystal formation, both of which may increase the likelihood of oxalate stone formation, especially in the presence of elevated **oxalic acid** (21).[328,329]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

AMINO ACID METABOLITES

(30) 3- Methylglutaric acid

3-Methylglutaric acid is involved in leucine metabolism and often accumulates due to mitochondrial dysfunction, particularly when acetyl-CoA is rerouted through the "acetyl-CoA diversion pathway" due to impaired Citric Acid Cycle function.[338] Elevated levels of this acid can indicate mitochondrial health issues, especially when the electron transport chain is compromised.[338,339] Rare genetic disorders, such as deficiencies in HMGCL or AUH, can also cause its accumulation.[338,339] Additionally, certain medications, the ketogenic diet, and components of parenteral nutrition can promote the formation of 3-methylglutaric acid.[230]

Mitochondrial Health

Elevations, especially in the presence of other mitochondrial metabolite elevations, can indicate issues with overall mitochondrial health and energy production. 3-methylglutaric acid levels are particularly elevated when the electron transport chain is impaired, causing the "acetyl-CoA diversion pathway" to be activated. This process prevents acetyl-CoA from entering the Citric Acid Cycle, leading to an increase in 3-methylglutaric acid.[338,339]

For more insight into mitochondrial health, reference the other **mitochondrial markers** (22)-(32) and **fatty acid oxidation markers** (45)-(49).

Genetics

In rare metabolic disorders such as deficiencies in 3-hydroxy-3-methylglutaryl-CoA lyase (HMGCL) or 3-methylglutaconyl-CoA hydratase (AUH), the breakdown of leucine is disrupted, causing the accumulation of intermediates like 3-methylglutaconyl-CoA. This intermediate may undergo side reactions, leading to the production of 3-methylglutaric acid.[338,339]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary Influences: The ketogenic diet can result in ketoaciduria and the accumulation of various organic acids, including 3-methylglutaric acid. This is especially significant for individuals with pre-existing mitochondrial dysfunction, as the diet may worsen the metabolic imbalance. Additionally, certain components of total parenteral nutrition (TPN), such as isolated amino acids, can cause abnormal organic acid profiles, including increased levels of 3-methylglutaric acid. This occurs because these substrates can be directly metabolized into 3-methylglutaric acid or related compounds.[230]

Medication/ Supplement Interactions: Some medications, such as valproate, may promote the formation of 3-methylglutaric acid. The American College of Medical Genetics and

Genomics states that valproate inhibits 3-methylcrotonyl-CoA carboxylase, resulting in increased urinary excretion of 3-hydroxyisovaleric acid and other related metabolites, which may include 3-methylglutaric acid. Other medications, such as levetiracetam, aspirin, benzoic acid, ibuprofen, and acetaminophen, can also affect organic acid profiles, potentially leading to elevated excretion of various organic acids, including 3-methylglutaric acid.[230]

Low Values There is no known clinical significance for low values.

(31) 3-Hydroxyglutaric acid

3-hydroxyglutaric acid is produced during **lysine** degradation and relies on the enzyme glutaryl-CoA dehydrogenase for its breakdown. Elevated levels of this acid can indicate mitochondrial dysfunction and may act as both an acidogen and a metabotoxin, potentially causing acidosis and other health issues. Chronic elevations are linked to the rare genetic disorder glutaric aciduria type I, which results from a deficiency in glutaryl-CoA dehydrogenase.[340] Dietary factors such as the ketogenic diet and medications such as valproate can also increase 3-hydroxyglutaric acid levels.[230]

Mitochondrial Health

Elevations, especially in the presence of other mitochondrial metabolite elevations, can indicate issues with overall mitochondrial health and energy production.

For more insight into mitochondrial health, reference the other **mitochondrial markers** (22)-(32) and **fatty acid oxidation markers** (45)-(49).

Genetics

Chronically elevated levels of 3-hydroxyglutaric acid may be linked to the rare inherited disorder, glutaric aciduria type I. This is a condition in which the body cannot fully metabolize the amino acids lysine, hydroxylysine, and tryptophan due to a deficiency of mitochondrial glutaryl-CoA dehydrogenase. As a result, excess intermediate breakdown products (such as glutaric acid, glutaryl-CoA, 3-hydroxyglutaric acid, and glutaconic acid) can accumulate, potentially causing damage to the brain, particularly the basal ganglia, as well as other organs.[340]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

The American College of Medical Genetics and Genomics notes that dietary factors (i.e., ketogenic diet) and medications (i.e., valproate) can affect organic acid metabolism, potentially leading to elevated levels like 3-hydroxyglutaric acid.[230]

Dietary Influences: The American College of Medical Genetics and Genomics notes that dietary factors such as the ketogenic diet can impact organic acid metabolism and potentially increase levels of 3-hydroxyglutaric acid.[230]

Medication/ Supplement Interactions: The American College of Medical Genetics and Genomics notes that some medications, such as valproate, may affect organic acid metabolism, potentially increasing levels of 3-hydroxyglutaric acid.[230]

Low Values There is no known clinical significance for low values.

(32) 3-Methylglutaconic acid

3-methylglutaconic acid is involved in leucine metabolism and the mevalonate shunt, connecting isoprenoid and mitochondrial acetyl-CoA metabolism. Elevated levels can indicate mitochondrial dysfunction and act as both an acidogen and a metabotoxin. Persistent elevations are linked to rare metabolic disorders such as 3-methylglutaconic aciduria and GAMT deficiency.[341] Total parenteral nutrition, the ketogenic diet, and medications such as valproate can also increase its levels.[230]

Mitochondrial Health

Elevations, especially in the presence of other mitochondrial metabolite elevations, can indicate issues with overall mitochondrial health and energy production.

For more insight into mitochondrial health, reference the other **mitochondrial markers** (22)-(32) and **fatty acid oxidation markers** (45)-(49).

Genetics

Persistently elevated levels of 3-methylglutaconic acid are linked to some rare inborn errors of metabolism, including 3-hydroxy-3-methylglutaryl-CoA lyase deficiency, 3-methylglutaconic aciduria type I, 3-methylglutaconic aciduria type III, 3-methylglutaconic aciduria type IV, and guanidinoacetate methyltransferase deficiency (GAMT deficiency).[341]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary Influences: Some dietary factors can impact 3-methylglutaconic acid, such as total parenteral nutrition (TPN), certain infant formulas, and the ketogenic diet.[230]

Medication/ Supplement Interactions: Medications also may play a role in increased 3-methylglutaconic acid levels. Drugs such as valproate, levetiracetam, aspirin, ibuprofen, and acetaminophen can increase 30-methylglutaconic acid.[230]

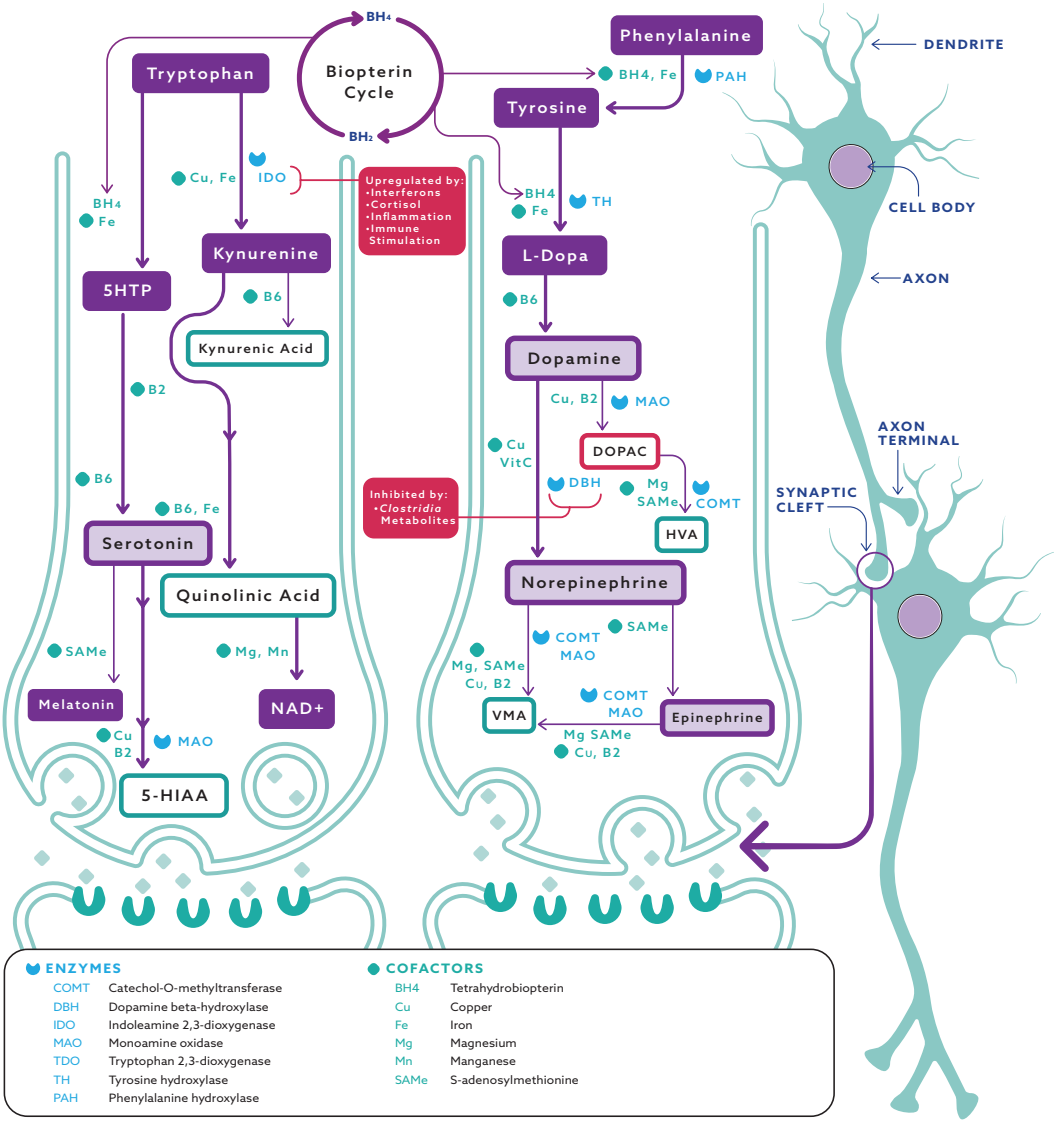
Associated Conditions: Some clinical conditions, such as infections, fever, and other stressors, can cause temporary increases.[230]

Low Values There is no known clinical significance for low values.

NEUROTRANSMITTER METABOLITES

Figure 4:

This diagram illustrates the interconnected biochemical pathways involved in neurotransmitter synthesis and metabolism, focusing on serotonin and catecholamines. It shows how tryptophan is converted through the biopterin cycle into serotonin to 5HIAA, while phenylalanine and tyrosine are transformed into dopamine, norepinephrine, and epinephrine, to ultimately form HVA and VMA, respectively. Key enzymes (e.g., TDO, IDO, TH, MAO, COMT) and cofactors (such as BH4, iron, copper, B vitamins, and SAMe) are required at multiple steps, with certain processes are inhibited by stress-related factors and microbial metabolites. This illustrates the complex regulation of mood-related neurotransmitters and their dependence on nutrient cofactors, enzymatic activity, and external influences.



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PHENYLALANINE AND TYROSINE METABOLITES

(33) Homovanillic acid (HVA) (dopamine)

Homovanillic acid (HVA) is the primary urinary metabolite of dopamine and serves as an indirect marker of dopamine metabolism.[342] Elevated HVA levels may suggest increased dopamine turnover, often due to Microbial Overgrowths (e.g., *Clostridia* or *Fusarium* species), toxic exposures (heavy metals, pesticides, mycotoxins), or nutritional deficiencies (e.g., vitamin C, copper, magnesium) that impair dopamine conversion via enzymes such as dopamine β-hydroxylase (DBH).[120,343-357] Stress, stimulant medications, certain dietary patterns, and methylation status can also influence HVA by altering dopamine synthesis or degradation pathways.[358-371] Low HVA may reflect impaired dopamine synthesis, enzyme dysfunction (COMT/MAO), methylation disturbances, or deficiencies in cofactors such as vitamin B6, B2, C, iron, or magnesium.[372-387] Genetic variations in DBH, COMT, or MAO may further modify dopamine metabolism and HVA levels.[388,389] Evaluation of related metabolites and cofactors can help contextualize HVA findings within broader biochemical and neurological patterns.

Microbial Overgrowth

Clostridia overgrowth has been linked to inhibition of dopamine beta hydroxylase (DBH), an enzyme crucial for converting dopamine to norepinephrine. This inhibition may disrupt normal dopamine metabolism, potentially increasing HVA levels.[120]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Neurotransmitter Metabolites

vHVA levels reflect dopamine activity, with elevated levels suggesting increased dopamine metabolism and low levels proposing reduced dopamine turnover or metabolic dysfunction.[342]

For a more in-depth evaluation into dopamine metabolites, assess the **Phenylalanine** and **Tyrosine metabolites** (33)-(37), along with **2-Hydroxyphenylacetic acid** (11), **Mandelic acid** (68), **Phenylacetic acid** (69), **Phenylpyruvic acid** (70), and **4-Hydroxyphenyllacetic acid** (72).

Toxic Exposures

Mycotoxins, such as ochratoxin A and fusaric acid, may cause elevated HVA levels by disrupting dopamine metabolism through mechanisms such as DBH inhibition, oxidative stress, and neuroinflammation.[120,351-353] Some pesticides increase HVA levels, possibly by inducing oxidative stress or causing dopaminergic neurodegeneration.[348-350] Exposure to heavy metals like lead, aluminum, manganese, arsenic, and mercury can result in elevated HVA levels, typically due to the inhibition of DBH activity.[343-347]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Methylation/Detoxification

Methylation plays a crucial role in dopamine metabolism by influencing the expression of key enzymes such as catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO).[374-376] Additionally, hypomethylation of dopamine-related regulatory elements, like the IGF2 enhancer, can upregulate dopamine synthesis by increasing tyrosine hydroxylase expression.[390]

VMA (34) and **DOPAC** (36) values may give additional insights into COMT as well as 5HIAA for MAO function. Additionally, refer to the Nutrient–Marker Cross-Reference Table for insights into corresponding organic acids that are associated with **methylation support** (**B2**, **B3**, **B6**, **B9**, **B12**, and **magnesium**).

Nutritional Needs

Magnesium deficiency can raise HVA levels by increasing oxidative stress, which upregulates enzymes such as MAO and ALDH.[356,357] Insufficient **copper** and **vitamin C** levels can also elevate HVA acid levels by reducing DBH activity.[354,355]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Genetic single-nucleotide polymorphisms (SNPs) in the DBH enzyme can lead to elevated HVA levels by altering the enzyme's activity, potentially affecting dopamine to norepinephrine conversion and influencing catecholamine balance.[388] Variations in the COMT and/or MAO enzymes can increase HVA levels by altering the enzymatic activity involved in dopamine and norepinephrine metabolism, influencing their related metabolites.[389]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary Influences: Foods rich in **phenylalanine** and **tyrosine**, such as meat, fish, dairy, eggs, soy, legumes, and nuts, can elevate HVA levels by providing the substrates necessary for dopamine synthesis.[362] Increased L-DOPA intake from foods can lead to elevated dopamine synthesis and subsequently higher HVA levels.[363,364] Aspartame consumption may elevate HVA levels and influence dopamine metabolism through mechanisms such as phenylalanine competition, oxidative stress, and inflammation. Additionally, the byproduct phenolic acid of 2-hydroxyhippuric acid, along with other phenolic compounds, can potentially inhibit DBH function by inactivating it, likely through hydrogen atom abstraction, with the phenolic structure itself being critical for this inhibition mechanism.[365-368] Salicylates raise HVA levels by inducing oxidative stress and enhancing dopamine metabolism through hydroxyl radical formation and cytochrome P450 enzyme activity, leading to increased dopamine turnover and higher metabolite levels.[369,370] Flavanol-rich foods, such as dark chocolate, tea, and berries, can increase HVA levels by enhancing enzyme activity and expression, leading to higher HVA production.[371]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients. For more insight into possible aspartame or salicylate intake, reference **2-Hydroxyhippuric acid** (61).

Medication/Supplement Interactions: Medications and supplements such as MAO inhibitors, tyrosine, L-dopa, dopamine medications (Levodopa, Sinemet, etc), SNRIs (Wellbutrin, etc), tricyclic antidepressants, amphetamines, appetite suppressants, caffeine, mucuna pruriens, and quercetin can increase HVA levels.[360,361,363,364,391-394] Disulfiram and Etamicastat help treat alcohol, drug, and gambling addictions by inhibiting the DBH enzyme, which increases dopamine, decreases norepinephrine, and elevates HVA levels, ultimately reducing addictive behaviors by modulating dopaminergic and adrenergic systems.[395,396]

Associated Conditions: Dopamine dysregulation in ADHD is thought to result from genetic, neurobiological, and environmental factors affecting dopamine transmission and receptor functioning, leading to symptoms like inattention and hyperactivity; elevated HVA levels are often linked to this dysregulation.[397] Elevated HVA levels may be found in autism, likely due to impaired dopamine metabolism, particularly the decreased conversion of dopamine to norepinephrine, which results in increased dopamine turnover and higher HVA production.[398,399] Stress can cause elevated HVA levels by triggering increased catecholamine output from the adrenal glands, which is further amplified by **vitamin C** depletion, as this deficiency disrupts the normal conversion of dopamine to norepinephrine, resulting in heightened dopamine metabolism to HVA.[358,359] Stress from post-traumatic stress disorder (PTSD) and general stress increases HVA levels, likely due to higher noradrenergic activity.[400]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

Low Values

Neurotransmitter Metabolites: Disruptions in COMT and MAO enzymes impair dopamine metabolism, leading to increased dopamine levels and the accumulation of toxic metabolites, which may explain the correlation with low HVA levels.[372,373] Evaluating **DOPAC** (36) in particular can give additional insight into dopamine levels prior to metabolizing to HVA. Moreover, deficiencies in cofactors involved in the dopamine generation pathway, particularly with tetrahydrobiopterin (BH4), can impair synthesis, and cause low dopamine levels, and subsequently low HVA.[401]

For more insights into dopamine metabolites, assess the **phenylalanine** and **tyrosine metabolites** (33)-(37), **2-Hydroxyphenylacetic acid** (11), **Mandelic acid** (68), **Phenylacetic acid** (69), and **Phenylpyruvic acid** (70).

Methylation/Detoxification: Methylation of the COMT gene can alter its expression, affecting dopamine degradation, while CpG methylation in the MAO-A promoter can regulate dopamine breakdown.[374-376] Increased methylation of dopamine-related genes, such as the dopamine transporter (DAT) gene, has been linked to reduced dopamine levels by enhancing DAT

availability and reducing synaptic dopamine.[377,378] Methylation also influences dopamine synthesis by regulating the availability of tetrahydrobiopterin (BH4), which is a critical cofactor for tyrosine hydroxylase (TH).[379-381]

VMA (34) and **DOPAC** (36) values make give additional insights into COMT, as well as **5HIAA** (38) for MAO, and BH4 functions. Additionally, refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with nutrients related to **methylation support** (**B2**, **B3**, **B6**, **B9**, **B12** and **magnesium**).

Nutritional Needs: **Vitamin B6** deficiency can decrease HVA levels by impairing enzymes, including monoamine oxidase (MAO), which are essential for dopamine metabolism.[382] **Vitamin B2** (riboflavin) deficiency may decrease levels by impairing the activity of flavoprotein enzymes like MAO and aldehyde dehydrogenase (ALDH), which are essential for dopamine metabolism.[383] Additionally, **vitamin C**, **iron**, **copper**, and **magnesium**, which are cofactors for MAO and COMT, can impair dopamine synthesis and metabolism, leading to reduced dopamine and norepinephrine levels, and consequently, lower HVA levels.[384-387]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Dietary: Low levels of the precursors **phenylalanine** and **tyrosine** can lead to low HVA levels, as these amino acids are essential for dopamine synthesis, and their deficiency disrupts normal dopamine metabolism.[402]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Medication/ Supplement Influences: Antidepressants like fluvoxamine and fluoxetine may decrease dopamine turnover and lower HVA levels through various mechanisms, such as reducing tetrahydrobiopterin levels and inhibiting dopamine release.[403,404] Quercetin may also potentially influence HVA levels by competing with dopamine transporters or inhibiting catechol-O-methyltransferase (COMT) activity, reducing the methylation of dopamine and consequently lowering HVA levels.[405-408]

(34) Vanillylmandelic acid (VMA) (norepinephrine, epinephrine)

Vanillylmandelic acid (VMA) is a metabolite of catecholamines (dopamine, epinephrine, and norepinephrine), produced from the amino acids tyrosine and phenylalanine during their metabolism, and excreted in urine as a marker for catecholamine activity in the body. VMA levels serve as markers for catecholamine imbalances, with elevated levels indicating increased metabolism and low levels suggesting reduced turnover or metabolic dysfunction.[409] Toxic exposures, including lead, mercury, manganese, and aluminum, can disrupt catecholamine metabolism, raising VMA levels.[410-414] nutritional insufficiencies, such as low magnesium or iron, and deficiencies in vitamins B2, B3, B6, C, and copper, can also impact VMA production by affecting enzymes such as dopamine beta hydroxylase (DBH).[386,415-422] Additionally, VMA levels can be affected by medications, stress, genetics, and metabolic disorders, with COMT/MAO impairment and mold toxins potentially causing low levels.[120,230,345,351,423-437]

Neurotransmitter Metabolites

VMA levels, along with other metabolites such as HVA, serve as markers for catecholamine imbalances and potential disruptions in the enzymes involved in their metabolic pathway. VMA levels reflect the activity of epinephrine and norepinephrine, with elevated levels indicating increased catecholamine metabolism and low levels suggesting reduced turnover or metabolic dysfunction (see below for more information on low values).

For a deeper look into dopamine metabolites, assess the **Phenylalanine and Tyrosine metabolites** (33)-(37).

Toxic Exposures

Exposure to lead, manganese, mercury, and aluminum influences catecholamine metabolism, including the metabolism of dopamine and epinephrine, resulting in increased HVA and VMA levels. Lead interferes with enzymes involved in catecholamine pathways, manganese affects neurochemical metabolism, mercury induces oxidative stress that alters enzyme activity, and aluminum may contribute through similar oxidative stress mechanisms, all of which may lead to elevated levels and highlight the impact of heavy metal exposure on catecholamine metabolism.[410-414]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Nutritional Needs

Low magnesium levels are linked to increased catecholamine excretion, which can elevate VMA levels, as **magnesium** plays a key role in regulating catecholamine release.[415]

Iron deficiency can increase DBH activity as a compensatory mechanism, which may lead to altered catecholamine metabolism and elevated VMA levels, as DBH is required for VMA synthesis.[386,416]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Elevated VMA levels can result from some rare inborn errors of metabolism, such as organic acidurias and amino acid metabolism disorders. Additionally, conditions like Costello Syndrome and vitiligo, which involve increased catecholamine release, can also contribute to elevated VMA levels.[230,432,433]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary Influences: VMA is used in artificial vanilla flavoring and intake can cause elevations.[409]

Medication/Supplement Interactions: Medications and supplements such as stimulants (amphetamines, ADHD medications, caffeine, ephedrine, appetite suppressants), and dopamine reuptake inhibitors (e.g., risperidone) may increase VMA levels. The use of L-DOPA, dopamine, phenylalanine, and tyrosine raises HVA levels by promoting dopamine synthesis and metabolism and therefore influences VMA.[426,427]

Associated Conditions: Increased stress activates the sympathetic nervous system and HPA axis, boosting catecholamine release and metabolism into VMA, which serves as a marker for stress-related sympathetic activity. Studies show a positive correlation between elevated VMA levels and both immediate and long-term stress responses, including psychological and physiological stress and PTSD.[428-431]

Low Values

Microbial Overgrowth: Clostridia overgrowth inhibits the DBH enzyme, which is essential for converting dopamine to norepinephrine, disrupting dopamine metabolism and potentially leading to low VMA levels due to impaired production of norepinephrine and its metabolites.[120,351]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Toxic Exposure: The mycotoxin, fusaric acid from Fusarium spp, can also inhibit the DBH enzyme, as can heavy metals such as aluminum and manganese, causing reduced conversion of Dopamine to norepinephrine, leading to lower VMA.[120,345,351,436,437]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Methylation/Detoxification: Downregulation of either the COMT or MAO enzyme leads to low VMA levels, as COMT activity is responsible for O-methylating catecholamines into metanephrines, and MAO further deaminates these intermediates into VMA.[434,435]

HVA (33) and DOPAC (36) values may give additional insights into COMT as well as 5HIAA (38) for MAO function. Additionally, refer to the Nutrient–Marker Reference Table for the corresponding

organic acids associated with nutrients related to **methylation support** (B2, B3, B6, B9, B12, and **magnesium**).

Nutritional Needs: **Iron** overload, along with deficiencies in **vitamins B2**, **C**, and **copper**, can decrease VMA levels by disrupting dopamine beta-hydroxylase (DBH) activity and impairing catecholamine metabolism through various mechanisms.[417-419] Insufficient **vitamin B3**, **B6**, or **tetrahydrobiopterin** (BH4) can lead to decreased VMA levels by impairing catecholamine synthesis or enhancing their degradation.[420-422]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics: Genetic SNPs that cause deficiencies in the DBH enzyme can also decrease VMA levels.[438]

Dietary: Low dietary intake of **phenylalanine** and **tyrosine** reduces catecholamine synthesis, leading to decreased production of dopamine, norepinephrine, and epinephrine, and consequently lower VMA levels.[439]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Medication/ Supplement Influences: Some pharmaceuticals such as disulfiram and etamicastat inhibit the DBH enzyme, which reduces norepinephrine production and impairs dopamine metabolism, potentially leading to low VMA levels.[363,364, 371]

35 HVA/VMA Ratio

The HVA/VMA ratio measures the balance between dopamine and norepinephrine/epinephrine production by catecholamine-producing neurons in the central nervous system, sympathetic nervous system, and adrenal glands. It reflects the conversion of dopamine to HVA and the conversion of dopamine to norepinephrine, processes regulated by the enzyme dopamine beta-hydroxylase (DBH).[342,409] An elevated HVA/VMA ratio typically suggests disruptions in dopamine metabolism, often due to impaired DBH activity, such as through *Clostridia* overgrowth, mycotoxin exposure, heavy metals, nutritional deficiencies in niacin, copper, or vitamin C, by medications, supplements, or rare genetic factors that affect dopamine to norepinephrine conversion.[120,345,351,354,355,388,395,396,436,440,441] In contrast, a low HVA/VMA ratio is usually indicative of reduced dopamine synthesis and turnover, often due to high cortisol levels or other factors inhibiting dopamine production.[442-444]

Microbial Overgrowth

Clostridia overgrowth inhibits DBH activity through byproducts like HPHPA, 4-cresol, and 4-hydroxyphenylacetic acid, disrupting dopamine metabolism and increasing the HVA/VMA ratio.[351]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Neurotransmitter Metabolites

The HVA/VMA ratio serves as a marker for catecholamine metabolism imbalances, with an elevated ratio suggesting disruptions in the conversion of dopamine to HVA, norepinephrine/epinephrine to VMA, and/or dopamine to norepinephrine, often due to impaired DBH activity.

For a more in-depth evaluation into dopamine metabolites, assess the **Phenylalanine** and **Tyrosine metabolites** (33)-(37), along with **2-Hydroxyphenylacetic acid** (11), **Mandelic acid** (68), **Phenylacetic acid** (69), **Phenylpyruvic acid** (70), and **4-Hydroxyphenyllacetic acid** (72).

Toxic Exposure

Fusaric acid, a mycotoxin produced by Fusarium species, inhibits the DBH enzyme, disrupting dopamine conversion to norepinephrine and causing an elevated HVA/VMA ratio due to increased dopamine and its metabolites.[120] Elements such as Aluminum and Manganese have been shown to inhibit DBH enzyme, which could cause an elevated HVA/VMA ratio.[345,436]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Nutritional Needs

Vitamin B3 (Niacin) supports dopamine to norepinephrine conversion by aiding in NAD/NADP production, and a deficiency could impair DBH activity, leading to an increased HVA/VMA ratio.[440,441] A deficiency in **copper** and **vitamin C** can reduce DBH activity, leading to an elevated HVA/VMA ratio.[354,355]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Genetic single nucleotide polymorphisms (SNPs) in the DBH enzyme can increase the HVA/VMA ratio by altering enzyme activity, which disrupts dopamine to norepinephrine conversion and affects catecholamine balance.[388] Other genetic diseases such as Menkes disease, a rare copper transport disorder that impairs DBH activity, lead to elevated HVA/VMA ratios.[354]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary Influences: Aspartame consumption may increase the HVA/VMA ratio by elevating HVA levels through mechanisms like phenylalanine competition, oxidative stress, and inflammation, which impact dopamine metabolism.[363-365]

Review **2-Hydroxyhippuric acid** (61) for further insights on aspartame intake.

Medication/Supplement Interactions: Certain pharmaceuticals, like disulfiram and etamicastat, inhibit the DBH enzyme, disrupting dopamine metabolism and reducing norepinephrine production, which can increase the HVA/VMA.[395,396]

Associated Conditions: Low cortisol levels may increase the HVA/VMA ratio by disrupting the normal regulation of dopamine metabolism, leading to elevated HVA levels due to the effects of HPA axis hormones.[445]

Low Values High cortisol output can lower HVA/VMA ratio by inhibiting dopamine synthesis and turnover.[442] Similarly, by increasing cortisol output, medications and supplements such as some psychostimulants, grapefruit juice, and licorice may decrease HVA/VMA ratio.[443,444]

(36) Dihydroxyphenylacetic acid (DOPAC) (dopamine)

Dihydroxyphenylacetic acid (DOPAC) is a key dopamine metabolite formed through the oxidative deamination of dopamine by monoamine oxidase (MAO), resulting in a neurotoxic byproduct, 3,4-dihydroxyphenylacetaldehyde (DOPAL), which is further metabolized into DOPAC by aldehyde dehydrogenase enzyme (ALDH2). DOPAC, along with HVA and VMA, is used to assess dopamine and norepinephrine metabolism, with fluctuations in these metabolites reflecting alterations in catecholamine turnover and balance.[342,409,446] DOPAC levels can be elevated due to disruptions in dopamine metabolism, which can be caused by DBH inhibition via clostridia or toxic exposures such as mycotoxins or heavy metals.[120,343-353] Nutritional deficiencies in vitamin B6, B2, magnesium, copper, and vitamin C, along with genetic variations in COMT or DBH, can also impact DOPAC levels.[354-357,382,383,388,438,447] Low precursors like phenylalanine and tyrosine, as well as deficiencies in cofactors like tetrahydrobiopterin and other enzymatic cofactors, can impair dopamine synthesis and metabolism, leading to lower DOPAC levels.[354-357,382,383,402,435,438,448] Additionally, dietary factors, medications, and certain pharmaceuticals can further affect dopamine metabolism and lead to either elevated or reduced DOPAC levels.[363,365-367,369,370,395,402-404,446,449-454]

Microbial Overgrowth

DOPAC can become elevated due to disruptions in dopamine metabolism from Clostridia byproducts inhibiting the dopamine beta hydroxylase (DBH) enzyme. These disruptions lead to impaired dopamine conversion to norepinephrine, causing an increase in dopamine levels and its metabolites, including DOPAC.[120,351]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Neurotransmitter Metabolites

Elevated DOPAC levels indicate increased dopamine breakdown, reflecting higher dopamine turnover. This can result from disruptions in dopamine metabolism and can contribute to alterations in catecholamine balance.

For a deeper look into dopamine metabolites, assess the **Phenylalanine** and **Tyrosine metabolites** (33)-(37), as well as **2-Hydroxyphenylacetic acid** (11), **Mandelic acid** (68), **Phenylacetic acid** (69), and **Phenylpyruvic acid** (70).

Toxic Exposure

Mycotoxins, such as ochratoxin A and fusaric acid, may lead to elevated DOPAC levels by disrupting dopamine metabolism through mechanisms like DBH inhibition, oxidative stress, and neuroinflammation. Similarly, some pesticides may increase DOPAC levels by inducing oxidative stress or causing dopaminergic neurodegeneration. Exposure to heavy metals like lead, aluminum, manganese, arsenic, and mercury can also result in elevated DOPAC levels, often due to the inhibition of DBH activity, which interferes with dopamine conversion.[120,343-350,352,353]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Nutritional Needs

Deficiencies in **vitamin B6**, **vitamin B2** (riboflavin), and **magnesium** can elevate DOPAC levels by impairing the activity of MAO, with magnesium deficiency also increasing oxidative stress and riboflavin influencing **tetrahydrobiopterin** (BH4). Additionally, insufficient levels of **copper** and **vitamin C** can reduce DBH activity, further contributing to higher DOPAC levels.[354-357,382,383,438] Catechol-O-methyltransferase (COMT) facilitates the conversion of DOPAC to HVA, and downregulation of COMT can result in elevated DOPAC levels. SAMe (S-adenosyl-L-methionine) and magnesium are essential cofactors for optimal COMT activity.[435,448]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Additional Insights

Dietary Influences: Certain foods like tea, citrus, and soy can increase DOPAC levels as they promote its formation through microbial fermentation.[363,446,449-452] Aspartame and salicylates can increase DOPAC levels by promoting oxidative stress and enhancing dopamine metabolism, with aspartame affecting dopamine through phenylalanine competition and salicylates via cytochrome P450 enzyme activity and hydroxyl radical formation.[365-367,369,370]

Medications/Supplement Interactions: Certain pharmaceuticals, such as disulfiram and etamicastat, inhibit the DBH enzyme, increasing dopamine metabolism to DOPAC.[395] Additionally, Lithium has been shown to modulate dopamine metabolism, and although it has been shown to inhibit COMT activity, it may vary depending on the current neurochemical state.[453,454]

Associated Conditions: Single-nucleotide polymorphisms (SNPs) in the DBH enzyme can impair dopamine-to-norepinephrine conversion, elevating DOPAC levels, and disrupting catecholamine balance.[355,388,447]

Low Values

Methylation/Detoxification: Inhibitions in dopamine-metabolizing enzymes such as MAO can result in elevated dopamine levels and the accumulation of toxic metabolites, preventing their conversion to DOPAC and ultimately lowering levels.[372,373]

HVA (33), VMA (34), and 5HIAA (38) values may give additional insights into MAO function.

Nutritional Needs: Deficiencies in cofactors involved in the dopamine pathway, such as **BH4**, **vitamin C**, **vitamin B6**, **iron**, and the enzymatic cofactors for MAO and COMT, can impair dopamine synthesis and metabolism, leading to reduced dopamine and norepinephrine levels, and consequently, lower DOPAC levels.[384-387]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Dietary: Low levels of the precursors **phenylalanine** and **tyrosine** can lead to low DOPAC levels, as these amino acids are essential for dopamine synthesis.[402]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Medications/Supplement Interactions: Antidepressants like fluvoxamine and fluoxetine decrease dopamine turnover and lower DOPAC levels through various mechanisms such as reducing tetrahydrobiopterin levels and inhibiting dopamine release.[403,404] Genetic SNPs in enzymes involved in dopamine metabolism can reduce DOPAC levels.[404]

(37) HVA/DOPAC Ratio

The HVA/DOPAC ratio reflects the balance in dopamine metabolism, with dopamine being first broken down into DOPAC by the monoamine oxidase (MAO) enzyme, and then DOPAC being converted to HVA by catechol-O-methyltransferase (COMT). A higher ratio can indicate increased COMT activity and conversion of DOPAC to HVA or decreased activity of MAO and DOPAC levels, while a lower ratio may suggest reduced COMT activity and slower conversion.[342,446] This ratio can be influenced by factors such as genetic variations, methylation donor availability, and nutrient levels such as magnesium and SAMe, which upregulate COMT activity.[389,408,448,455-457] Medications, supplements, and environmental factors can also impact COMT and MAO enzyme activity, leading to changes in the HVA/DOPAC ratio and reflecting various metabolic and genetic influences.[458-463]

Neurotransmitter Metabolites

An elevated HVA/DOPAC ratio reflects increased dopamine metabolism and turnover, indicating more conversion of DOPAC to HVA. This can suggest heightened dopamine activity or a shift in the balance of metabolic processes involved in dopamine breakdown.

For a more in-depth evaluation into dopamine metabolites, assess the **Phenylalanine** and **Tyrosine metabolites** (33)-(37), along with **2-Hydroxyphenylacetic acid** (11), **Mandelic acid** (68), **Phenylacetic acid** (69), **Phenylpyruvic acid** (70), and **4-Hydroxyphenyllacetic acid** (72).

Methylation/Detoxification

An increased HVA/DOPAC ratio indicates enhanced methylation activity, as the enzyme COMT plays a key role in transferring a methyl group from S-adenosyl-L-methionine (SAMe) to DOPAC, converting it to HVA. This process reflects an upregulation of methylation, which is important for the inactivation and elimination of dopamine and its metabolites. Factors such as genetic variations or methyl donor availability can influence this ratio, affecting overall methylation efficiency.[389,408,457]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with nutrients related to **methylation support** (**B2**, **B3**, **B6**, **B9**, **B12**, and **magnesium**).

Nutritional Needs

Increased levels or intake of methylation factors, such as magnesium and SAMe, can upregulate COMT activity and increase HVA/DOPAC ratio. COMT enzyme activity can be upregulated by methylation factors like magnesium, which stabilizes the enzyme, and S-adenosylmethionine (SAMe), which acts as a methyl donor. Additionally, **methylcobalamin (B12)** and **methylfolate (B9)** enhance COMT activity by promoting the conversion of homocysteine to methionine, supporting SAMe production.[448,464]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

COMT enzymatic activity can be upregulated by factors such as genetic variants), while MAO activity may be downregulated, potentially resulting in elevated HVA/DOPAC ratio levels.[455,456]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Medication/Supplement Interactions: Some medications and supplements such as L-Dopa, insulin, dihydrotestosterone (DHT), all-trans retinoic acid (ATRA) from vitamin A, and epigallocatechin-3-gallate (EGCG) have been shown to upregulate COMT activity through various mechanisms leading to an increased HVA/DOPAC ratio.[458-460] The use of MAO inhibiting medications such as MAOIs for depression and supplements such as curcumin, guaiacol, resveratrol, and zingerone can also lead to an increase in HVA/DOPAC ratio by decreasing conversion of dopamine to DOPAC.[461,462]

Low Values

Toxic Exposure: Certain environmental toxicants, particularly the Polychlorinated Biphenyls (PCBs) have been shown to influence COMT function, potentially causing low HVA/DOPAC ratios.[463]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Methylation/Detoxification: Downregulation of the COMT enzyme from low methylation factors such as SAMe, or genetic variants, may lead to decreased HVA/DOPAC ratios.448,455,464 Upregulation of the MAO enzyme or genetic variants may also decrease the HVA/DOPAC ratio.[465,466]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with nutrients related to **methylation support** (**B2**, **B3**, **B6**, **B9**, **B12**, and **magnesium**).

Nutrient Needs: High levels of **calcium**, **iron**, and **boron** may potentially impair COMT function leading to decreased HVA/DOPAC ratios.[448,455,464] Additionally, decreased levels of **magnesium**, a major cofactor for COMT, as well as methylation supporting nutrients such as **methylcobalamin**, or **methylfolate**, **may decrease COMT activity**.[448,455,464]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

TRYPTOPHAN METABOLITES

(38) 5-Hydroxindoleacetic acid (serotonin)

5-Hydroxy indoleacetic acid (5-HIAA) is the primary metabolite of serotonin, formed when serotonin is enzymatically broken down by monoamine oxidase A (MAO-A) in the liver or synaptic cleft. It is used as a marker for serotonin levels and plays a role in various metabolic processes.[470,471] Elevated 5-HIAA levels reflect increased serotonin breakdown, which can be influenced by factors such as dysbiosis, toxic exposure, nutritional status, medications and supplements, and conditions such as celiac disease and in more rare instances, carcinoid syndrome.[472-478] On the other hand, disruptions in the microbiome, nutrient deficiencies, and downregulation of MAO can result in lower serotonin and 5-HIAA levels.[376,478-483]

Microbial Overgrowth

Dysbiosis, or an imbalance in gut microbiota, can lead to elevated serotonin levels by influencing enterochromaffin (EC) cells, which produce serotonin in the gastrointestinal tract. Certain gut bacteria, through the production of short-chain fatty acids, promote the synthesis of serotonin, while other bacteria stimulate serotonin release directly from EC cells.[484-486]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Neurotransmitter Metabolites

Elevated 5-HIAA levels serve as an indicator of serotonin status, reflecting the breakdown of serotonin by MAO-A.

For a deeper look into neurotransmitter metabolites, assess the **Phenylalanine** and **Tyrosine metabolites** (33)-(37) and **Tryptophan metabolites** (38)-(40).

Toxic Exposure

Toxic exposures, especially from acrylamide, cause elevated 5-HIAA levels through mechanisms involving oxidative stress, neuroinflammation, and impaired neurotransmitter metabolism.[472-474]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Methylation/Detoxification

Hypomethylation may upregulate MAO-A activity and increase 5-HIAA levels.[376]

For additional insights into MAO, assess **HVA** (33), **VMA** (34), and **DOPAC** (36). Additionally, refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with nutrients related to **methylation support** (**B2**, **B3**, **B6**, **B9**, **B12**, and **magnesium**).

Additional Insights

Dietary Influences: Some foods, such as bananas, pineapple, walnuts, soybeans, chicken, and tuna, can elevate 5-HIAA levels because of their high tryptophan and serotonin content.[475-478]

Medications/Supplement Interactions: Some medications and supplements such as SSRIs and 5-HTP, among others can elevate 5-HIAA levels by increasing serotonin availability, which is then metabolized by MAO into 5-HIAA.[487,488]

Associated Conditions: Celiac disease and tropical sprue can raise 5-HIAA levels by causing hyperplasia of serotonin-producing enterochromaffin cells in the intestinal mucosa, leading to increased serotonin production and its subsequent conversion to 5-HIAA.[489,490] Carcinoid syndrome, which is rare and requires a 24-hour urine collection, among other testing to further evaluate, causes elevated 5-HIAA levels due to increased serotonin production from neuroendocrine tumors.[491]

Low Values

Microbial Overgrowth: Disruption of the gut microbiome, such as through antibiotic treatment, can reduce serotonin production and therefore 5-HIAA levels, emphasizing the role of a balanced microbiome in regulating serotonin levels.[479]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Methylation/Detoxification: Hypermethylation can lead to downregulated MAO-A and lower 5-HIAA levels.[376] MAO downregulation due to medications such as MAOIs and genetic SNPs, can lead to lower 5-HIAA levels.[456,461]

For additional insights into MAO, assess **HVA** (33), **VMA** (34), and **DOPAC** (36).

Nutritional Needs: Deficiencies in key nutrients like **vitamin B6**, **tetrahydrobiopterin (BH4)**, **vitamin B2**, **zinc**, **tryptophan**, **Vitamin D**, and **magnesium** can impair serotonin synthesis by disrupting the enzymes, cofactors and precursors necessary for serotonin production, resulting in lower serotonin and 5-HIAA levels.[478,480-483]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients. **Phosphoric acid** (76) may give insights into vitamin D status.

39 Quinolinic acid

Quinolinic acid (QA) is a neuroactive metabolite that is primarily produced through the kynurenine pathway, where tryptophan is degraded by the enzyme indoleamine 2,3-dioxygenase (IDO). This pathway is activated during inflammatory responses, leading to the accumulation of quinolinic acid, which serves a crucial role in NAD+ synthesis but also acts as an NMDA receptor agonist and neurotoxin. Elevated quinolinic acid levels are associated with excitotoxicity, inflammation, neurodegeneration, and conditions such as neurological and psychiatric disorders.[492,493] Factors such as Microbial Overgrowth, nutrient deficiencies, toxic exposures, immune modulation, high cortisol, and inflammatory states can modulate quinolinic acid production, increasing its neurotoxic effects.[493-507]

Microbial Overgrowth

The gut microbiome can influence elevated quinolinic acid levels by altering tryptophan metabolism through the kynurenine pathway, particularly by enzymatic modulation of IDO1, which is upregulated during inflammation and may lead to increased quinolinic acid levels. Additionally, systemic inflammation triggered by lipopolysaccharide (LPS) activates macrophages, which are a significant source of quinolinic acid production.[494,495]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Neurotransmitter Metabolites

Elevated quinolinic acid levels indicate potential disruptions in neurotransmitter balance, as it acts as an NMDA receptor agonist, contributing to excitotoxicity, neuroinflammation, and neurodegeneration. Its presence suggests heightened activation of the kynurenine pathway, which may also affect NAD+ synthesis and cellular energy, as well as reduced serotonin production.

For a deeper look into neurotransmitter metabolites, assess the **Phenylalanine** and **Tyrosine metabolites** 33-37 and **Tryptophan metabolites** 38-40.

Toxic Exposure

Phthalates, such as DEHP and MEHP, inhibit ACMS decarboxylase (ACMSD), disrupting tryptophan metabolism and leading to increased production of quinolinic. Elevated quinolinic levels impair NAD+ synthesis, as phthalate exposure also inhibits quinolinic acid phosphoribosyltransferase (QPRT), an enzyme crucial for NAD+ biosynthesis.[497,498]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Nutritional Needs

B3 (niacin) deficiency can cause elevated quinolinic acid levels due to the disruption of the kynurenine pathway, where excessive inflammation-induced IDO enzymatic activity depletes tryptophan and leads to the accumulation of kynurenine and quinolinic acid. This can impair

NAD+ production, as quinolinic acid is a precursor in the synthesis of nicotinamide.[493] Low levels of **vitamins B2** and **B6** can elevate quinolinic acid levels by impairing the kynurenine pathway, as both vitamins are essential cofactors for its proper metabolism.[496]

Elevated quinolinic acid acts as a metal chelator, binding transition metals like **iron** and **copper**, reducing their availability. This can disrupt essential redox reactions and lead to oxidative stress, which not only contributes to reactive oxygen species (ROS) production but also potentially depletes key nutrients, further impairing metabolic and immune function.[508]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Additional Insights

Dietary Influences: Foods rich in tryptophan, such as chicken, soy, tuna, certain cereals, nuts, and bananas, may potentially raise quinolinic acid levels. Quinolinic acid has also been found in foods like Ceylon cinnamon, pitanga, Oregon yampahs, red bell peppers, and durians.[477,492]

Refer to the Nutrient–Marker Cross-Reference Table for insights into corresponding organic acids that are associated with **tryptophan**.

Medications/Supplement Interactions: Some medications, such as interferon-gamma and pyrazinamide are known to increase quinolinic acid levels through their effects on the kynurenine pathway.[509,510] Oral contraceptive use is associated with lower neuroprotective kynurenic acid, a decreased kynurenic acid to quinolinic acid ratio, and higher CRP levels, potentially contributing to increased quinolinic acid levels.[511]

Associated Conditions: Quinolinic acid is strongly associated with inflammation and immune modulation, playing a central role in several health conditions. Estrogen has been shown to increase quinolinic acid levels by boosting pro-inflammatory cytokines and neurotoxic kynurenine metabolites.[503] Elevated quinolinic acid levels are linked to neurological and psychiatric disorders, such as Alzheimer's disease, stroke, schizophrenia, depression, and possibly autism, where they contribute to neuroinflammation and excitotoxicity.[504-507] Additionally, high quinolinic acid levels are implicated in cardiovascular conditions, particularly atherosclerosis and ischemic injury, due to their connection with oxidative stress, inflammation, and early signs of systemic atherosclerosis.[512,513] Immune activation, such as from cytokines stimulates increased quinolinic acid production, which is linked to inflammation and neurological damage.[499-501] High cortisol levels can exacerbate the damaging effects of quinolinic, suggesting that elevated cortisol may increase quinolinic acid's neurotoxic effects.[502] Furthermore, quinolinic acid inhibits gluconeogenesis by binding to divalent metal ions required for phosphoenolpyruvate carboxykinase (PEPCK), thereby reducing glucose production.[514] Elevated levels may also be associated with Lyme disease and multiple sclerosis as well as general increased viral load due to interferons upregulating the IDO enzyme.[515]

Benefits: Quinolinic acid may play a beneficial role in certain contexts, such as being a precursor for NAD+ synthesis, which is essential for energy production, DNA repair, and enzyme activity,

as well as helping modulate immune responses during neuroinflammation. However, despite these potential benefits, elevated quinolinic levels are also linked to neurotoxicity, contributing to excitotoxicity, neuroinflammation, and neuronal damage.[506,516]

Low Values Low quinolinic acid levels are less concerning than elevated levels and can result from factors affecting the kynurenine pathway, such as enzyme inhibition (e.g., kynureninase inhibitors), the use of Highly Active Antiretroviral Therapy (HAART) in HIV patients, genetic mutations like the knockout of the QPRT gene, or nutritional influences such as low protein intake influencing enzymes like ACMSD.[517-520] These factors can reduce the synthesis or conversion of quinolinic acid, offering potential therapeutic avenues for modulating its levels in clinical settings.

(40) Kynurenic acid

The kynurenine pathway is a major metabolic route for tryptophan, where it is converted into several metabolites, including kynurenic acid and quinolinic acid, and is a key source of NAD+, essential for cellular energy production. While the pathway is beneficial for NAD+ synthesis and regulating physiological functions, it can become problematic when upregulated due to inflammation or stress, potentially leading to a deficiency in serotonin production and the accumulation of neuroactive metabolites like quinolinic acid, which can contribute to neurotoxicity, excitotoxicity, and neuroinflammation.[492,521-524] Kynurenic acid levels are influenced by factors such as inflammation, stress, and nutritional deficiencies in B vitamins (B3, B2, B6), which disrupt the kynurenine pathway, as well as dietary intake of tryptophan-rich foods and certain medications.[477,493,496,522-528] Elevated kynurenic acid is associated with conditions such as neurodegenerative diseases, psychiatric disorders, and inflammatory diseases, while low levels can result from high estrogen states, certain treatments, or insufficient protein intake.[503,518,520-523]

Neurotransmitter Metabolites

Elevated kynurenic acid levels may indicate an upregulated kynurenine pathway due to inflammation or stress, leading to a disruption in serotonin production and an accumulation of neuroactive metabolites like quinolinic acid. While kynurenic acid has neuroprotective effects, increased levels could contribute to neuroinflammation, excitotoxicity, and neurodegenerative or psychiatric disorders.

For a deeper look into neurotransmitter metabolites, assess the **Phenylalanine** and **Tyrosine metabolites** (33)-(37) and **Tryptophan metabolites** (38)-(40).

Nutritional Needs

Insufficient levels of **B3 (Niacin)**, **B2 (Riboflavin)**, and **B6** can increase kynurenic acid levels by disrupting the kynurenine pathway.[493,496]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Additional Insights

Dietary Influences: Foods rich in tryptophan, such as chicken, soy, tuna, certain cereals, nuts, and bananas, may potentially increase kynurenic acid levels.[477] Some foods contain kynurenic acid and will increase levels such as cacao powder, fermented foods (beer, red wine, yeast-fermented foods), honeybee products (propolis honey, bee pollen), tea, and coffee.[529-531]

Refer to the Nutrient–Marker Reference Table for insights into corresponding organic acids that are associated with tryptophan.

Medications/Supplement Interactions: Medications that may increase kynurenic acid levels include anticonvulsants, antidepressants, beta-adrenergic agonists, and angiotensin-converting enzyme inhibitors.[525-528]

Associated Conditions: Elevated kynurenic acid levels can be influenced by neurodegenerative conditions such as Alzheimer's, Parkinson's, and Huntington's disease, as well as by infections like HIV-1 and Lyme neuroborreliosis. Additionally, increased kynurenic acid metabolism is linked to cognitive decline in disorders like schizophrenia and Down syndrome, and it has been identified as a uremic toxin in renal dysfunction.[521] Increased stress in conditions such as major depressive disorder and more activates the tryptophan-kynurenine pathway, suppressing enzymatic function and leading to elevated kynurenic acid levels, which are linked to stress-induced behavioral changes and cognitive impairments.[293] High kynurenic levels are associated with various inflammatory diseases, including ulcerative colitis and systemic lupus erythematosus, where elevated levels correlate with disease severity, activity, and clinical manifestations.[522,523]

Benefits: Kynurenic acid may provide neuroprotection through multiple mechanisms, including NMDA receptor antagonism to reduce excitotoxicity, antioxidant properties to scavenge reactive oxygen species, and the induction of neprilysin to degrade amyloid-beta peptides. Additionally, it stimulates BDNF-TrkB signaling, protects mitochondria, and modulates redox homeostasis to maintain neuronal survival and prevent oxidative damage.[532-536]

Low Values

Nutrient Needs: Vitamin B6 is an important cofactor for kynurenine aminotransferase (KAT), an enzyme crucial for converting kynurenine to kynurenic acid in the tryptophan metabolism pathway. Deficiency may lead to low kynurenic acid levels.[537]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

Dietary: Low protein intake, influencing the availability of the precursor tryptophan, may influence Kynurenic acid to be produced.[520]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

Medications/Supplement Interactions: The use of treatments such as Highly Active

Antiretroviral Therapy (HAART) in HIV patients has been associated with low Kynurenic acid.[518] Oral contraceptive use is linked to decreased kynurenic acid levels and reduced kynurenic to quinolinic ratios, potentially contributing to altered immune function and increased systemic inflammation.[511]

Associated conditions: Low kynurenic levels can result from high estrogen states.[503] A hormone panel may give further assessment, if this is a potential.

PYRIMIDINE METABOLITES – FOLATE METABOLISM Methylation/Detoxification

(41) Uracil

Uracil is a pyrimidine primarily found in RNA, where it pairs with adenine during transcription and translation, and is replaced by thymine in DNA.[538] It plays a vital role in enzyme synthesis, cellular function, and biochemical regulation by serving as a coenzyme, an allosteric regulator, and a precursor to phosphorylated nucleotides (UMP, UDP, and UTP), which influence carbamoyl phosphate synthetase II activity, polysaccharide biosynthesis, and sugar transport.[539-541] The conversion of uracil to **thymine** (42) is dependent on folate and the methylation of uracil, with 5,10-methylene tetrahydrofolate donating a methyl group via thymidylate synthase.[542,543] Elevated uracil levels can indicate impaired methylation due to folate deficiency and various genetic variants.[542,544,545] Other contributing factors include liver dysfunction and certain cancer treatments such as 5-fluorouracil.[546,547]

Methylation/Detoxification

The conversion of uracil to thymine depends on 5,10-methylene tetrahydrofolate, which donates a methyl group via thymidylate synthase.[543] When folate metabolism is impaired, methylation is disrupted, leading to uracil accumulation in the nucleus.[543] Impacts on the conversion of 5-methyltetrahydrofolate into SAM, which regulates gene transcription, is driven by folate, and without it, SAM is depleted, leading to DNA hypomethylation and altered gene expression.[548] Uracil has been used as a potential biomarker for folate and methylation status from either genetic or micronutrient deficiencies.[548]

Review of **2-hydroxybutyric acid** (59), a byproduct of the homocysteine to cystathionine pathway, may also provide insight, along with a **homocysteine** level. Additionally, refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with nutrients related to **methylation support** (B2, B3, B6, B9, B12, and **magnesium**).

Nutrient Needs

Folate (Vitamin B9) deficiency may lead to excessive uracil incorporation into DNA, causing chromosome breaks from impaired methylation of dUMP to dTMP.[549] These damages have

been linked to cognitive risks and defects in cellular replication, and folate supplementation has demonstrated reversal.[549] Moreover, deficiencies in **vitamins B12**, **B6** (pyridoxine), and **B2** (riboflavin) can also impact methylation capacity, impairing uracil-to-thymine conversion, leading to uracil accumulation in DNA, which may contribute to genetic instability and disease risk.[550,551] In the presence of folate deficiency, this pathway can be preserved at the expense of homocysteine re-methylation.[552]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Urea cycle disorders, particularly Ornithine Transcarbamylase Deficiency (OTCD), can cause excess carbamoylphosphate diversion into pyrimidine synthesis, leading to elevated uracil and **orotic acid** (60) levels.[545] Elevated uracil can also come from genetic variants in dihydropyrimidine dehydrogenase (DPD) enzyme through the DPYD gene, as it can impact the catabolism of uracil, **thymine** (42), and the analog 5-fluorouracil.[544,553] Genetic variations affecting thymidylate synthase (TYMS) activity, which is the enzyme responsible for converting deoxyuridine monophosphate (dUMP) to thymidine monophosphate (dTMP), may also lead to elevated uracil levels.[542] SNPs in the production of methyl tetrahydrofolate dehydrogenase I (MTHFD1) will influence the conversion of uracil to thymine as well as methionine.[543]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Medication/ Supplement Influences: Cancer treatments such as 5-fluorouracil (5-FU) can increase uracil excretion in the urine.[547]

Associated Conditions: Liver dysfunction can disrupt uracil metabolism, leading to elevated urinary uracil levels.[546] Uracil elevations related to folate deficiency have been shown in neuronal damage.[549, 554] MTHFD1 is folate dependent, and when deficient can play a role in megaloblastic anemia, and severe combined immunodeficiency (SCID).[555]

Low Values There is no known clinical significance for low values.damage.[556]

(42) Thymine

Thymine, also known as 5-methyluracil, is one of the four essential nucleobases in DNA, where it pairs with adenine to stabilize the double-helix structure. Thymine is synthesized by uracil methylation, and when bound to deoxyribose, forms thymidine, which can be phosphorylated to dTDP for DNA incorporation. Thymine metabolism can be influenced by abnormalities in methylation pathways and mutations in dihydropyrimidine dehydrogenase (DPD) production.[551,553] It has also been shown to act as a biomarker for UV-induced DNA damage.[556]

Methylation/Detoxification

The conversion of uracil to thymine depends on 5,10-methylene tetrahydrofolate, which donates a methyl group via thymidylate synthase.[552] Thymine can be influenced by the polymorphism MTHFR C677T at the de novo dTMP synthesis, which can influence uracil's misincorporation into DNA.[551]

Nutrient Needs

Folate deficiency, along with deficiencies in **vitamins B12**, **B6** (pyridoxine), and **B2** (riboflavin) can all impact methylation capacity, impairing uracil-to-thymine conversion.[550,551] In the presence of folate deficiency, this pathway can be preserved at the expense of homocysteine remethylation.[552]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Dihydropyrimidine dehydrogenase (DPD) deficiency is a rare genetic condition that impairs the breakdown of pyrimidines, leading to elevated urinary levels of **uracil** (41), thymine, and the analog 5-fluorouracil.[544,553] The DPD enzyme relies on flavin and NADP (nicotinamide adenine dinucleotide phosphate) as cofactors for this process.[557] While some individuals with DPD deficiency remain asymptomatic, severe cases have been associated with seizures, autism, microcephaly, hypotonia, and delayed myelination.[558,559]

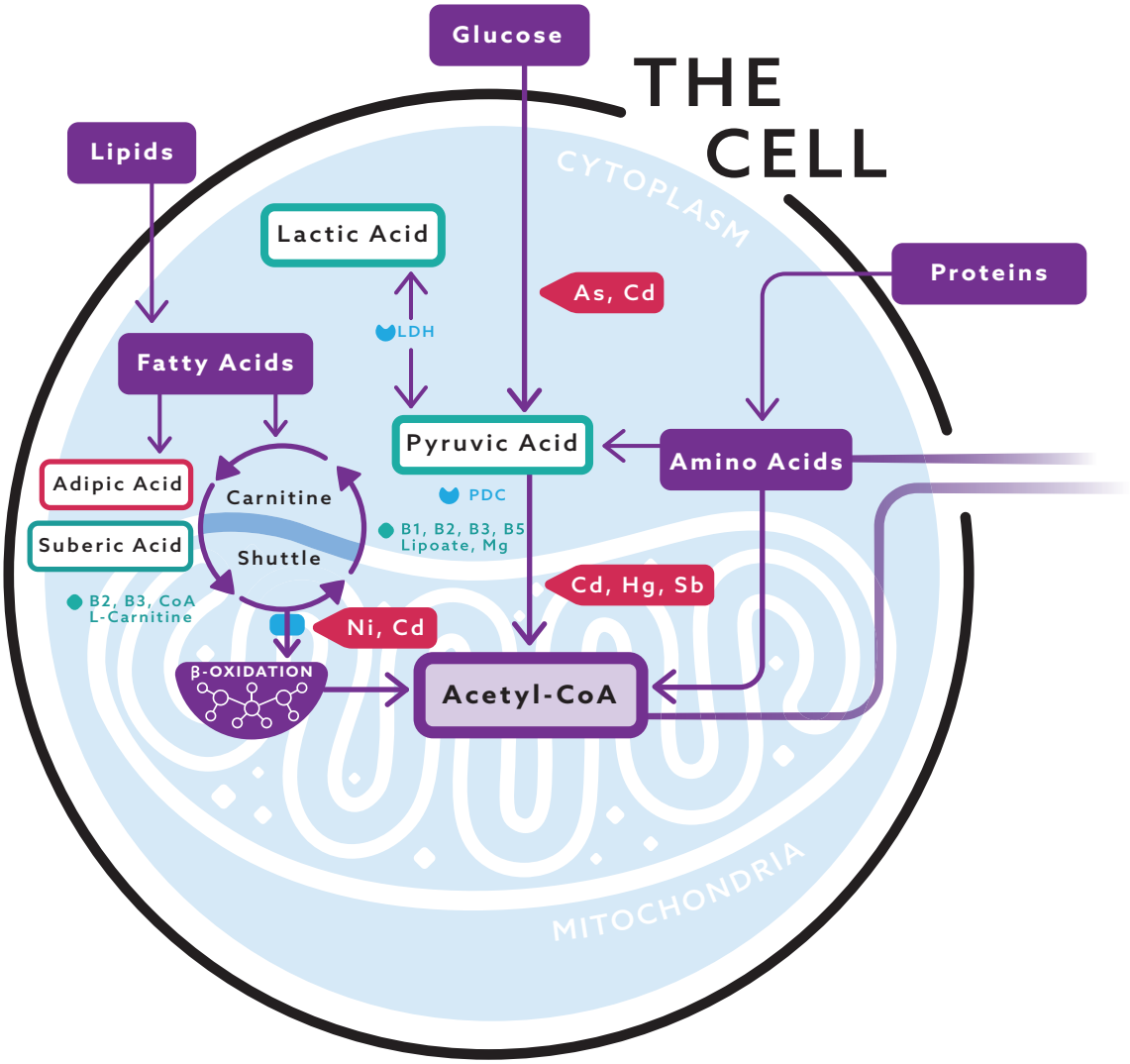
Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Associated Conditions: Thymine can act as a biomarker for UV-induced DNA damage in humans, as exposure to UV radiation can cause DNA lesions, such as thymine dimers, leading to elevated urinary thymine levels.[556,560] Research studies have shown increased thymine levels in psoriasis patients receiving PUVA therapy (psoralen with UVA radiation), a treatment known to induce DNA damage, and in lifeguards and agricultural workers with UV exposure consecutively for 12-18 days.[560,561]

Low Values There is no known clinical significance for low values.

KETONE AND FATTY ACID OXIDATION



This diagram shows how lipids are broken down into fatty acids, which require the carnitine shuttle to cross into the mitochondria for β-oxidation. In the cytoplasm, fatty acids are first transported with the help of L-carnitine and converted into acylcarnitine, which is shuttled across the mitochondrial membranes and reconverted to acyl-CoA. Once inside the mitochondrial matrix, β-oxidation removes two-carbon units to form acetyl-CoA, a critical substrate for the TCA cycle and ketone production. If the carnitine shuttle is impaired or insufficient, fatty acid transport into mitochondria is blocked, leading to an accumulation of intermediates such as adipic and suberic acids and reduced energy generation from fats. Additionally, when fatty acid oxidation is limited, the body may rely more heavily on glycolysis and amino acid metabolism, with ketone body production (like 3-hydroxybutyric acid) reduced as an alternative energy source.

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(43) 3-Hydroxybutyric acid

3-Hydroxybutyric acid (β-hydroxybutyrate) and **acetoacetic acid** (42) are two main ketones involved in fatty acid metabolism and energy production.[562] Their levels increase during fasting, carbohydrate-restricted diets, diabetes, or metabolic disorders. [563] Ketones serve as an essential alternative energy source, particularly for the brain and muscles, and play a role in lipid biosynthesis (e.g. cholesterol, phospholipids, etc.) and myelination.[564] Elevated ketone levels can indicate metabolic shifts, such as prolonged fasting, vigorous exercise, or more serious conditions such as uncontrolled diabetes, or in rare cases, genetic disorders.[564]

Mitochondrial Health

Ketone production occurs in the mitochondria, after coenzyme A bound fatty acids (Fatty acyl CoA) are transported into the mitochondrial membrane via the carnitine shuttle.[565] Once inside the mitochondria, the bound fatty acids undergo beta- oxidation generating acetyl CoA, for the citric acid cycle for ATP production, lipid biosynthesis, or for the synthesis of **acetoacetate** (44).[562] Additionally, certain amino acids, like leucine, can metabolize into acetoacetate and acetyl CoA.[566] Acetoacetate can be further reduced to 3-hydroxybutyrate (3HB) via 3HB dehydrogenase, which is reversible based on NADH levels, and tends to be higher than acetoacetate in prolonged fasted states.[564] Mitochondrial function regulates ketogenesis, and disruptions in this process, such as mitochondrial disorders or fatty acid oxidation defects, can lead to excessive ketone accumulation.[564]

Additional insights into the cascading effects of ketone generation can be found in **acetoacetic acid** (44), the **fatty acid oxidation markers** (45)-(49), and the other **mitochondrial markers** (22)-(32).

Genetics

Two common inherited genetic conditions associated with abnormal ketone metabolism are **systemic primary carnitine deficiency (CDSP)**, preventing fatty acyl CoA molecules from being transported into the mitochondria, and **medium-chain acyl CoA dehydrogenase (MCAD) deficiency**, a disorder that impairs the conversion of 4–12 carbon fatty acyl CoA molecules into acetyl CoA.[567,568]

Markers also associated with MCAD, include **Acetoacetic acid** (44), **Ethylmalonic acid** (45) , **Methylsuccinic acid** (46), **Adipic acid** (47), **Suberic acid** (48), and **Sebacic acid** (49).

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Information

Dietary: Restricted diets such as strict ketogenic, GAPS, and other diets with elimination of carbohydrates can increase ketone production.[563]

Medication/ Supplement Influence: Valproate has been shown to elevate ketones.[183] Exogenous ketone supplementation, typically a variation of beta-hydroxybutyrate, has been shown to significantly increase blood and urinary levels.[570-573]

Associated Conditions: Ketones, though not diagnostic, can be associated with dysglycemia, diabetes, alcohol intoxication, strenuous exercise, corticoid steroid deficiencies, and infections.[574,575]

Developing Discussions: When evaluating 3HB and acetoacetate, blood tests are beginning to use their ratio to evaluate abnormal redox states of the mitochondria and give insights into the respiratory chain.[190] Since the conversion of acetoacetate to 3HB is driven by NADH, if 3HB is higher than acetoacetate, **Vitamin B3** (niacin), may be helpful in supporting the reaction.[577,578] Furthermore, lactate and pyruvate ratio analysis are being evaluated to additionally evaluate the cystolic redox state since pyruvate is converted to lactate to re-oxidize NADH.[578]

For additional insights into NAD, one can also assess **Quinolinic acid** (39) elevations, as well as **Lactic acid** (22) and **Pyruvic acid** (23) for redox associations. Additionally, refer to the Nutrient-Marker Reference Table for the corresponding organic acids associated with that nutrient.

Low Values There is no known clinical significance for low values.

(44) Acetoacetic acid

Acetoacetic acid and **3-Hydroxybutyric acid (3HB)** (43) are two main ketones involved in fatty acid metabolism and energy production.[562] Their levels increase during fasting, carbohydrate-restricted diets, diabetes, or metabolic disorders.[563] Ketones serve as an essential alternative energy source, particularly for the brain and muscles, and play a role in lipid biosynthesis (e.g., cholesterol, phospholipids, etc.) and myelination.[564] Elevated ketone levels can indicate metabolic shifts, such as prolonged fasting, vigorous exercise, or more serious conditions, such as uncontrolled diabetes, or in rare cases, genetic disorders.[564]

Mitochondrial Health

Ketone production occurs in the **mitochondria** after **fatty acyl-CoA** is transported across the mitochondrial membrane via the carnitine shuttle.[565] Once inside the mitochondria, fatty acids undergo beta-oxidation, generating acetyl-CoA, which can enter the citric acid cycle, contribute to lipid biosynthesis, or serve as a precursor for acetoacetate synthesis.[562] Additionally, certain amino acids, like leucine, can metabolize into acetoacetate and acetyl CoA.[566] Acetyl CoA is then converted to acetoacetyl CoA by 3-ketothiolase, to HMG CoA by HMG CoA synthase, and finally broken down into acetoacetate by HMG CoA lyase.[65] Acetoacetate can be further reduced to 3-hydroxybutyrate (3HB) via 3HB dehydrogenase, which is reversible based on NADH levels, and tends to be higher than acetoacetate in

prolonged fasted states.[202] Mitochondrial function regulates ketogenesis, and disruptions in this process, such as mitochondrial disorders or fatty acid oxidation defects, can lead to excessive ketone accumulation.[564]

Additional insights into the cascading effects of ketone generation can be found in **3HB** (43), the **fatty acid oxidation markers** (45)-(49), the other **mitochondrial markers** (22)-(32), and **3-hydroxy-3-methylglutaric acid** (55).

Genetics

Two common inherited genetic conditions associated with abnormal ketone metabolism are systemic primary carnitine deficiency (CDSP), preventing fatty acyl CoA molecules from being transported into the mitochondria, and medium-chain acyl CoA dehydrogenase (MCAD) deficiency, a disorder that impairs the conversion of 4–12 carbon fatty acyl CoA molecules into acetyl CoA.[567,568]

Markers also associated with MCAD, include **3-Hydroxybutyric acid** (43), **Ethylmalonic acid** (45), **Methylsuccinic acid** (46), **Adipic acid** (47), **Suberic acid** (48), and **Sebacic acid** (49).

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Information

Dietary: Restricted diets such as strict ketogenic, GAPS, and other diets with elimination of carbohydrates can increase ketone production.[563]

Medication/Supplementation Influences: Valproate has been shown to elevate ketones.[569]

Associated Conditions: Ketones, though not diagnostic, can be associated with dysglycemia, diabetes, alcohol intoxication, strenuous exercise, corticoid steroid deficiencies, and infections.[574,575]

Developing Discussions: When evaluating 3HB and acetoacetate, blood tests are beginning to use their ratio to evaluate abnormal redox states of the mitochondria, and give insights into the respiratory chain.[576] Since the conversion of acetoacetate to 3HB is driven by NADH, if 3HB is higher than acetoacetate, **Vitamin B3** (niacin), may be helpful in supporting the reaction.[577,578] Furthermore, lactate and pyruvate ratio analysis are being evaluated to additionally evaluate the cystolic redox state since pyruvate is converted to lactate to re-oxidize NADH.[578]

For additional insights into NAD, one can also assess **Quinolinic acid** (39) elevations, as well as **Lactic acid** (22) and **Pyruvic acid** (23) for redox associations. Additionally, refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

Low Values There is no known clinical significance for low values.

(45) Ethylmalonic acid

Ethylmalonic acid (EMA) is a key metabolic marker associated with fatty acid oxidation disorders and mitochondrial dysfunction.[579] It is derived from butyrate metabolism and can accumulate due to high-fat or vegan diets, riboflavin or carnitine insufficiencies, or in more rare instances, genetic mutations.[580-582]

Microbial Overgrowth

Although there is no direct association between butyrate-producing organisms, butyrate production, and ethylmalonic acid, theoretically, if there is a significant amount of butyrate production, it may have an influence on ethylmalonic levels.[583,584]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Mitochondrial Health

Since EMA is linked to fatty acid oxidation and energy metabolism, reduced function of the pathway can have significant impacts on mitochondrial processes 62 EMA can also disrupt mitochondrial function by inhibiting key complexes within the electron transport chain (ETC), leading to impaired ATP production and increased oxidative stress, leading to further mitochondrial inefficiencies and imbalances.[581,585] It can also interfere with succinate and glutamate, partly by inhibiting α-ketoglutarate dehydrogenase (KGDH) and compromising membrane potential.[586,587]

The mitochondrial metabolite **2-Oxoglutaric acid** (27) is also influenced by KGDH, and additional changes in **Succinic acid** (24) may give further insights into EMA's direct influence on the Citric Acid Cycle. Insights into the cascading effects on the other **mitochondrial markers** (22)-(32) might also be supportive.

Nutritional Needs

Deficiencies in **carnitine** or **Vitamin B2 (Riboflavin)** can lead to abnormal EMA levels, as carnitine is required for transporting fatty acids for oxidation and riboflavin is crucial for flavin adenine dinucleotide (FAD)-dependent enzymes involved in fatty acid metabolism.[588,589]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Conditions like **MCAD deficiency**, **glutaric acidemia II**, **ethylmalonic acidemia**, and **ethylmalonic encephalopathy** caused by mutations in ETHE1 or SLC25A32 genes that disrupt butyrate metabolism can all disrupt fatty acid metabolism and lead to EMA accumulation.[589-592] Genetic mutations in the **short-chain acyl-CoA dehydrogenase** (SCAD) enzyme that controls butyrate oxidative pathways could also increase ethylmalonic acid.[579]

Markers associated with MCAD include **3-Hydroxybutyric acid** (43), **Acetoacetic acid** (44), **Methylsuccinic acid** (46), **Adipic acid** (47), **Suberic acid** (48), and **Sebacic acid** (49). Glutaric acidemia is associated with **3-hydroxyglutaric acid** (31), **Methylsuccinic acid** (46), **Adipic acid** (47), **Suberic acid** (48), **Sebacic acid** (49), and **Glutaric acid** (53). **Methylsuccinic acid** (46), together with EMA, can be associated with ethylmalonic acidemia.

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary: Very high-fat diets (Ketogenic, GAPS, etc.) or extreme carbohydrate restriction, without proper intake of carnitine and Vitamin B2 (Riboflavin) can cause altered fatty acid metabolism and may influence elevations in EMA.[582] Additionally, vegan diets without proper protein complementing may also increase the risk of carnitine deficiency, and stress fatty acid metabolism. Additional fatty acid oxidation markers that could also be influenced include **Methylsuccinic acid** (46), **Adipic acid** (47), **Suberic acid** (48), and **Sebacic acid** (49).[582]

Medication/ Supplement Influences: Since EMA is derived from butyrate, supplemental butyrate intake may increase EMA excretion levels.[580] Medium-chain triglyceride (MCT) supplements and coconut oil may also influence elevations due to their ability to promote rapid oxidation of medium-chain fatty acids.[582,593]

Methylsuccinic acid (46), **Adipic acid** (47), **Suberic acid** (48), and **Sebacic acid** (49) can also be influenced by MCT-containing foods and supplements.

Low Values There is no known clinical significance for low values.

(46) Methylsuccinic acid

Methylsuccinic acid (MSA), is a fatty acid metabolite involved in isoleucine metabolism.[594] It is associated with mitochondrial dysfunction from abnormal fatty acid utilization and has been associated with type 2 diabetes and various inborn errors of metabolism.[595,596]

Mitochondrial Health

MSA is linked to fatty acid oxidation and energy metabolism, and reduced function of the pathway can have significant impacts on mitochondrial dysfunction and cellular health. In reducing oxidative phosphorylation (OXPHOS) efficiency of fatty acids, ATP production is decreased, and energy deficits occur.[597,598] This dysfunction also causes structural mitochondrial abnormalities, calcium homeostasis disruption, and increased reactive oxygen species (ROS), further damaging mitochondrial integrity.[595,599]

Additional insights into the cascading effects of mitochondrial issues include the other **fatty acid oxidation markers** (45)-(49), and **mitochondrial markers** (22)-(32).

Nutritional Needs

Deficiencies in **carnitine** or **Vitamin B2 (Riboflavin)** can lead to abnormal MSA levels, as carnitine is required for transporting fatty acids for oxidation and riboflavin is crucial for flavin adenine dinucleotide (FAD)-dependent enzymes involved in fatty acid metabolism.[600,601]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Conditions such as **medium-chain acyl-CoA dehydrogenase deficiency** (MCAD), **ethylmalonic encephalopathy**, **glutaric acidemia**, and **isovaleric acidemia**, have all been associated with MSA elevations.[591,592,602] **Short-chain acyl-CoA dehydrogenase** (SCAD) enzyme defects can also cause elevations in MSA, along with **ethylmalonic acid** (45).[603]

Markers also associated with MCAD include **3-Hydroxybutyric acid** (43), **Acetoacetic acid** (44), **Ethylmalonic acid** (45), **Adipic acid** (47), **Suberic acid** (48), and **Sebacic acid** (49). **Ethylmalonic acid** (45) combined with MSA is associated with ethylmalonic encephalopathy. **3-Hydroxyglutaric acid** (31), **Ethylmalonic acid** (45), **Adipic acid** (47), **Suberic acid** (48), **Sebacic acid** (49), and **Glutaric acid** (53) are all associated with glutaric acidemia. **3-Hydroxy-3-methylglutaric acid** (55), **Methylcitric acid** (57), **2-Hydroxyisovaleric acid** (62), and **3-Methyl- 2-oxovaleric acid** (64) are also associated with isovaleric acidemia.

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary: Very high fat diets (Ketogenic, GAPS, etc.) or extreme carbohydrate restriction, without proper intake of carnitine and Vitamin B2 (Riboflavin) can cause altered fatty acid metabolism and may influence elevations in EMA.[582] Additionally vegan diets with improper protein complementing may also increase the risk of carnitine deficiency, and stress fatty acid metabolism.[582] Additional fatty acid oxidation markers that could also be influenced include; **Ethylmalonic acid** (45), **Adipic acid** (47), **Suberic acid** (48), and **Sebacic acid** (49).

Medication/ Supplement Influences: Medium chain triglyceride (MCT) supplements and coconut oil may influence elevations due to their ability to promote rapid oxidation of medium-chain fatty acids.[582,593]

Ethylmalonic acid (45), **Adipic acid** (47), **Suberic acid** (48), and **Sebacic acid** (49) can also be influenced by MCT containing foods and supplements.

Associated Conditions: MSA has been shown to be associated with type 2 diabetes.[596]

Low Values There is no known clinical significance for low values.

(47) Adipic acid

Adipic acid is a dicarboxylic acid that serves as a key marker of fatty acid metabolism that undergoes omega-oxidation, when beta oxidation is impaired.[579] High adipic acid may indicate mitochondrial dysfunction, carnitine or Vitamin B2 (Riboflavin) insufficiencies, metabolic stressors, dietary intake, or, in rare cases, genetic abnormalities.[582,592,600,601,603]

Mitochondrial Health

When fatty acid oxidation is impaired, alternative metabolic pathways such as beta and omega oxidation become active, leading to the potential accumulation of Adipic and **Suberic acids** (48).[579] Deficiencies in key mitochondrial enzymes or disruptions in oxidative phosphorylation can also contribute to elevations.[604] Furthermore, the buildup of adipic and suberic acid as byproducts of lipid peroxidation and fatty acid oxidation can generate additional oxidative stress, leading to more stress on the mitochondria.[605]

Additional insights into the cascading effects of mitochondrial issues include the other **fatty acid oxidation markers** (45)-(49) and **mitochondrial markers** (22)-(32).

Nutritional Needs

Deficiencies in **carnitine** or **Vitamin B2 (Riboflavin)** can lead to abnormal adipic levels, as carnitine is required for transporting fatty acids for oxidation and riboflavin is crucial for flavin adenine dinucleotide (FAD)-dependent enzymes involved in fatty acid metabolism.[600,601] Moreover, magnesium can also influence the optimization of omega oxidation directly or through reducing the effects of oxidative stress.[606,607]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

There are numerous genetic and mitochondrial disorders that can influence both adipic and suberic acids (48), and are classified into mitochondrial, peroxisomal, and fatty acid oxidation disorders 62 The more well known conditions that can influence adipic acid include **medium-chain acyl-CoA dehydrogenase deficiency** (MCAD), **multiple acyl-CoA dehydrogenase deficiency** (MADD), **glutaric acidemia**, and **short-chain acyl-CoA dehydrogenase** (SCAD).[592,603] Markers also associated with MCAD, include **3-Hydroxybutyric acid** (43), **Acetoacetic acid** (44), **Ethylmalonic acid** (45), **Methylsuccinic acid** (46), **Suberic acid** (48), and **Sebacic acid** (49). **3-hydroxyglutaric acid** (31), **Ethylmalonic acid** (45), **Methylsuccinic acid** (46), **Suberic acid** (48), **Sebacic acid** (49), and **Glutaric acid** (53) are all associated with glutaric acidemia.

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary: Intake of gelatin, processed foods that contain it, and coconut oil can all increase adipic, as can very high-fat diets (Ketogenic, GAPS, etc.), fasting, or very limited carbohydrate intake without proper intake of carnitine and Vitamin B2 (Riboflavin).[08]

Additionally, vegan diets with improper protein complementing may also increase the risk of carnitine deficiency, and stress fatty acid metabolism.[582] Additional fatty acid oxidation markers that could also be influenced include **Ethylmalonic acid** (45), **Methylsuccinic acid** (46), **Suberic acid** (48), and **Sebacic acid** (49).

Medication/Supplementation Influences: Valproate has been shown to elevate ketones.[569]

Associated Conditions: Adipic acid has been shown to be commonly elevated in children with autism spectrum disorders (ASD).[609,610]

Low Values There is no known clinical significance for low values.

(48) Suberic acid

Suberic acid is a dicarboxylic acid that serves as a key marker of fatty acid metabolism that undergoes omega-oxidation when beta oxidation is impaired.[579] High suberic acid may indicate mitochondrial dysfunction, carnitine or Vitamin B2 (Riboflavin) insufficiencies, metabolic stressors, dietary intake, or in rare cases, genetic abnormalities.[582,592,600,601,603]

Mitochondrial Health

When fatty acid oxidation is impaired, alternative metabolic pathways such as beta and omega oxidation become active, leading to the accumulation of Suberic and **Adipic acids** (47).[579] Deficiencies in key mitochondrial enzymes or disruptions in oxidative phosphorylation can also contribute to elevations.[604] Furthermore, the buildup of adipic and suberic acid as byproducts of lipid peroxidation and fatty acid oxidation can generate additional oxidative stress, leading to more stress on the mitochondria.[605]

Additional insights into the cascading effects of mitochondrial issues include the other **fatty acid oxidation markers** (45)-(49) and **mitochondrial markers** (22)-(32).

Nutritional Needs

Deficiencies in **carnitine** or **Vitamin B2 (Riboflavin)** can lead to abnormal adipic levels, as carnitine is required for transporting fatty acids for oxidation and riboflavin is crucial for flavin adenine dinucleotide (FAD)-dependent enzymes involved in fatty acid metabolism.[600,601] Moreover, **magnesium** can also influence the optimization of omega oxidation directly, or through reducing the effects of oxidative stress.[606,607]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

There are numerous genetic and mitochondrial disorders that can influence both **adipic** (47) and suberic acids, and are classified into mitochondrial, peroxisomal, and fatty acid oxidation disorders.[62] The more well-known conditions that can influence adipic acid include **medium-chain acyl-CoA dehydrogenase deficiency** (MCAD), **multiple acyl-CoA dehydrogenase deficiency** (MADD), **glutaric acidemia**, and **short-chain acyl-CoA dehydrogenase** (SCAD).[592,603] Markers also associated with MCAD, include **3-Hydroxybutyric acid** (43), **Acetoacetic acid** (44), **Ethylmalonic acid** (45), **Methylsuccinic acid** (46), **Adipic acid** (47), and **Sebacic acid** (49). **3-hydroxyglutaric acid** (31), **Ethylmalonic acid** (45), **Methylsuccinic acid** (46), **Adipic acid** (47), **Sebacic acid** (49) and **Glutaric acid** (53) are all associated with glutaric acidemia.

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary: Intake of gelatin, processed foods, and coconut oil can increase suberic acid, as can very high-fat diets (Ketogenic, GAPS, etc.), fasting, or very limited carbohydrate intake without proper intake of carnitine and Vitamin B2 (Riboflavin).[608] Additionally, vegan diets with improper protein complementing may also increase the risk of carnitine deficiency, and stress fatty acid metabolism.[582] Additional fatty acid oxidation markers that could also be influenced include **Ethylmalonic acid** (45), **Methylsuccinic acid** (46), **Adipic acid** (47), and **Sebacic acid** (49).

Associated Conditions: Suberic acid has been shown to be commonly elevated in children with autism spectrum disorders (ASD).[610]

Low Values There is no known clinical significance for low values.

(49) Sebacic acid

Sebacic acid is a medium-chain dicarboxylic acid obtained by oxidizing a fatty acid called ricinoleic acid (castor oil).[611] It is produced through the oxidation of decanoyl-CoA to sebacoyl-CoA, a process facilitated by acyl-CoA dehydrogenase.[611] Elevated sebacic acid is impaired fatty acid oxidation due to mitochondrial dysfunction, carnitine or riboflavin insufficiencies, or certain rare genetic disorders. Additionally, certain toxicants, high-fat diets, and MCT supplementation may impact its levels.[595,598, 600,601,612,613]

Mitochondrial Health

Linked to fatty acid oxidation and energy metabolism, reduced function of these pathways can have significant impacts on mitochondrial dysfunction and cellular health. In reducing oxidative phosphorylation (OXPHOS) efficiency of fatty acids, ATP production is decreased, and energy deficits occur.[597,598] This dysfunction also causes structural mitochondrial abnormalities, calcium

homeostasis disruption, and increased reactive oxygen species (ROS), further damaging mitochondrial integrity.[595,599]

Additional insights into the cascading effects of mitochondrial issues include the other **fatty acid oxidation metabolites** (45)-(49), and **mitochondrial metabolites** (22)-(32).

Toxic Exposure

Sebacic acid and its derivatives, such as pimelic acid, have diverse industrial applications, including use in plasticizers, lubricants, hydraulic fluids, cosmetics, and candles.[612] It also plays a role in producing polyester and epoxy resins and serves as an intermediate in the synthesis of fragrances, disinfectants, and coating materials.[614] It has not been well studied if sebacic acid is found in urine from these exposures, and itself is not toxic; however, it may help support investigations into exposures to toxicants found in the aforementioned products.

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Nutritional Needs

Deficiencies in **carnitine** or **Vitamin B2 (Riboflavin)** can lead to abnormal sebacic acid levels, as carnitine is required for transporting fatty acids for oxidation and riboflavin is crucial for flavin adenine dinucleotide (FAD)-dependent enzymes involved in fatty acid metabolism.[600,601]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Genetic conditions including **multiple acyl-CoA dehydrogenase deficiency** (MADD), **medium-chain acyl-CoA dehydrogenase deficiency**, **carnitine-acylcarnitine translocase deficiency**, **Adrenoleukodystrophy** (ALD), and peroxisome disorders such as **Zellweger syndrome** and **neonatal adrenoleukodystrophy**, can cause elevated sebacic acid levels.[613,615,616]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary: Very high-fat diets (Ketogenic, GAPS, etc.) or extreme carbohydrate restriction, without proper intake of carnitine and Vitamin B2 (Riboflavin), can cause altered fatty acid metabolism and may influence elevations in Sebacic acid.[82] Additionally, vegan diets with improper protein complementing may also increase the risk of carnitine deficiency, and stress fatty acid metabolism.[82] Additional fatty acid oxidation markers that could also be influenced include **Ethylmalonic acid** (45), **Methylsuccinic acid** (46), **Adipic acid** (47), and **Suberic acid** (48).

Medication/ Supplement Influences: Medium-chain triglyceride (MCT) supplements and coconut oil may influence elevations due to their ability to promote rapid oxidation of medium-chain fatty acids.[582,593] Consumption of castor oil may also influence elevations.[611] **Ethylmalonic acid (45)**, **Methylsuccinic acid** (46), **Adipic acid** (47), and **Suberic acid** (48) may also be influenced by MCT-containing foods and supplements.

Low Values There is no known clinical significance for low values.

NUTRITIONAL MARKERS

(50) Methylmalonic acid

Vitamin B12 is essential for propionic acid metabolism, as it enables the conversion of methylmalonyl-CoA to succinyl-CoA through the B12-dependent enzyme methylmalonyl-CoA mutase (MMUT).[617] When B12 is deficient, this process is disrupted, causing the accumulation of methylmalonic acid (MMA). Propionic acid metabolism connects branched-chain amino acid and odd-chain fatty acid oxidation to the Citric Acid Cycle, and disturbances in this pathway can have widespread metabolic consequences.[618,619] Vitamin B12 not only plays a role in mitochondrial function, but it can also disrupt the methylation processes, which can have cascading effects, particularly in neurotransmitter metabolism and detoxification pathways.[617]

Microbial Overgrowth

Elevated MMA levels may signal gut microbiota imbalances due to an increase in the production of the short-chain fatty acid, propionic acid, which can interfere with metabolism.[230,620]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Mitochondrial Health

Vitamin B12, in the form of adenosylcobalamin, is essential for mitochondrial health as it serves as a cofactor for methylmalonyl-CoA mutase (MUT), an enzyme that catalyzes the conversion of methylmalonyl-CoA to succinyl-CoA.[617] This step in propionate catabolism enables the breakdown of branched-chain amino acids, odd-chain fatty acids, and cholesterol, allowing them to be funneled into the citric acid cycle.[618]

Review **Markers** (24)-(29) for insights on the citric acid cycle, **3-methylglutaric acid** (30), **3 Methylglutaconic acid** (32), and **Markers** (62)-(67) for further evaluation of branched-chain amino acid utilization, and **Markers** (43)-(49) for fatty acid utilization for energy.

Neurotransmitter Metabolites

Vitamin B12 acts as a cofactor for methionine synthase in the conversion of homocysteine to methionine, which is then used to produce S-adenosylmethionine (SAM), a key methyl donor for neurotransmitter methylation via COMT.[621,622] It also modulates cholinergic signaling by influencing choline availability for acetylcholine synthesis and helps regulate glutamate release to prevent excitotoxicity.[623-625] Deficiency can impair myelin integrity, elevate neurotoxic homocysteine levels, and disrupt neurotransmitter metabolism.[622,626]

Review **neurotransmitter metabolites** (33)-(39) for further insights.

Methylation/Detoxification

Vitamin B12 is essential for coordinating the folate and methionine cycles, which regulate methylation.[617] As a cofactor for methionine synthase (MS), B12 enables the conversion of homocysteine to methionine using 5-methyltetrahydrofolate (5-mTHF), and sustains S-adenosylmethionine (SAM) production, which is a primary methyl donor for DNA, protein, and neurotransmitter methylation.[617]

For additional markers influencing methylation and SAM, look to **HVA/DOPAC ratio** (37), **Uracil** (41), and **2-Hydroxybutryic acid** (58). A homocysteine serum test may be helpful. Additionally, refer to the Nutrient–Marker Cross-Reference Table for insights into corresponding organic acids that are associated with **methylation support** (**B2**, **B3**, **B6**, **B9**, and **magnesium**).

Nutritional Needs

MMA serves as a functional biomarker for **B12** deficiency since vitamin B12 is the cofactor for the enzyme methylmalonyl-CoA mutase, and its absence leads to the accumulation of MMA instead of the formation of succinyl-CoA.[19] **Biotin** also plays a role in the metabolism of propionic acid, potentially aiding in reducing MMA accumulation.[620]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Conditions such as methylmalonic acidemia and propionic acidemia are inherited metabolic disorders that severely disrupt detoxification and cellular pathways, leading to extreme developmental and neurological issues.[620]

Methylmalonic acidemia is also associated with **Methyl citric acid** (57) and **3-Methyl-2-oxovaleric acid** (64), but a normal homocysteine. **Pyroglutamic acid** (58), **2-Hydroxybutryic acid** (59), **2-Hydroxyisovaleric acid** (62), and **3-Methyl-2-oxovaleric acid** (64) are associated with propionic acidemia.

Elevated MMA may also indicate mitochondrial disorders such as Pearson syndrome, which affects the respiratory chain, along with mitochondrial DNA mutations further impairing energy metabolism.[620] Other associated genetic disorders include Malonyl CoA decarboxylase deficiency, Malonic Aciduria, Methylmalonate Semialdehyde Dehydrogenase Deficiency, and Methylmalonic Aciduria.[627-629] Malonyl CoA decarboxylase deficiency is also associated with **malonic acid** (74).

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary: Individuals who do not consume animal products and do not supplement with B12 are at risk for insufficiencies.[630,631]

Medication/Supplement Influences: Medications such as metformin, proton pump inhibitors, or H2 receptor blockers may impair B12 absorption.[632,633] There is also some evidence that oral contraceptives may influence B12 insufficiencies.[634]

Associated Conditions: MMA elevations have been associated with Alzheimer's disease, advanced age, pregnancy, and kidney disease.[635-637] Individuals with short bowel syndrome, SIBO, gastritis, or other gastrointestinal conditions that impair B12 absorption, as well as those who have undergone bariatric surgery, are at a significantly higher risk for B12 deficiencies.[638-640]

Low Values There is no known clinical significance for low values.

51 Pyridoxic Acid

Pyridoxic acid is the primary metabolite of vitamin B6, serving as a biomarker for assessing status.[641] Abnormal vitamin B6 levels may indicate excessive intake, medication influences affecting metabolism and excretion, or, in rare instances, genetic disorders such as pyridoxine-dependent epilepsy.[642,643] Low levels may stem from inadequate intake, Microbial Overgrowths, or mitochondrial dysfunction, and may impact neurotransmitter synthesis, methylation, and detoxification pathways.[230,421,644-646] Moreover, certain medications, hormonal factors, and conditions such as celiac disease, diabetes, or chronic kidney disease may further influence B6 status.[647,648]

Nutritional Needs

Elevated levels may indicate excessive vitamin B6 intake from diet or supplements.[641]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

Genetics

Pyridoxine-dependent epilepsy, a rare genetic disorder caused by mutations in the PNPO gene encoding pyridox(am)ine 5′-phosphate oxidase, disrupts the rate-limiting step in B6 metabolism, leading to excess pyridoxic acid elimination.[642]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Supplement/Medications Influences: Isoniazid and penicillamine may increase excretion of pyridoxic acid.[643]

Associated conditions: Pyridoxic acid levels can accumulate due to impaired renal clearance and an increase in catabolic states such as fever, fasting, or metabolic acidosis, which accelerate protein turnover and amino acid oxidation.[230]

Low Values

Microbial Overgrowth: There is evidence that B6 can be produced by various bacteria in the microbiome (e.g. *B. fragilis* and *P. copri* (Bacteroidetes), *Bifidobacterium longum* and *Collinsella aerofaciens* (Actinobacteria), and *H. Pylori*), and if reduced in abundance, may influence insufficiencies.[644,649] There is also some data that suggests a lack of B6 can influence the microbiome, as various Firmicutes (*Veillonella*, *Ruminococcus*, *Faecalibacterium*, and *Lactobacillus* spp.) are unable to produce their own and require their hosts to provide it.[649]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Mitochondrial Health: Vitamin B6 supports Coenzyme A production, which is essential for energy metabolism.[645] It also aids in the absorption and storage of **vitamin B12**, a key cofactor in mitochondrial pathways.[645] Additionally, B6 influences hormone synthesis, including cortisol and glucagon, which regulate mitochondrial energy balance and metabolic processes.[645]

Assessing **Markers** (22)-(32) for mitochondrial insights, as well as refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

Neurotransmitter Metabolites: Vitamin B6 is essential for neurotransmitter synthesis, serving as a cofactor for aromatic L-amino acid decarboxylase (AADC), which converts L-DOPA to dopamine and 5-hydroxytryptophan to serotonin.[21] Deficiency in B6 can impair AADC activity, leading to reduced dopamine and serotonin levels.[385]

Evaluate **HVA** (33), **VMA** (34), **DOPAC** (37), and **5-HIAA** (38) for further insights.

B6 also supports the **biopterin** cycle by aiding in the regeneration of tetrahydrobiopterin (BH4), which is the enzyme involved in dopamine, norepinephrine, and serotonin synthesis.[650,651]

For additional insights into Biopterin pathways, review **phenylalanine** and **tyrosine metabolites** (33)-(37), **2-Hydroxyphenylacetic acid** (11), **Mandelic acid** (68), **Phenylacetic acid** (69), and **Phenylpyruvic acid** (70).

B6 is a cofactor for various enzymes involved in the tryptophan-to-kynurenine pathway, and insufficient levels may lead to abnormal levels of **Quinolinic acid** (39) and **Kynurenic acid** (40).[652]

Methylation/Detoxification: In the methylation pathway, B6 supports serine hydroxymethyltransferase (SHMT), facilitating the conversion of serine to glycine and providing one-carbon units for methionine and S-adenosylmethionine (SAM) synthesis, crucial for methylation reactions.[646,653] Vitamin B6 is also essential for the transsulfuration pathway as a coenzyme for cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE), which convert homocysteine to cysteine for glutathione production.[653-655]

Review **2-hydroxybutyric acid** (58) and **Pyroglutamic acid** (59) to gain further insights into methylation and detoxification components, as well as refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with nutrients related to **methylation support** (B2, B3, B6, B9, B12, and **magnesium**) and **glutathione**.

Nutritional Needs: Measuring pyridoxic acid may reflect **B6** insufficiency.[641] Moreover, vitamin **B2 (Riboflavin)** insufficiency can influence low B6 levels as it affects B6 activation.

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Dietary: Restrictions in intake of fish or beef, starchy vegetables, and grains may increase risk of inadequate intake.[648,656,657]

Supplement/Medications Influences: Cycloserine, various antiepileptic medications, and theophylline may influence B6 insufficiencies.[647,658,659] Various birth controls or supplemental estrogen or progesterone may require an increased need for B6.[634,660]

Associated Conditions: Maladies such as celiac disease, diabetes, inflammatory bowel disease, or chronic renal failure can influence B6 absorption.[648] Low B6 levels may contribute to calcium **oxalate** stone formation, as B6 helps convert glyoxylate into glycine instead of oxalate.[185]

Evaluate **Oxalic acid** (21) for further insights into oxalates.

(52) Pantothenic Acid

Pantothenic acid (B5) plays a crucial role in metabolism, primarily through its involvement in Coenzyme A (CoA) synthesis, which is essential for energy production.[661] Levels of B5 can be influenced by dietary intake, microbial activity, supplementation, including products containing B5 derivatives or royal jelly.[662-664] Rare genetic mutations, such as those in the PANK2 gene linked to PKAN, can lead to significantly elevated levels due to impaired conversion to CoA.[665]

Additionally, low B5 levels may have a significant influence on mitochondrial dysfunction, potentially affecting the Citric Acid Cycle and energy metabolism.[666]

Microbial Overgrowth

There is evidence that suggests B5, in the form of pantothenic acid phosphate, can be produced by *Lactobacillus plantarum*, and if in high abundance, may influence high levels.[662]

Evaluate **DHPPA** (14), **2-Hydroxyisocaproic acid** (65), and **4-Hydroxyphenyllactic acid** (72) for more insights into *Lactobacillus* activity.

Nutritional Needs

High levels may reflect recent intake and may give insights into nutritional status.[663]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

Genetics

Genetic mutations in the PANK2 gene are linked to PKAN, a disorder that impairs the

conversion of pantothenic acid to its active form, CoA, causing significant elevations of pantothenic acid.[665]

Evaluate **Lactic acid** (22), **Pyruvic acid** (23), and the **Citric Acid Cycle metabolites** (24)-(29), particularly **2-oxoglutaric acid** (27), for further insights.

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary: Pantothenic acid is abundant in whole grains, legumes, eggs, meat, shitake mushrooms, and high intakes of these foods the day before may influence levels.[656]

Medication/Supplement Influences: Supplements that contain royal jelly may influence elevations, as can any supplement containing Vitamin B5 (various forms).[664]

Low Values

Microbial Overgrowth: Pantothenic acid phosphate is produced by *Lactobacillus*, and if in insufficient amounts, may influence low levels.[662]

Evaluate **DHPPA** (14), **2-Hydroxyisocaproic acid** (65), and **4-Hydroxyphenyllactic acid** (72) for more insights into *Lactobacillus* activity.

Mitochondrial Health: Pantothenic acid aids in the synthesis of coenzyme A (CoA), which is required for the Citric Acid Cycle and energy production. If deficiencies are present, significant mitochondrial influences may occur.[666]

Evaluate **Lactic acid** (22), **Pyruvic acid** (23), and the **Citric Acid Cycle markers** (24)-(29), particularly **2-oxoglutaric acid** (27), for further insights.

Nutritional Needs: Low levels may suggest insufficient intake.

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

(53) Glutaric Acid

Glutaric acid metabolism relies on riboflavin (B2) as a cofactor for glutaryl-CoA dehydrogenase, and a deficiency can lead to its accumulation, impacting amino acid and fatty acid metabolism.[667] Riboflavin is essential for mitochondrial energy production, neurotransmitter synthesis, and detoxification through its role in FAD-dependent enzymes.[401,668,669] Insufficient B2 levels can affect ATP synthesis, methylation, and oxidative stress balance, potentially contributing to metabolic dysfunction.[668,670,671] Dietary restrictions, medications such as oral contraceptives, and inadequate riboflavin intake may further influence these processes, increasing the risk of deficiency-related complications.[672,673]

Mitochondrial Health

Riboflavin is absorbed from the diet, transported into mitochondria, and converted into FAD through the Rf-FAD cycle.[668] The various FAD-dependent enzymes involved in fatty acid metabolism support the acetyl-CoA generation for the citric acid cycle.[668] B2 also plays a role in the electron transport chain (ECT), which can have significant impacts on ATP production.[668]

Evaluate other **fatty acid oxidation markers** (45)-(49) for B2 influence, and **Succinic acid** (24) for further insights into the ECT.

Neurotransmitter Metabolites

Tetrahydrobiopterin (BH4), a key cofactor for enzymes involved in dopamine, norepinephrine, and serotonin **production**, requires FAD for dihydropteridine reductase (DHPR) to recycle BH4 and maintain neurotransmitter synthesis.[379,401,600,650,651] Moreover, FAD plays a role in monamine oxidase (MAO), the enzyme involved in the **metabolism** of dopamine, norepinephrine, and serotonin.[674] B2 has also been shown to help restore dopamine levels and reduce oxidative stress in the brain.[671]

For further insights into influences on biopterin cycles and MAO pathways, look to **2-Hydroxyphenylacetic acid** (11), **HVA** (33), **VMA** (34), **5HIAA** (38), **Mandelic acid** (68), **Phenylacetic acid** (69), and **Phenylpyruvic acid** (70).

Methylation/Detoxification

Vitamin B2 activates methylenetetrahydrofolate reductase (MTHFR), which converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, facilitating homocysteine remethylation and sustaining S-adenosylmethionine (SAM) levels for DNA and protein methylation.[669,670] Moreover, FAD-dependent enzymes, such as dimethylglycine dehydrogenase, drive oxidative demethylation processes that generate tetrahydrofolate, linking riboflavin to one-carbon metabolism and xenobiotic clearance.[675]

Review of **HVA/DOPAC ratio** (37), **Uracil** (41), and **2-hydroxybutyric acid** (59) for additional insights into methylation dysfunction. Additionally, refer to the Nutrient–Marker Reference Table for the

corresponding organic acids associated with nutrients related to **methylation support** (**B2**, **B3**, **B6**, **B9**, **B12**, and **magnesium**).

Nutritional Needs

Glutaric acid metabolism relies on **riboflavin (B2)** as a cofactor for the enzyme glutaryl-CoA dehydrogenase.[672] A deficiency in vitamin B2 can impair this enzyme's function, leading to the accumulation of glutaric acid.[667,676]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

Genetics

Glutaric acidemia type I (GA-1) and glutaryl-CoA dehydrogenase deficiency are autosomal recessive disorders caused by a deficiency in glutaryl-CoA dehydrogenase, which influences the breakdown of amino acids lysine, hydroxylysine, and tryptophan. **3-hydroxyglutaric acid (31)** may also be influenced by GA-1.[677]

Glutaric acidemia type II (GA-2), or multiple acyl-CoA dehydrogenase deficiency (MADD), arises from a defect in either electron transfer flavoprotein (ETF) or electron transfer flavoprotein dehydrogenase (ETFDH), leading to impaired fatty acid, amino acid, and choline metabolism, which disrupts ATP synthesis, reduces gluconeogenesis, and causes excessive lipid accumulation.[677]

3-hydroxyglutaric acid (31), **Ethylmalonic acid** (45), **Methylsuccinic acid** (46), **Adipic acid** (47), and **Sebacic acid** (49) are all associated with glutaric acidemias.

An additional rare genetic disorder, Riboflavin transporter deficiency (formerly known as Brown-Vialetto-Van Laere or Fazio-Londe syndrome), is caused by mutations in the *SLC52A3* or *SLC52A2* genes, which encode riboflavin transporters.[678]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary: A diet that excludes meat, dairy, and fortified grains may lack a significant amount of Vitamin B2 (Riboflavin), increasing the risk of deficiencies.[679]

Medication/Supplement Influences: Valproic acid and oral contraceptives may influence B2 insufficiencies.[673,680]

Low Values There is no known clinical significance for low values.

54 Ascorbic Acid (Vitamin C)

Ascorbic acid, also known as vitamin C, is a water-soluble nutrient found in citrus fruits and vegetables, essential for collagen synthesis, various biological functions, and antioxidant protection.[681] Ascorbic acid levels are influenced by factors such as Microbial Overgrowth, mitochondrial health, neurotransmitter metabolism, and nutritional needs such as iron or zinc deficiency.[682-689] Foods rich in vitamin C and supplements, as well as medications, can increase its levels, while conditions such as critical illness, infections, and smoking raise the body's demand for it.[689-698] Vitamin C levels are commonly low, due to its ability to be rapidly metabolized and excreted as well as its short half-life.[699]

Microbial Overgrowth

Fungal species, including yeast such as Saccharomyces cerevisiae, produce the stereoisomer D-erythroascorbic acid through a biosynthesis pathway similar to L-ascorbic acid, starting from D-arabinose.[682]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Nutritional Needs

Iron deficiency increases the need for vitamin C, as it enhances the absorption of non-heme iron, with studies showing that iron regulates the uptake of ascorbic acid in the intestines. Similarly, zinc deficiency can impact vitamin C requirements due to zinc's role in immune function and wound healing, processes also supported by vitamin C.[688,689]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Additional Insights

Dietary Influences: Foods high in vitamin C, such as citrus fruits, strawberries, kiwi, bell peppers, and acerola juice, can increase ascorbic acid levels.[690]

Medication/Supplement Interactions: Medications and supplements such as microsomal enzyme inducers (e.g., phenobarbital and diallyl sulfide), aspirin, certain types of dietary fiber, such as hemicellulose, and vitamin C supplementation have been shown to boost urinary excretion of ascorbic acid, likely by affecting its metabolism or enhancing its absorption.[691-694]

Associated Conditions: High doses of vitamin C, particularly in the presence of copper, can increase oxalate levels in the body, as it is metabolized to oxalate, which is then excreted in the urine.[700]

To further assess oxalate status, reference **glyceric** (19), **glycolic** (20), and **oxalic** (21).

Low Values

Mitochondrial Health: Insufficiencies in ascorbic acid levels could impair mitochondrial function

by increasing oxidative stress, increase the potential for damage to the mitochondrial DNA, reduce ATP production, and disrupt energy metabolism, ultimately compromising overall mitochondrial efficiency.[683-686]

For more insight into mitochondrial health, reference the other **mitochondrial markers** (22)-(32) and **fatty acid oxidation markers** (45)-(49).

Neurotransmitter Metabolites: Ascorbic acid is essential for the proper function of dopamine beta-hydroxylase (DBH), as it acts as a cofactor for converting dopamine to norepinephrine. Deficiency in vitamin C impairs DBH activity, leading to decreased norepinephrine synthesis.[687] For more insight into neurotransmitter activity, reference the **phenylalanine** and **tyrosine metabolites** (33)-(37).

Nutritional Needs: Ascorbic acid is rapidly metabolized and excreted primarily due to its renal handling, which involves a renal threshold mechanism, where excess vitamin C is cleared in the urine once plasma levels exceed a certain threshold. Its conversion to oxalate, short half-life, and saturable reabsorption in the kidneys contribute to this quick clearance from the body.[699]

If deficiency is suspected, refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

Associated Conditions: Conditions such as cirrhosis, malnutrition, critical illness, trauma, infections, diabetes, obesity, smoking, and strenuous exercise increase the need for vitamin C due to heightened oxidative stress, inflammation, and metabolic demands. Patients with these conditions often require higher vitamin C intake or supplementation to support immune function, wound healing, and to counteract oxidative damage. Smokers and athletes, in particular, have higher daily requirements, while individuals with chronic illnesses may need vitamin C to compensate for impaired absorption or increased turnover.[689,695-698]

(55) 3-Hydroxy-3-methylglutaric Acid * (Vitamin Q10 (CoQ10))

3-Hydroxy-3-methylglutaric acid (HMG) is an intermediate in leucine degradation, formed when the enzyme 3-hydroxy-3-methylglutaryl-CoA lyase (HMG-CoA lyase) is deficient or impaired. This enzymatic influence disrupts ketone body synthesis and leads to the accumulation of HMG, contributing to metabolic imbalances. Low coenzyme Q10 (CoQ10) levels can exacerbate this by impairing mitochondrial function, leading to increased acetyl-CoA accumulation and further diversion into pathways such as those that produce 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA), which is a substrate for HMG-CoA lyase. The disruption in metabolism also impacts cholesterol and CoQ10 synthesis, as the accumulation of HMG-CoA, a precursor in both pathways, can impair their downstream processes. Similarly, disruptions in the mevalonate pathway, where HMG-CoA is a key intermediate, hinder the synthesis of CoQ10.[388,701-705]

Mitochondrial Health

Mitochondrial dysfunction caused by low CoQ10 levels may impair the electron transport chain, reduce ATP production, and increase oxidative stress. This inefficiency leads to acetyl-CoA accumulation, which is diverted into pathways that produce 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA), affecting the activity of HMG-CoA lyase and increasing levels of 3-hydroxy-3-methylglutaric acid.[338,702,705]

For more insight into mitochondrial health, reference the other **mitochondrial markers** (22)-(32) and **fatty acid oxidation markers** (45)-(49).

Nutritional Needs

CoQ10 deficiency or insufficiency can impair mitochondrial function and ATP production, leading to increased oxidative stress. This dysfunction results in acetyl-CoA accumulation, which is diverted into pathways that may increase levels of 3-hydroxy-3-methylglutaric acid.[338,702,705]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

Genetics

Elevated levels of 3-hydroxy-3-methylglutaric acid are often seen in individuals with the rare condition, 3-hydroxy-3-methylglutaric aciduria, a disorder caused by a deficiency in the enzyme HMG-CoA lyase. This enzyme defect disrupts leucine degradation, leading to the accumulation of HMG in the mitochondria and urine. Other disorders, such as maple syrup urine disease, isovaleric acidemia, and methylcrotonylglycinemia, which also affect leucine degradation, as well as mitochondrial disorders, can lead to increased levels of 3-hydroxy-3-methylglutaric acid due to disrupted enzyme activity in the metabolic pathways.[701]

Other markers associated with MSUD include; **2-Hydroxyisovaleric acid** (62), **2-Oxoisovaleric acid** (63), **3-Methyl-2-oxovaleric acid** (64), **2-Hydroxyisocaproic acid** (65), and **2-Oxoisocaproic acid** (66), while **Methylsuccinic acid** (46), **Methylcitric acid** (57) , **2-Hydroxyisovaleric acid** (62), and **3-Methyl-2-oxovaleric acid** (64) are associated with isovaleric acidemia.

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Medication/Supplement Interactions: Statins main mechanism of action is blocking HMG-CoA reductase, which blocks the conversion of HMG-CoA to mevalonate.[706]

Associated Conditions: 3-hydroxy-3-methylglutaric acid has been found to be significantly more elevated in patients with diabetes and those using statins.[707,708]

Low Values There is no known clinical significance for low values.

(56) N-Acetylcysteine (NAC) (Glutathione Precursor and Chelating Agent)

N-Acetylcysteine (NAC) is a derivative of L-cysteine and a precursor to the antioxidant glutathione. It helps replenish glutathione levels, neutralizes free radicals, and protects cells from oxidative damage.[709] Elevated NAC levels may result from high supplemental intake, deficiencies, or rare conditions involved in acylation. Low levels can be physiologically normal and expected.[709-714]

Methylation/Detoxification

Being an important cofactor to the antioxidant **glutathione**, assessing NAC levels and conversion can provide more insight into detoxification, especially under circumstances of oxidative stress.[709]

Refer to the Nutrient–Marker Reference Table for insights into corresponding organic acids that are associated with **glutathione**.

Genetics

It is theorized that when NAC is elevated alongside **pyroglutamic acid** (58), there may be a dysfunction in an acylase enzyme, which would compromise NAC to cysteine conversion, potentially influencing glutathione status.[714]

For more insight into this conversion, assess with **pyroglutamic acid** (58).

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Medication/Supplement Interactions: NAC is mostly converted to glutathione in the body, therefore, elevated levels are often related to intake, such as through intravenous formulations, oral supplementation.[710-713]

Additional Benefits: NAC offers several benefits, including replenishing glutathione levels to protect against liver damage from acetaminophen overdose, reducing the viscosity of mucus in respiratory conditions such as COPD, and providing antioxidant effects by reducing free radicals. It also shows promise in managing psychiatric disorders, such as bipolar disorder and schizophrenia, and may have antiviral properties.[709]

Low Values: Low values of NAC are often less clinically significant as most is converted efficiently, but may indicate an increase in utilization of antioxidants such as glutathione in the context of supplementation.[709]

(57) Methylcitric Acid* Biotin (Vitamin B7)

Methylcitric acid serves as a key marker for assessing biotin sufficiency, as biotin is essential for the propionyl-CoA carboxylase (PCC)-catalyzed conversion of propionyl-CoA to methylmalonyl-CoA.[167] If biotin is insufficient, methylcitrate from propionyl CoA is elevated, and prevents succinyl CoA formation to support the citric acid cycle.[715] Increased levels of methylcitric acid can also be influenced by Microbial Overgrowths that affect biotin synthesis or by biotinidase deficiency, which impairs biotin recycling and biotin-dependent enzymes. Additionally, conditions such as vitamin B12 deficiency, Crohn's disease, and certain dietary factors can also contribute to elevated methylcitric acid levels.[716-719]

Microbial Overgrowth

The microbiome influences methylcitric acid levels through biotin synthesis, with specific bacteria such as *Bifidobacterium longum* shown to enhance biotin production. Other gut bacteria, such as *Lactobacillus* species, also contribute to biotin availability, affecting biotin-dependent enzymes and, consequently, methylcitric acid accumulation.[720,721]

Candida species, such as *Candida albicans*, are unable to synthesize biotin and rely on external sources for its acquisition, using specialized transporters to ensure survival and virulence.[722] Moreover, biotin availability can promote growth and proliferation.[723]

Additionally, excessive production of the short-chain fatty acid propionic acid by gut microbiota can contribute to increased propionyl-CoA levels, diverting its metabolism towards methylcitric acid accumulation.[177] This imbalance can result from dysbiosis or an overgrowth of specific bacteria that produce propionic acid during the breakdown of dietary components.[724]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Mitochondrial Health

Propionyl-CoA levels, produced by certain amino acids and fatty acids, are converted to succinyl–CoA to be utilized in the Citric Acid Cycle, and this conversion is influenced by biotin. A backup in this pathway can disrupt the function of pyruvate dehydrogenase and reduce the synthesis of key metabolic compounds like citrate and ATP.[725]

For more insight into mitochondrial health, reference the other **mitochondrial markers** (22)-(32) and **fatty acid oxidation markers** (45)-(49).

Nutritional Needs

Biotin (Vitamin B7) is a critical cofactor for propionyl-CoA carboxylase, and its deficiency leads to impaired metabolism of propionyl-CoA, causing an increase in methylcitric acid.[715]

Vitamin B12 deficiency impairs the enzyme methylmalonyl-CoA mutase, leading to the accumulation of methylmalonyl-CoA, which is converted into both **methylmalonic acid** (50) and

methylcitric acid. Elevated levels of both metabolites may serve as markers for vitamin B12 deficiency, as well.[726-728]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Biotinidase deficiency impairs biotin recycling, leading to secondary deficiencies in biotin-dependent enzymes such as propionyl-CoA carboxylase, which results in elevated levels of methylcitric acid.[729] Another condition, methylcitric acidemia, results from a deficiency in methylcitrate synthase, an enzyme involved in propionate metabolism.[725,730] Methylcitric acid is also associated with methylmalonic acidemia as well as isovaleric acidemia.[230]

Other metabolites associated with methylmalonic acidemia include **methylmalonic acid** (50), **3-Methyl-2-oxovaleric acid** (64). For isovaleric acidemia, associated metabolites include **Methylsuccinic acid** (46), **3-Hydroxy-3-methylglutaric acid** (55), **2-Hydroxyisovaleric acid** (62), and **3-Methyl-2-oxovaleric acid** (64).

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary Influences: Consuming raw egg whites can affect biotin levels because they contain avidin, a protein that binds to biotin and influences its bioavailability.[731]

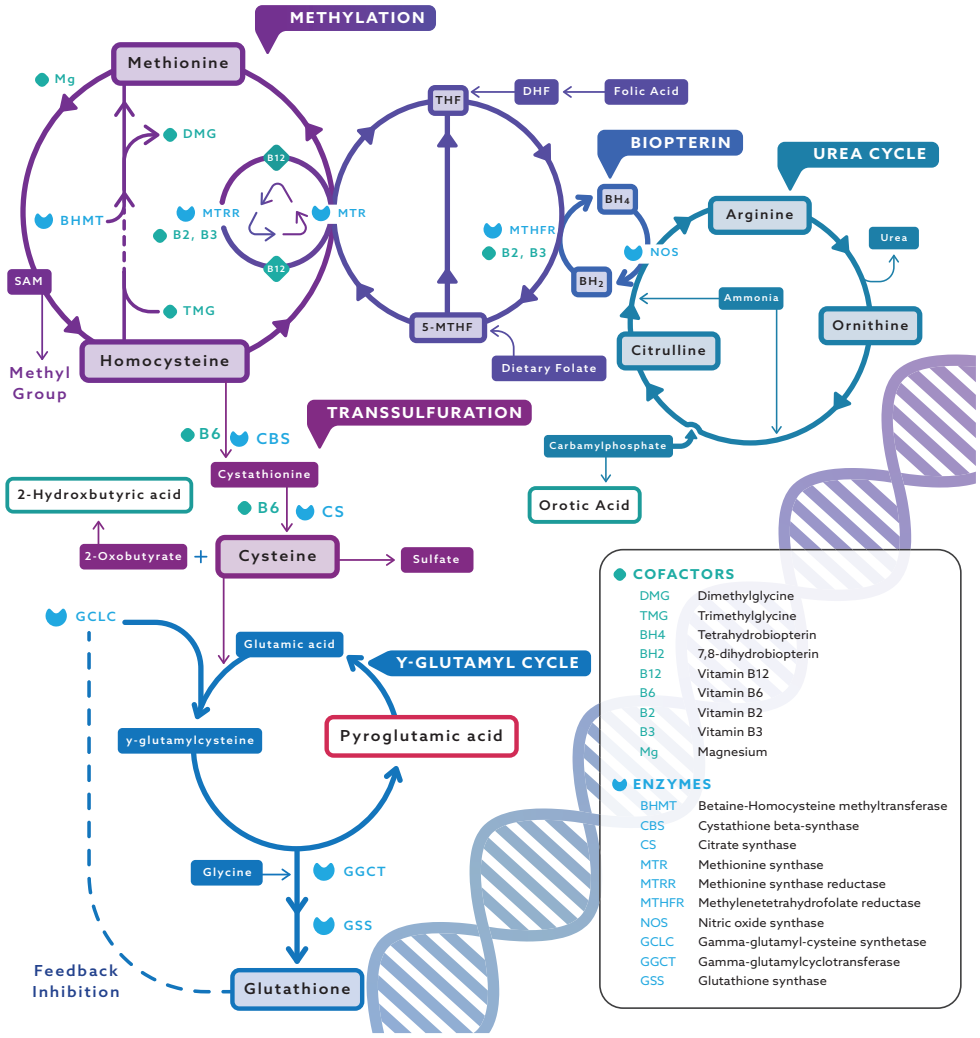
Methylcitric acid has also been detected in foods such as duck, chicken, swine, and cow's milk, suggesting it could serve as a potential biomarker for the consumption of these foods.[716]

Associated Conditions: In Crohn's disease, dysbiosis and the presence of adherent-invasive *Escherichia coli* (AIEC) bacteria lead to the degradation of propionate, resulting in increased methylcitric acid production. This accumulation is linked to the metabolic shifts and inflammation characteristic of the disease.[732,733]

Low Values There is no known clinical significance for low values.

INDICATORS OF DETOXIFICATION

Figure 6:



This figure explains the interconnections between the detoxification, methylation, biopterin, and urea cycles, displaying the collective role these pathways play in maintaining cellular health and supporting detoxification. Methylation is essential for DNA repair, neurotransmitter synthesis, and detoxification, relying on enzymes like MTHFR and BHMT to convert homocysteine into methionine, which produces S-Adenosyl Methionine (SAMe), a universal methyl donor. Biopterin, specifically tetrahydrobiopterin (BH4), is a critical cofactor in several enzymatic processes, including the synthesis of neurotransmitters and nitric oxide, and is influenced by MTHFR. The urea cycle also complements these processes by removing excess ammonia, a toxic byproduct of protein metabolism, through its conversion into urea for excretion. Detoxification pathways, particularly glutathione metabolism, are also critical, as described by elevated pyroglutamic acid levels, which may indicate impaired glutathione synthesis needed to neutralize free radicals and process toxins. Nutritional cofactors such as vitamins B6, B12, magnesium, and folate are essential for supporting methylation, detoxification, and the urea cycle. Disruptions in any of these pathways, whether due to genetic mutations, Microbial Overgrowths, or toxic exposures, can lead to oxidative stress, impaired cellular function, and toxin accumulation, emphasizing the interconnected nature of these biochemical processes.

58 Pyroglutamic acid (Glutathione)

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

Pyroglutamic acid (5-oxoproline) is formed from glutamate, glutamine, and gamma-glutamylated peptides through gamma-glutamylcyclotransferase and is involved in glutathione metabolism. When intracellular glutathione synthesis is impaired, pyroglutamic acid levels rise, prompting increased cystine uptake to support restoration and reduce its accumulation.[734-736] Factors such as Microbial Overgrowth, mitochondrial dysfunction, toxic exposures, methylation, and nutritional deficiencies (e.g., magnesium, vitamin B6, precursor amino acids) can elevate pyroglutamic acid levels by disrupting glutathione metabolism and related cycles.[735,737-745] Conversely, genetic mutations, severe nutritional deficiencies, and metabolic disorders may influence low levels, though this is mainly theoretical.[744,746,747]

Microbial Overgrowth

Some bacteria of the microbiome, including Bacteroidetes species and thermophilic lactic acid bacteria, can increase pyroglutamic acid levels by converting glutamine to pyroglutamate, potentially affecting its accumulation in the gastrointestinal system.[737,738]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Mitochondrial Health

Mitochondrial dysfunction related to ATP depletion disrupts the gamma-glutamyl cycle, impairing glutathione synthesis, leading to the accumulation of pyroglutamic acid. This dysfunction also affects glutamine metabolism, further contributing to increased pyroglutamic acid levels.[735,739]

For more insight into mitochondrial health, reference the other **mitochondrial markers** 22-32 and **fatty acid oxidation markers** 45-49.

Toxic Exposure

Various toxins and toxicants can influence pyroglutamic acid levels by disrupting glutathione metabolism, leading to oxidative stress, redox imbalances, and impaired glutathione recycling. These disturbances also affect amino acid and glutathione intermediates, further elevating pyroglutamic acid levels.[740,748] Metals, mycotoxins, and various toxicants like styrene, benzene, acrylonitrile, 1-bromopropane, 1,3 butadiene, ethylene oxide, vinyl chloride, and acrylamide can increase pyroglutamic acid levels by inducing oxidative stress and depleting glutathione. Specific mycotoxins, such as gliotoxin and roridin, either use or deplete glutathione, which impacts the formation of pyroglutamic acid.[741,749,750]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Methylation/Detoxification

Methylation processes, particularly those involving S-adenosylmethionine (SAMe) and

S-adenosylhomocysteine (SAH), influence amino acid metabolism and may elevate pyroglutamic acid levels by disrupting the regulation of key intermediates involved in the glutathione cycle, such as glutamate, **glycine**, and **cysteine**.[742]

Refer to the Nutrient–Marker Reference Table for insights into corresponding organic acids that are associated with **glycine** and **glutathione**. Additionally, reviewing **HVA/DOPAC ratio** (37) may give additional information with regard to SAMe, and **2-Hydroxybutyric acid** (59) for insights into homocysteine's conversion to **cysteine**.

Nutritional Needs

Deficiencies of **magnesium**, **vitamin B6**, **glycine**, **cysteine**, and **glutamine** can lead to increased pyroglutamic acid levels by disrupting the gamma-glutamyl cycle and glutathione synthesis. These nutrients are essential for ATP production, enzymatic reactions in amino acid metabolism, and the synthesis of glutathione, and their deficiencies can impair glutathione production, resulting in the accumulation of pyroglutamic acid.[735,743-745] Low antioxidant levels can increase pyroglutamic acid levels by activating a futile ATP-depleting cycle in the gamma-glutamyl pathway.[751]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Conditions such as nephropathic cystinosis, 5-oxoprolinase deficiency, glutathione synthetase deficiency (GSSD), urea cycle disorders, hawkinsinuria, and homocystinuria can elevate pyroglutamic acid levels by disrupting glutathione metabolic processes.[734,751]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary Influences: Low protein intake, especially of cysteine, glycine, and glutamine, can elevate pyroglutamic acid levels by disrupting the gamma-glutamyl cycle and impairing glutathione synthesis. Additionally, a vegetarian diet may increase pyroglutamic acid excretion due to differences in protein intake and nutrient synthesis compared to omnivorous diets.[735,752] Long-ripened cheeses like Grana Padano and Parmigiano Reggiano Thermophilic can cause elevations due to the lactic acid bacteria that are important in processing, cyclizing glutamine through the action of glutamine to pGlu cyclase.[738]

Medication/Supplement Interactions: Use of certain medications such as acetaminophen, vigabatrin, flucloxacillin, and more can lead to increased pyroglutamic acid levels by depleting key metabolites like glutathione and cysteine and disrupting metabolic cycles.[744,753,754] Theoretically, any medication or supplement that undergoes glutathione conjugation may stress glutathione levels and therefore influence pyroglutamic acid levels depending on dose, frequence, and other comorbidities.

Associated Conditions: Type 2 diabetes and Alzheimer's may contribute to elevated pyroglutamic acid through glutathione depletion or impaired synthesis.[746,755-761]

Additional benefits: Pyroglutamate supplementation may offer benefits such as improving glucose tolerance, cholesterol levels, and cognitive function, as well as providing anti-inflammatory and antidepressant-like effects. However, it may also disrupt glutathione homeostasis, potentially increasing risks.[762-766]

Low Values Low pyroglutamic acid levels and their clinical significance are largely theoretical, but may result from genetic mutations affecting enzymes in the gamma-glutamyl cycle, severe nutritional deficiencies (particularly in amino acid precursors), metabolic disorders that impact amino acid synthesis, or pharmacological interventions that disrupt glutathione metabolism, such as acetaminophen.[744,746,747] Some studies have observed low levels of pyroglutamic acid, along with decreased levels of essential amino acids in autism spectrum disorder (ASD).[767] Additional amino acid testing may give further insights, if this were the case.

59 2-Hydroxybutyric acid** (Methylation, Toxic Exposure)

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

2-Hydroxybutyric acid, a byproduct of metabolism during oxidative stress or detoxification, is produced from alpha-ketobutyrate, which forms during the catabolism of threonine and methionine or glutathione synthesis, reflecting shifts in glutathione production.[768] Changes in 2-hydroxybutyric acid levels can result from toxic exposures that induce oxidative stress and disrupt amino acid metabolism, impairing detoxification and promoting its accumulation.[769-771] Deficiencies in methylation nutrients (e.g., folate, B12, methionine, B6, B2, and B3) and factors such as low protein intake, ketosis, diabetes, alcohol abuse, and genetic disorders can all elevate 2-hydroxybutyric acid by disrupting amino acid catabolism and metabolism.[496,743,767,768,770-780]

Toxic Exposure

Oxidative stress, potentially from toxic exposures, increases 2-hydroxybutyric acid levels by disrupting amino acid metabolism through the conversion of methionine and threonine to 2-oxobutyric acid, which is reduced to 2-hydroxybutyric acid. Additionally, oxidative stress depletes glutathione, impairing detoxification pathways and contributing to the accumulation of 2-hydroxybutyric acid as a byproduct.[769-771]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Methylation/Detoxification

Impaired methylation, caused by deficiencies in methyl donors like **folate (B9)**, **B12**, and methionine or genetic mutations in methylation enzymes, disrupts the methionine cycle and increases levels of S-adenosylhomocysteine (SAH). Elevated SAH inhibits methylation

processes, leading to a buildup of homocysteine. Through the transsulfuration pathway, homocysteine is converted into cystathionine and then into alpha-ketobutyrate, which is reduced to 2-hydroxybutyric acid, thereby increasing its levels.[781-784]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with nutrients related to **methylation support** (**B2**, **B3**, **B6**, **B9**, **B12**, and **magnesium**). A serum homocysteine test may also provide additional insight.

Nutritional Needs

Deficiencies in **folate**, **B12**, or **methionine** can elevate 2-hydroxybutyric acid levels by increasing homocysteine. **B6**, **B2**, and **B3** deficiencies, along with low **cysteine** and **taurine**, can further disrupt amino acid metabolism and redox balance, leading to the accumulation of 2-hydroxybutyric acid through impaired transsulfuration and enzyme regulation.[496,743,767,770-773]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Several genetic disorders such as 3-hydroxyisobutyryl-CoA hydrolase deficiency (HIBCHD), primary hyperoxaluria type 2, and a genetic variant in the cystathionine beta-synthase (CBS) enzyme among others involving metabolic disruptions leading to the accumulation of 2-hydroxybutyric acid.[778-780]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary Influences: Low protein intake can increase 2-hydroxybutyric acid levels by promoting the catabolism of amino acids like methionine and threonine, inducing a metabolic shift towards ketogenesis, and impairing the breakdown of branched-chain amino acids, which leads to their conversion into 2-hydroxybutyric.[774,775]

Associated Conditions: In ketosis, diabetes, and alcohol abuse, elevated fatty acid oxidation increases ketone bodies and raises the NADH/NAD ratio, promoting the conversion of 2-oxobutyric acid to 2-hydroxybutyric acid. This shift occurs in response to insulin deficiency, chronic alcohol consumption, and metabolic states like diabetic ketoacidosis and alcoholic ketoacidosis.[768,776,777]

Review **3-hydroxybutyric acid** (43) and **Acetoacetic acid** (44) for insights into ketones.

Low Values

Toxic Exposure: Phthalate exposure can decrease 2-hydroxybutyric acid levels by disrupting metabolic pathways related to oxidative stress and fatty acid oxidation.[785] **Quinolinic acid** (39) can also be influenced by Phthalates. Look to **Markers** (44)-(49) for more insights into fatty acid oxidation disruptions. Refer to the Toxin Exposure Tables for additional insights into

corresponding metabolites and patterns.

Dietary: High **cysteine** intake can decrease 2-hydroxybutyric acid levels by inhibiting some enzymatic activity and the ability to produce metabolites like 2-oxobutanoate, a precursor of 2-hydroxybutyric acid. Disruptions in the transsulfuration pathway can lead to increased 2-hydroxybutyric acid levels due to the accumulation of metabolic intermediates like 2-oxobutyric acid.[786]

(60) Orotic acid (Ammonia Excess)

Orotic acid is a key intermediate in pyrimidine nucleotide synthesis, formed in the body from carbamoyl phosphate and aspartic.[787] Elevated levels can indicate urea cycle dysfunction, where excess carbamoyl phosphate is diverted into orotic acid synthesis.[784,788,789] Imbalances in the gut microbiome, particularly overgrowth of *E. coli* or *Candida*, may raise orotic acid levels, while low arginine, B12, B2, magnesium, or zinc can impair enzymes needed to process orotic acid.[790-795] Disruptions in methylation pathways and BH4 deficiency can also lead to elevated levels.[792,796-798] Liver dysfunction, high-protein diets, and certain medications or supplements (e.g., diuretics, lithium/magnesium orotate) can further contribute to orotic acid accumulation.[784,788,789,791,799-801] Orotic acid elevations have been linked to hyperammonemia, oxidative stress, and impaired nitric oxide signaling.[784,788,789,792,796,797,802]

Microbial Overgrowth

Disruptions in the microbiome may increase orotic acid levels through bacteria like *Escherichia coli*, which produce orotic acid via the pyrimidine biosynthesis pathway, converting carbamoyl phosphate and aspartate into orotate and then orotic acid. Additionally, some Candida albicans strains can generate orotic acid.[790,791]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Neurotransmitter Metabolites

Elevated orotic acid can result from tetrahydrobiopterin (BH4) deficiency, particularly in dihydropteridine reductase (DHPR) deficiency, which impairs BH4 recycling.[798] This disruption affects the urea cycle, leading to secondary hyperammonemia and increased orotic acid levels.[03] Since BH4 is crucial for neurotransmitter synthesis, its deficiency can also impact dopamine, serotonin, and nitric oxide production.[804]

Evaluate **HVA** (33), **VMA** (34), **5HIAA** (38) to gain further insights into insufficient biopterin pathways. **2-Hydroxyphenylacetic acid** (11), **Mandelic acid** (68), **Phenylactic acid** (69), and **Phenylpyruvic acid** (70) may also be influenced.

Methylation/Detoxification

Methylation impairments can elevate orotic acid levels by disrupting the one-carbon

metabolism pathway, which affects the availability of S-adenosylmethionine (SAMe), a key methyl donor. Deficiencies in methylation cofactors, or genetic variations in the MTHFR enzyme, can reduce SAMe levels, impair methylation, and may lead to the accumulation of intermediates like orotic acid.[792,796,797]

For more insight into methylation, refer to the **Uracil** (41), **2-hydroxybutyric** (59), as well as **HVA/DOPAC ratio** (37) may give additional information with regards to SAMe. Additionally, refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with nutrients related to **methylation support** (**B2**, **B3**, **B6**, **B9**, **B12**, and **magnesium**).

Nutritional Needs

Ornithine deficiency and low **arginine** intake can both lead to the accumulation of carbamoyl phosphate, which is shunted into the pyrimidine biosynthesis pathway, resulting in increased orotic acid production and excretion. Low **vitamin B12** causes high orotic acid levels by impairing the conversion of orotic acid to uridine monophosphate (UMP) due to reduced activity of key enzymes in pyrimidine metabolism. Deficiencies in vitamins and minerals such as **magnesium**, **B2 (riboflavin)**, and **zinc** can impair key enzymes in the pyrimidine biosynthesis pathway, leading to the accumulation of intermediates like orotic acid.[791-795]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Rare conditions, such as urea cycle defects (e.g., OTC deficiency, citrullinemia, and argininemia), Hyperornithinemia-Hyperammonemia-Homocitrullinuria (HHH) Syndrome, hereditary orotic aciduria, and megaloblastic anemia from pyrimidine synthesis defects, can result in elevated orotic acid levels due to impaired urea cycle function or defective enzymes in the pyrimidine biosynthesis pathway.[805-807]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary Influences: Orotic acid levels may be influenced by some dietary factors, such as cow's milk and dairy products or a high-protein diet.[799,800]

Medication/Supplement Interactions: Some medications, such as diuretics like thiazides, some chemotherapy agents, and allopurinol, may increase orotic acid levels by either inhibiting enzymes in the pyrimidine biosynthetic pathway or disrupting the urea cycle, leading to the accumulation of intermediates.[791,801] Because lithium or magnesium orotate is made up of a mineral salt and orotic acid, their intake may lead to increased levels of orotic acid being eliminated.

Associated Conditions: Conditions like liver cirrhosis, liver failure, chronic liver disease, gastrointestinal bleeding, and systemic portal shunting increase orotic acid levels due to

hyperammonemia, which overwhelms the urea cycle and causes excess carbamoyl phosphate to enter the pyrimidine biosynthesis pathway.[784,788,789] This leads to elevated orotic acid production and may contribute to hypertension and insulin resistance by impairing endothelial nitric oxide synthesis and disrupting insulin-stimulated NO production.[802]

Low Values: Low protein intake can result in reduced urinary orotic acid levels due to the decreased availability of nitrogen required for carbamoyl phosphate synthesis, a precursor in the pyrimidine biosynthesis pathway.[800,808]

(61) 2-Hydroxyhippuric acid (61) (Aspartame, Salicylates, or GI Bacteria)

2-hydroxyhippuric acid is a compound formed in the body to eliminate excess salicylates by conjugating with glycine after salicylic acid undergoes hydrolysis and further metabolism, and has no anti-inflammatory effects. Salicylates, including salicylic acid and its derivatives like aspirin, are commonly used in medicine as antipyretics, analgesics, and anti-inflammatory agents, but they also occur naturally in foods and can cause hypersensitivity reactions in some.[809-811] Elevated 2-hydroxyhippuric acid levels can result from dysbiosis or certain medications and dietary factors, including foods high in salicylates and aspartame intake, topical treatments that contain salicylic acid, environmental pollutants, and medications such as aspirin may potentially alter metabolic pathways.[61,805,812-824]

Microbial Overgrowth

The microbiome increases 2-hydroxyhippuric acid levels by metabolizing dietary phenolic compounds and aromatic amino acids, such as phenylalanine, into intermediates like phenylpropionic acid and benzoic acid. Specific gut bacteria, including *Pseudomonas*, *Bacillus*, *Azospirillum*, *Salmonella*, *Achromobacter*, *Vibrio*, *Yersinia*, and *Mycobacteria*, play a crucial role in this process by reducing phenylalanine to phenylpropionic acid, which is further metabolized in the liver to form 2-hydroxyhippuric.[812-814] Clostridia overgrowth can lead to elevated 2-hydroxyhippuric acid levels by metabolizing dietary aromatic compounds into benzoate, which is then conjugated with glycine to form hippurate and its derivatives.[61]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Neurotransmitter Metabolites

While there is no direct evidence that 2-hydroxyhippuric acid inhibits dopamine beta-hydroxylase (DBH) activity, its structural similarity to other known DBH inhibitors, such as 4-hydroxypyrazole, suggests it could potentially act through mechanisms like competitive inhibition or interference with the enzyme's electron donors.[123,825]

For more insight into neurotransmitter activity, reference the **phenylalanine and tyrosine metabolites** (33)-(37).

Toxic Exposures

Environmental toxicants, such as organic solvents and pollutants, can elevate 2-hydroxyhippuric acid levels by altering metabolic pathways. Exposure to toxicants may lead to increased levels of 2-hydroxyhippuric acid due to changes in renal metabolism and the uptake of these compounds by the kidneys. This process can contribute to oxidative stress and kidney injury.[823,824]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Additional Insights

Dietary Influences: Foods high in salicylates include various fruits such as blueberries, oranges, tangerines, tomatoes, and lemons, and beverages like tea and wine.[816-819] Aspartame intake can increase 2-hydroxyhippuric acid levels by influencing metabolic pathways through its byproducts, methanol and formaldehyde, which may alter aromatic compound metabolism and contribute to oxidative stress.[820-822] Glycine enhances the production and excretion of 2-hydroxyhippuric acid by conjugating with aromatic acids like benzoic acid, with higher glycine intake increasing this process.[826,827]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

Medication/ Supplement Interactions: Aspirin increases 2-hydroxyhippuric acid levels through its metabolism, where salicylic acid is hydroxylated by cytochrome P450 enzymes to form dihydroxybenzoic acids, which are then conjugated with glycine to produce 2-hydroxyhippuric acid. The use of salicylic acid, such as in skincare products, may also increase 2-hydroxyhippuric acid levels.[805,815] High salicylate herb concentrations, including basil, cumin, oregano, and clove, may cause elevations.[810, 817]

Low Values There is no known clinical significance for low values.

AMINO ACID METABOLITES

(62) 2-Hydroxyisovaleric acid

2-Hydroxyisovaleric acid (2-HIVA) is a catabolite of the branched-chain amino acid (BCAA) **valine**. It is formed from α-ketoisovalerate (also known as **2-oxoisovalerate** (63)) via 2-hydroxyisovalerate dehydrogenase, a component of the branched-chain alpha-ketoacid dehydrogenase (BCKDH) complex on the mitochondrial inner membrane.[828-830] Elevated levels can provide insights into mitochondrial health, nutritional needs such as Vitamin B1 (Thiamin), and potential genetic predispositions.[828,831,832] 2-HIVA has been associated with conditions such as lactic acidosis and alcoholic or diabetic ketoacidosis, and with extreme elevations, which can give insights into metabolic disorders such as maple syrup urine disease (MSUD), and other inborn errors of metabolism.[230,832-834]

Mitochondrial Health

2-HIVA is a product of ketogenesis and BCAA metabolism, which are crucial for mitochondrial energy production. 2-hydroxyisovaleric acid is metabolized into acetyl-CoA and acetoacetate via the BCKDH complex, which can enter both the ketogenic pathway and the citric acid cycle for energy production.[828-830,835]

For additional insights, evaluate the **mitochondrial markers** (22)-(32), **fatty acid oxidation section** (45)-(49), and the other **amino acid metabolites** (63)-(66) influenced by BCKDH complex.

Nutritional Needs

The diphosphate form of **thiamine** (known as TPP) serves as a major cofactor for BCKDH, which catalyzes the oxidation of BCAA valine, as well as the other BCAA isoleucine and leucine, to form the respective thioesters with acetyl CoA.[831] Additional nutrients also influential for BCKDH include **Vitamin B2** (riboflavin), **Vitamin B3** (Niacin), **Vitamin B5** (pantothenic acid), **alpha-lipoic acid**, and **magnesium**.[836]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Elevated 2-HIVA is associated with several genetic metabolic disorders, primarily involving defects in branched-chain amino acid metabolism from enzyme deficiencies or impairment. These include maple syrup urine disease (MSUD), phenylketonuria (PKU), methylmalonic acidemia, propionic acidemia, isovaleric acidemia, and multiple carboxylase deficiency, among others.[832]

Corresponding markers to the aforementioned genetic diseases include; **Hippuric acid (10)**, **2-Oxoisovaleric acid** (63), **3-Methyl-2-oxovaleric acid** (64), **2-Hydroxyisocaproic acid** (65), or **2-Oxoisocaproic acid** (66) for MSUD, **Hippuric acid** (10), **2-Hydroxyphenylacetic acid** (11), **3-Indoleacetic acid** (18), **2-hydorxyisovaleric acid** (62), **Mandelic acid** (68), **Phenylactic acid** (69), or **Phenylpyruvic acid** (70) for PKU, **Methylmalonic acid** (50), **Pyroglutamic acid** (58), **2-Hydroxybutryic acid** (59), and **3-Methyl-2-oxovaleric acid** (64) for propionic acidemia.

Additionally, 2-HIVA elevations have been noted in genetic disorders affecting mitochondrial function, such as glutaric aciduria and ornithine transcarbamylase deficiency.[832]

Glutaric acidemia is associated with **3-hydroxyglutaric acid** (31), **Ethylmalonic acid** (45), **Methylsuccinic acid** (46), **Adipic acid** (47), **Suberic acid** (48), **Sebacic acid** (49), and **Glutaric acid** (53)

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary influence: Consumption of BCAA supplementation containing valine may increase this metabolite, particularly if there is a dysfunction in the enzyme complex.[837-840]

Medication/Supplement Influences: Certain drugs, such as antivirals and valproic acid, can potentially elevate 2-oxoisovaleric acids, and ultimately 2-hydroxyisovaleric acid, due to their impact on mitochondrial function or the blocking of certain enzymes associated with BCAA pathways.[230,841] Medications that can cause thiamin depletion, such as loop diuretics, chemotherapy agents, and certain antibiotics, may impair BCAA metabolism.[227,666,842] BCAA supplementation may also cause elevations.[838]

Associated Conditions: Extreme exercise increases flux through the BCKDH pathway; however, if cofactors are insufficient, it can lead to a buildup of **2-oxoisovaleric (63)** and/or 2-hydroxyisovaleric acids.[843] Elevated levels have also been observed in individuals with severe neonatal asphyxia, lactic acidosis, and diabetic or alcoholic ketoacidosis.[230,833,834,844]

Low Values There is no known clinical significance for low values.

(63) 2-Oxoisovaleric acid

2-Oxoisovaleric acid (also known as alpha-ketoisovaleric acid) is a metabolite of the branched-chain amino acid **valine**.[838] The enzyme branched-chain aminotransferase (BCAT) catalyzes the transfer of the amino group from valine to alpha-ketoglutarate, producing the branched-chain keto acid 2-oxoisovaleric acid, ultimately to be used for energy production.[828,845] Impaired metabolism causing elevations can often be due to deficiencies in key cofactors such as Vitamin B1 (Thiamine) or enzymatic dysfunction, leading to metabolic imbalances, energy deficits, and increased risk for disorders such as insulin resistance.[842,846] This metabolite provides insight into mitochondrial function, nutritional status, and potential genetic predispositions.[847-849]

Mitochondrial Health

Once 2-oxoisovaleric acid is formed, it undergoes oxidative decarboxylation by the branched chain alpha ketoacid dehydrogenase (BCKDH) complex in the mitochondrial matrix, yielding isobutyryl-CoA, which then enters further catabolic pathways leading to the production of succinyl-CoA, a citric acid cycle intermediate.[830,845,848,850] If unable to support this pathway, it may lead to decreased activity of respiratory chain complexes, reduced ATP synthesis, and increased oxidative stress.[847,851]

For additional insights, evaluate the **mitochondrial markers (22)-(32)**, **fatty acid oxidation section (45)-(49)**, and the other **amino acid metabolites (62)-(66)** influenced by BCKDH complex.

Nutritional Needs

Several key nutrients are required for the optimal function of the BCKDH complex, particularly in the subunits E1, E2, and E3. **Vitamin B1 (Thiamine)** is essential for the E1 subunit, **Vitamin B2 (Riboflavin)** is required for the FAD-dependent E3 component, and **Vitamin B3 (Niacin)** is necessary for NAD+ synthesis, which is also a cofactor for E3. **Pantothenic acid (vitamin B5)** is

the precursor for coenzyme A, required for the E2 component. **Alpha-lipoic acid** is a coenzyme for the E2 component, and **magnesium** is necessary for the proper function of thiamine pyrophosphate-dependent enzymes.[666,842,846,848,852]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Genetic mutations affecting the BCKDH complex can lead to metabolic disorders such as MSUD, where BCAA and keto acid accumulation resulting in neurotoxicity, metabolic acidosis, and severe developmental impairments.[230,849]

Additional markers associated with MSUD include **Hippuric acid** (10), **3-Methyl-2-oxovaleric acid** (64), **2-Hydroxyisocaproic acid** (65), and **2-Oxoisocaproic acid** (66).

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary influence: Excessive dietary intake of BCAAs can potentially overwhelm BCKA metabolism, especially if the necessary micronutrients that support the BCKDH enzyme complex are lacking.[837-840]

Medication/Supplement Influences: Certain drugs, such as antivirals and valproic acid, can potentially elevate **2-oxoisocaporic acid** (66) and 2-oxoisovaleric acids due to their impact on mitochondrial function.[841] Medications that can cause thiamin depletion, such as loop diuretics, chemotherapy agents, and certain antibiotics, may impair BCAA metabolism.[227,666,842] BCAA supplementation may also cause elevations.[838]

Associated Conditions: Elevated levels have been linked to insulin resistance and type 2 diabetes, potentially due to impaired BCKDH function.[852] While exercise enhances BCAA breakdown, if there are insufficiencies in enzyme cofactors or increased inhibitory products such as NADH and acyl-CoA esters, it can lead to a buildup of 2-oxoisovaleric acid, especially if the exercise is excessive.[843,852] Liver cirrhosis, chronic kidney disease, and hyperthyroidism can disrupt BCAA metabolism, contributing to accumulation.[52] Malabsorption disorders, inflammatory bowel disease, or gut dysbiosis may impact the metabolism of BCAA, contributing to elevated levels.[853]

Low Values There is no known clinical significance for low values.

(64) 3-Methyl-2-oxovaleric acid

3-Methyl-2-oxovaleric acid (also known as α-keto-β-Methylvaleric acid-KMV) is a branched-chain keto acid (BCKA) derived from **isoleucine** metabolism.[828] Elevations can reflect impaired mitochondrial function, with disruptions in the citric acid cycle and therefore reduced ATP production.[854] Inadequate activity of the branched chain alpha ketoacid dehydrogenase (BCKDH) enzyme complex, often due to nutrient deficiencies such as Vitamin B1 (thiamine), can contribute to these elevations.[227,846] Additional factors to consider for elevations include excessive BCAA intake, certain medications that impair mitochondrial or BCAA metabolism, or, in atypical instances, genetic disorders such as Maple Syrup Urine Disease (MSUD).[227,230,839]

Mitochondrial Health

3-methyl-2-oxovaleric acid (KMV), from isoleucine, can further metabolize to form acetyl CoA and Succinyl CoA, and can be both glycogenic and ketogenic.[855,856] It modulates mitochondrial respiration by competitively inhibiting the alpha-ketoglutarate dehydrogenase complex (KGDHC), impairing the citric acid cycle, and reducing ATP production.[854] Accumulation of KMV and related BCKAs further disrupts mitochondrial energy homeostasis, promotes oxidative stress, and can alter calcium signaling, contributing to neurometabolic dysfunction.[855,857]

For additional insights, evaluate the **mitochondrial markers** (22)-(32), **fatty acid oxidation section** (45)-(49), and the other **amino acid metabolites** (62)-(66) influenced by BCKDH complex

Nutritional Needs

Several key nutrients are required for the optimal function of the branched-chain alpha-ketoacid dehydrogenase (BCKDH) complex, particularly in the subunits E1, E2, and E3. **Vitamin B1 (Thiamine)** is essential for the E1 subunit, **Vitamin B2 (Riboflavin)** is required for the FAD-dependent E3 component, and **Vitamin B3 (Niacin)** is necessary for NAD+ synthesis, which is also a cofactor for E3. **Pantothenic acid (vitamin B5)** is the precursor for coenzyme A, required for the E2 component. **Alpha-lipoic acid** is a coenzyme for the E2 component, and **magnesium** is necessary for the proper function of thiamine pyrophosphate-dependent enzymes.[666,842,846,848,852]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Severe elevations of 3-methyl-2-oxovaleric acid are typically associated with **Maple Syrup Urine Disease (MSUD)**, which can present in infancy or later in life during periods of metabolic stress.[87] Other genetic diseases, including **methylmalonic acidemia (MMA)**, **propionic acidemia (PA)**, and **isovaleric acidemia (IVA)**, have been associated with elevations.[230]

Other associated metabolites with MSUD include, **Hippuric acid** (10), **2-Hydroxyisovaleric acid** (62), **2-Oxoisovaleric acid** (63), **2-Hydroxyisocaproic acid** (65), or **2-Oxoisocaproic acid** (66).

MMA can be also associated with **Methylmalonic acid** (50) and **Methylcitric acid** (57) metabolites. **Methylmalonic acid** (50), **Pyroglutamic acid** (58), **2-Hydroxybutryic acid** (59), and **2-Hydroxyisovaleric acid** (62) are associated with propionic acidemia, and **Methylsuccinic acid** (46), **3-Hydroxy-3-methylglutaric acid** (55), **Methylcitric acid** (57), and **2-Hydroxyisovaleric acid** (62), are associated with isovaleric acidemia.

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary influence: Excessive dietary intake of BCAAs can potentially overwhelm BCKA metabolism, especially if the necessary micronutrients that support the BCKDH enzyme complex are lacking.[837-840]

Medication/Supplement Influences: Certain drugs, such as antivirals and valproic acid, can potentially elevate BCKAs due to their impact on mitochondrial function.[841] Medications that can cause thiamin depletion, such as loop diuretics, chemotherapy agents, and certain antibiotics, may impair BCAA metabolism.[227,666,842] BCAA supplementation may also cause elevations.[838]

Associated conditions: Elevated levels have been linked to insulin resistance and type 2 diabetes, potentially due to impaired BCKDH function.[852] While exercise enhances BCAA breakdown, if there are insufficiencies in enzyme cofactors or increased inhibitory products such as NADH and acyl-CoA esters, it may lead to a buildup of BCKA, especially if the exercise is excessive.[843,852] Liver cirrhosis, chronic kidney disease, and hyperthyroidism can disrupt BCAA metabolism, contributing to accumulation.[852] Malabsorption disorders, inflammatory bowel disease, or gut dysbiosis may impact the metabolism of BCAA, contributing to elevated levels.[853] Additionally, elevations in BCAA metabolites have been associated with cardiometabolic risks, though varying in age and disease state.[858]

Low Values There is no known clinical significance for low values.

(65) 2- Hydroxyisocaproic acid

2-Hydroxyisocaproic acid (HICA) is a downstream metabolite of the branched-chain amino acid **leucine**, formed when leucine is first transaminated by branched-chain aminotransferase (BCAT) into alpha-ketoisocaproic acid (KIC), which is then reduced by cytosolic alpha-ketoisocaproate reductase (KICD).[828-830] Elevations in HICA can arise from both endogenous metabolic shifts and microbial activity. Mitochondrial dysfunction or nutrient deficiencies affecting the BCKDH complex (e.g. thiamine, riboflavin, niacin, B5, B6, magnesium) can impair the normal conversion of leucine-derived KIC to isovaleryl-CoA, instead favoring its reduction to HICA. Additionally, certain microbial species (fungi, lactic acid bacteria, and *Clostridium*) can produce HICA, and high intake of fermented foods or probiotics may further contribute. Genetic conditions such as MSUD or dihydrolipoyl dehydrogenase (E3) deficiency can also elevate HICA, though they are less likely.

Microbial Overgrowth

2-Hydroxyisocaproic acid has been identified as a microbial metabolite produced by certain fungi, lactic acid bacteria, and *Clostridium* species, and also possesses antimicrobial properties.[859,860]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Mitochondrial Health

Leucine is transaminated by BCAT to form KIC, which can either convert to isovaleryl-CoA via BCKDH complex or to HICA via KICD; dysfunction of branched-chain alpha ketoacid dehydrogenase (BCKDH) complex could theoretically shift excess KIC toward HICA production, with excess KIC potentially inhibiting alpha-ketoglutarate dehydrogenase, reducing mitochondrial membrane potential, and increasing reactive oxygen species.[835,854,861,862] Moreover, if Isovaleryl-CoA was less available, it could influence yields of acetyl-CoA and **acetoacetate** (44) for energy synthesis.[830,852,863]

For additional insights, evaluate the **mitochondrial markers** (22)-(32), **fatty acid oxidation section** (45)-(49), and the other **amino acid metabolites** (62)-(66) influenced by BCKDH complex.

Nutritional Needs

The main enzymes involved in leucine to get to HICA are branched-chain aminotransferase (BCAT) and cystosolic alpha-ketoisocaproate reductase (KICD). BCAT requires pyridoxal 5′-phosphate (PLP), which is associated with **Vitamin B6**, and KICD requires NADH or NADPH, which is associated with **Vitamin B3**.[829,864-867]

Moreover, the diphosphate form of **thiamine** (known as TPP), serves as a major cofactor for BCKDH, which catalyzes the oxidation of KIC to isovaleryl-CoA.[831] Additional nutrients also influential for BCKDH include **Vitamin B2** (riboflavin), **Vitamin B3** (Niacin), **Vitamin B5**

(pantothenic acid), **alpha-lipoic acid**, and **magnesium**.[122]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

HICA has been associated with MSUD.[230,849]

Additional markers associated with MSUD include **Hippuric acid** (10), **3-Methyl-2-oxovaleric acid** (64), **2-Hydroxyisocaproic acid** (65), and **2-Oxoisocaproic acid** (66).

HICA has also been found to be elevated in individuals with dihydrolipoyl dehydrogenase (E3) deficiency.[868]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary influence: High intake of **fermented foods**, which serve as dietary sources of certain bacteria that may produce this metabolite.[859,860]

Medication/Supplement Influences: Probiotics that contain lactic acid bacteria, may influence elevations.[859,860]

Associated Conditions: HICA has been observed in individuals with **short bowel syndrome**.[869]

Low Values There is no known clinical significance for low values.

(66) 2-Oxoisoaproic acid

2-Oxoisocaproic acid (also known as alpha ketoisocaporic acid (KIC)) is the transamination product of leucine and is a key intermediate in branched-chain amino acid (BCAA) catabolism. Elevated levels suggest dysfunction in this pathway—whether due to nutrient deficiencies (e.g., thiamin, riboflavin, niacin, B6, magnesium), metabolic stress, or in rare instances, genetic conditions such as Maple Syrup Urine Disease (MSUD). Excess KIC can impair mitochondrial oxidative phosphorylation and lead to reduced energy production and neurological or metabolic disturbances. Contributing factors may also include high-protein or leucine-rich diets, BCAA supplementation, certain medications (e.g., valproic acid, chemotherapy), or underlying conditions such as insulin resistance, liver or kidney dysfunction, or gut dysbiosis.[870]

Mitochondrial Health

2-oxoisocaproic acid is primarily metabolized in the mitochondria by the branched-chain α-keto acid dehydrogenase complex (BCKDC) to produce isovaleryl-CoA, ultimately contributing to acetyl-CoA, acetoacetate, and energy production via the TCA cycle and

ketogenesis.[132,133,134] At physiological concentrations, it can modulate mitochondrial respiration, but at pathophysiological levels (such as in maple syrup urine disease (MSUD)), KIC inhibits mitochondrial oxidative phosphorylation, particularly by inhibiting α-ketoglutarate dehydrogenase, leading to impaired TCA cycle flux, reduced NAD(P)H, and decreased mitochondrial membrane potential.[854,861,862]

For additional insights, evaluate the **mitochondrial markers** (22)-(32), **fatty acid oxidation section** (45)-(49), and the other **amino acid metabolites** (62)-(66) influenced by BCKDH complex.

Nutritional Needs

Several nutrients and cofactors impact these pathways. Vitamin B6 is required for the initial transamination step, while BCKDC activity depends on **thiamine** (vitamin B1), **Vitamin B2** (riboflavin), **Vitamin B3** (Niacin), **Vitamin B5** (pantothenic acid), **alpha-lipoic acid**, and **magnesium**.[829]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Marked elevations in 2-oxoisocaproic and related BCAA metabolites can signal inborn errors of metabolism, especially Maple Syrup Urine Disease (MSUD). MSUD is caused by a deficiency in the BCKDH complex and can range in severity from classic infantile onset to milder intermittent forms230. This condition results in a toxic accumulation of BCAAs and their corresponding ketoacids in the brain and blood, leading to symptoms like seizures, ataxia, encephalopathy, behavioral changes, and metabolic crises.[230]

Additional markers associated with MSUD include **Hippuric acid** (10), **3-Methyl-2-oxovaleric acid** (64), **2-Hydroxyisocaproic acid** (65), and **2-Oxoisocaproic acid** (66).

In other rare cases, **isovaleric acidemia (IVA)**, a branched-chain organic aciduria caused by deficiency of isovaleryl-CoA dehydrogenase.[230]

Methylsuccinic acid (46), **3-Hydroxy-3-methylglutaric acid** (55), **Methylcitric acid** (57), and **2-Hydroxyisovaleric acid** (62) are also associated with isovaleric acidemia.

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary influence: High-protein diets, especially if predominating with leucine-rich foods, can overload the system and lead to elevations, especially in individuals with impaired BCAA processing capacity.[837-840]

Medication/ Supplement Influences: Certain drugs, such as antivirals and valproic acid, can potentially elevate 2-oxoisocaporic acid and **2-oxoisovaleric acid** (63) due to their impact on mitochondrial function.[841] Medications that can cause thiamin depletion, such as loop diuretics,

chemotherapy agents, and certain antibiotics, may impair BCAA metabolism.[227,666,842] BCAA supplementation may also cause elevations.[838]

Associated Conditions: Elevated levels have been linked to insulin resistance and type 2 diabetes, potentially due to impaired BCKDH function.[852] While exercise enhances BCAA breakdown, if there are insufficiencies in enzyme cofactors or increased inhibitory products such as NADH and acyl-CoA esters, it may lead to a buildup of BCKA, especially if the exercise is excessive.[843,852] Liver cirrhosis, chronic kidney disease, and hyperthyroidism can disrupt BCAA metabolism, contributing to accumulation.[852] Malabsorption disorders, inflammatory bowel disease, or gut dysbiosis may impact the metabolism of BCAA, contributing to elevated levels.[853]

Low Values There is no known clinical significance for low values.

(67) 2-Oxo-4-methiolbutyric acid

2-oxo-4-methylthiobutyric acid (also known as 4-methylthio-2-oxobutyric acid or MTOB), an intermediate in **methionine** metabolism, suggests a disruption in the transamination pathway and may lead to the accumulation of toxic byproducts such as 3-methylthiobutyrate, methanethiol, and hydrogen sulfide.[156] This metabolite may accumulate due to excessive methionine intake, vitamin B6 deficiency, or genetic defects in sulfur amino acid metabolism. If not properly metabolized, KMBA can give rise to toxic byproducts that impact cellular health, liver function, and energy regulation.[872]

Its elevation is often seen in the context of hypermethioninemia or inherited genetic disorders.

Methylation/Detoxification

MTBO is a key intermediate in the methionine salvage pathway, which maintains methionine and S-adenosylmethionine pools necessary for cellular methylation reactions.[873,874] If elevated, it could give insights into methylation and SAM homeostasis.[873]

For additional markers influencing methylation and SAM, look to **HVA/DOPAC ratio** (37) and **2-Hydroxybutryic acid** (58).

Nutritional Needs

Vitamin B6 (pyridoxal phosphate) is a key cofactor required for directing methionine metabolism through the transsulfuration pathway.[875] A deficiency can shift methionine metabolism toward the transamination route, increasing KMBA production.[875]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

Genetics

Various different genetic SNPs involved in methionine recycling or clearance could potentially influence elevations, and include S-adenosylhomocysteine (SAH) hydrolase, Methionine adenosyltransferase (MAT), Methylenetetrahydrofolate reductase (MTHFR), Glycine N-methyltransferase (GNMT), Cystathionine beta-synthase (CBS).[876]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary influence: While a high-protein or methionine-rich diet may contribute to elevated MTBO, dietary intake alone is generally not the primary driver unless paired with other metabolic impairments.[875]

Medication/Supplement Influences: Methionine supplements in theory could potentially elevate KMBA, though it is not usually the primary influence.[875]

Associated Conditions: Elevations have been shown in hypermethioninemia, which is linked to changes in liver function, hemolytic anemia, and glucose regulation.[872,877]

Low Values There is no known clinical significance for low values.

(68) Mandelic acid

Mandelic acid is a primary metabolite of phenylethylamine, which is formed from phenylalanine in an alterative pathway to **phenylacetic acid** (69). Elevated mandelic acid is most commonly associated with toxic exposure to styrene or ethylbenzene, which are metabolized in the body and excreted as mandelic acid. These compounds are found in tobacco smoke, vehicle exhaust, synthetic rubber, plastics, resins, and food containers, especially when heated, making environmental exposure a primary concern. As a secondary mechanism, mandelic acid may also result from altered phenylalanine metabolism, where phenylalanine is diverted to phenylethylamine and subsequently to mandelic acid, particularly when dopamine metabolism is impaired. This diversion may be slightly influenced by deficiencies in iron or vitamin B2, which are cofactors for phenylalanine hydroxylase; however, genetic factors such as PKU, although rare, can also elevate mandelic acid when phenylalanine processing is disrupted.

Neurotransmitter Metabolites

When phenylalanine is unable to convert to tyrosine via phenylalanine hydroxylase (PAH) to generate dopamine, norepinephrine, and epinephrine, it goes an alternate path to ultimately generate mandelic acid.[875,879]

Additionally, neurotoxic aromatic hydrocarbons from styrene exposure (see below) can impair dopamine metabolism.[880]

For a more in-depth evaluation into dopamine metabolites, assess the **Phenylalanine** and **Tyrosine metabolites** (33)-(37), along with **2-Hydroxyphenylacetic acid** (11), **Phenylacetic acid** (69) , **Phenylpyruvic acid** (70), and **4-Hydroxyphenyllacetic acid** (72).

Toxic Exposure

Mandelic acid is a major urinary metabolite formed from styrene and ethylbenzene metabolism via cytochrome P450 oxidation and subsequent enzymatic steps, making it a widely used biomarker for assessing contact.[880-883] Exposures to these toxicants can occur through inhalation via tobacco smoke, off-gassing of synthetic rubber, resins, polyesters, vehicle exhaust, and food contact materials like Styrofoam or plastic containers, especially when heated.[884]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Nutritional Needs

Iron and **B2** influence PAH, and if deficient, may reduce the processing of phenylalanine to tyrosine, shunting phenylalanine back to phenylethylamine.[885-887]

BH4 synthesis and regeneration is essential to optimize phenylalanine metabolism, with **folate** (especially folinic acid in DHPR deficiency) aiding its regeneration and **vitamin C** and other antioxidants stabilizing BH4 by preventing oxidation and preserving its role in neurotransmitter and endothelial function.[888-890]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

In rare cases, **inborn errors** like **PKU (phenylketonuria)** may elevate mandelic acid due to impaired metabolism of phenylalanine. However, this is usually accompanied by **elevations in Hippuric acid** (10), **2-hydroxyphenylacetic acid** (11), **2-Hydorxyisovaleric acid** (62), **phenylacetic acid** (69), and **phenylpyruvic acid** (70).[230]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary Influence: Dietary intake of phenylethylamine or excessive grain consumption can influence elevations.[884,887]

Medication/Supplement Influences: Skincare products or dyes may contain mandelic acid derivatives, but these are less common contributors.[891]

Low Values There is no known clinical significance for low values.

(69) Phenyllactic acid

Phenyllactic acid is formed when phenylalanine is transaminated to phenylpyruvic acid and then reduced. Elevated phenyllactic acid may result from impaired phenylalanine metabolism, particularly when phenylalanine hydroxylase (PAH) activity is reduced, diverting phenylalanine away from tyrosine and neurotransmitter synthesis toward alternative pathways. This can occur due to disruptions in BH4, a critical cofactor for PAH, which may be influenced by deficiencies in iron, vitamin B2, folate, or antioxidants such as vitamin C. Gastrointestinal overgrowth of certain *Clostridium* species may also contribute to mild elevations, although this connection is less established than with other phenylalanine metabolites. Genetic conditions such as phenylketonuria (PKU) and BH4 synthesis defects can lead to significant increases in phenyllactic acid and related metabolites.

Microbial Overgrowth

Slight elevations of phenyllactic acid can potentially be due to gastrointestinal overgrowth of *Clostridium spp*, including *C. botulinium* and *C. sporogenes* as well as other species.[115,892]

For additional insights into clostridia metabolites, review **4-Hydroxyphenylacetic acid** (15), **HPHPA (3-(3-hydroxyphenyl)-3-hydroxypropionic acid)** (16), **4-cresol** (17), and **3-Indolacetic acid** (18).

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Neurotransmitter Metabolites

The pathway that generates phenyllactic acid from phenylalanine becomes more prominent when phenylalanine hydroxylase (PAH) activity is impaired, diverting phenylalanine away from its primary role in producing tyrosine, a critical precursor for dopamine, norepinephrine, and epinephrine synthesis.[893-896] Disruptions in Tetrahydrobiopterin (BH4), an essential cofactor for PAH, may also be a factor.

For a more in-depth evaluation into dopamine metabolites, assess the **Phenylalanine** and **Tyrosine metabolites** (33)-(37), along with **2-Hydroxyphenylacetic acid** (11), **Mandelic acid** (68), **Phenylpyruvic acid** (70), and **4-Hydroxyphenyllacetic acid** (72).

Nutritional Needs

Iron and **B2** influence PAH, and if deficient, may reduce the processing of phenylalanine to tyrosine, shunting phenylalanine back to phenyllactic acid.[885-887] Support for BH4 synthesis and regeneration is essential to optimize phenylalanine metabolism and reduce phenyllactic acid accumulation, with **folate** (especially folinic acid in DHPR deficiency) aiding its regeneration and **vitamin C** and other antioxidants stabilizing BH4 by preventing oxidation and preserving its role in neurotransmitter and endothelial function.[803,889,890]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Inborn errors such as **phenylketonuria (PKU)**, a genetic deficiency of **PAH**, can lead to the accumulation of phenylalanine and its byproducts, including phenyllactic acid. Genetic factors affecting BH4 production may also contribute.[230]

Metabolites also associated with PKU include **Hippuric acid** (10), **2-hydroxyphenylacetic acid** (11), **2-Hydorxyisovaleric acid** (62), and **phenylpyruvic acid** (70).

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary Influence: Dietary intake of excessive phenylalanine, especially in the presence of decreased PAH function, could elevate phenyllactic acid.[897]

Low Values: There is no known clinical significance for low values.

(70) Phenylpyruvic acid

Phenylpyruvic acid is formed from phenylalanine by transamination, in which phenylalanine is converted to phenylpyruvate by aminotransferase enzymes. This reaction occurs when the primary pathway for phenylalanine metabolism, hydroxylation to tyrosine by phenylalanine hydroxylase (PAH), is impaired. Elevations typically indicate impaired metabolism of phenylalanine due to reduced activity of phenylalanine hydroxylase (PAH), often caused by nutrient deficiencies (iron, B2) or dysfunction in its cofactor tetrahydrobiopterin (BH4). This diversion away from tyrosine production affects neurotransmitter synthesis, particularly dopamine, norepinephrine, and epinephrine. Nutritional support for BH4 regeneration, such as folate, vitamin C, and antioxidants, may help reduce phenylpyruvic acid accumulation. Genetic conditions such as phenylketonuria (PKU), which involves a deficiency of PAH, are a potential cause, as are variants affecting BH4 metabolism. Excessive dietary phenylalanine may also contribute, especially when PAH activity is already compromised.

Neurotransmitter Metabolites

The pathway that generates phenylpyruvic acid from phenylalanine becomes more prominent when phenylalanine hydroxylase (PAH) activity is impaired, diverting phenylalanine away from its primary role in producing tyrosine, a critical precursor for dopamine, norepinephrine, and epinephrine synthesis.[893-896] Disruptions in Tetrahydrobiopterin (BH4), an essential cofactor for PAH, is also a factor.

For a more in-depth evaluation into dopamine metabolites, assess the **phenylalanine** and **tyrosine metabolites** (33)-(37), along with **2-Hydroxyphenylacetic acid** (11), **Mandelic acid** (68), **Phenyllactic acid** (69), and **4-Hydroxyphenyllacetic acid** (72).

Nutritional Needs

Iron and **B2** influence PAH, and if deficient, may reduce the processing of phenylalanine to tyrosine, shunting phenylalanine back to phenylpyruvic acid.[885-887] Support for BH4 synthesis and regeneration is essential to optimize phenylalanine metabolism and reduce phenypyruvic acid accumulation, with **folate** (especially folinic acid in DHPR deficiency) aiding its regeneration and **vitamin C** and other antioxidants stabilizing BH4 by preventing oxidation and preserving its role in neurotransmitter and endothelial function.[803,889,890]

Refer to the Nutrient-Marker Reference Table for the corresponding organic acids associated with those nutrients.

Genetics

Inborn errors such as phenylketonuria (PKU), a genetic deficiency of PAH, can lead to the accumulation of phenylalanine and its byproducts, including phenyllactic acid. Genetic factors affecting BH4 production may also contribute.[230]

Metabolites also associated with PKU include: **Hippuric acid** (10), **2-Hydroxyphenylacetic acid** (11), **2-Hydorxyisovaleric acid** (62), and **Phenyllacetic acid** (69).

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary Influence: Dietary intake of excessive phenylalanine, especially in the presence of decreased PAH function, could elevate phenylpyruvic acid.[897]

Low Values There is no known clinical significance for low values.

(71) Homogentisic acid

Homogentisic acid (HGA) is a byproduct of tyrosine breakdown via the enzyme homogentisate 1,2-dioxygenase (HGD), which processes tyrosine when it diverges from neurotransmitter synthesis. A deficiency in HGD, as seen in the genetic disorder alkaptonuria, impairs this catabolic pathway, disrupting energy metabolism and leading to elevated HGA levels.

Mitochondrial Health

From tyrosine, HGA converts to maleylacetoacetate via homogentisate 1,2-dioxygenase, which is ultimately further degraded to fumarate and acetoacetate, entering the Citric Acid Cycle for energy production.[898]

For more insight into mitochondrial health, reference the other **mitochondrial markers** (22)-(32) and **fatty acid oxidation markers** (45)-(49).

Neurotransmitter Metabolites

Homogentisic acid is a key intermediate in the breakdown of tyrosine, when it diverges from the pathway of synthesizing dopamine, norepinephrine, and epinephrine.[898]

For a more in-depth evaluation of dopamine metabolites, assess the **phenylalanine** and **tyrosine metabolites** (33)-(37).

Genetics

Alkaptonuria is inherited in an autosomal recessive pattern that involves a mutation in the HGD gene, impairing the conversion of HGA to maleylacetoacetate, leading to systemic buildup of toxic byproducts like benzoquinone acetic acid.[899]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Associated Conditions: Elevated HGA has also been observed in individuals with uncontrolled hyperglycemia.[900]

Low Values There is no known clinical significance for low values.

(72) 4-Hydroxyphenllactic acid

4-Hydroxyphenyllactic acid (4-HPLA) is formed when L-tyrosine is first transaminated into 4-hydroxyphenylpyruvic acid, which is then reduced by the enzyme hydroxyphenylpyruvate reductase. Certain gut bacteria, such as *Bifidobacteria*, *Lactobacillus*, and *Clostridium*, can produce D-4-HPLA, linking elevations to microbial overgrowth or dysbiosis, while excessive dietary tyrosine intake may further contribute. In rare cases, elevations may be associated with tyrosinemia due to mutations in the *HPD* gene.

Microbial Overgrowth

4-HPLA (D form) is produced by various gut bacteria, including *Bifidobacteria*, *Lactobacillus*, and *Clostridium*, and elevations may reflect bacterial overgrowth or dysbiosis.[115,901]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Neurotransmitter Metabolites

Markedly elevated plasma tyrosine, as seen in tyrosinemia, has been shown in computational and clinical studies to competitively inhibit other large neutral amino acids (LNAAs) at the LAT1 transporter, reducing their entry into the brain. This may disrupt neurotransmitter synthesis and amino acid balance, particularly by limiting tryptophan availability, ultimately influencing the serotonin synthesis pathway.[902,903] Additionally, excessive tyrosine levels have been shown to cause neurotoxicity.[904]

For a more in-depth evaluation of dopamine metabolites, assess the **phenylalanine** and **tyrosine metabolites** (33)-(37).

Genetics

Elevated 4-hydroxyphenyllactic acid (4-HPLA) is most directly linked to mutations in the HPD gene, which impair the enzyme 4-hydroxyphenylpyruvate dioxygenase, leading to tyrosinemia types I- III. This enzymatic block causes upstream accumulation of 4-HPLA.[230]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Dietary Influence: Dietary intake of excessive tyrosine, especially in the presence of decreased enzyme function, could elevate 4-HPLA.[905]

Low Values There is no known clinical significance for low values.

(73) N-Acetylaspartic acid

N-Acetylaspartic acid (NAA) is synthesized in neurons from aspartate and acetyl-CoA and plays roles in fluid balance, myelin synthesis, and neurotransmitter function. Elevated NAA is most commonly associated with **Canavan disease**, a rare autosomal recessive neurodegenerative disorder caused by mutations in the ASPA gene, leading to a deficiency of the enzyme aspartoacylase.

Genetics

N-acetylaspartic acid (NAA) is most commonly associated with **Canavan disease**, a rare autosomal recessive neurodegenerative disorder caused by mutations in the ASPA gene, leading to a deficiency of the enzyme aspartoacylase.[906]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Low Values There is no known clinical significance for low values.

(74) Malonic acid

Malonic acid is a dicarboxylic acid involved in fatty acid metabolism and energy production. Elevations may result from impaired mitochondrial function or acrolein exposure from polluted air or burning cooking oils past their smoke point. Markedly high levels are associated with malonyl-CoA decarboxylase deficiency, often alongside elevated methylmalonic acid.

Mitochondrial Health

Elevated malonic acid can impair energy production by inhibiting both succinic acid dehydrogenase in the citric acid cycle and carnitine palmitoyltransferase I (CPT-I), limiting mitochondrial fatty acid oxidation.[907-910]

For more insight into mitochondrial health, reference the other **mitochondrial markers** (22)-(32) and **fatty acid oxidation markers** (45)-(49).

Toxic Exposures

Acrolein can be metabolized into malonic acid through oxidative degradation pathways following initial epoxidation or hydration.[911] While **acrolein** is primarily detoxified via glutathione conjugation and excreted as mercapturic acids, its conversion to small dicarboxylic acids like malonic acid and oxalic acid is a recognized secondary route.[912] Acrolein exposure can occur through inhalation of polluted air from sources like tobacco smoke, vehicle exhaust, industrial emissions, and burning fuels, with smaller amounts also found in fried foods and cooking oils, though it is rarely present in drinking or surface water.[913]

Refer to the Toxin Exposure Tables for corresponding metabolites and patterns.

Genetics

In very high elevations, malonic acid is associated with the rare genetic metabolic disorder, malonyl-CoA decarboxylase deficiency.[230]

Malonyl CoA decarboxylase deficiency is also associated with methylmalonic acid (50).

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Associated Conditions: Malonic acid has been associated with several conditions, including eosinophilic esophagitis and early preeclampsia.

Low Values There is no known clinical significance for low values.

75 4-Hydroxybutyric acid

4-Hydroxybutyric acid (4-HBA), also known as gamma-hydroxybutyric acid (GHB), is primarily produced in the brain and liver through the degradation of gamma-aminobutyric acid (GABA), where GABA is converted to succinic semialdehyde (SSA) and then is either reduced to GHB or oxidized to succinate.[914-917] Elevations in 4-HBA may result from microbial production by species like *Clostridium aminobutyricum*, *Pseudomonas*, and *Saccharomyces cerevisiae*, or GABA degradation in the brain and liver. As a neurotransmitter metabolite, it influences GABA and glutamate signaling by acting on GABA receptors, affecting inhibitory and excitatory balance. 4-HBA can also be elevated due to GHB ingestion, whether illicit or pharmaceutical, and its metabolism depends on NAD^+, making **B3** status a potential modulating factor. Genetically, elevations may be associated with inherited metabolic disorders such as SSADH deficiency, though this is rare.

Microbial Overgrowth

4-Hydroxybutyric acid (4-HBA) has been shown to be produced by various microbes, including *Clostridium aminobutyricum*, *Saccharomyces cerevisiae*, and *Pseudomonas spp*, through the conversion of GABA or related precursors.[918]

Refer to Microbial Overgrowth Tables for corresponding metabolites and patterns.

Neurotransmitter Metabolites

4-HBA is produced during gamma-aminobutyric acid (GABA) degradation and can influence both GABA and glutamate signaling, potentially disrupting excitatory and inhibitory neurotransmission. Gamma-hydroxybutyric acid (GHB) can cycle back to GABA and modulate neurotransmission by acting on both GABA B and high-affinity GHB receptors, while also indirectly affecting GABAA signaling by reducing presynaptic GABA release.[919-921] This influences both inhibitory (GABAergic) and excitatory (glutamatergic) pathways in a region- and dose-dependent manner.[922]

Refer to **phenylalanine** and **tyrosine** 33-37 and **tryptophan** 38-40 metabolites for further review of neurotransmitters.

Toxic Exposures

4-HBA is chemically identical to GHB, which is a prototypical date rape drug used in drug-facilitated sexual assault due to its sedative, amnestic, and incapacitating effects.[923,924]

Nutritional Needs

The oxidation of 4-hydroxybutyric acid to succinic semialdehyde is catalyzed by 4-hydroxybutyrate dehydrogenase, an NAD^+-dependent enzyme.[925,926] Considering **Vitamin B3** (Niacin) is a precursor to NAD, slight elevations may be influenced by B3 insufficiencies.[927]

Refer to the Nutrient–Marker Reference Table for the corresponding organic acids associated with that nutrient.

Genetics

Elevated 4-HBA is most closely linked to inherited disorders such as SSADH deficiency, GABA transaminase deficiency, and 4-hydroxybutyric acid-CoA transferase deficiency.[230]

Note: This test is not diagnostic for genetic conditions, and specialized genetic testing may be warranted if a disorder is suspected.

Additional Insights

Medications/Supplements: Illicit or pharmaceutical use of GHB can significantly increase urinary 4-HBA.

Low Values There is no known clinical significance for low values.

MINERAL METABOLISM

76 Phosphoric

Phosphoric acid forms phosphate ions, which are essential for energy metabolism, DNA/RNA structure, and bone homeostasis.[928] High phosphoric acid levels can be caused by toxic exposures such as uranium or lead, high vitamin D and phosphorus intake, certain medications, and conditions that enhance bone resorption or impair phosphate reabsorption.[821,928-941] Low phosphate levels stimulate the production of 1,25-dihydroxyvitamin D3, to regulate phosphate and calcium levels, supporting the relationship between low vitamin D and low phosphate levels. Otherwise, low values may suggest low dietary intake or absorption, kidney disease, liver disease, and conditions such as hypoparathyroidism.[815,821,827,934,942-945]

Toxic Exposure

Toxic exposures, such as heavy metals like uranium and lead, can increase phosphoric acid levels by causing metabolic acidosis and renal tubular dysfunction, which reduces phosphate reabsorption and leads to increased urinary phosphate excretion.[929,930]

Refer to the Toxic Marker Comparison Table for corresponding metabolites and patterns.

Nutritional Needs

High phosphorus and **vitamin D** intake can increase phosphoric acid levels by enhancing the absorption and reabsorption of phosphate in the intestine and kidneys. Vitamin D, through its active metabolite 1,25-dihydroxyvitamin D3, stimulates phosphate absorption and helps regulate phosphate homeostasis. This leads to increased levels of phosphate in the blood, which, in turn, can elevate phosphoric acid levels, particularly in the context of dietary phosphate loading.[821,928]

Additional Insights

Dietary Influences: Meat and poultry, dairy products, and grains and cereals contribute to increased phosphoric acid levels by providing natural phosphorus.[946] Processed foods increase phosphoric acid levels through the use of phosphate additives, which are commonly found in bakery items, processed meats, cheeses, and beverages like colas. These additives, containing highly bioavailable inorganic phosphorus, and are rapidly absorbed by the body, leading to elevated phosphoric acid levels.[947,948]

Medication/Supplement Interactions: Medications that increase phosphoric acid levels include phosphate-containing laxatives, which can significantly raise serum phosphate levels, especially in individuals with compromised renal function. Additionally, drugs like K-Phos No. 2, certain proton pump inhibitors (e.g., omeprazole), calcium carbonate therapy with famotidine or lansoprazole, and medications with phosphate as an excipient, such as some antidiabetic, antidepressant, and antihypertensive medications, can contribute to elevated phosphate levels and potentially cause hyperphosphatemia.[931-935]

Associated Conditions: Conditions like hyperparathyroidism, vitamin D-resistant rickets, increased bone turnover, renal tubular damage, and kidney disease increase phosphoric acid levels by either enhancing bone resorption or impairing phosphate reabsorption in the kidneys. Other factors like familial hypophosphatemia, immobilization, metabolic acidosis, and active bone growth during pediatric development also contribute by promoting phosphate release from bones or impairing phosphate balance, resulting in higher phosphoric acid levels.[936-941]

Low Values

Nutritional Needs: Low phosphoric acid levels can be linked to low **vitamin D** and low phosphorus due to inadequate dietary intake or malabsorption.

Associated Conditions: Kidney disease may exacerbate low phosphoric acid levels due to impairments in phosphate reabsorption. Liver disease, acute liver failure, and conditions like hypoparathyroidism or pseudohypoparathyroidism reduce phosphate excretion, contributing to low phosphate levels.[815,821,827,934,942-945]

THERAPEUTIC CONSIDERATIONS

This section provides a structured framework to support clinicians when any of the six categories of clinical insight on the summary page are found to be imbalanced. These include Microbial Overgrowth, Mitochondrial Health, Neurotransmitter Metabolites, Methylation/ Detoxification, Toxic Exposure, and Nutritional Needs. For each category, targeted interventions are presented, outlining key metabolites associated with certain clinical insights and suggested supports for those particular markers and patterns. This systematic approach is intended to facilitate the development by practitioners of individualized care plans aimed at addressing underlying dysfunction and improving clinical outcomes.

MICROBIAL OVERGROWTH

THE 5RS FOR GENERAL SUPPORT

Remove	Reduce microbial load	• **Antimicrobials**: Oregano oil (150-200 mg BID), Garlic extract (Allicin 300-600 mg/day), Berberine (500 mg TID), Caprylic acid (500 mg BID)[949-956] • **Binders** (if mycotoxins suspected or possible Herxheimer): Activated charcoal (500-1000 mg/day), Zeolite clay (1 tsp/day)[957-960]	Rotate antimicrobials every 2-4 weeks to minimize resistance
Replace	Support digestion	• **Digestive Enzymes** such as Amylase, Lipase, Protease, or HCl (1-2 caps with meals)[961, 962] • **Bile salts** (250-500 mg with fatty meals if needed)[963, 964]	Helps reduce fermentable substrates for microbial overgrowth
Reinoculate	Restore healthy flora	• **Probiotics**: *Saccharomyces boulardii* (5-10 billion CFU BID for yeast overgrowth), *Lactobacillus* & *Bifido* blends (20-50 billion CFU/day)[965-969]	Start after 2 weeks of antimicrobials
Repair	Gut lining support	• L-Glutamine (5 g/day)[970-972] • Zinc carnosine (75 mg BID)[973,974] • Omega-3 fatty acids (1000-3000mg/day)[975-978]	Begin mid-protocol to aid mucosal healing
Rebalance	Support systemic health	• **Lifestyle**: Low sugar, varied, anti-inflammatory, high-fiber diet • **Stress management**	Avoid rapid die-off with aggressive interventions

SPECIFIC ORGANISM/MARKER CONSIDERATIONS

Marker Type	Elevated Findings Suggest	Therapeutic Focus	Example Interventions
Yeast/Mold (e.g., Arabinose, Furan-2,5-Dicarboxylic acid)	Candida or other fungal overgrowth	Antifungal botanicals, Pharmaceuticals, Probiotics, Mycotoxin clearance	• Caprylic acid, Cinnamon/ cinnamon leaf extract, Thyme essential oil, Oil of Oregano[955,956,979-986] • Nystatin, Fluconazole, Itraconazole, or Amphotericin B.[987-990] • Probiotics: *Saccharomyces boulardii*, *Lactobacillus kefiri*, *L. Pentosis*, *L. Brevis*, *L. plantarum* and *Bacillus coagulans* and *B. subtilis*.[966,991-998]
Bacterial (e.g., Hippuric, Benzoic, DHPPA)	Bacterial imbalance	Probiotics Fiber for SCFA production	• *Lactobacillus spp, Bifidobacterium spp*, and *Bacillus spp*.[1001-1004]
Clostridial (e.g., HPHPA, 4-Cresol)	Clostridia overgrowth (esp. neurotoxic species)	Targeted antimicrobials, Toxin neutralization	• High-dose *S. boulardii*, *Lactobacillus species*[966,1005-1007] • Ginger, garlic, Oil of Oregano[1008-1016] • Focus on detox pathways (e.g., NAC 600-1200 mg/day)[1017, 1018]
Oxalates (e.g., Glyceric, Glycolic, Oxalic)	Endogenous production of oxalate (often yeast or mold-related) or exogenous sources, such a certain plant-based foods	Microbial + oxalate-lowering support	• Address fungal overgrowth • Calcium + Magnesium citrate; 3:1 ratio with medium-high oxalates foods[1019-1023] • Vitamin B6[1024-1026] • Low-oxalate diet if sensitive to medium-high oxalate foods • Low sodium intake

ASSOCIATED PATTERNS FROM OTHER CATEGORIES

Category	Markers	Microbial Impacts
Neurotransmitter Metabolites	HVA (33), VMA (34), HVA/VMA ratio (35)	Clostridia inhibits dopamine → norepinephrine conversion.
Toxic Exposure	Succinic (24), Pyroglutamic (58), 2-Hydroxybutyric (59) acids	Various herbicides can impact the microbiome. Mycotoxins can be antimicrobial and impact imbalances in the microbiome.

CLINICAL TIPS *See Disclaimer on Page 154

- **Rotational Strategy**: Rotate antimicrobials every 2-4 weeks to reduce development of resistance.
- **Die-off Awareness**: Always start low and go slow—support detox pathways with adequate hydration, increased fiber intake, sweating, magnesium, and vitamin C.
- **Retesting Window**: Consider retesting OAT after 8–12 weeks of intervention.
- **Combination Therapy**: Use synergistic approaches—e.g., berberine + probiotic + glutamine—rather than mono-strategy.
- **Oxalate Alert**: Elevations in this section may reflect yeast or mold-associated endogenous oxalate production. Correlate with other yeast and fungal markers.
- **Environmental Cross-Talk**: If markers 1-9 and 19-21 persist, screen for mold/mycotoxins (MycoTOX) and environmental toxicants (TOXDetect) to address upstream root causes.

TESTING CONSIDERATIONS

Consider the following testing for further insights:

- **GI360 (with Zonulin and H. Pylori add-ons)**: A complement to the OAT, it can further assess additional organisms contributing to dysbiosis, as well as insights into inflammation and digestion.
- **IgG Food Map**: Food sensitivities are common with dysbiosis and may also give insights into immune response to Candida, if present.
- **MycoTOX**: Elevated mold-related metabolites or clinical signs of mycotoxin-induced microbiome impacts may warrant additional assessment.
- **IgE Mold**: If mold is suspected, this panel may provide insights into how the immune system is responding to the exposure.
- **TOXDetect**: Consider when microbial patterns, particularly with Clostridia, allude to possible toxicant- related influences, based on clinical history.

MITOCHONDRIAL HEALTH

KEY ORGANIC ACID MARKERS

Category	Marker(s)	Clinical Insight
Glycolytic Markers	Lactic (22), Pyruvic (23) acids	Could indicate mitochondrial dysfunction, impaired glucose metabolism, or tissue hypoxia.
Citric Acid Cycle Intermediates	Succinic (24), Fumaric (25), Malic (26), 2-Oxoglutaric (27), Citric (29), Aconitic (28), Citric (29) acids	Abnormal values may indicate impaired enzyme function or cofactor deficiencies (e.g., Mg, B vitamins).
Amino Acid Metabolism	3-Methylglutaric (30), 3-Hydroxyglutaric (31), 3-Methylglutaconic (32) acids	Impaired amino acid utilization for energy production, potentially causing oxidative stress.
Fatty Acid Metabolism	Ethylmalonic (45), Methylsuccinic (46), Adipic (47), Suberic (48), Sebacic (49) acids	Elevated in carnitine or B2 deficiencies, or β-oxidation impairments, leading to increased oxidative stress and reduced energy production.
Ketone Metabolism	3-Hydroxybutyric (43), Acetoacetic (44) acids	May reflect impaired carbohydrate utilization, ketogenic adaptation, or mitochondrial overload.

NUTRIENT COFACTOR ASSOCIATIONS *See disclaimer on Page 154

Organic Acid Marker	Likely Cofactor Deficiency	Suggested Support	General Dosage Range Guideline*
Pyruvic Acid (23)	B1 (Thiamine), Lipoic Acid[846,1027-10310]	Benfotiamine or thiamine HCl, R-lipoic acid	Benfotiamine: 150-600 mg/day; Thiamine HCl: 50-100 mg/day; R-lipoic acid: 100-300 mg/day
Succinic (24), Fumaric (25), Malic (26) acids	B2 (Riboflavin), CoQ10[1032-1035]	Riboflavin 5′-phosphate, ubiquinol	Riboflavin (as R5P or Riboflavin HCl): 10-30 mg/day; Ubiquinol: 100-300 mg/day

3-Methylglutaric (30), 3-Hydroxyglutaric (31), 3-Methylglutaconic (32) acids	B3 (Niacin), Mg, B6[772,829,830,1036,1037]	Niacinamide, magnesium glycinate, P5P/ Pyridoxine HCl	Niacinamide: 50-150 mg/day; Magnesium glycinate: 200-400 mg/day; P5P: 25-75 mg/day (or Pyridoxine HCl: 50-150 mg/day)
Ethylmalonic (45), Methylsuccinic (46), Adipic (47), Suberic (48), Sebacic (49) acids	Carnitine, B2[1033,1038-1041]	Acetyl-L-carnitine or L-carnitine tartrate; Riboflavin	Acetyl-L-carnitine: 500-2,000 mg/day; L-carnitine tartrate: 1-3 g/day; Riboflavin 10-30 mg/day

* Dosages represent typical adult clinical ranges used in mitochondrial and metabolic support protocols. Dosing should be individualized based on patient characteristics, such as age, weight, comorbidities, efficacy, and contraindications, as well as practitioner judgment.

THERAPEUTIC INTERVENTION GRID *See disclaimer on Page 154

Clinical Scenario	OAT Pattern	Intervention Strategy
Fatigue, muscle weakness, mild cognitive impairment	Elevated Citric Acid Cycle (24)-(29) + fatty acid (44)-(49) metabolites	Mitochondrial nutrient blend (CoQ10, carnitine+ ALA, Mg, B-complex)
Hypoglycemia vs hyperglycemia-related symptoms	Elevated Glycolytic (22),(23) and ketone (43),(44) and/or fatty acid (44)-(49) metabolites	Add carnitine + B2, optimize blood sugar using diet strategies, and if able, a Continuous Glucose Monitoring (CGM) device.[1042-1044]
Toxin-induced mitochondrial disruption	Elevated multiple metabolites + history of exposure	Mitochondrial repair + toxin binders + detox support (sweating, GI clearance, antioxidants)

ASSOCIATED PATTERNS FROM OTHER SECTIONS

Influencing Section	Marker(s)	Mitochondrial Impact
Microbial Overgrowth	Markers:①-⑱; molds, yeast, and various bacteria	Can produce similar metabolites, impacting elevations.
Toxic Exposure	Succinic ㉔, Pyroglutamic ㊽, 2-Hydroxybutyric ㊾ acids	Direct mitochondrial impairment or contributes to associated oxidative stress.
Nutrient Needs	Markers associated with low iron, magnesium, amino acids, B vitamins (see nutrient chart)	May generate a higher demand for these nutrients, or insufficiencies can impact the enzymatic reactions for these pathways.

CLINICAL TIPS *See disclaimer on Page 154

- **Assess nutrient status** before assuming mitochondrial dysfunction — many abnormalities reflect cofactor depletion.
- **Consider toxic exposure interference** (e.g., mold, heavy metals, environmental toxicants, certain medications) when multiple energy metabolism markers are elevated.
- **Evaluate upstream fuel delivery issues**, such as blood sugar dysregulation or gut malabsorption, which can impair mitochondrial input.
- **Fatty acid and ketone metabolism markers** can be early indicators of mitochondrial stress, especially in neurologic or fatigue cases.
- **Use a layered support approach**: mitochondrial nutrient repletion → reducing toxic burden → metabolic rehabilitation (e.g., gentle exercise, PQQ, NAD+).

TESTING CONSIDERATIONS

Consider the following testing for further insights:

- **Metal-Toxic + Nutrient Elements, TOXDetect,** and/or **MycoTOX**: Various toxic exposures can influence several mitochondrial enzymes in addition to contributing to a significant amount of oxidative stress that can impact the health of the mitochondria.
- **Amino Acid Profile**: Some data suggest, in extreme cases, insufficient amino acids can influence the mitochondrial pathways.

NEUROTRANSMITTER PATHWAYS

KEY NEUROTRANSMITTER MARKERS

Neurotransmitter	Key Marker(s)	Interpretive Notes
Dopamine	HVA (33), DOPAC (36), HVA/DOPAC ratio (37)	HVA: dopamine turnover. Low: depletion or impaired synthesis; high: increased breakdown/stimulation.
Norepinephrine/ Epinephrine	VMA (34), HVA/VMA ratio (35)	High VMA: stress response, sympathetic activation. Low: catecholamine depletion or decreased breakdown.
Serotonin	5-HIAA (38)	Low: precursor depletion, poor synthesis. High: rapid production/metabolism.
Kynurenine Pathway	Quinolinic (39), Kynurenic (40) acids	High quinolinic: neurotoxicity, inflammation, need for NAD+; High kynurenic: neuroprotection.

COFACTORS & INFLUENCING FACTORS *See Disclaimer on Page 154

Pathway	Nutrient Cofactors	General Dosage Range Guideline*	Clinical Influences
Dopamine/ Norepinephrine	Iron, B6, Vit C, Copper, B2, Mg, SAMe[671,1045-1053]	**Iron** (as ferritin repletion, typically 50-200 mg elemental/day if deficient); P5P: 25–75 mg/day (or pyridoxine HCl: 10-25 mg/day); **Vitamin C**: 100-200 mg/day; **Copper** (only if deficient): 5-10 mg/day; **Riboflavin** (R-5-P or HCl): 10-50 mg/day; **Magnesium** (glycinate or malate): 300–400 mg/day; SAMe: 400–1,200 mg/day	Stimulants, stress, infection, MAO inhibitors, COMT polymorphisms
Serotonin	5HTP, B6, Folate, Mg, B2, Iron[1032,1045,1054-1060]	**5-HTP**: 50–300 mg/day (often divided); **Pyridoxine HCl**: 10-25 mg/day; **Folate** (L-5-MTHF): 400–1,000 mcg/day; **Magnesium** (glycinate or malate): 200–400 mg/day; **Riboflavin**: 5-15 mg/day; Iron (if deficient): 50-200 mg elemental/day	SSRIs, inflammation, gut dysbiosis, IDO activation

Kynurenine Pathway (to assist shifting tryptophan towards serotonin instead of Kynurenic)	B2, B6, Niacin (B3)[496,1061-1064] **Other supportive nutrients:** Zinc, Omega 3s, Rosmarinic acid, Curcumin[1065-1072]	**Riboflavin**: 5-10 mg/day; **v**: 25–75 mg/day; **Niacinamide**: 250–500 mg/day **Other supportive nutrients:** **Zinc** (5-15 mg/day); **Omega-3s** (EPA+DHA): 1–3 g/day **Rosmarinic acid**: 200–500 mg/day; **Curcumin** (500-1500 mg/day)	Inflammation, stress, infection (e.g. viral, Lyme), chronic illness, upregulation of IDO/TDO

Dosages represent typical adult clinical ranges used in mitochondrial and metabolic support protocols. Dosing should be individualized based on patient characteristics, such as age, weight, comorbidities, efficacy, and contraindications, as well as practitioner judgment.

ASSOCIATED PATTERNS FROM OTHER SECTIONS

Influencing Section	Marker(s)	Neurotransmitter Impact
Microbial Overgrowth	Elevated Clostridia markers (15)-(18)	Inhibition of dopamine → norepinephrine conversion
Toxic Exposure	Markers associated with heavy metals, solvents, mycotoxins (see Mold, Toxicant, and Heavy Metal charts) and Markers (24),(58),(59)	Direct neurotoxicity, mitochondrial impairment
Methylation/ Detoxification	Markers (41),(50),(51),(53), and (59) are associated with methylation Methylation can impact Biopterin and COMT, major cofactors in the generation and metabolism of NTs	Could cause levels to look low, when they could actually be elevated.
Nutrient Needs	Markers associated with low iron, magnesium, amino acids, and B vitamins (see nutrient chart)	Limits neurotransmitter precursor availability and enzymatic activity

CLINICAL TIPS *See Disclaimer on Page 154

- Inflammation drives tryptophan down the kynurenine pathway, potentially raising quinolinic acid.
- 5-HIAA may be low due to precursor issues, high cortisol dampening serotonin synthesis, or excessive dopamine.

- Review mitochondrial and microbial sections for upstream drivers of neurotransmitter disruption (e.g., Clostridia can inhibit Dopamine Beta Hydroxylase)

TESTING CONSIDERATIONS

Consider the following testing for further insights:

- **Amino Acid Profile**: Assessing amino acid precursors for neurotransmitter synthesis provides insight into potential limitations or excesses in the pathways governing production.
- **DNA Methylation Pathway Profile**: If metabolite patterns suggest disruption of methylation, COMT, or MAO pathways, this testing may help identify genetic influences.
- **Saliva Hormone Profile**: Provides insights into the neuroendocrine influences on certain neurotransmitter metabolites.
- **Lyme and Co-infection testing** (Lyme Direct Detect, Tickborne BB Direct Detect, and Bartonella IgG Detect): If Quinolinic acid (39) is elevated, and clinical history aligns with potential for Lyme- and co-infections, testing may be warranted.

METHYLATION & DETOXIFICATION

KEY ORGANIC ACID MARKERS

Marker	Primary Pathway	Clinical Significance
Pyroglutamic acid (58)	Glutathione recycling	Elevated with glutathione depletion or oxidative stress; common in toxic burden or chronic illness.
2-Hydroxybutyric acid (59)	Transsulfuration (CBS path)	Reflects increased demand for glutathione or methylation defects; rises with oxidative stress, methylation impairment, or increased detox demands.
Orotic acid (60)	Urea cycle & nucleotide synthesis	Elevated with ammonia overload, urea cycle dysfunction, or methylation impairments.
2-Hydroxyhippuric acid (61)	Glycine conjugation (Phase II)	May indicate xenobiotic exposure or impaired Phase II liver detox; also gut microbiome-influenced.

FUNCTIONAL NUTRIENT & DETOX SUPPORT

*See Disclaimer on Page 154

Marker	Suggested Support	General Dosage Range Guideline*	Mechanistic Focus
Pyroglutamic acid (58)	NAC, glycine, glutamine, liposomal glutathione[740,751,1073-1079]	NAC: 600–1,800 mg/day (divided doses); Glycine: 1–3 g/day; L-Glutamine: 2–5 g/day; Liposomal Glutathione: 250–500 mg/day	Supports glutathione regeneration; key in redox homeostasis.
2-Hydroxybutyric acid (59)	Sulfur amino acids (taurine, methionine), B6, selenium[655,1080-1090]	Taurine: 1–3 g/day; L-Methionine: 500–2,000 mg/day; P5P: 25–75 mg/day (or pyridoxine HCl: 50–150 mg/day); Selenium (selenomethionine or yeast-bound): 100–200 mcg/day	Supports transsulfuration; indicates stress on glutathione demand.
Orotic acid (60)	Citrulline, arginine, methylation support (B2,B6, B12)[669,670,782,1086,1091-1096]	L-Citrulline: 2–6 g/day; L-Arginine: 3–6 g/day; L-Ornithine: 1–3 g/day; Riboflavin: 20–100 mg/day; P5P: 25–75 mg/day; Methylcobalamin: 1,000–5,000 mcg/day	Supports urea cycle and methylation
2-Hydroxyhippuric acid (61)	Glycine, liver detox herbs (milk thistle, dandelion), probiotics[75,827,1097-1108]	Glycine: 1–3 g/day; Milk thistle extract (80% silymarin): 200–600 mg/day; Dandelion root extract: 500–1,500 mg/day; Probiotics (multi-strain): 10–50 billion CFU/day	Reflects need for Phase II conjugation or microbial rebalancing.

*Dosages reflect typical adult integrative medicine ranges; pediatric dosing should be weight-adjusted. All supplementation should be guided by clinical context, laboratory monitoring, and patient tolerability.

PATTERN INTERVENTION GRID

Pattern on OAT	Targeted Support Strategy
↑ Pyroglutamic (58), ↑ 2-Hydroxybutyric (59) acids	NAC or glutathione, Methylation support, mitochondrial antioxidants, sauna/sweating therapy, binders
↑ Orotic acid (60)	Citrulline, arginine, liver support, methylation nutrients
↑ 2- Hydroxybutyric acid (59)	Support Methylation, B6 for CBS enzyme, and may consider Homocysteine panel.

ASSOCIATED PATTERNS FROM OTHER SECTIONS

Influencing Section	Marker(s)	Neurotransmitter Impact
Toxic Exposure	Markers associated with heavy metals, toxicants, mycotoxins (see Mold, Toxicant, and Heavy Metal charts) and Markers (24),(58),(59)	Direct neurotoxicity, mitochondrial impairment
Nutrient Needs	Markers (41),(50),(51), and (53) are associated with nutrients that are needed for methylation.	Without proper support for methylation, dysfunction is likely to occur.

CLINICAL TIPS *See Disclaimer on Page 154

- **High pyroglutamate + fatigue** → Consider glutathione depletion or oxidative load from toxic exposure or infections.
- **2-hydroxybutyric elevation** → Suggests acute glutathione demand, transsulfuration pathway overload, or methylation stress.
- **Orotic acid spike** → Screen for ammonia overload (especially with fatigue, cognitive impairment); support urea cycle and methylation.
- **Elevated 2-hydroxyhippuric** → Consider gut dysbiosis or toxic exposure; enhance glycine and Phase II liver detox.
- Combine markers with clinical presentation: e.g., **Pyroglutamate + 2-HB** in a mold-exposed patient often suggests oxidative + detoxification burden.

TESTING CONSIDERATIONS

Consider the following testing for further insights:

- **Amino Acid Profile**: Assesses the status of amino acids involved in detoxification, methylation, and the urea cycle.
- **DNA Methylation Pathway Panel**: Can give insights into genetic SNPs associated with various points in the methylation cycle and transsulfuration pathway.
- **Homocysteine**: Provides more insight into the function of the methylation and transsulfuration pathways. **This is also on the amino acid profiles (both urine and plasma), but can also be a separate test if needed, particularly for reassessment or monitoring.*

TOXIC EXPOSURE

KEY ORGANIC ACID MARKERS

Organic Acid Marker	Potential Toxic Exposure	Clinical Insight
Mold-related metabolites (Markers 1, 2, 4, 5, 6, 9)	Mold activity or exposure	May indicate mold overgrowth or mycotoxin exposure.
Succinic acid 24	Toxicants, heavy metals, and/or mycotoxins	Suggests mitochondrial impacts from toxic exposures
Pyroglutamic acid 58	Glutathione depletion from toxic burden	Reflects oxidative stress and detox demand
2-Hydroxybutyric acid 59	Oxidative stress from toxic or inflammatory sources	Homocysteine favoring the transsulfuration pathway either to support GSH production or as a result of methylation stress.

FUNDAMENTAL DETOX STRATEGIES *See Disclaimer on Page 154

1. Reduce ongoing exposure by identifying and eliminating sources (e.g., moldy environments, contaminated water, occupational chemicals) and prioritizing organic foods to reduce pesticide intake, using HEPA air filtration and remove dust to limit airborne pollutants and mold spores, and avoiding plastics, synthetic fragrances, and other common environmental toxic exposures in the home and workplace.[1109-1116]
2. Support biotransformation pathways, especially glutathione conjugation, glucuronidation, sulfation, and methylation, using nutrients such as NAC, glycine, selenium, B6, B12, folate, and magnesium. More detailed information can be found in the following blog: The Liver: Supportive Nutrients in Detoxification - MosaicDX.
3. Enhance glutathione status via liposomal glutathione, N-acetyl cysteine (NAC), or other precursors like glycine
4. Target mitochondrial repair with CoQ10, acetyl-L-carnitine, alpha-lipoic acid, and B complex.
5. Bind and eliminate toxins and toxicants using agents like activated charcoal, zeolite clay, chlorella, humic and fulvic acids, fibers, or prescription binders (e.g., cholestyramine), depending on toxic exposure type.

6. Support Phase II detoxification with sulforaphane, calcium-D-glucarate, taurine, and cruciferous vegetables. Additional information can be found in the following blog: The Liver: Its Important Role in Detoxification - MosaicDX
7. Address secondary dysbiosis or fungal overgrowth, which may be exacerbated by toxin-induced immune suppression or antimicrobial activity, using targeted botanicals and gut repair strategies.
8. Replenish key vitamins (e.g. B vitamins, C, etc.) and minerals (e.g., zinc, magnesium, molybdenum) displaced by toxic exposure to restore enzyme function.
9. Consider adjunct therapies such as sauna, lymphatic support, and detox protocols based on individual tolerance and clinical presentation.

CLINICAL TIPS *See Disclaimer on Page 154

- **Elevated pyroglutamic acid** often signals glutathione depletion—consider supporting glutathione synthesis via NAC, glutathione, or precursors.
- Elevations in **succinic acid** and related Citric Acid Cycle markers warrant assessment for toxic exposures that influence mitochondria (heavy metals, toxicants, mycotoxins).
- **Fungal and Mycotoxin-Linked Markers to Screen for Mold Exposure**: Elevated levels of **5-Hydroxymethyl-2-furoic acid**, **Furan-2,5-dicarboxylic acid**, **Furancarbonylglycine**, **Citramalic**, **Tartaric**, and **Tricarballylic acid** can indicate mold exposure (especially *Aspergillus* or *Fusarium* species). Evaluate these in the context of clinical history and potential environmental exposure.
- **Identify Environmental and Heavy Metal Toxicity Through Patterned Marker Changes**: Look for elevated **HVA**, **VMA**, **pyruvic**, **citric**, **quinolinic**, **mandelic**, **hippuric**, **oxalic**, and **malonic acids** as possible indicators of toxic exposures from **heavy metals** (**arsenic**, **mercury**, **cadmium**), **pesticides**, **phthalates**, **solvents**, **parabens**, and **combustion byproducts**. Assess in conjunction with symptomatology and known or suspected exposure sources.
- Integrate these markers with clinical context—lab abnormalities alone don't confirm exposure, but guide further investigation.

TESTING CONSIDERATIONS

Consider the following testing for further insights:

- **Metal-Toxic + Nutrient Elements, TOXDetect**, and/or **MycoTOX**: Based on clinical presentation, history, and patterns with OAT metabolites, one or all of the toxic exposure testing modalities may be warranted.

NUTRIENT NEEDS

The following table highlights metabolites linked to specific nutrients and may support clinical interpretation by revealing patterns suggestive of insufficiencies.

NUTRIENT-MARKER REFERENCE TABLE

Nutrient / Category	Relevant OAT Marker(s)	Interpretation
B1 (Thiamin)	• Glycolytic markers (22), (23) • 2-Oxoglutaric acid (27) • 2-Hydroxyhippuric acid (61) • BCKA Metabolites (62)-(66)	Required for pyruvate dehydrogenase; elevation: impaired carbohydrate metabolism, potential thiamin need, or mitochondrial stress.
B2 (Riboflavin)	• Pyruvic acid (23) • Succinic acid (24), 2-Oxoglutaric acid (27) • HVA (33), VMA (34), DOPAC (36), HVA/DOPAC (37) • Tryptophan metabolites (38)-(40) • Folate metabolites (41), (42) • Ketone and Fatty Acid markers (45)-(49) • Glutaric acid (53) • Indicators of Detoxification (59)-(60) • Amino Acid metabolites (62)-(66), (68)-(70)	Needed for acyl-CoA dehydrogenase and glycolate oxidase; elevations in Krebs or fatty acid markers may reflect B2 need.
B3 (Niacin)	• Glyceric acid (19) • Glycolytic markers (22)-(23) • Malic acid (26), 2-Oxoglutaric acid (27) • VMA (33), HVA/VMA (35) • Quinolinic acid (39), Kynurenic acid (40) • 3-Hydroxybutyric acid (43), acetoacetic acid (44) • 2-Hydroxybutyric acid (59) • Amino acid metabolites (62)-(66), (75)	Niacin is required for NAD^+/$NADP^+$ production; abnormal tryptophan metabolites or Citric Acid Cycle imbalances may indicate B3 insufficiency or inflammation-driven demand.
B5 (Pantothenic Acid)	• Hippuric acid (10) • Pyruvic acid (23) • 2-Oxoglutaric acid (27) • Pantothenic acid (52) • BCKA metabolites (62)-(66)	Pantothenic acid is a precursor to CoA; elevations in Krebs or fatty acid markers may suggest impaired energy metabolism and B5 need.

B6 (Pyridoxine)	• 2-Hydroxyphenylacetic acid (11) • Oxalate metabolites (20),(21) • HVA (33), VMA (34), DOPAC (36) • Tryptophan metabolites (38)-(40) • Pyrimidine metabolites (41)-(42) • Pyridoxic acid (51) • Indicators of Detoxification (58),(59) • 2-Hydroxyisocaproic (65) and 2-Oxo-4-methiolbutyric acids (67)	Cofactor for transamination and neurotransmitter synthesis; elevations in oxalates and neurotransmitter markers may indicate a functional B6 deficiency. Influential in methylation and energy production.
B7 (Biotin)	• Methylmalonic acid (50), • Methylcitric acid (57)	Cofactor for carboxylase enzymes; elevations in methylmalonic or methylcitric acids may reflect biotin deficiency or dysbiosis-related interference.
B9 (Folate)	• HVA/DOPAC (37) • Pyrimidine metabolites (41)-(42) • 2-Hydroxybutyric acid (59) • Amino Acid metabolites (68)-(70)	Essential for methylation and nucleotide synthesis; abnormalities in folate metabolites or 2-hydroxybutyric acid may suggest B9 deficiency or MTHFR-related need.
B12 (Cobalamin)	• Succinic acid (L) (24) • HVA/DOPAC (37) • Pyrimidine Metabolites (41)-(42) • Methylmalonic acid (50) • Methylcitric acid (57) • Indicators of Detoxification (59),(60)	Abnormal: functional or genetic B12 deficiency.
Vitamin C	• Aconitic acid (28) • HVA (33), VMA (34), HVA/VMA (35), DOPAC (36) • Ascorbic acid (54) • Amino Acid Metabolites (68)-(70)	Excess can potentially raise oxalates; deficiency may impact immunity and antioxidant defenses.
CoQ10 (Ubiquinone)	• 4-hydroxybenzoic acid (12) • Lactic acid (22) • Succinic acid (24) • 3-Hydroxy-3-Methylglutaric acid (CoQ10) (55)	Essential for the electron transport chain; low CoQ10 may impair mitochondrial function.

Calcium	• Tricarballylic acid (9) • Oxalic acid (21) • 2-Oxoglutaric acid (27) • Citric acid (29) • HVA/DOPAC ratio (37)	Can be depleted by tricarballylic or oxalic acids, while an insufficiency can influence enzymatic function in mitochondrial function. Excess can impair neurotransmitter metabolism.
Magnesium	• Tricarballylic acid (9) • Oxalic acid (21) • Pyruvic acid (23) • Citric Acid Cycle metabolites (26), (27), (29) • HVA (33), VMA (34), DOPAC (36), HVA/DOPAC (37) • 5-HIAA (38) • Ketone and Fatty Acid markers (47), (48) • Indicators of Detoxification (58), (60) • Amino Acid metabolites (62)-(65)	Needed for ATP-dependent enzymes; deficiency can impair oxalate, Krebs, and ketone metabolism. Also necessary for proper catecholamine metabolism.
Zinc	• Tricarballylic acid (9) • Lactic acid (22) • 2-Oxoglutaric acid (27) • 5-HIAA (38) • Ascorbic acid (54) • Orotic acid (60)	Cofactor for kynureninase; deficiency may shift tryptophan pathway toward quinolinic, zinc can inhibit (27) as well as support reactions.
Iron	• Oxalic acid (21) • Lactic acid (22) • Mitochondrial – Citric Acid Cycle markers (24), (25), (26), (28), (29) • HVA (33), VMA (34), DOPAC (36), HVA/DOPAC (37) • Quinolinic acid (39) • Ascorbic acid (54) • Amino Acid metabolites (68)-(70)	Cofactor in mitochondrial SOD and metabolism of oxalate precursors.
Glutathione	• Glycolic acid (20) • Aconitic acid (28), Citric acid (29)	Markers of oxidative stress, methylation support; elevation: tglutathione depletion or detox strain.

Glycine	• Hippuric acid (10), 4-Hydroxyhippuric acid (13) • Pyroglutamic acid (58)	Building block of glutathione; elevated pyroglutamic acid could indicate glycine deficiency.
Carnitine	• Ketone and Fatty Acid Oxidation markers (45)-(49)	Needed for FA transport into mitochondria; elevations suggest carnitine need or mitochondrial block.
Phenylalanine/Tyrosine	• 2-Hydroxyphenylacetic acid (11) • HVA (33), VMA (34), DOPAC (36), Mandelic (68), Phenyllactic acid (69), Phenylpyruvic acid (70)	Involved in the synthesis of dopamine, norepinephrine, and epinephrine.
Tryptophan	• 5-Hydroxyindoleacetic acid (5-HIAA) (38) Quinolinic acid (39), Kynurenic acid (40)	Precursor to these neurotransmitters has the potential to go down the kynurenine pathway vs serotonin.
Lipoic Acid	• Pyruvic acid (23) • 2-Oxoglutaric acid (27)	Coenzyme in pyruvate and α-KG dehydrogenase; need suspected if elevations + oxidative stress markers.

CLINICAL TIPS *See Disclaimer on Page 154

- Elevations in **2-hydroxybutyric acid**, **pyrimidine metabolites**, and imbalance in **HVA/DOPAC** may be related to **Vitamin B9** insufficiencies.
- Imbalances in tryptophan metabolites (↑ **quinolinic** and ↓ **kynurenic acids**), and **mitochondrial dysfunction** (**Citric Acid Cycle**, **ketones**) → often linked to **Vitamin B3** demand.
- Imbalanced **fatty acid metabolism markers** --> information on **carnitine** or **Vitamin B2** needs
- Abnormal **oxalic** (21), **mitochondrial** and **fatty acid metabolites** (23),(26),(27),(29),(47),(48), and **catecholamine metabolites** (33),(34),(36),(37),(38) may suggest **magnesium** deficiency.
- Elevations in **oxalic acid** (21), **lactic acid** (22), **Citric Acid Cycle intermediates** (24),(25), and **amino acid markers** (68),(69),(70) may suggest **Iron** deficiency.

TESTING CONSIDERATIONS

Consider the following testing for further insights;

- **Omega-3 Index Complete**: Offers a more comprehensive review of essential fatty acids that are vital in cellular health, neurological function, regulating inflammation, hormonal imbalance, and many other biological functions.
- **Amino Acid Profile**: Provides a more complete assessment of amino acids.
- **Metals –Toxic + Nutrient Elements**: If minerals are suspected to be inadequate based on corresponding markers, may use this testing for further insights.
- **Vitamin D**: When **Phosphoric acid** (76) is abnormal, may need further review of Vitamin D status.
- **GI360 (with H. Pylori add-ons)**: Can provide insights into deficiencies that may be related to insufficient digestion or inadequate microbial abundance and/or diversity.

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