Sick, Tired and on Fire: Nutrition and Inflammation

Jamie Wright, DO, MS

Genova Diagnostics LiveGDX

24 February 2016

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Christine Stubbe, ND

Medical Education Specialist - Asheville

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Jamie Wright DO, MS

Board Certified OB/GYN
ABAARM, FACOOG

Director of Metabolic Medicine & Healthy Aging,
Garden of the Gods Club and Resort

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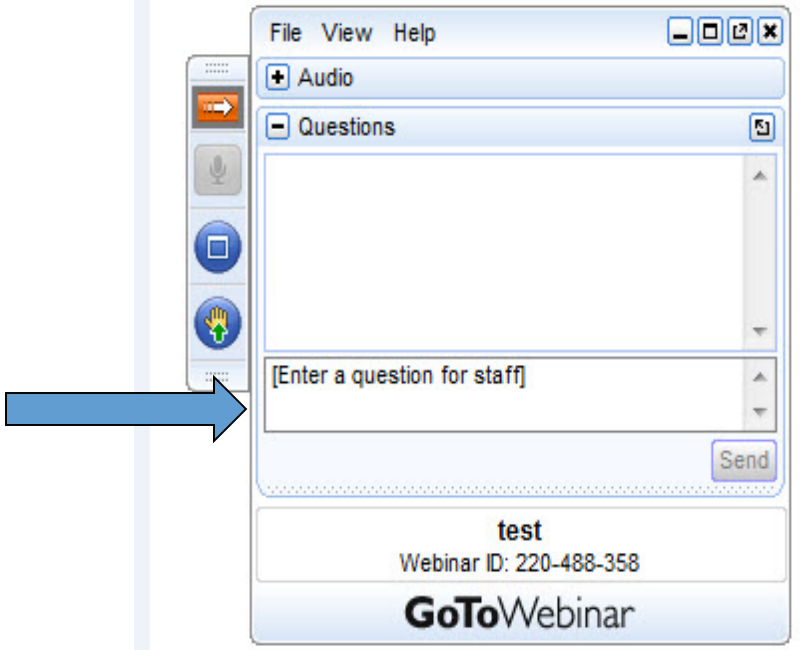
Technical Issues & Clinical Questions

Please type any technical issue or clinical question into either the “Chat” or “Questions” boxes, making sure to send them to “Organizer” at any time during the webinar.

We will be compiling your clinical questions and answering as many as we can the final 15 minutes of the webinar.



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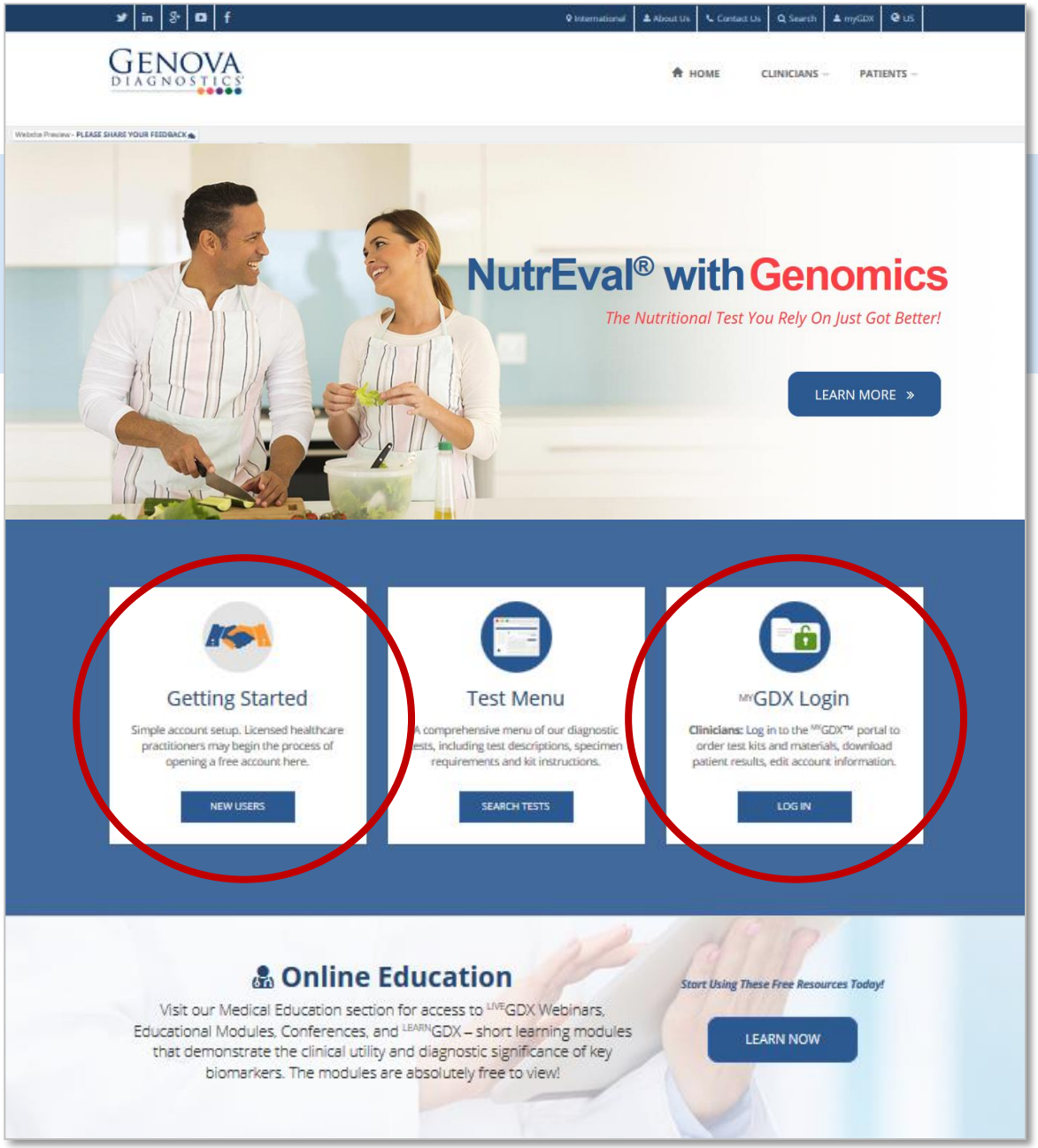
DISCLAIMER: *Please note that any and all emails provided may be used for follow up correspondence and/or for further communication.*

Need More Resources?

Ensure you have an account!



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Problem

"…the rising cost of health care represents perhaps the **most significant threat** to the long-term economic security of workers and retirees."

Social Security Advisory Board, September 2009. The Unsustainable Cost of Healthcare.

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The Problem is… Chronic Disease

75%

Sylvester J. Schieber, Chairman, Dana K. Bilyeu,Dorcas R. Hardy,Marsha Rose Katz, Barbara B. Kennelly, Mark J. Warshawsky. The Unsustainable Cost of Health Care. Social Security Advisory Board, September 2009.

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The Problem is… Diabetes

$13,000

White JR. Economic Considerations in Treating Type 2 Diabetes. Am J Health Syst Pharm. 2002;59 Suppl 9:S14-7.

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The Problem is… Behavior

"Behavioral **choices** that result in an increased incidence of chronic disease are also extremely costly in terms of the affordability of health care coverage."

Why Public Health Is Necessary to Improve Healthcare. The National Association of Chronic Disease Directors (NACDD). Accessed 2014-11-30 at www.chronicdisease.org

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Risk Behaviors are?

- _____,
- _____,
- _____,
- _____.

Why Public Health Is Necessary to Improve Healthcare. The National Association of Chronic Disease Directors (NACDD). Accessed 2014-11-30 at www.chronicdisease.org

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The Problem is Really…

- Poor diet,
- Lack of physical activity,
- Tobacco,
- Family history.

Why Public Health Is Necessary to Improve Healthcare. The National Association of Chronic Disease Directors (NACDD). Accessed 2014-11-30 at www.chronicdisease.org

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Really?

FITNESS

Coca-Cola Funds Scientists Who Shift Blame for Obesity Away From Bad Diets

By ANAHAD O'CONNOR AUGUST 9, 2015 5:25 PM 1088 Comments

An image from a video by the Coca-Cola Foundation. In November 2012, the foundation announced a $3 million grant to Chicago's Garfield Park Conservatory Alliance. The grant was intended to establish a wellness program.

Email

Share

Coca-Cola, the world's largest producer of sugary beverages, is backing a new "science-based" solution to the obesity crisis: To maintain a healthy weight, get more exercise and worry less about cutting calories.

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The Problem: NCD

"Already in every region except Africa, NCDs account for greater mortality than communicable, maternal, perinatal and nutritional conditions combined."

Singhal A. The global epidemic of non-communicable disease: the role of early-life factors. Nestle Nutr Inst Workshop Ser. 2014;78:123-32. doi: 10.1159/000354951. Epub 2014 Jan 27.

Physical Inactivity

- 4th leading risk for global death

- Obesity linked to:
  - 3.4M deaths per year
  - Inactivity
  - Chronic inflammatory state
  - DM2

Sarvas JL1, Niccoli S2, Walser E3, Khaper N1, Lees SJ4. Interleukin-6 deficiency causes tissue-specific changes in signaling pathways in response to high-fat diet and physical activity. Physiol Rep. 2014 Jul 4;2(7). pii: e12064. doi: 10.14814/phy2.12064. Print 2014 Jul 1

Use it, or…

"…physical activity… [promotes] the biogenesis and function of the mitochondria and **as a consequence** help maintain cellular and whole body health."

Aaron P. Russell , Victoria C. Foletta, Rod J. Snow, Glenn D.Wadley. Skeletal muscle mitochondria: A major player in exercise, health and disease. Biochimica et Biophysica Acta 1840 (2014) 1276–1284.

“Disease is of man’s own building…”

J. H. TILDEN, M. D. DENVER, COLORADO,
Toxemia Explained, copyright 1926

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The Problem: Noncommunicable Diseases (NCD)

“…the most important global health problem of the 21st century.”

Singhal A. The global epidemic of non-communicable disease: the role of early-life factors. Nestle Nutr Inst Workshop Ser. 2014;78:123-32. doi: 10.1159/000354951. Epub 2014 Jan 27.

Inflammation

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Br J Nutr. 2015 Oct 14;114(7):999-1012. doi: 10.1017/S0007114515002093. Epub 2015 Jul 31.

Low-grade inflammation, diet composition and health: current research evidence and its translation.

Minihane AM[1], Vinoy S[2], Russell WR[3], Baka A[4], Roche HM[5], Tuohy KM[6], Teeling JL[7], Blaak EE[8], Fenech M[9], Vauzour D[1], McArdle HJ[3], Kremer BH[10], Sterkman L[11], Vafeiadou K[12], Benedetti MM[13], Williams CM[14], Calder PC[15].

Author information

Abstract

The importance of chronic low-grade inflammation in the pathology of numerous age-related chronic conditions is now clear. An unresolved inflammatory response is likely to be involved from the early stages of disease development. The present position paper is the most recent in a series produced by the International Life Sciences Institute's European Branch (ILSI Europe). It is co-authored by the speakers from a 2013 workshop led by the Obesity and Diabetes Task Force entitled 'Low-grade inflammation, a high-grade challenge: biomarkers and modulation by dietary strategies'. The latest research in the areas of acute and chronic inflammation and cardiometabolic, gut and cognitive health is presented along with the cellular and molecular mechanisms underlying inflammation-health/disease associations. The evidence relating diet composition and early-life nutrition to inflammatory status is reviewed. Human epidemiological and intervention data are thus far heavily reliant on the measurement of inflammatory markers in the circulation, and in particular cytokines in the fasting state, which are recognised as an insensitive and highly variable index of tissue inflammation. Potential novel kinetic and integrated approaches to capture inflammatory status in humans are discussed. Such approaches are likely to provide a more discriminating means of quantifying inflammation-health/disease associations, and the ability of diet to positively modulate inflammatic
product development and associated health cla

An unresolved inflammatory response is likely to be involved from the early stages of disease development. There is a substantial amount of evidence to suggest that many foods, nutrients and non-nutrient food components modulate inflammation both acutely and chronically.

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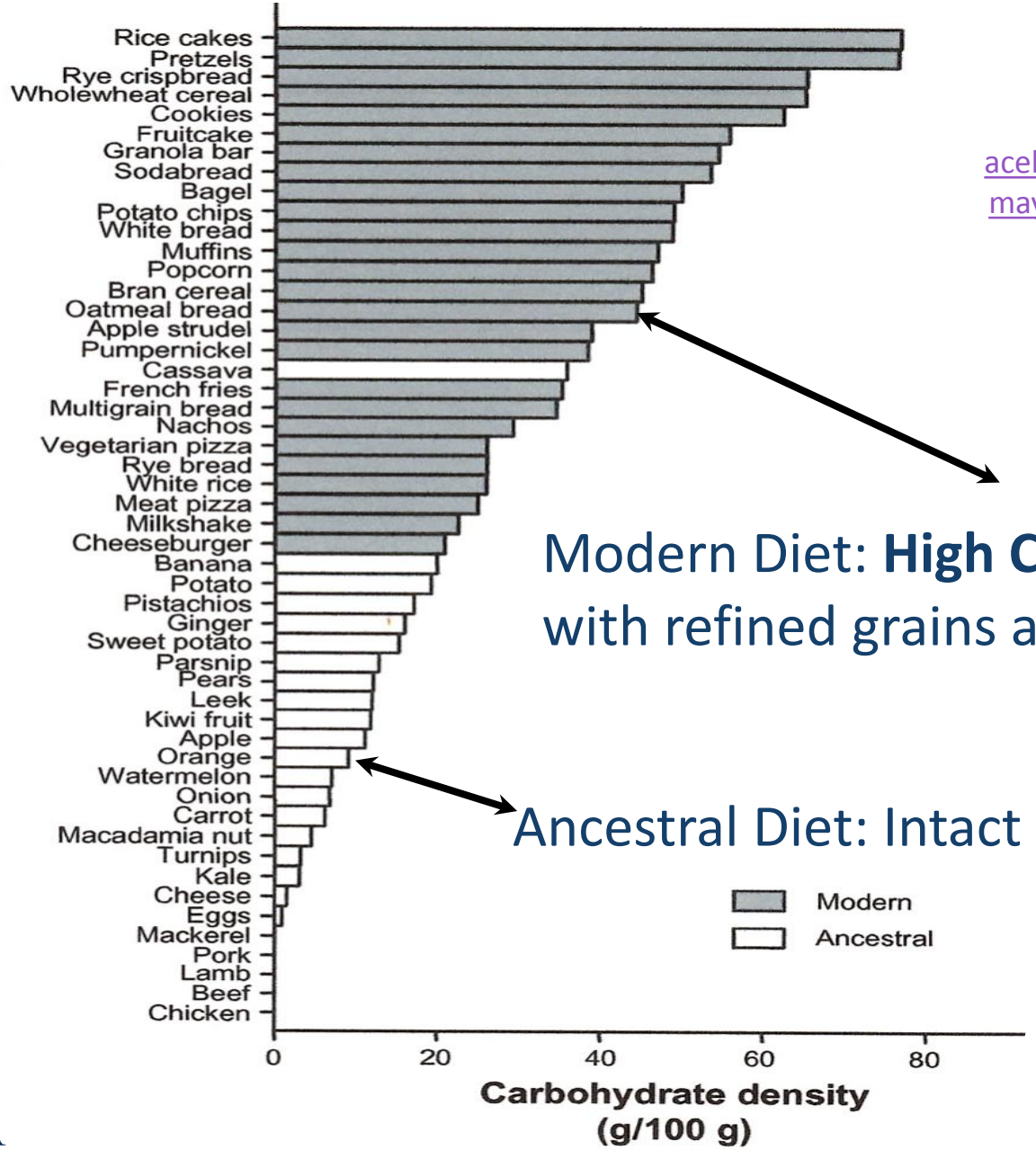

Spreadbury I. Comparison with ancestral diets suggests dense acellular carbohydrates promote an inflammatory microbiota, and may be the primary dietary cause of leptin resistance and obesity. Diabetes Metab Syndr Obes. 2012;5:175-89. Epub 2012 Jul 6.
Used with author's permission.

Modern Diet: **High Carbohydrate Density** is associated with refined grains and acellular "food" products

Ancestral Diet: Intact cellular whole foods

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Complex Chronic Disease and Inflammation

- Inflammation is involved in virtually every chronic disease process:
  - Cardiometabolic Disease
  - Cardiovascular Disease
  - Brain Disease
  - Degenerative Disease
  - Autoimmune Disease
  - Mental Illness

Metabolic Dysfunction

- Chronic inflammation = metabolic dysfunction
  - Atherosclerosis, CAD, MI
  - Diabetes 1 & 2, Insulin Resistance, Obesity
  - Non-alcoholic Fatty Liver Disease

Erridge C. Diet, commensals and the intestine as sources of pathogen-associated molecular patterns in atherosclerosis, type 2 diabetes and non-alcoholic fatty liver disease. Atherosclerosis. 2011 May;216(1):1-6. Epub 2011 Feb 26

Cardiometabolic Disease

"**…chronic inflammation** is recognized to be a key player in the pathogenesis of cardio-metabolic disease, including both **atherosclerosis and type 2 diabetes**."

Kosei Eguchi, Manabe I. Toll-Like Receptor, Lipotoxicity and Chronic Inflammaiton: The Pathological Link Between Obesity and Cardiometabolic Disease. J Atheroscler Thromb, 2014; 21:000-000.

Cardiometabolic Disease

- C-reactive protein is an independent risk factor for cardiovascular disease

- “Elevated CRP… associated with T2D”

Kosei Eguchi, Manabe I. Toll-Like Receptor, Lipotoxicity and Chronic Inflammaiton: The Pathological Link Between Obesity and Cardiometabolic Disease. J Atheroscler Thromb, 2014; 21:000-000.

Metabolic Syndrome

"Metabolic syndrome is associated with a **pro-inflammatory state**, and the role of visceral obesity is thought to be central to this."

S.A. Ritchie, J.M.C. Connell. The link between abdominal obesity, metabolic syndrome and cardiovascular disease. Nutrition, Metabolism & Cardiovascular Diseases (2007) 17, 319e326

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Conventional Assessment

Nutritional Deficiency

Inflammation

Genetic Factors

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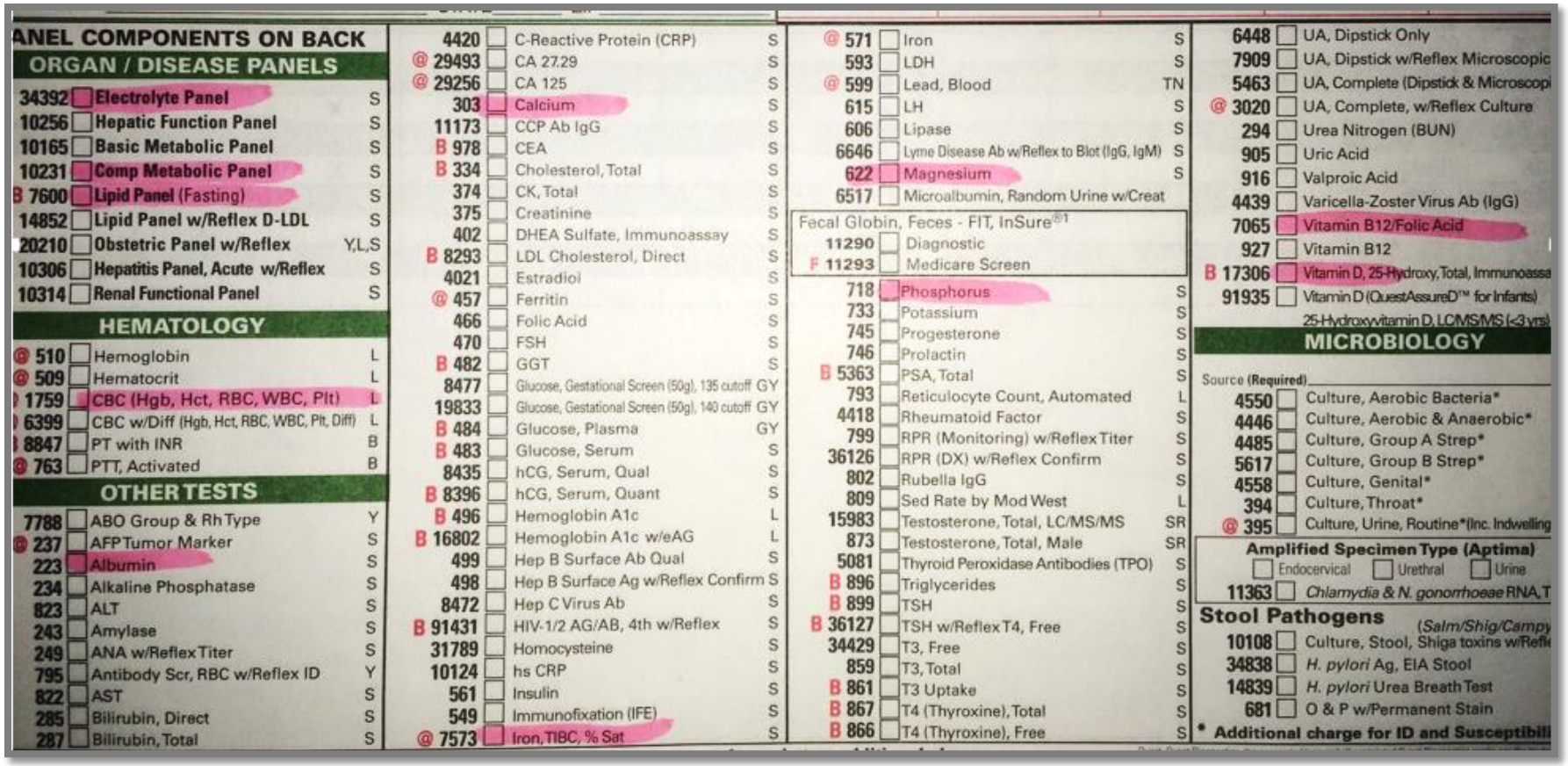
How Does Traditional Medicine Assess "Nutritional Status?"

- The Expeditious Evaluation
- Just use the Lab Form!



ANEL COMPONENTS ON BACK

ORGAN / DISEASE PANELS

34392	Electrolyte Panel	S
10256	Hepatic Function Panel	S
10165	Basic Metabolic Panel	S
10231	Comp Metabolic Panel	S
B 7600	Lipid Panel (Fasting)	S
14852	Lipid Panel w/Reflex D-LDL	S
20210	Obstetric Panel w/Reflex	Y,L,S
10306	Hepatitis Panel, Acute w/Reflex	S
10314	Renal Functional Panel	S

HEMATOLOGY

@ 510	Hemoglobin	L
@ 509	Hematocrit	L
1759	CBC (Hgb, Hct, RBC, WBC, Plt)	L
6399	CBC w/Diff (Hgb, Hct, RBC, WBC, Plt, Diff)	L
8847	PT with INR	B
@ 763	PTT, Activated	B

OTHER TESTS

7788	ABO Group & Rh Type	Y
@ 237	AFP Tumor Marker	S
223	Albumin	S
234	Alkaline Phosphatase	S
823	ALT	S
243	Amylase	S
249	ANA w/Reflex Titer	S
795	Antibody Scr, RBC w/Reflex ID	Y
822	AST	S
285	Bilirubin, Direct	S
287	Bilirubin, Total	S
4420	C-Reactive Protein (CRP)	S
@ 29493	CA 27.29	S
@ 29256	CA 125	S
303	Calcium	S
11173	CCP Ab IgG	S
B 978	CEA	S
B 334	Cholesterol, Total	S
374	CK, Total	S
375	Creatinine	S
402	DHEA Sulfate, Immunoassay	S
B 8293	LDL Cholesterol, Direct	S
4021	Estradiol	S
@ 457	Ferritin	S
466	Folic Acid	S
470	FSH	S
B 482	GGT	S
8477	Glucose, Gestational Screen (50g), 135 cutoff	GY
19833	Glucose, Gestational Screen (50g), 140 cutoff	GY
B 484	Glucose, Plasma	GY
B 483	Glucose, Serum	S
8435	hCG, Serum, Qual	S
B 8396	hCG, Serum, Quant	S
B 496	Hemoglobin A1c	L
B 16802	Hemoglobin A1c w/eAG	L
499	Hep B Surface Ab Qual	S
498	Hep B Surface Ag w/Reflex Confirm	S
8472	Hep C Virus Ab	S
B 91431	HIV-1/2 AG/AB, 4th w/Reflex	S
31789	Homocysteine	S
10124	hs CRP	S
561	Insulin	S
549	Immunofixation (IFE)	S
@ 7573	Iron, TIBC, % Sat	S
@ 571	Iron	S
593	LDH	S
@ 599	Lead, Blood	TN
615	LH	S
606	Lipase	S
6646	Lyme Disease Ab w/Reflex to Blot (IgG, IgM)	S
622	Magnesium	S
6517	Microalbumin, Random Urine w/Creat	
	Fecal Globin, Feces - FIT, InSure®1	
11290	Diagnostic	
F 11293	Medicare Screen	
718	Phosphorus	S
733	Potassium	S
745	Progesterone	S
746	Prolactin	S
B 5363	PSA, Total	S
793	Reticulocyte Count, Automated	L
4418	Rheumatoid Factor	S
799	RPR (Monitoring) w/Reflex Titer	S
36126	RPR (DX) w/Reflex Confirm	S
802	Rubella IgG	S
809	Sed Rate by Mod West	L
15983	Testosterone, Total, LC/MS/MS	SR
873	Testosterone, Total, Male	SR
5081	Thyroid Peroxidase Antibodies (TPO)	S
B 896	Triglycerides	S
B 899	TSH	S
B 36127	TSH w/Reflex T4, Free	S
34429	T3, Free	S
859	T3, Total	S
B 861	T3 Uptake	S
B 867	T4 (Thyroxine), Total	S
B 866	T4 (Thyroxine), Free	S
6448	UA, Dipstick Only	
7909	UA, Dipstick w/Reflex Microscopic	
5463	UA, Complete (Dipstick & Microscopi	
@ 3020	UA, Complete, w/Reflex Culture	
294	Urea Nitrogen (BUN)	
905	Uric Acid	
916	Valproic Acid	
4439	Varicella-Zoster Virus Ab (IgG)	
7065	Vitamin B12/Folic Acid	
927	Vitamin B12	
B 17306	Vitamin D, 25-Hydroxy, Total, Immunoassa	
91935	Vitamin D (QuestAssureD™ for Infants)	
	25-Hydroxyvitamin D, LC/MS/MS (<3 yrs)	

MICROBIOLOGY

Source (Required)

4550	Culture, Aerobic Bacteria*
4446	Culture, Aerobic & Anaerobic*
4485	Culture, Group A Strep*
5617	Culture, Group B Strep*
4558	Culture, Genital*
394	Culture, Throat*
@ 395	Culture, Urine, Routine* (Inc. Indwelling

Amplified Specimen Type (Aptima)

Endocervical Urethral Urine

11363	*Chlamydia & N. gonorrhoeae* RNA, T

Stool Pathogens (*Salm/Shig/Campy*

10108	Culture, Stool, Shiga toxins w/Refle
34838	*H. pylori* Ag, EIA Stool
14839	*H. pylori* Urea Breath Test
681	O & P w/Permanent Stain

* Additional charge for ID and Susceptibili

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How Does Traditional Medicine Assess "Nutritional Status?"

It's hard… because we try to look for disease, not function…

TABLE 1 Overview of the plasma concentrations and examples of functional biomarkers (nonexhaustive) for selected micronutrients[1]

Plasma concentration cutoffs for status assessment	Functional biomarkers	Clinical signs of deficiency
Vitamin A		
>1.05 μmol/L, normal <0.7 μmol/L, markedly deficient	Retinol-binding protein	Night blindness, xerophthalmia, anemia
Vitamin D [as 25(OH)D_3]		
>50 nmol/L, desirable <25 nmol/L, deficient	Alkaline phosphatase activity; serum osteocalcin	Decline of bone density, rickets in children, osteomalacia in adults, disturbed immune function
Vitamin B-6 (as pyridoxal phosphate)		
>30 nmol/L, normal <20 nmol/L, deficient	α-EGOT activity	Rare; neurologic symptoms, seborrhea, dermatitis, eczema, cheilosis, anemia (microcytic, hypochromic)
Folate (as folic acid)		
≥13.4 nmol/L, normal <6.8 nmol/L, markedly deficient In erythrocytes: ≥356 nmol/L, normal <317 nmol/L, deficient	HCys, urinary excretion of FIGLU	Anemia (macrocytic, hyperchromic), cheilosis, glossitis, neurologic symptoms in elderly, higher risk of cardiovascular diseases (through HCys)
Vitamin B-12		
≥147 pmol/L, normal <110 nmol/L, markedly deficient	HCys, methylmalonic acid	Anemia (macrocytic, hyperchromic), neurologic symptoms
Calcium		
Excretion in urine, 2.5–6.0 mmol/d, normal	Excretion of hydroxyproline in urine	Decline of bone density, osteoporosis, rickets in children, osteomalacia in adults
Iron		
Ferritin ≥15 μg/L, normal ≥12 μg/L (in children aged <5 y), normal	Hemoglobin, hematocrit, total iron binding capacity	Anemia (microcytic, hypochromic)
Zinc		
Adults 13–19 μmol/L, normal <11.5 μmol/L, deficient Children <10 y: <9.9 μmol/L, deficient Pregnant women Trimester 1: <8.6 μmol/L, deficient Trimester 2: 7.6 μmol/L, deficient	Activity of zinc superoxide dismutase, zinc binding capacity in thalassemia	Growth retardation in children, disturbed immune function (especially cellular), reduced glucose tolerance, skin lesions, impaired wound healing

[1] Based on data from references 49,79. α-EGOT, erythrocyte α-glutamate oxaloacetate transferase; FIGLE, formiminoglutamic acid; HCy, homocysteine.

By the time we see this…we've missed the boat!

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Integrative Assessment

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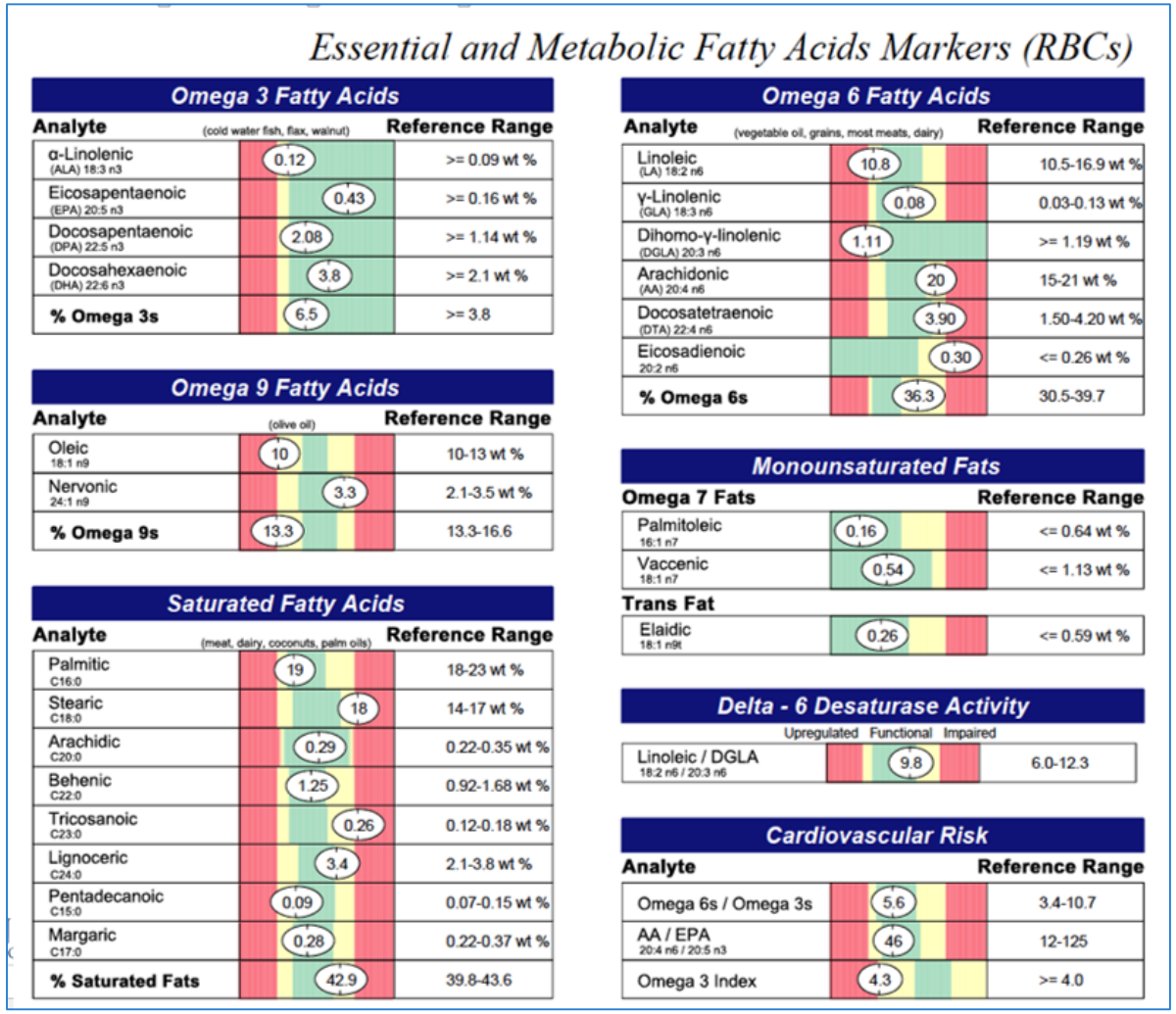
44-year old female



Essential and Metabolic Fatty Acids Markers (RBCs)

Omega 3 Fatty Acids

Analyte (cold water fish, flax, walnut)		Reference Range
α-Linolenic (ALA) 18:3 n3	0.12	>= 0.09 wt %
Eicosapentaenoic (EPA) 20:5 n3	0.43	>= 0.16 wt %
Docosapentaenoic (DPA) 22:5 n3	2.08	>= 1.14 wt %
Docosahexaenoic (DHA) 22:6 n3	3.8	>= 2.1 wt %
% Omega 3s	6.5	>= 3.8

Omega 9 Fatty Acids

Analyte (olive oil)		Reference Range
Oleic 18:1 n9	10	10-13 wt %
Nervonic 24:1 n9	3.3	2.1-3.5 wt %
% Omega 9s	13.3	13.3-16.6

Saturated Fatty Acids

Analyte (meat, dairy, coconuts, palm oils)		Reference Range
Palmitic C16:0	19	18-23 wt %
Stearic C18:0	18	14-17 wt %
Arachidic C20:0	0.29	0.22-0.35 wt %
Behenic C22:0	1.25	0.92-1.68 wt %
Tricosanoic C23:0	0.26	0.12-0.18 wt %
Lignoceric C24:0	3.4	2.1-3.8 wt %
Pentadecanoic C15:0	0.09	0.07-0.15 wt %
Margaric C17:0	0.28	0.22-0.37 wt %
% Saturated Fats	42.9	39.8-43.6

Omega 6 Fatty Acids

Analyte (vegetable oil, grains, most meats, dairy)		Reference Range
Linoleic (LA) 18:2 n6	10.8	10.5-16.9 wt %
γ-Linolenic (GLA) 18:3 n6	0.08	0.03-0.13 wt %
Dihomo-γ-linolenic (DGLA) 20:3 n6	1.11	>= 1.19 wt %
Arachidonic (AA) 20:4 n6	20	15-21 wt %
Docosatetraenoic (DTA) 22:4 n6	3.90	1.50-4.20 wt %
Eicosadienoic 20:2 n6	0.30	<= 0.26 wt %
% Omega 6s	36.3	30.5-39.7

Monounsaturated Fats

Omega 7 Fats		Reference Range
Palmitoleic 16:1 n7	0.16	<= 0.64 wt %
Vaccenic 18:1 n7	0.54	<= 1.13 wt %
Trans Fat		
Elaidic 18:1 n9t	0.26	<= 0.59 wt %

Delta - 6 Desaturase Activity

	Upregulated Functional Impaired	
Linoleic / DGLA 18:2 n6 / 20:3 n6	9.8	6.0-12.3

Cardiovascular Risk

Analyte		Reference Range
Omega 6s / Omega 3s	5.6	3.4-10.7
AA / EPA 20:4 n6 / 20:5 n3	46	12-125
Omega 3 Index	4.3	>= 4.0

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44-year old female

Elemental Markers (RBCs)

Nutrient Elements

Element	Reference Range	Reference Range
Copper	0.443	0.466-0.721 mcg/g
Magnesium	41.4	30.1-56.5 mcg/g
Manganese	0.016	0.007-0.038 mcg/g
Potassium	3,678	2,220-3,626 mcg/g
Selenium	0.28	0.25-0.76 mcg/g
Zinc	10.6	7.8-13.1 mcg/g

Toxic Elements

Element	Reference Range	Reference Range
Lead	0.028	<= 0.048 mcg/g
Mercury	<dl	<= 0.0039 mcg/g
Antimony	0.001	<= 0.002 mcg/g
Arsenic	0.019	<= 0.071 mcg/g
Cadmium	0.000	<= 0.001 mcg/g
Tin	<dl	<= 0.0009 mcg/g

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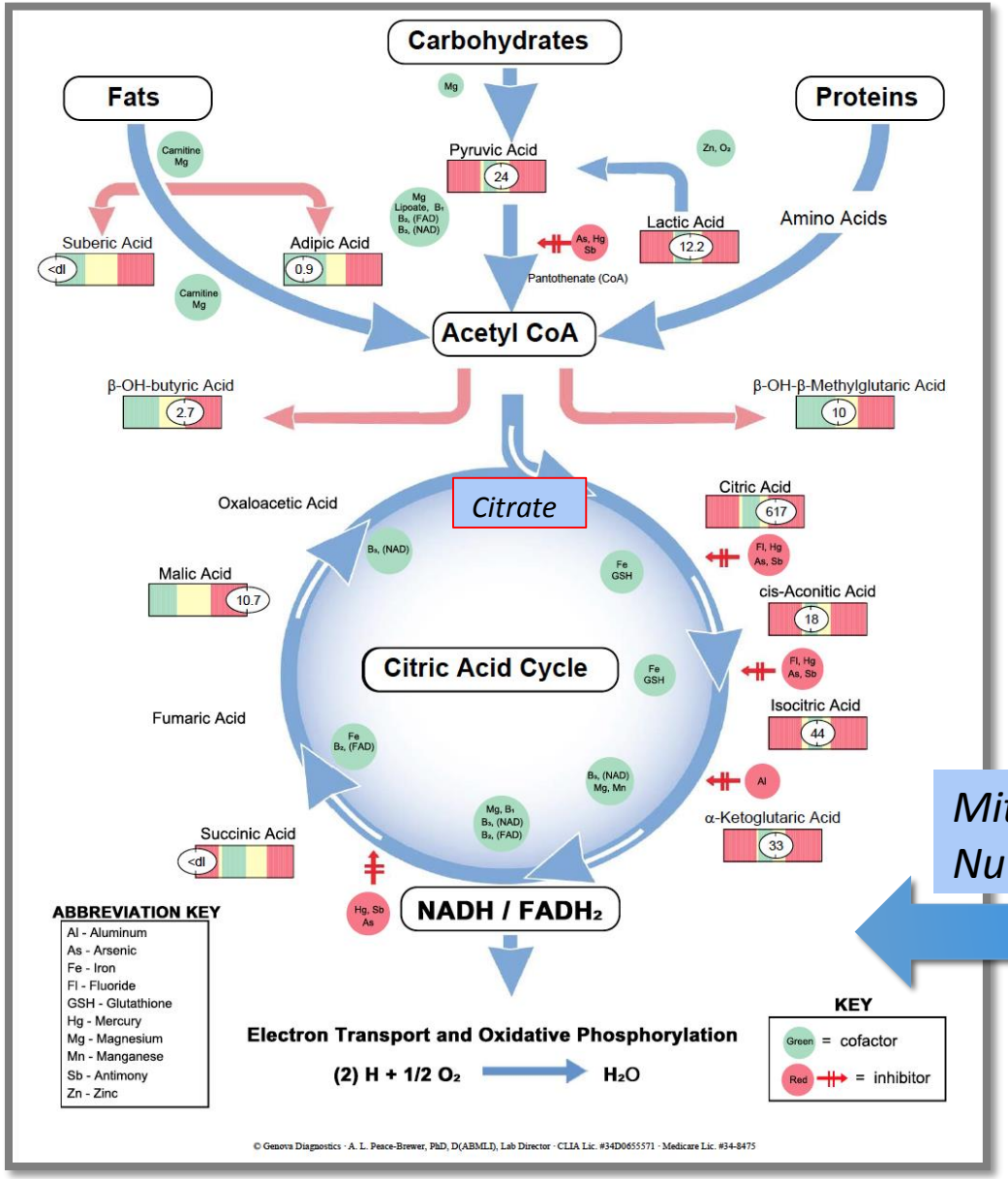
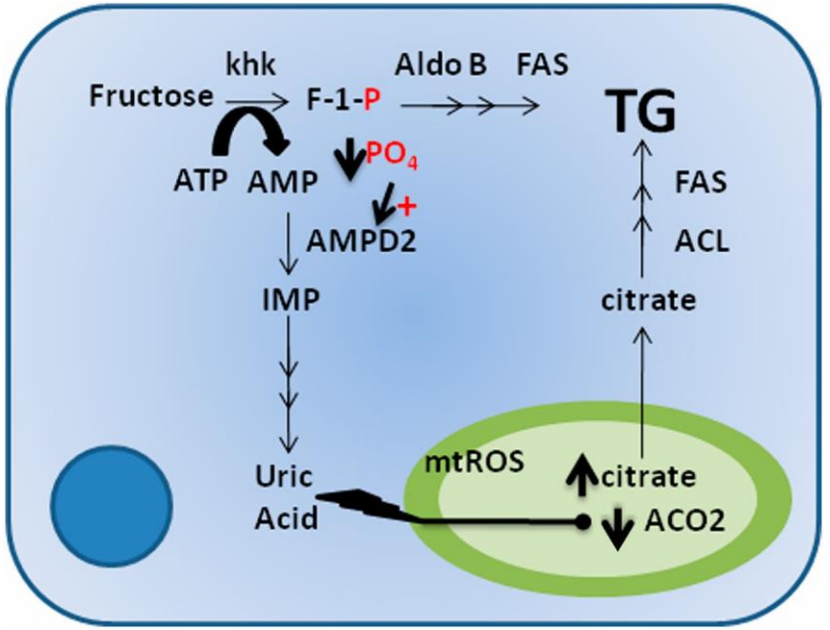


Fructose metabolism demands ATP



Mitochondrial performance demands Nutritional elements

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23-year old female

WHY TEST?

You know they Probably need D3….

Oxidative Stress Markers

Oxidative Stress Markers

		Reference Range
Glutathione (whole blood)	1,138	>= 669 micromol/L
Lipid Peroxides (urine)	4.2	<=10.0 micromol/g Creat.
8-OHdG (urine)	9	<=16 mcg/g Creat.
Coenzyme Q10, Ubiquinone (plasma)	0.28	0.43-1.49 mcg/mL

The Oxidative Stress reference ranges are based on an adult population.

Vitamin D

	Inside Range	Outside Range	Reference Range
25 - OH Vitamin D •		28	50-100 ng/mL

Deficiency = < 20 ng/mL (< 50 nmol/L)
Insufficiency = 20-49 ng/mL (50-124 nmol/L)
Optimal = 50-100 ng/mL (125-250 nmol/L)
Excessive = > 100 ng/mL (> 250 nmol/L)

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23-year old female

WHY TEST?

How would you know a 23-year old needs CoQ10???

Oxidative Stress Markers

Oxidative Stress Markers

		Reference Range
Glutathione (whole blood)	1,138	>= 669 micromol/L
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WHY TEST?

44-year old female

Omega 3 Fatty Acids

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α-Linolenic (ALA) 18:3 n3	0.12	>= 0.09 wt %
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23-year old female

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Docosahexaenoic (DHA) 22:6 n3	3.1	>= 2.1 wt %
% Omega 3s	4.5	>= 3.8

Cardiovascular Risk

Analyte		Reference Range
Omega 6s / Omega 3s	8.0	3.4-10.7
AA / EPA 20:4 n6 / 20:5 n3	49	12-125
Omega 3 Index	3.5	>= 4.0

The Essential Fatty Acid reference ranges are based on an adult population.

*Because you **can't predict** the need!!!*

GENOVA DIAGNOSTICS

Acta Psychiatrica Scandinavica

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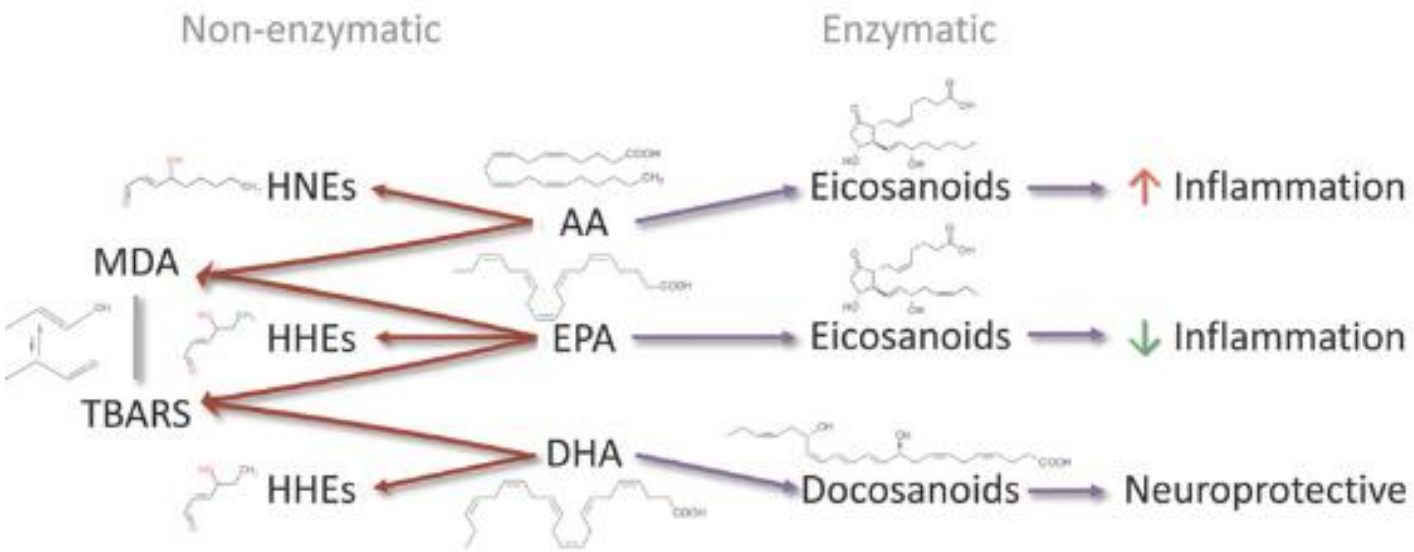
ACTA PSYCHIATRICA SCANDINAVICA



Non-enzymatic lipid peroxidation products of AA, EPA and DHA.

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http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4171779/pdf/acps0130-0163.pdf

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Review

Effects of oxidative stress on fatty acid- and one-carbon-metabolism in psychiatric and cardiovascular disease comorbidity

Summations

- Oxidative stress and its effects on fatty acid and 1-carbon cycle metabolism may underlie co-occurrence of cardiovascular and psychiatric disorders.
- During oxidative stress, fatty acids shorten in chain length and decrease in unsaturation and peroxidation, while the 1-carbon cycle shifts from the methylation to the transsulfuration pathway.
- While these changes initially may enhance oxidative stress resistance, persisting chronically, they may cause damage.

Results: Oxidative stress, mainly generated in mitochondria, is implicated in both psychiatric and cardiovascular pathophysiology. Oxidative stress affects the intrinsically linked FA and 1-C cycle metabolism: FAs decrease in chain length and unsaturation (particularly omega-3 polyunsaturated FAs), and lipid peroxidation

Nijmegen, the Netherlands and "Donders Institute for Brain, Cognition and Behavior, Radboud University, Nijmegen, the Netherlands

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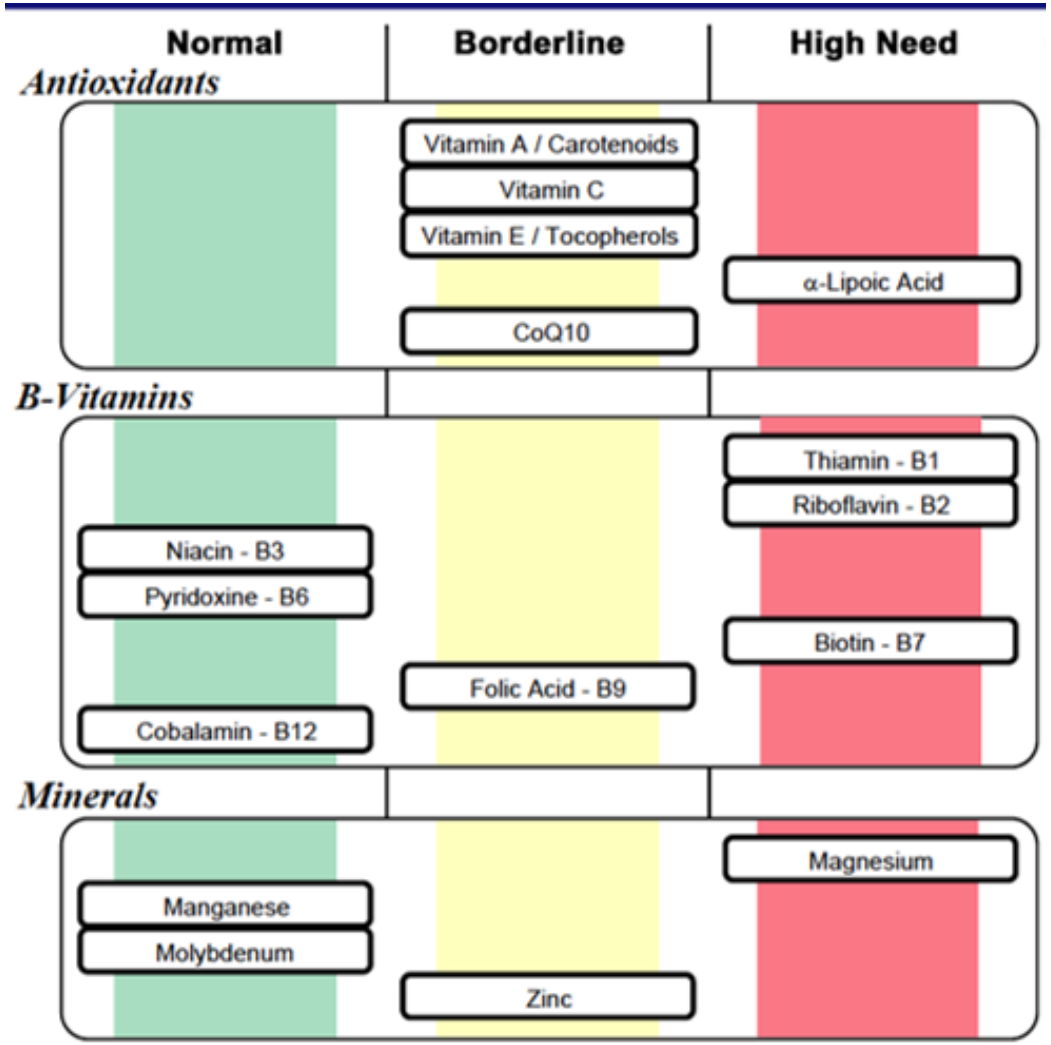

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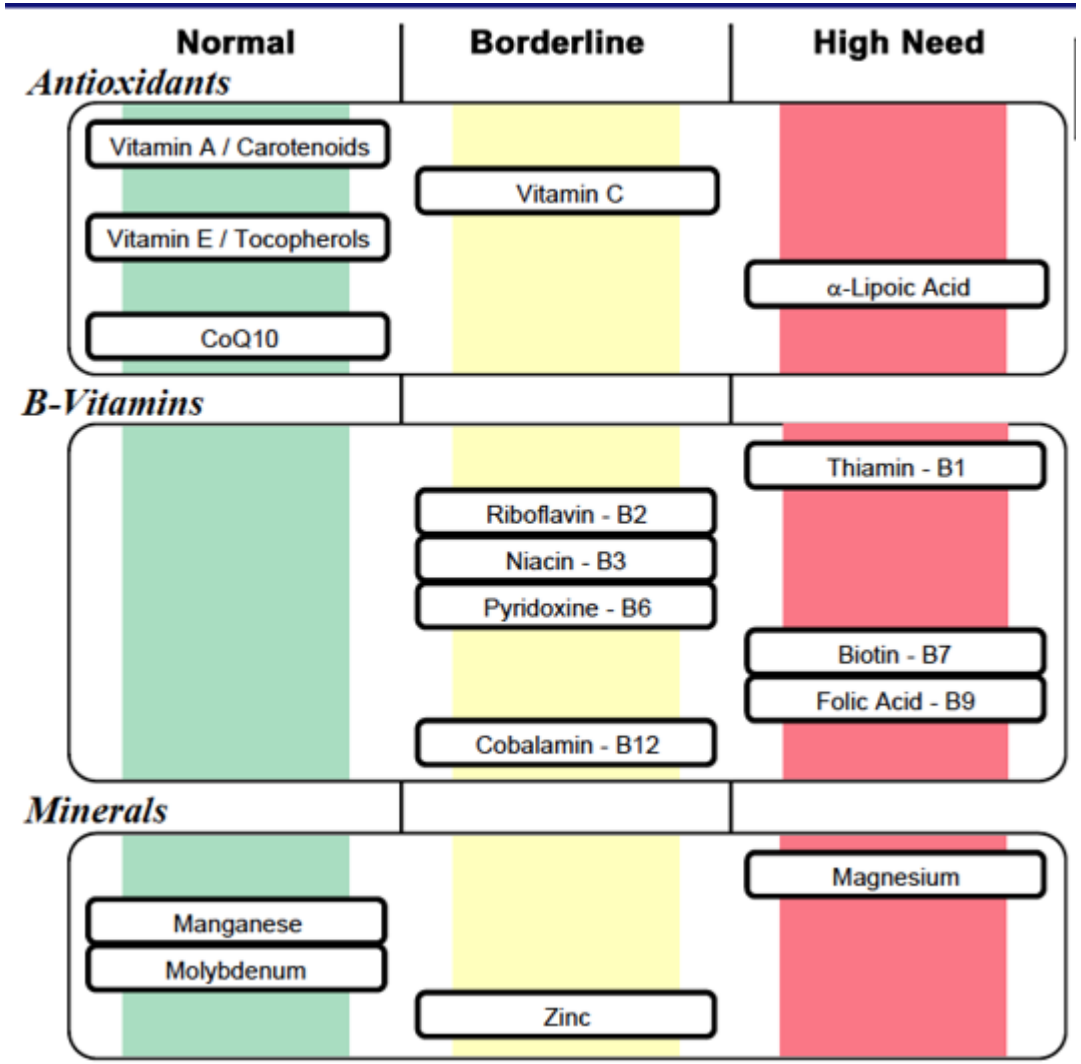

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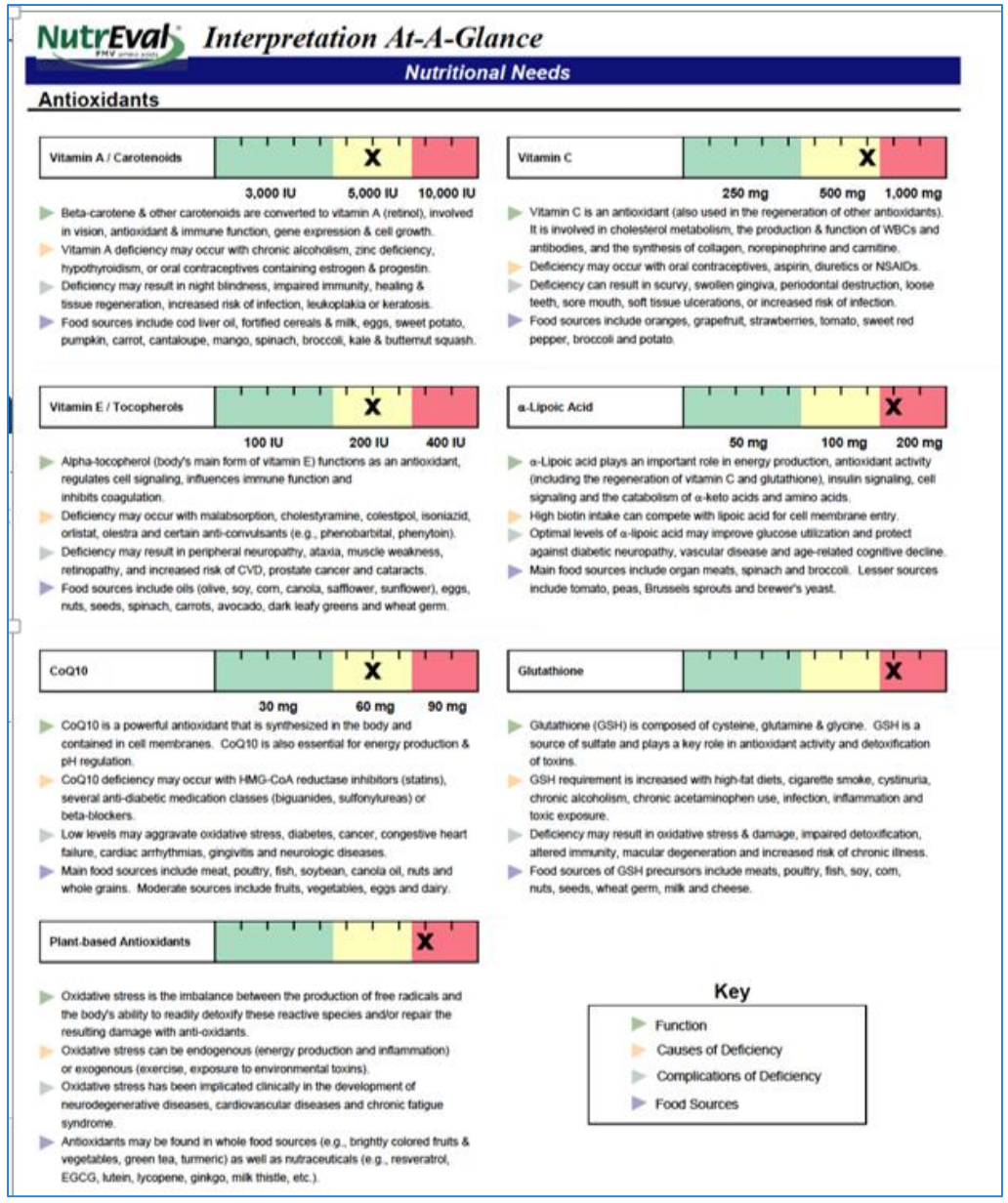


NutrEval Interpretation At-A-Glance

Nutritional Needs

Antioxidants

Vitamin A / Carotenoids

3,000 IU | 5,000 IU | 10,000 IU

- Beta-carotene & other carotenoids are converted to vitamin A (retinol), involved in vision, antioxidant & immune function, gene expression & cell growth.
- Vitamin A deficiency may occur with chronic alcoholism, zinc deficiency, hypothyroidism, or oral contraceptives containing estrogen & progestin.
- Deficiency may result in night blindness, impaired immunity, healing & tissue regeneration, increased risk of infection, leukoplakia or keratosis.
- Food sources include cod liver oil, fortified cereals & milk, eggs, sweet potato, pumpkin, carrot, cantaloupe, mango, spinach, broccoli, kale & butternut squash.

Vitamin C

250 mg | 500 mg | 1,000 mg

- Vitamin C is an antioxidant (also used in the regeneration of other antioxidants). It is involved in cholesterol metabolism, the production & function of WBCs and antibodies, and the synthesis of collagen, norepinephrine and carnitine.
- Deficiency may occur with oral contraceptives, aspirin, diuretics or NSAIDs.
- Deficiency can result in scurvy, swollen gingiva, periodontal destruction, loose teeth, sore mouth, soft tissue ulcerations, or increased risk of infection.
- Food sources include oranges, grapefruit, strawberries, tomato, sweet red pepper, broccoli and potato.

Vitamin E / Tocopherols

100 IU | 200 IU | 400 IU

- Alpha-tocopherol (body's main form of vitamin E) functions as an antioxidant, regulates cell signaling, influences immune function and inhibits coagulation.
- Deficiency may occur with malabsorption, cholestyramine, colestipol, isoniazid, orlistat, olestra and certain anti-convulsants (e.g., phenobarbital, phenytoin).
- Deficiency may result in peripheral neuropathy, ataxia, muscle weakness, retinopathy, and increased risk of CVD, prostate cancer and cataracts.
- Food sources include oils (olive, soy, corn, canola, safflower, sunflower), eggs, nuts, seeds, spinach, carrots, avocado, dark leafy greens and wheat germ.

α-Lipoic Acid

50 mg | 100 mg | 200 mg

- α-Lipoic acid plays an important role in energy production, antioxidant activity (including the regeneration of vitamin C and glutathione), insulin signaling, cell signaling and the catabolism of α-keto acids and amino acids.
- High biotin intake can compete with lipoic acid for cell membrane entry.
- Optimal levels of α-lipoic acid may improve glucose utilization and protect against diabetic neuropathy, vascular disease and age-related cognitive decline.
- Main food sources include organ meats, spinach and broccoli. Lesser sources include tomato, peas, Brussels sprouts and brewer's yeast.

CoQ10

30 mg | 60 mg | 90 mg

- CoQ10 is a powerful antioxidant that is synthesized in the body and contained in cell membranes. CoQ10 is also essential for energy production & pH regulation.
- CoQ10 deficiency may occur with HMG-CoA reductase inhibitors (statins), several anti-diabetic medication classes (biguanides, sulfonylureas) or beta-blockers.
- Low levels may aggravate oxidative stress, diabetes, cancer, congestive heart failure, cardiac arrhythmias, gingivitis and neurologic diseases.
- Main food sources include meat, poultry, fish, soybean, canola oil, nuts and whole grains. Moderate sources include fruits, vegetables, eggs and dairy.

Glutathione

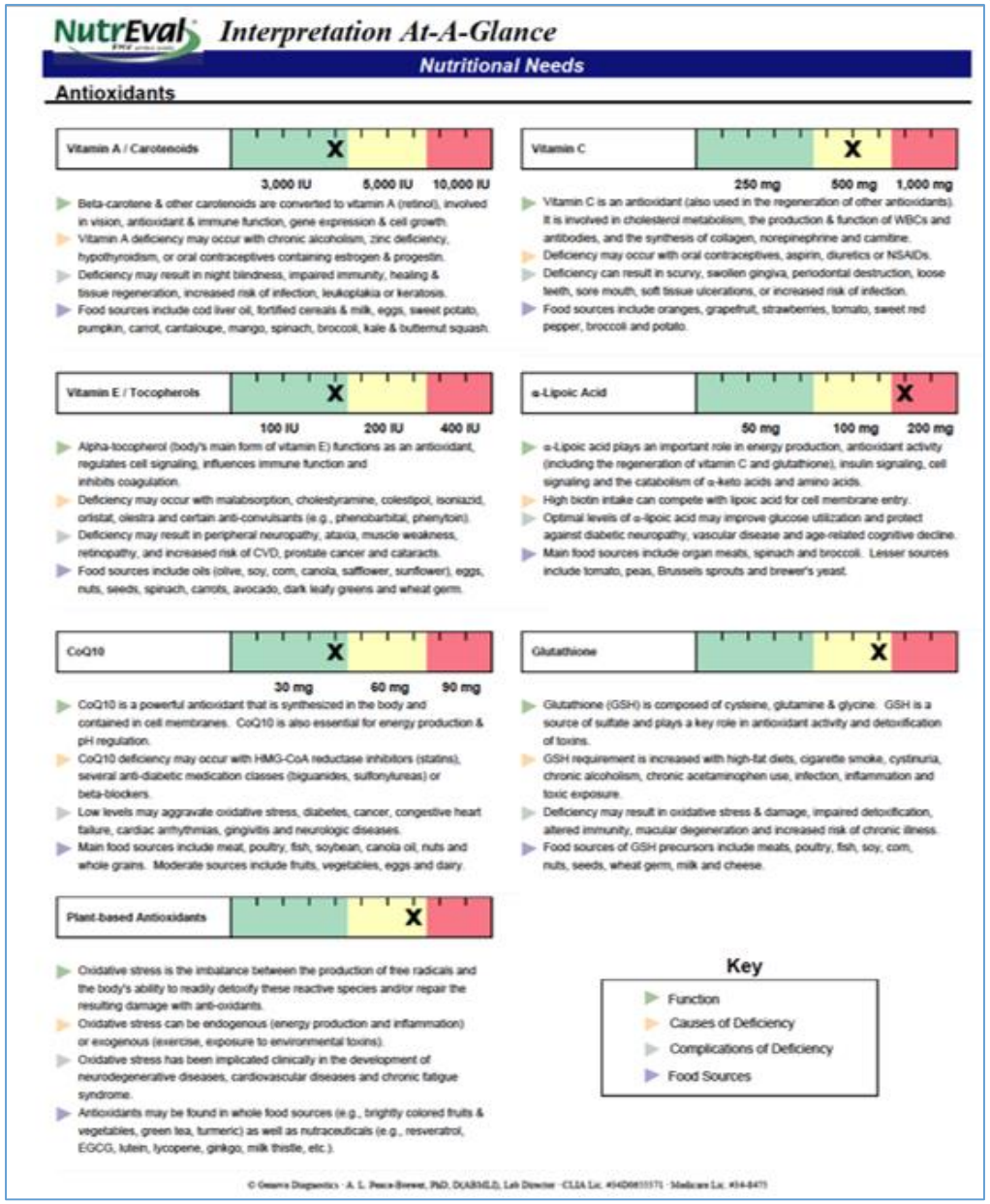
- Glutathione (GSH) is composed of cysteine, glutamine & glycine. GSH is a source of sulfate and plays a key role in antioxidant activity and detoxification of toxins.
- GSH requirement is increased with high-fat diets, cigarette smoke, cystinuria, chronic alcoholism, chronic acetaminophen use, infection, inflammation and toxic exposure.
- Deficiency may result in oxidative stress & damage, impaired detoxification, altered immunity, macular degeneration and increased risk of chronic illness.
- Food sources of GSH precursors include meats, poultry, fish, soy, corn, nuts, seeds, wheat germ, milk and cheese.

Plant-based Antioxidants

- Oxidative stress is the imbalance between the production of free radicals and the body's ability to readily detoxify these reactive species and/or repair the resulting damage with anti-oxidants.
- Oxidative stress can be endogenous (energy production and inflammation) or exogenous (exercise, exposure to environmental toxins).
- Oxidative stress has been implicated clinically in the development of neurodegenerative diseases, cardiovascular diseases and chronic fatigue syndrome.
- Antioxidants may be found in whole food sources (e.g., brightly colored fruits & vegetables, green tea, turmeric) as well as nutraceuticals (e.g., resveratrol, EGCG, lutein, lycopene, ginkgo, milk thistle, etc.).

Key

- Function
- Causes of Deficiency
- Complications of Deficiency
- Food Sources



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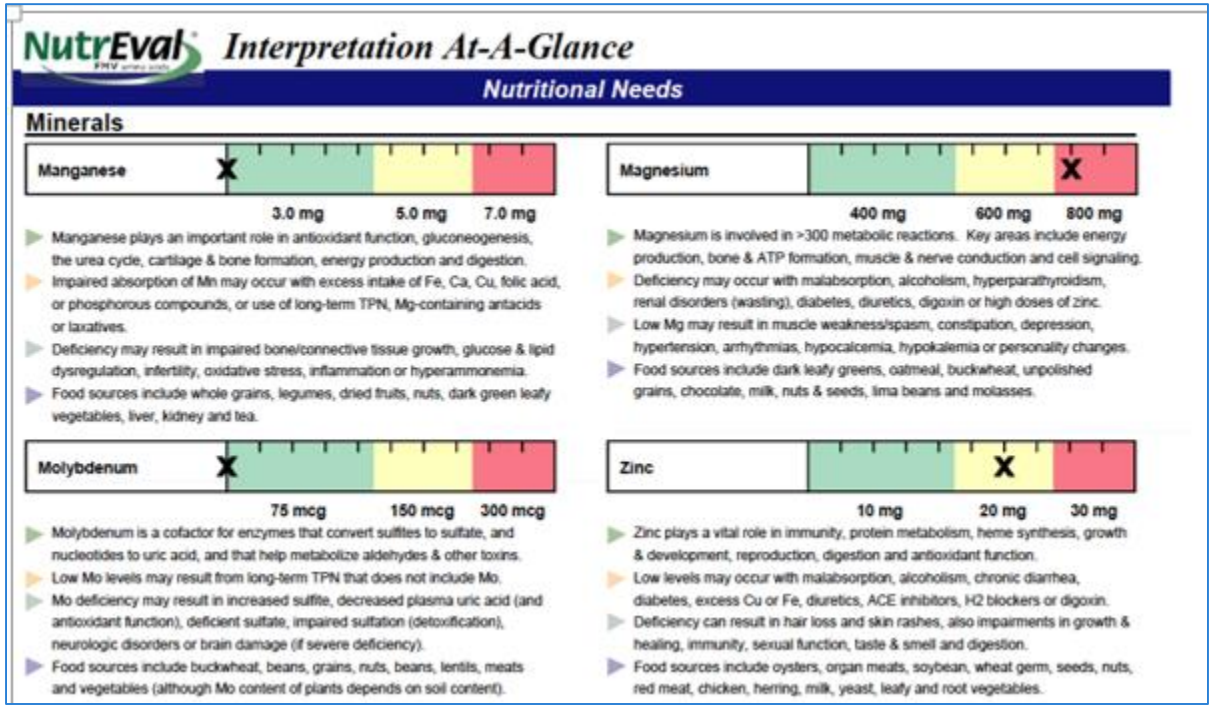


NutrEval FMV amino acids

Interpretation At-A-Glance

Nutritional Needs

Minerals

Manganese

3.0 mg | 5.0 mg | 7.0 mg

- Manganese plays an important role in antioxidant function, gluconeogenesis, the urea cycle, cartilage & bone formation, energy production and digestion.
- Impaired absorption of Mn may occur with excess intake of Fe, Ca, Cu, folic acid, or phosphorous compounds, or use of long-term TPN, Mg-containing antacids or laxatives.
- Deficiency may result in impaired bone/connective tissue growth, glucose & lipid dysregulation, infertility, oxidative stress, inflammation or hyperammonemia.
- Food sources include whole grains, legumes, dried fruits, nuts, dark green leafy vegetables, liver, kidney and tea.

Magnesium

400 mg | 600 mg | 800 mg

- Magnesium is involved in >300 metabolic reactions. Key areas include energy production, bone & ATP formation, muscle & nerve conduction and cell signaling.
- Deficiency may occur with malabsorption, alcoholism, hyperparathyroidism, renal disorders (wasting), diabetes, diuretics, digoxin or high doses of zinc.
- Low Mg may result in muscle weakness/spasm, constipation, depression, hypertension, arrhythmias, hypocalcemia, hypokalemia or personality changes.
- Food sources include dark leafy greens, oatmeal, buckwheat, unpolished grains, chocolate, milk, nuts & seeds, lima beans and molasses.

Molybdenum

75 mcg | 150 mcg | 300 mcg

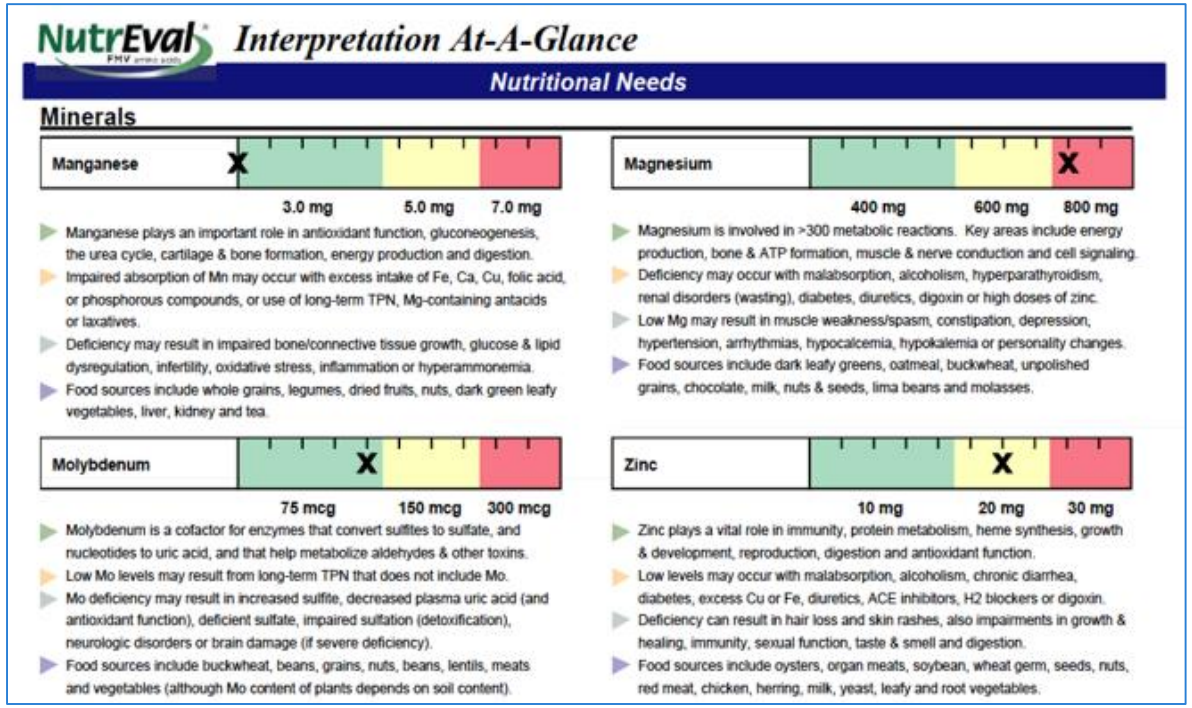
- Molybdenum is a cofactor for enzymes that convert sulfites to sulfate, and nucleotides to uric acid, and that help metabolize aldehydes & other toxins.
- Low Mo levels may result from long-term TPN that does not include Mo.
- Mo deficiency may result in increased sulfite, decreased plasma uric acid (and antioxidant function), deficient sulfate, impaired sulfation (detoxification), neurologic disorders or brain damage (if severe deficiency).
- Food sources include buckwheat, beans, grains, nuts, beans, lentils, meats and vegetables (although Mo content of plants depends on soil content).

Zinc

10 mg | 20 mg | 30 mg

- Zinc plays a vital role in immunity, protein metabolism, heme synthesis, growth & development, reproduction, digestion and antioxidant function.
- Low levels may occur with malabsorption, alcoholism, chronic diarrhea, diabetes, excess Cu or Fe, diuretics, ACE inhibitors, H2 blockers or digoxin.
- Deficiency can result in hair loss and skin rashes, also impairments in growth & healing, immunity, sexual function, taste & smell and digestion.
- Food sources include oysters, organ meats, soybean, wheat germ, seeds, nuts, red meat, chicken, herring, milk, yeast, leafy and root vegetables.

Mother



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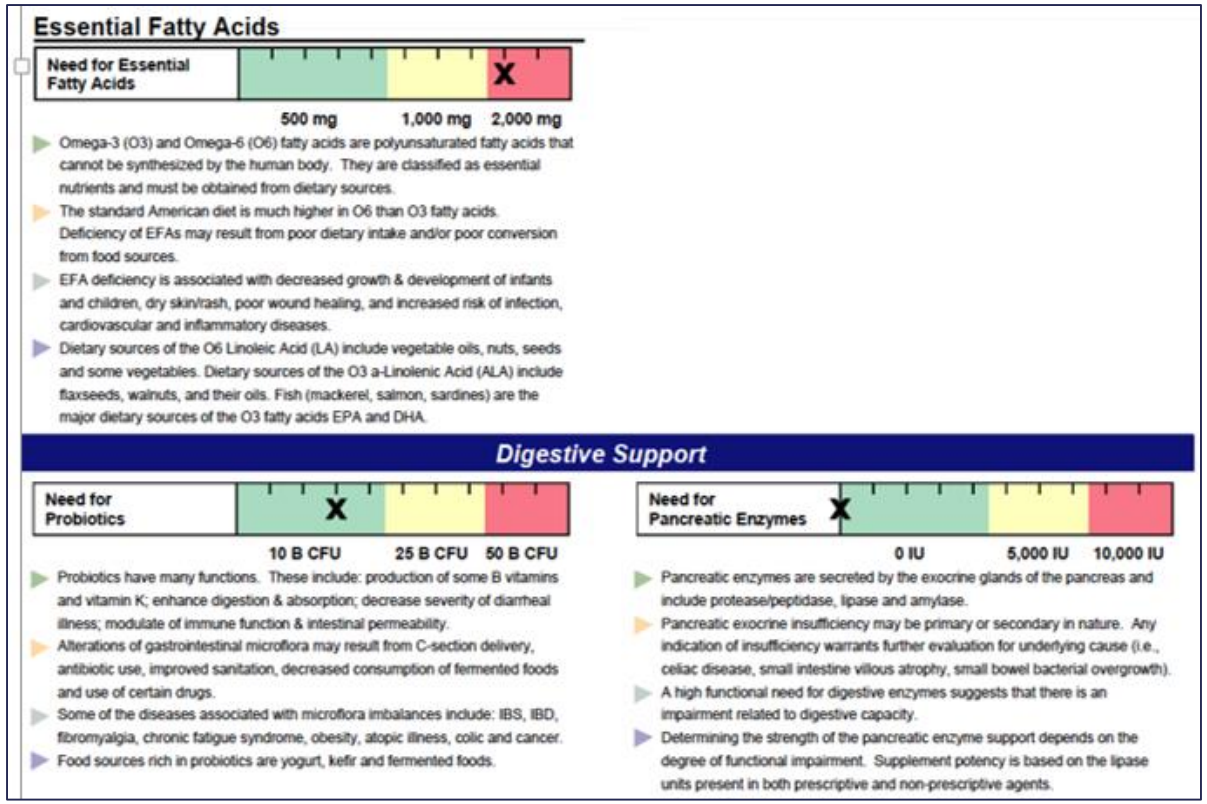
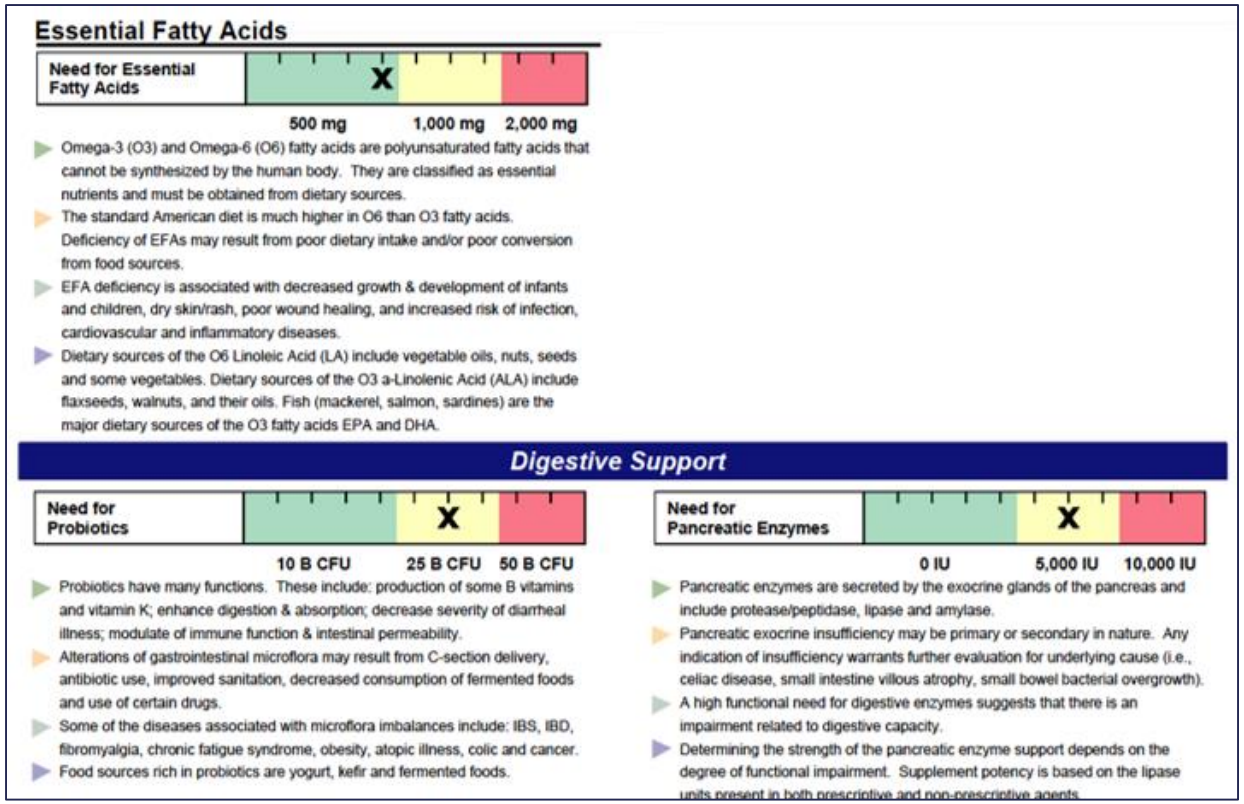


Daughter



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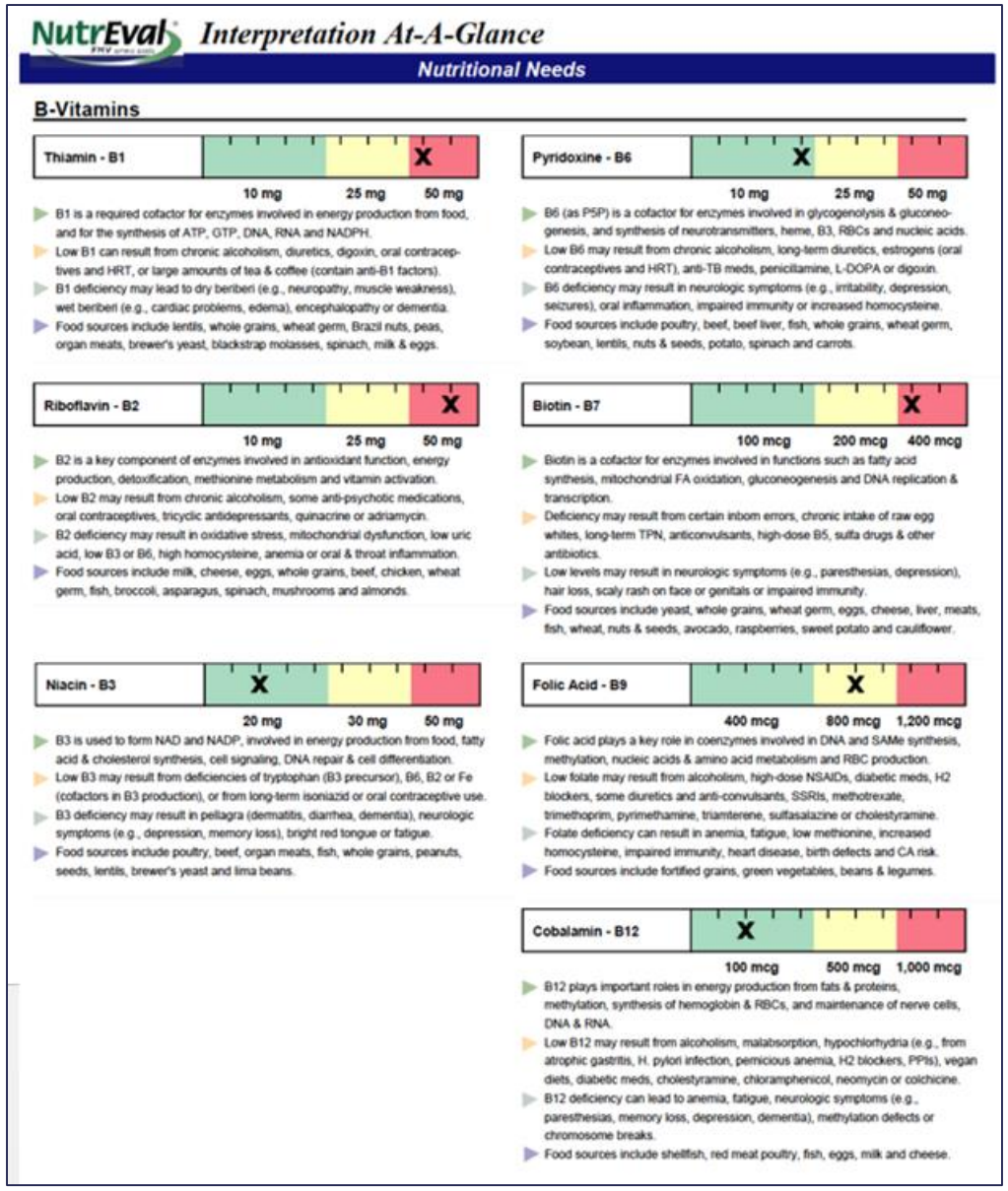


NutrEval® Interpretation At-A-Glance

Nutritional Needs

B-Vitamins

Thiamin - B1

10 mg | 25 mg | 50 mg — X

- B1 is a required cofactor for enzymes involved in energy production from food, and for the synthesis of ATP, GTP, DNA, RNA and NADPH.
- Low B1 can result from chronic alcoholism, diuretics, digoxin, oral contraceptives and HRT, or large amounts of tea & coffee (contain anti-B1 factors).
- B1 deficiency may lead to dry beriberi (e.g., neuropathy, muscle weakness), wet beriberi (e.g., cardiac problems, edema), encephalopathy or dementia.
- Food sources include lentils, whole grains, wheat germ, Brazil nuts, peas, organ meats, brewer's yeast, blackstrap molasses, spinach, milk & eggs.

Pyridoxine - B6

10 mg | 25 mg | 50 mg — X

- B6 (as P5P) is a cofactor for enzymes involved in glycogenolysis & gluconeogenesis, and synthesis of neurotransmitters, heme, B3, RBCs and nucleic acids.
- Low B6 may result from chronic alcoholism, long-term diuretics, estrogens (oral contraceptives and HRT), anti-TB meds, penicillamine, L-DOPA or digoxin.
- B6 deficiency may result in neurologic symptoms (e.g., irritability, depression, seizures), oral inflammation, impaired immunity or increased homocysteine.
- Food sources include poultry, beef, beef liver, fish, whole grains, wheat germ, soybean, lentils, nuts & seeds, potato, spinach and carrots.

Riboflavin - B2

10 mg | 25 mg | 50 mg — X

- B2 is a key component of enzymes involved in antioxidant function, energy production, detoxification, methionine metabolism and vitamin activation.
- Low B2 may result from chronic alcoholism, some anti-psychotic medications, oral contraceptives, tricyclic antidepressants, quinacrine or adriamycin.
- B2 deficiency may result in oxidative stress, mitochondrial dysfunction, low uric acid, low B3 or B6, high homocysteine, anemia or oral & throat inflammation.
- Food sources include milk, cheese, eggs, whole grains, beef, chicken, wheat germ, fish, broccoli, asparagus, spinach, mushrooms and almonds.

Biotin - B7

100 mcg | 200 mcg | 400 mcg — X

- Biotin is a cofactor for enzymes involved in functions such as fatty acid synthesis, mitochondrial FA oxidation, gluconeogenesis and DNA replication & transcription.
- Deficiency may result from certain inborn errors, chronic intake of raw egg whites, long-term TPN, anticonvulsants, high-dose B5, sulfa drugs & other antibiotics.
- Low levels may result in neurologic symptoms (e.g., paresthesias, depression), hair loss, scaly rash on face or genitals or impaired immunity.
- Food sources include yeast, whole grains, wheat germ, eggs, cheese, liver, meats, fish, wheat, nuts & seeds, avocado, raspberries, sweet potato and cauliflower.

Niacin - B3

20 mg | 30 mg | 50 mg — X

- B3 is used to form NAD and NADP, involved in energy production from food, fatty acid & cholesterol synthesis, cell signaling, DNA repair & cell differentiation.
- Low B3 may result from deficiencies of tryptophan (B3 precursor), B6, B2 or Fe (cofactors in B3 production), or from long-term isoniazid or oral contraceptive use.
- B3 deficiency may result in pellagra (dermatitis, diarrhea, dementia), neurologic symptoms (e.g., depression, memory loss), bright red tongue or fatigue.
- Food sources include poultry, beef, organ meats, fish, whole grains, peanuts, seeds, lentils, brewer's yeast and lima beans.

Folic Acid - B9

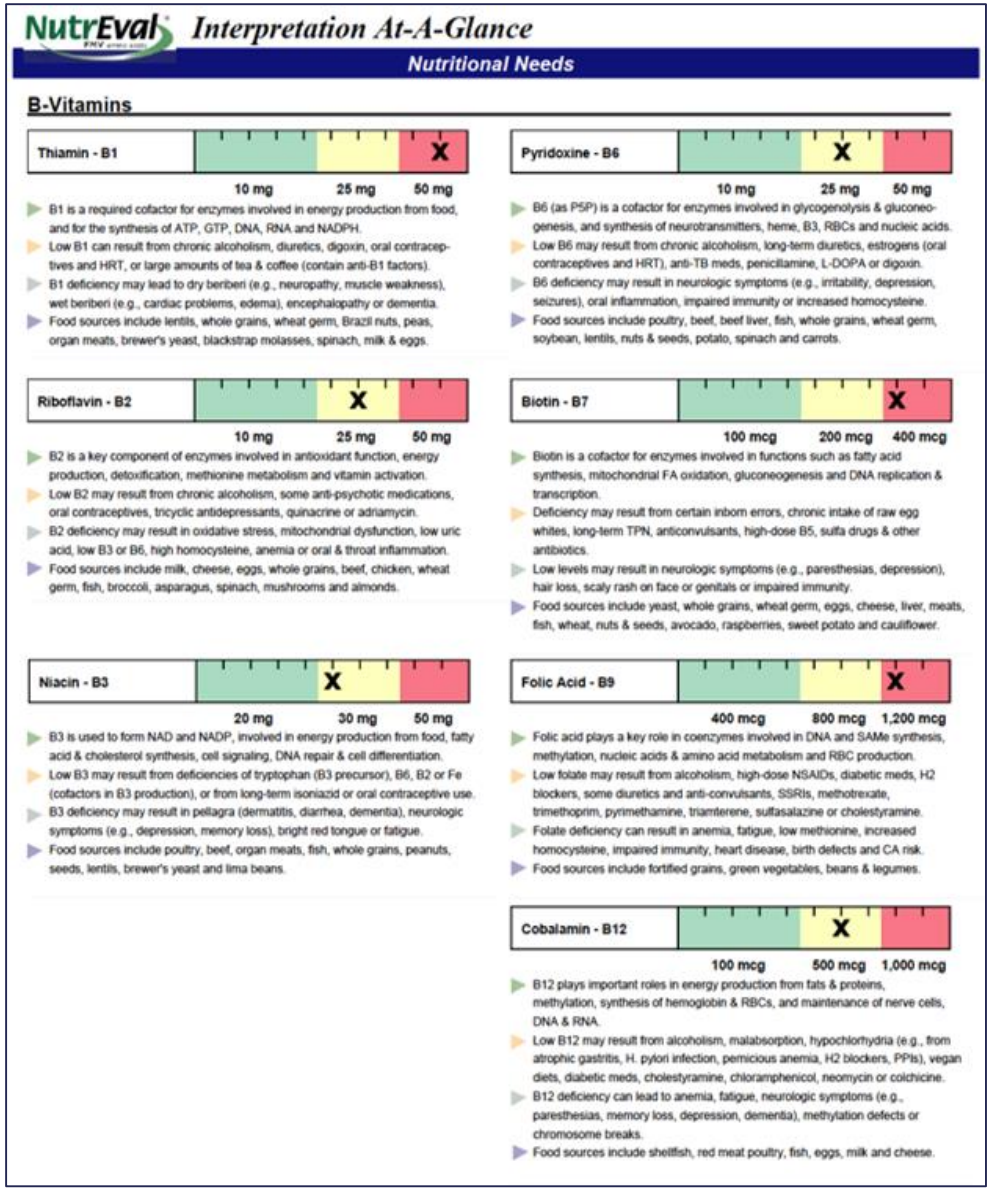
400 mcg | 800 mcg | 1,200 mcg — X

- Folic acid plays a key role in coenzymes involved in DNA and SAMe synthesis, methylation, nucleic acids & amino acid metabolism and RBC production.
- Low folate may result from alcoholism, high-dose NSAIDs, diabetic meds, H2 blockers, some diuretics and anti-convulsants, SSRIs, methotrexate, trimethoprim, pyrimethamine, triamterene, sulfasalazine or cholestyramine.
- Folate deficiency can result in anemia, fatigue, low methionine, increased homocysteine, impaired immunity, heart disease, birth defects and CA risk.
- Food sources include fortified grains, green vegetables, beans & legumes.

Cobalamin - B12

100 mcg | 500 mcg | 1,000 mcg — X

- B12 plays important roles in energy production from fats & proteins, methylation, synthesis of hemoglobin & RBCs, and maintenance of nerve cells, DNA & RNA.
- Low B12 may result from alcoholism, malabsorption, hypochlorhydria (e.g., from atrophic gastritis, H. pylori infection, pernicious anemia, H2 blockers, PPIs), vegan diets, diabetic meds, cholestyramine, chloramphenicol, neomycin or colchicine.
- B12 deficiency can lead to anemia, fatigue, neurologic symptoms (e.g., paresthesias, memory loss, depression, dementia), methylation defects or chromosome breaks.
- Food sources include shellfish, red meat poultry, fish, eggs, milk and cheese.



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400 mcg | 800 mcg | 1,200 mcg — X

- Folic acid plays a key role in coenzymes involved in DNA and SAMe synthesis, methylation, nucleic acids & amino acid metabolism and RBC production.
- Low folate may result from alcoholism, high-dose NSAIDs, diabetic meds, H2 blockers, some diuretics and anti-convulsants, SSRIs, methotrexate, trimethoprim, pyrimethamine, triamterene, sulfasalazine or cholestyramine.
- Folate deficiency can result in anemia, fatigue, low methionine, increased homocysteine, impaired immunity, heart disease, birth defects and CA risk.
- Food sources include fortified grains, green vegetables, beans & legumes.

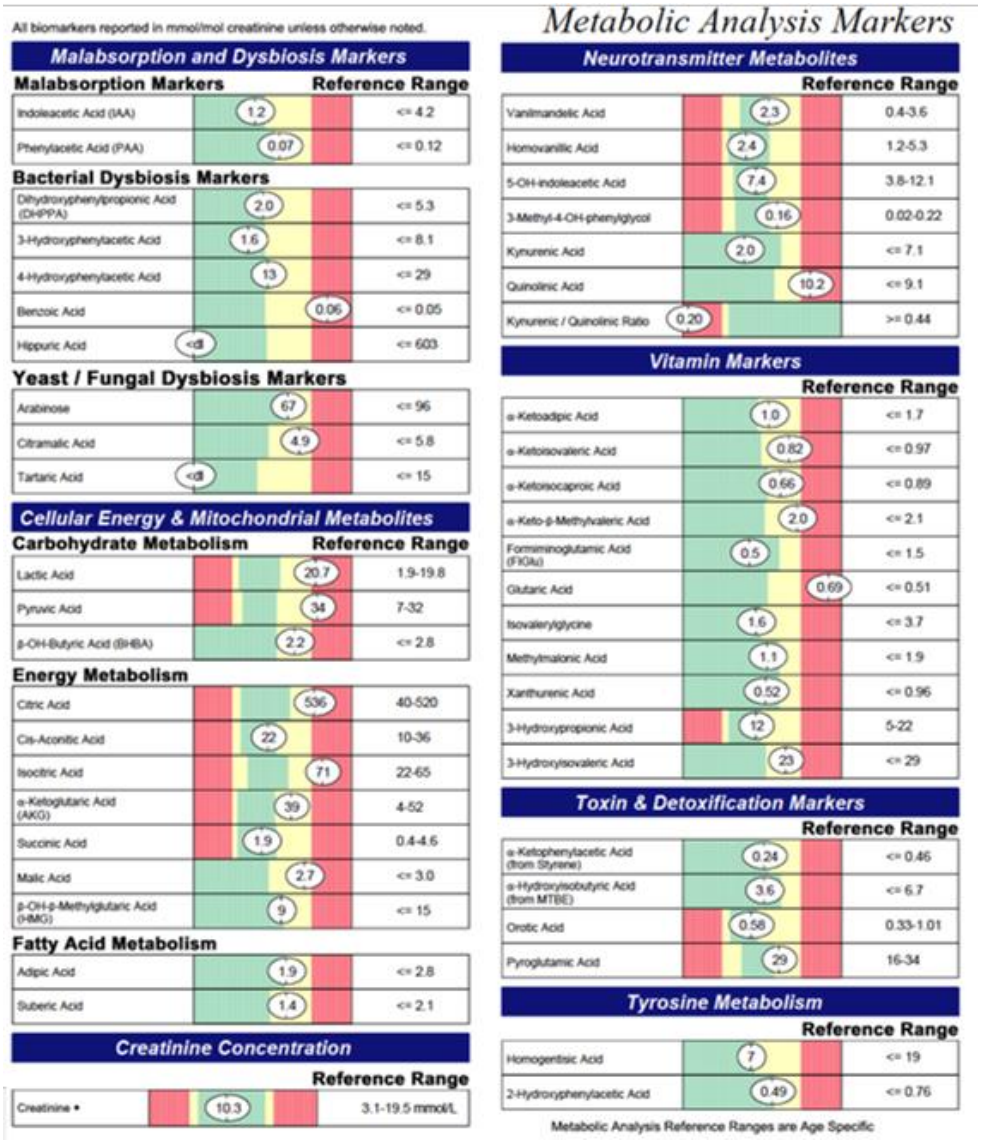
Cobalamin - B12

100 mcg | 500 mcg | 1,000 mcg — X

- B12 plays important roles in energy production from fats & proteins, methylation, synthesis of hemoglobin & RBCs, and maintenance of nerve cells, DNA & RNA.
- Low B12 may result from alcoholism, malabsorption, hypochlorhydria (e.g., from atrophic gastritis, H. pylori infection, pernicious anemia, H2 blockers, PPIs), vegan diets, diabetic meds, cholestyramine, chloramphenicol, neomycin or colchicine.
- B12 deficiency can lead to anemia, fatigue, neurologic symptoms (e.g., paresthesias, memory loss, depression, dementia), methylation defects or chromosome breaks.
- Food sources include shellfish, red meat poultry, fish, eggs, milk and cheese.

GENOVA DIAGNOSTICS

Daughter



All biomarkers reported in mmol/mol creatinine unless otherwise noted.

Malabsorption and Dysbiosis Markers

Malabsorption Markers		Reference Range
Indoleacetic Acid (IAA)	1.2	<= 4.2
Phenylacetic Acid (PAA)	0.07	<= 0.12
Bacterial Dysbiosis Markers		
Dihydroxyphenylpropionic Acid (DHPPA)	2.0	<= 5.3
3-Hydroxyphenylacetic Acid	1.6	<= 8.1
4-Hydroxyphenylacetic Acid	13	<= 29
Benzoic Acid	0.06	<= 0.05
Hippuric Acid	<dl	<= 603
Yeast / Fungal Dysbiosis Markers		
Arabinose	67	<= 96
Citramalic Acid	4.9	<= 5.8
Tartaric Acid	<dl	<= 15

Cellular Energy & Mitochondrial Metabolites

Carbohydrate Metabolism		Reference Range
Lactic Acid	20.7	1.9-19.8
Pyruvic Acid	34	7-32
β-OH-Butyric Acid (BHBA)	2.2	<= 2.8
Energy Metabolism		
Citric Acid	536	40-520
Cis-Aconitic Acid	22	10-36
Isocitric Acid	71	22-65
α-Ketoglutaric Acid (AKG)	39	4-52
Succinic Acid	1.9	0.4-4.6
Malic Acid	2.7	<= 3.0
β-OH-β-Methylglutaric Acid (HMG)	9	<= 15
Fatty Acid Metabolism		
Adipic Acid	1.9	<= 2.8
Suberic Acid	1.4	<= 2.1

Creatinine Concentration

		Reference Range
Creatinine •	10.3	3.1-19.5 mmol/L

Metabolic Analysis Markers

Neurotransmitter Metabolites

		Reference Range
Vanilmandelic Acid	2.3	0.4-3.6
Homovanillic Acid	2.4	1.2-5.3
5-OH-indoleacetic Acid	7.4	3.8-12.1
3-Methyl-4-OH-phenylglycol	0.16	0.02-0.22
Kynurenic Acid	2.0	<= 7.1
Quinolinic Acid	10.2	<= 9.1
Kynurenic / Quinolinic Ratio	0.20	>= 0.44

Vitamin Markers

		Reference Range
α-Ketoadipic Acid	1.0	<= 1.7
α-Ketoisovaleric Acid	0.82	<= 0.97
α-Ketoisocaproic Acid	0.66	<= 0.89
α-Keto-β-Methylvaleric Acid	2.0	<= 2.1
Formiminoglutamic Acid (FIGlu)	0.5	<= 1.5
Glutaric Acid	0.69	<= 0.51
Isovalerylglycine	1.6	<= 3.7
Methylmalonic Acid	1.1	<= 1.9
Xanthurenic Acid	0.52	<= 0.96
3-Hydroxypropionic Acid	12	5-22
3-Hydroxyisovaleric Acid	23	<= 29

Toxin & Detoxification Markers

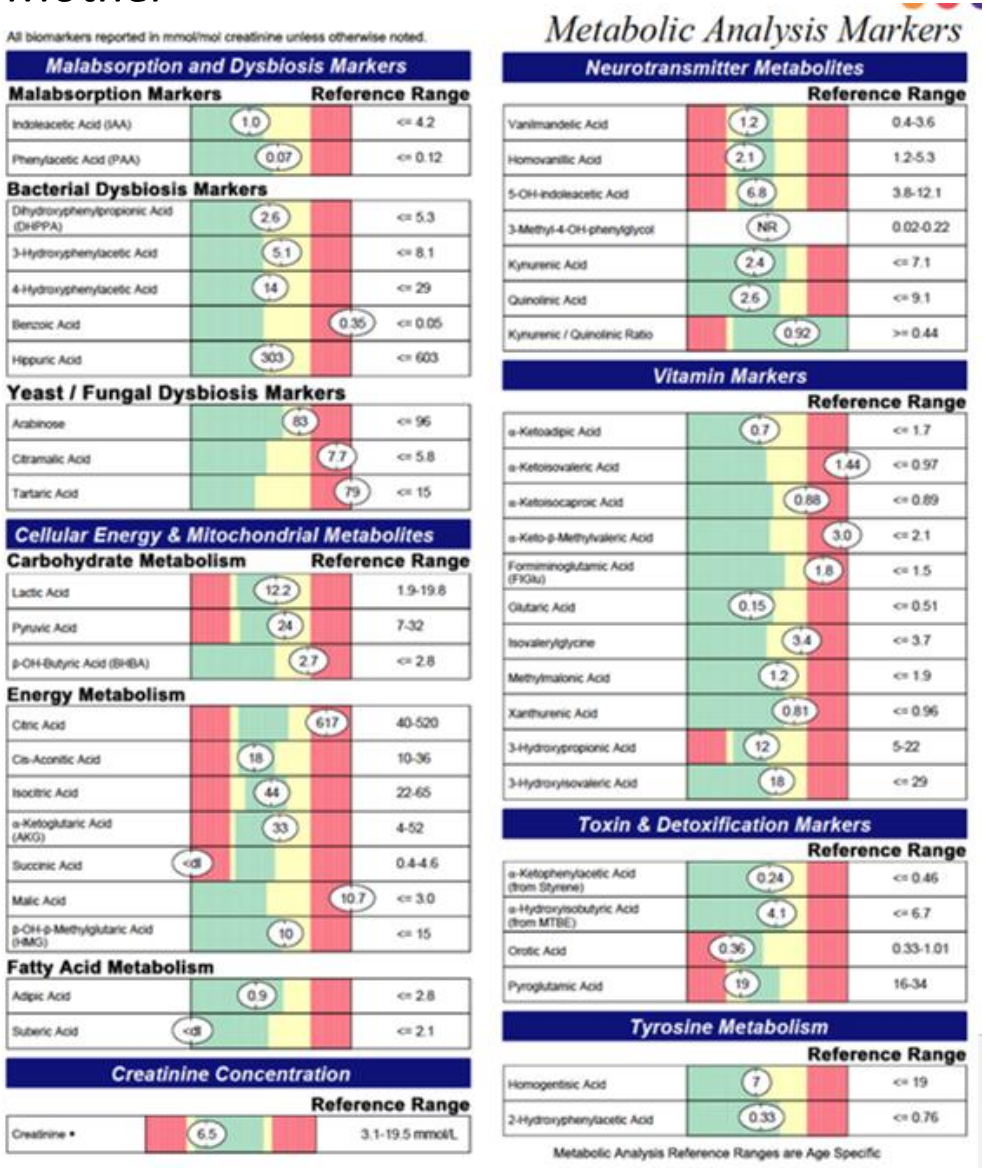
		Reference Range
α-Ketophenylacetic Acid (from Styrene)	0.24	<= 0.46
α-Hydroxyisobutyric Acid (from MTBE)	3.6	<= 6.7
Orotic Acid	0.58	0.33-1.01
Pyroglutamic Acid	29	16-34

Tyrosine Metabolism

		Reference Range
Homogentisic Acid	7	<= 19
2-Hydroxyphenylacetic Acid	0.49	<= 0.76

Metabolic Analysis Reference Ranges are Age Specific

Mother



All biomarkers reported in mmol/mol creatinine unless otherwise noted.

Malabsorption and Dysbiosis Markers

Malabsorption Markers		Reference Range
Indoleacetic Acid (IAA)	1.0	<= 4.2
Phenylacetic Acid (PAA)	0.07	<= 0.12
Bacterial Dysbiosis Markers		
Dihydroxyphenylpropionic Acid (DHPPA)	2.6	<= 5.3
3-Hydroxyphenylacetic Acid	5.1	<= 8.1
4-Hydroxyphenylacetic Acid	14	<= 29
Benzoic Acid	0.35	<= 0.05
Hippuric Acid	303	<= 603
Yeast / Fungal Dysbiosis Markers		
Arabinose	83	<= 96
Citramalic Acid	7.7	<= 5.8
Tartaric Acid	79	<= 15

Cellular Energy & Mitochondrial Metabolites

Carbohydrate Metabolism		Reference Range
Lactic Acid	12.2	1.9-19.8
Pyruvic Acid	24	7-32
β-OH-Butyric Acid (BHBA)	2.7	<= 2.8
Energy Metabolism		
Citric Acid	617	40-520
Cis-Aconitic Acid	18	10-36
Isocitric Acid	44	22-65
α-Ketoglutaric Acid (AKG)	33	4-52
Succinic Acid	<dl	0.4-4.6
Malic Acid	10.7	<= 3.0
β-OH-β-Methylglutaric Acid (HMG)	10	<= 15
Fatty Acid Metabolism		
Adipic Acid	0.9	<= 2.8
Suberic Acid	<dl	<= 2.1

Creatinine Concentration

		Reference Range
Creatinine •	6.5	3.1-19.5 mmol/L

Metabolic Analysis Markers

Neurotransmitter Metabolites

		Reference Range
Vanilmandelic Acid	1.2	0.4-3.6
Homovanillic Acid	2.1	1.2-5.3
5-OH-indoleacetic Acid	6.8	3.8-12.1
3-Methyl-4-OH-phenylglycol	NR	0.02-0.22
Kynurenic Acid	2.4	<= 7.1
Quinolinic Acid	2.6	<= 9.1
Kynurenic / Quinolinic Ratio	0.92	>= 0.44

Vitamin Markers

		Reference Range
α-Ketoadipic Acid	0.7	<= 1.7
α-Ketoisovaleric Acid	1.44	<= 0.97
α-Ketoisocaproic Acid	0.88	<= 0.89
α-Keto-β-Methylvaleric Acid	3.0	<= 2.1
Formiminoglutamic Acid (FIGlu)	1.8	<= 1.5
Glutaric Acid	0.15	<= 0.51
Isovalerylglycine	3.4	<= 3.7
Methylmalonic Acid	1.2	<= 1.9
Xanthurenic Acid	0.81	<= 0.96
3-Hydroxypropionic Acid	12	5-22
3-Hydroxyisovaleric Acid	18	<= 29

Toxin & Detoxification Markers

		Reference Range
α-Ketophenylacetic Acid (from Styrene)	0.24	<= 0.46
α-Hydroxyisobutyric Acid (from MTBE)	4.1	<= 6.7
Orotic Acid	0.36	0.33-1.01
Pyroglutamic Acid	19	16-34

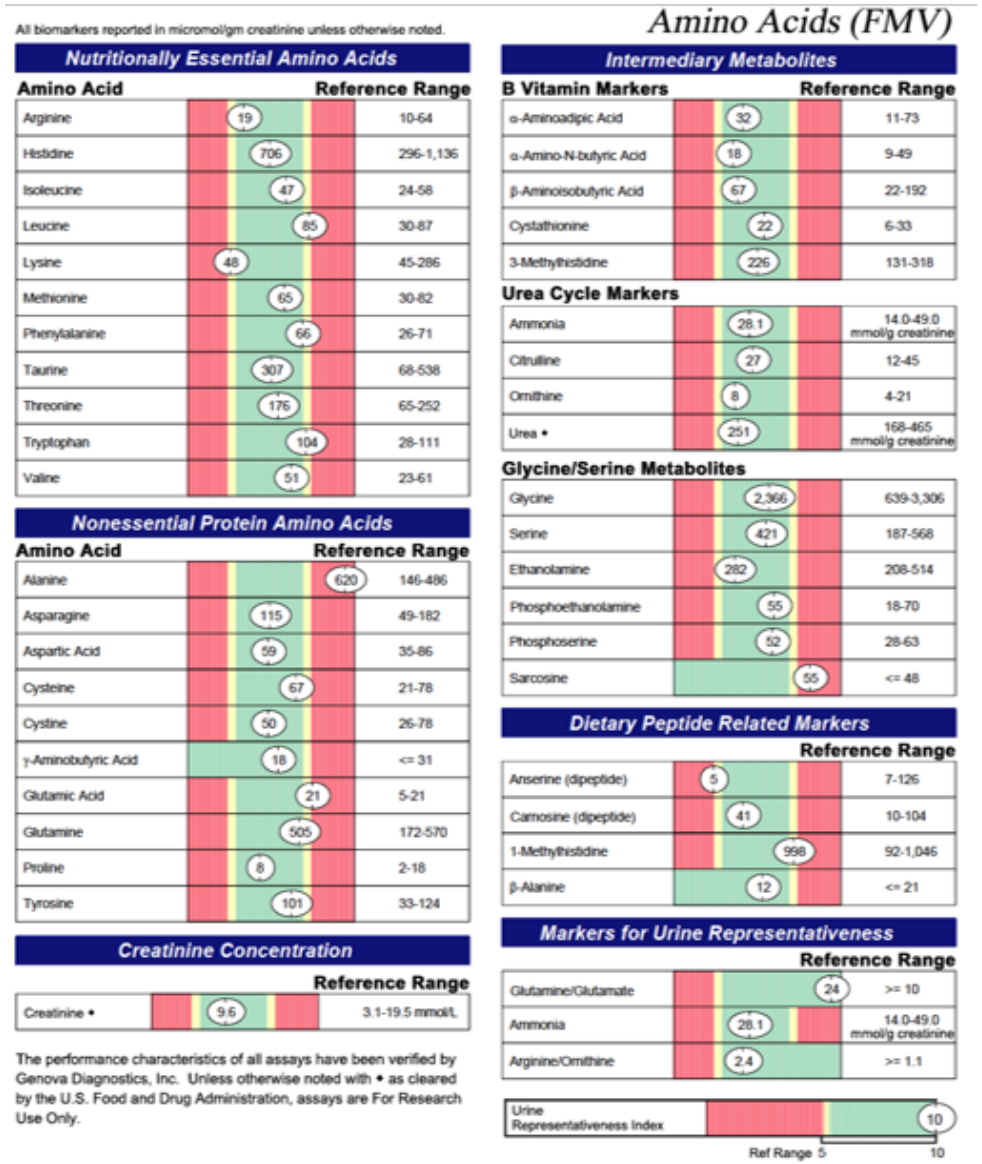
Tyrosine Metabolism

		Reference Range
Homogentisic Acid	7	<= 19
2-Hydroxyphenylacetic Acid	0.33	<= 0.76

Metabolic Analysis Reference Ranges are Age Specific

GENOVA DIAGNOSTICS

Daughter



All biomarkers reported in micromol/gm creatinine unless otherwise noted.

Amino Acids (FMV)

Nutritionally Essential Amino Acids

Amino Acid		Reference Range
Arginine	19	10-64
Histidine	706	296-1,136
Isoleucine	47	24-58
Leucine	85	30-87
Lysine	48	45-286
Methionine	65	30-82
Phenylalanine	66	26-71
Taurine	307	68-538
Threonine	176	65-252
Tryptophan	104	28-111
Valine	51	23-61

Nonessential Protein Amino Acids

Amino Acid		Reference Range
Alanine	620	146-486
Asparagine	115	49-182
Aspartic Acid	59	35-86
Cysteine	67	21-78
Cystine	50	26-78
γ-Aminobutyric Acid	18	<= 31
Glutamic Acid	21	5-21
Glutamine	505	172-570
Proline	8	2-18
Tyrosine	101	33-124

Creatinine Concentration

		Reference Range
Creatinine •	9.6	3.1-19.5 mmol/L

The performance characteristics of all assays have been verified by Genova Diagnostics, Inc. Unless otherwise noted with • as cleared by the U.S. Food and Drug Administration, assays are For Research Use Only.

Intermediary Metabolites

B Vitamin Markers		Reference Range
α-Aminoadipic Acid	32	11-73
α-Amino-N-butyric Acid	18	9-49
β-Aminoisobutyric Acid	67	22-192
Cystathionine	22	6-33
3-Methylhistidine	226	131-318

Urea Cycle Markers		Reference Range
Ammonia	28.1	14.0-49.0 mmol/g creatinine
Citrulline	27	12-45
Ornithine	8	4-21
Urea •	251	168-465 mmol/g creatinine

Glycine/Serine Metabolites		Reference Range
Glycine	2,366	639-3,306
Serine	421	187-568
Ethanolamine	282	208-514
Phosphoethanolamine	55	18-70
Phosphoserine	52	28-63
Sarcosine	55	<= 48

Dietary Peptide Related Markers

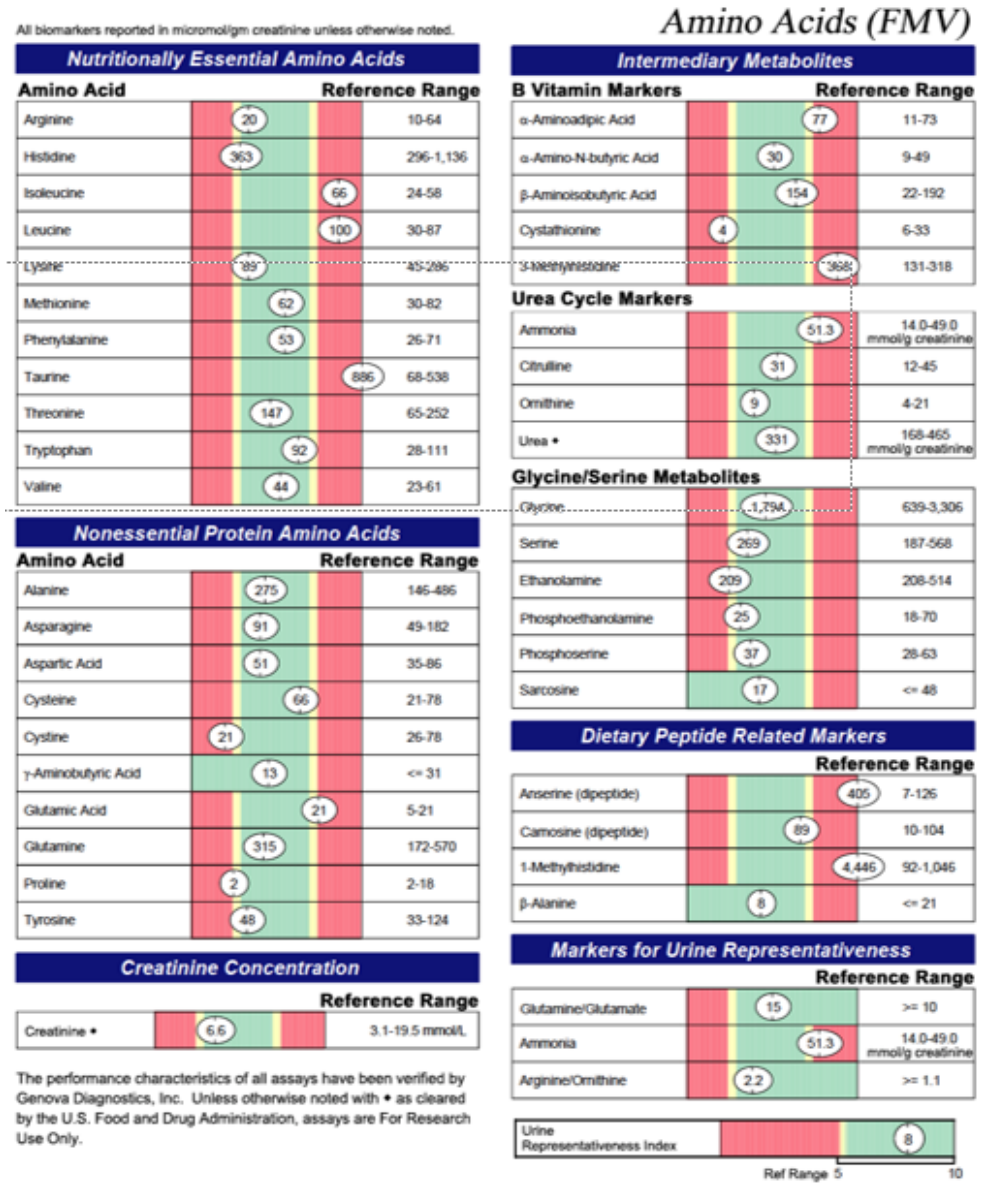
		Reference Range
Anserine (dipeptide)	5	7-126
Carnosine (dipeptide)	41	10-104
1-Methylhistidine	998	92-1,046
β-Alanine	12	<= 21

Markers for Urine Representativeness

		Reference Range
Glutamine/Glutamate	24	>= 10
Ammonia	28.1	14.0-49.0 mmol/g creatinine
Arginine/Ornithine	2.4	>= 1.1

Urine Representativeness Index: 10 (Ref Range 5 – 10)

Mother



All biomarkers reported in micromol/gm creatinine unless otherwise noted.

Amino Acids (FMV)

Nutritionally Essential Amino Acids

Amino Acid		Reference Range
Arginine	20	10-64
Histidine	363	296-1,136
Isoleucine	66	24-58
Leucine	100	30-87
Lysine	89	45-286
Methionine	62	30-82
Phenylalanine	53	26-71
Taurine	886	68-538
Threonine	147	65-252
Tryptophan	92	28-111
Valine	44	23-61

Nonessential Protein Amino Acids

Amino Acid		Reference Range
Alanine	275	146-486
Asparagine	91	49-182
Aspartic Acid	51	35-86
Cysteine	66	21-78
Cystine	21	26-78
γ-Aminobutyric Acid	13	<= 31
Glutamic Acid	21	5-21
Glutamine	315	172-570
Proline	2	2-18
Tyrosine	48	33-124

Creatinine Concentration

		Reference Range
Creatinine •	6.6	3.1-19.5 mmol/L

The performance characteristics of all assays have been verified by Genova Diagnostics, Inc. Unless otherwise noted with • as cleared by the U.S. Food and Drug Administration, assays are For Research Use Only.

Intermediary Metabolites

B Vitamin Markers		Reference Range
α-Aminoadipic Acid	77	11-73
α-Amino-N-butyric Acid	30	9-49
β-Aminoisobutyric Acid	154	22-192
Cystathionine	4	6-33
3-Methylhistidine	3688	131-318

Urea Cycle Markers		Reference Range
Ammonia	51.3	14.0-49.0 mmol/g creatinine
Citrulline	31	12-45
Ornithine	9	4-21
Urea •	331	168-465 mmol/g creatinine

Glycine/Serine Metabolites		Reference Range
Glycine	1,794	639-3,306
Serine	269	187-568
Ethanolamine	209	208-514
Phosphoethanolamine	25	18-70
Phosphoserine	37	28-63
Sarcosine	17	<= 48

Dietary Peptide Related Markers

		Reference Range
Anserine (dipeptide)	405	7-126
Carnosine (dipeptide)	89	10-104
1-Methylhistidine	4,446	92-1,046
β-Alanine	8	<= 21

Markers for Urine Representativeness

		Reference Range
Glutamine/Glutamate	15	>= 10
Ammonia	51.3	14.0-49.0 mmol/g creatinine
Arginine/Ornithine	2.2	>= 1.1

Urine Representativeness Index: 8 (Ref Range 5 – 10)

GENOVA DIAGNOSTICS

Daughter

Essential and Metabolic Fatty Acids Markers (RBCs)

Omega 3 Fatty Acids

Analyte (cold water fish, flax, walnut)		Reference Range
α-Linolenic (ALA) 18:3 n3	0.16	>= 0.09 wt %
Eicosapentaenoic (EPA) 20:5 n3	0.19	>= 0.16 wt %
Docosapentaenoic (DPA) 22:5 n3	1.58	>= 1.14 wt %
Docosahexaenoic (DHA) 22:6 n3	1.8	>= 2.1 wt %
% Omega 3s	3.8	>= 3.8

Omega 6 Fatty Acids

Analyte (vegetable oil, grains, most meats, dairy)		Reference Range
Linoleic (LA) 18:2 n6	14.0	10.5-16.9 wt %
γ-Linolenic (GLA) 18:3 n6	0.10	0.03-0.13 wt %
Dihomo-γ-linolenic (DGLA) 20:3 n6	2.14	>= 1.19 wt %
Arachidonic (AA) 20:4 n6	17	15-21 wt %
Docosatetraenoic (DTA) 22:4 n6	4.17	1.50-4.20 wt %
Eicosadienoic 20:2 n6	0.37	<= 0.26 wt %
% Omega 6s	37.7	30.5-39.7

Omega 9 Fatty Acids

Analyte (olive oil)		Reference Range
Oleic 18:1 n9	10	10-13 wt %
Nervonic 24:1 n9	3.1	2.1-3.5 wt %
% Omega 9s	13.4	13.3-16.6

Monounsaturated Fats

Omega 7 Fats		Reference Range
Palmitoleic 16:1 n7	0.17	<= 0.64 wt %
Vaccenic 18:1 n7	0.68	<= 1.13 wt %
Trans Fat		
Elaidic 18:1 n9t	0.55	<= 0.59 wt %

Saturated Fatty Acids

Analyte (meat, dairy, coconuts, palm oils)		Reference Range
Palmitic C16:0	19	18-23 wt %
Stearic C18:0	19	14-17 wt %
Arachidic C20:0	0.27	0.22-0.35 wt %
Behenic C22:0		
Tricosanoic C23:0		
Lignoceric C24:0		
Pentadecanoic C15:0		
Margaric C17:0		
% Saturated Fats		

Delta - 6 Desaturase Activity

	Upregulated	Functional	Impaired	
Linoleic / DGLA		6.6		6.0-12.3

Cardiovascular Risk

Analyte		Reference Range
Omega 6s / Omega 3s	10.0	3.4-10.7
AA / EPA 20:4 n6 / 20:5 n3	88	12-125
Omega 3 Index	2.0	>= 4.0

Mother

Essential and Metabolic Fatty Acids Markers (RBCs)

Omega 3 Fatty Acids

Analyte (cold water fish, flax, walnut)		Reference Range
α-Linolenic (ALA) 18:3 n3	0.12	>= 0.09 wt %
Eicosapentaenoic (EPA) 20:5 n3	0.43	>= 0.16 wt %
Docosapentaenoic (DPA) 22:5 n3	2.08	>= 1.14 wt %
Docosahexaenoic (DHA) 22:6 n3	3.8	>= 2.1 wt %
% Omega 3s	6.5	>= 3.8

Omega 6 Fatty Acids

Analyte (vegetable oil, grains, most meats, dairy)		Reference Range
Linoleic (LA) 18:2 n6	10.8	10.5-16.9 wt %
γ-Linolenic (GLA) 18:3 n6	0.08	0.03-0.13 wt %
Dihomo-γ-linolenic (DGLA) 20:3 n6	1.11	>= 1.19 wt %
Arachidonic (AA) 20:4 n6	20	15-21 wt %
Docosatetraenoic (DTA) 22:4 n6	3.90	1.50-4.20 wt %
Eicosadienoic 20:2 n6	0.30	<= 0.26 wt %
% Omega 6s	36.3	30.5-39.7

Omega 9 Fatty Acids

Analyte (olive oil)		Reference Range
Oleic 18:1 n9	10	10-13 wt %
Nervonic 24:1 n9	3.3	2.1-3.5 wt %
% Omega 9s	13.3	13.3-16.6

Monounsaturated Fats

Omega 7 Fats		Reference Range
Palmitoleic 16:1 n7	0.16	<= 0.64 wt %
Vaccenic 18:1 n7	0.54	<= 1.13 wt %
Trans Fat		
Elaidic 18:1 n9t	0.26	<= 0.59 wt %

Saturated Fatty Acids

Analyte (meat, dairy, coconuts, palm oils)		Reference Range
Palmitic C16:0	19	18-23 wt %
Stearic C18:0	18	14-17 wt %
Arachidic C20:0	0.29	0.22-0.35 wt %
Behenic C22:0		
Tricosanoic C23:0		
Lignoceric C24:0		
Pentadecanoic C15:0		
Margaric C17:0		
% Saturated Fats		

Delta - 6 Desaturase Activity

	Upregulated	Functional	Impaired	
Linoleic / DGLA		9.8		6.0-12.3

Cardiovascular Risk

Analyte		Reference Range
Omega 6s / Omega 3s	5.6	3.4-10.7
AA / EPA 20:4 n6 / 20:5 n3	46	12-125
Omega 3 Index	4.3	>= 4.0

GENOVA DIAGNOSTICS

Where do we start?

- “He won’t change his diet...”
- “My dad was a diabetic...”
- “It’s genetic...”
- “I really don’t eat that bad...”
- “I do a lot of cardio...”
- “I hardly eat but can’t lose weight...”

How do we begin to change our life?

GENOVA DIAGNOSTICS

It’s In The Genes

- Historical Thought Paradigm
  - Common Variants - Common Disease
  - International HapMap Project
  - Genome-Wide Association Studies

Risch, N, et. al. (1996) The future of genetic studies of complex human diseases. Science 273:1516-17.
Lander ES (1996) The new genomics: Global views of biology. Science 274:536-539.
International HapMap Consortium (2003) The International HapMap Project. Nature 426:789-796.

It’s In The Genes

- Common Variant - Common Disease
  - Coronary Heart Disease
  - Breast Cancer
  - DM-2

Easton DF, et. al. (2007) Genome-wide association study identifies novel breast cancer loci. Nature 447: 1087-1093.
McPherson R, et. al. (2007) A common allele on Chromosome 9 associated with coronary heart disease. Science 316: 1488-1491.
Saxena R, et. al. (2007) Genome-wide... loci for type 2 DM and triglycerides. Nature 445: 881-885.

It’s In The Genes

- Common Variant - Common Disease
  - Assumes a FEW common genetic variants are responsible for a common complex disease

- What about RARE VARIANTS?

It’s In The Genes

- New Paradigm:
  - Common Allele Variants
    - “Represent only a fraction of the existing disease variants”

Iles MM. What can genome-wide association studies tell us about the genetics of common diseases? PLoS Genet. 2008 Feb;4(2)Naomi R. Wray, et. al. Predictions of individual genetic risk to disease from genome-wide associate studies. Genome Res. 2007 Oct; 17(10): 1520-8.

GENOVA DIAGNOSTICS

It’s In The Genes

- New Paradigm
  - Common Disease Genetics:
    - Multi-variant Genetics + Environment

It’s In The Genes

- New Paradigm
  - Common Disease Genetics:
    - Multi-variant Genetics + Environment
  - But… It’s Complicated....

It NOT Genetic… It's Epigenetic!

"…the study of any potentially stable and, ideally, heritable **change in gene expression** or cellular phenotype that occurs **without** changes in Watson-Crick base-pairing of DNA (Goldberg et al, 2007)."

Johannes Bohacek and Isabelle M Mansuy. Epigenetic Inheritance of Disease and Disease Risk. Neuropsychopharmacology REVIEWS (2013) 38, 220–236.

GENOVA DIAGNOSTICS

It NOT Genetic… It's Epigenetic!

"…the study of any potentially stable a… …table **change in gene expression** or cellular ph… …**hout** changes in Watson-Crick base-pairi… …al, 2007)."

GENETIC CHANGES THAT OCCUR **WITHOUT** CHANGING THE DNA!!

Johannes Bohacek and Isabelle M Mansuy. Epigenetic Inheritance of Disease and Disease Risk. Neuropsychopharmacology REVIEWS (2013) 38, 220–236.

GENOVA DIAGNOSTICS

What is Epigenetics?

- The study of:
  - Changes to gene expression that are
  - **Independent** of genotype.
  - May be trans-generationally heritable
    - Imprinting of the genome with other signals

The Epigenome

- The constellation of **mechanisms** that:
  - **Impact DNA expression** through
    - modification of a specific site on the gene (not a change in base code)
    - conformational changes to the chromatin

- NOTE: Epigenome refers to DNA expression, NOT RNA

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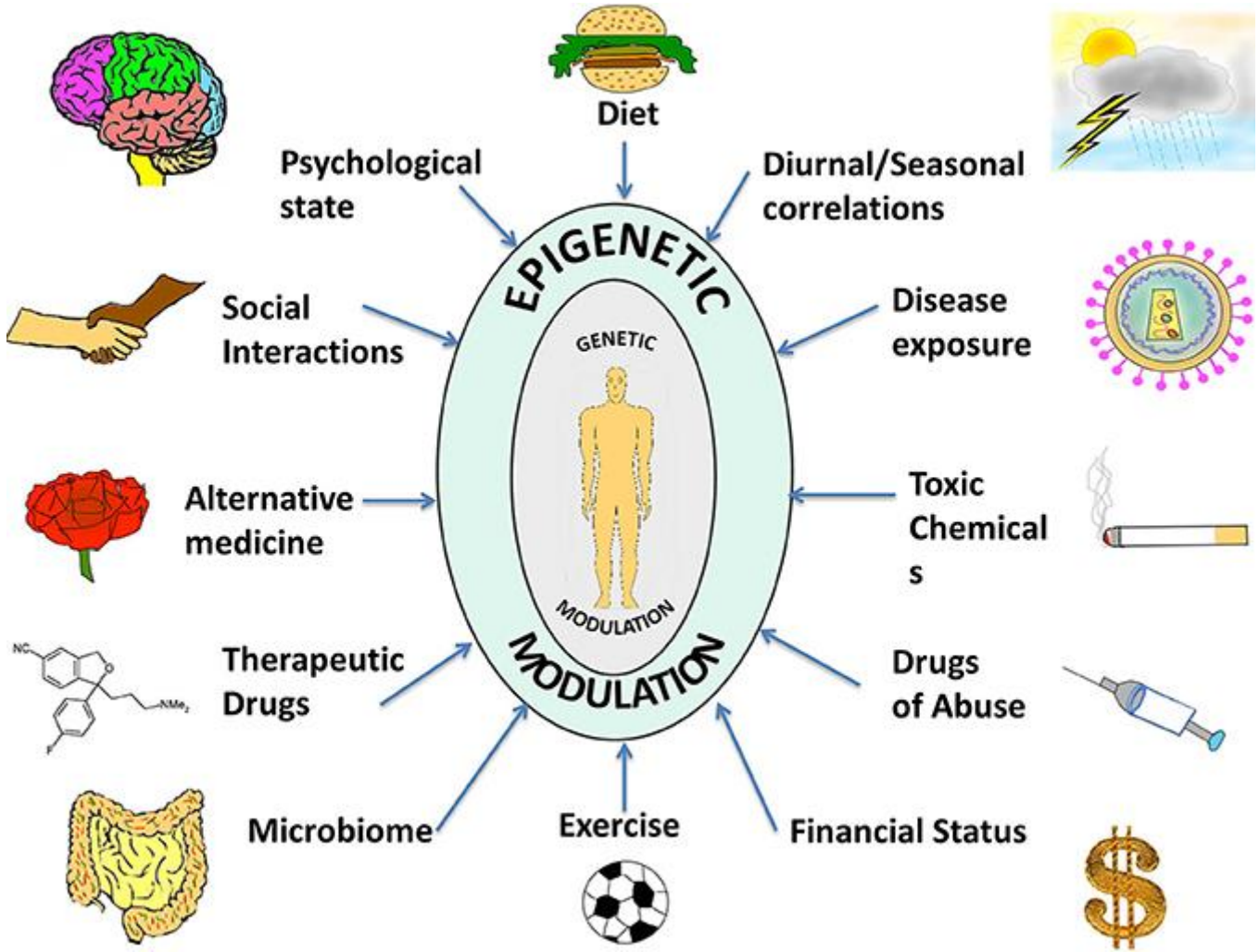

Epigenetics Across the Human Lifespan by Kanherkar, Bhatia-Dey and Csoka
http://journal.frontiersin.org/article/10.3389/fcell.2014.00049/full

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Epigenetic Mechanism

- Plasticity of the genome
  - **The genome is fixed, but functionally modular**
- DNA mechanisms (epigenome)
  - DNA methylation
  - Histone acetylation
- Phenotype
  - Net sum of the environmental influence on genomic expression

GENOVA DIAGNOSTICS

Kouzarides T. Chromatin modifications and their function. Cell. 2007;27:363-88.

So What?

- Layered mechanisms to modify the expression of DNA
- Communication among the mechanisms
- Infinitely adaptive organism?

Epigenomics and Disease

"Aberrant" epigenetic profiles are associated with disease.

Bartlett TE, Zaikin A, et al. Corruption of the intragene DNA methylation architecture is a hallmark of cancer. PLoS One. 2013;8

Wang X, et al. A genome-wide methylation study on essential hypertension in young AA males. Plos One/ 2013;8.

GENOVA DIAGNOSTICS

Clinical Indications NutrEval + Genomics Add-Ons

- Depression
- Anxiety
- Cardio-metabolic Syndrome/Metabolic Syndrome
- Cardiovascular disease
- Inflammatory conditions
- Chronic Pain Syndromes

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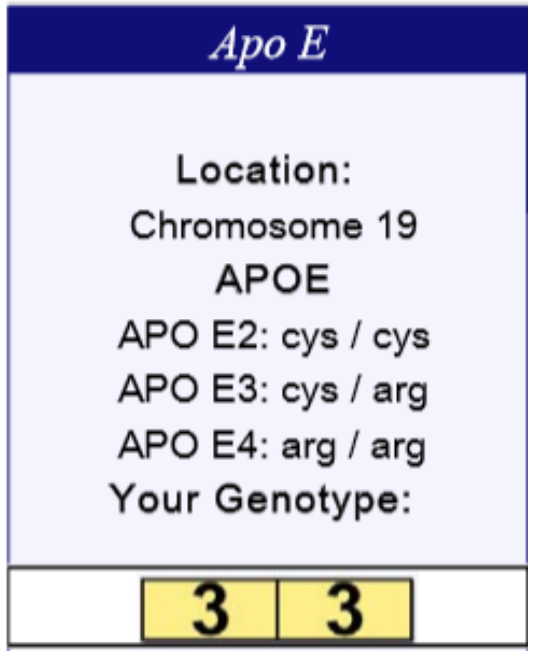
Apolipoprotein E (APOE)

APOE plays a key role in the metabolism of cholesterol and triglycerides by helping to mediate the clearance of chylomicrons and VLDL (remnants from dietary fats) from the bloodstream.

- 3 major isoforms - APO2, APO3 and APO4
- 6 common phenotypes
- Epigenetic Factors: diet, stress, smoking, and physical activity
- Consider testing in
  - Patients with **inflammatory conditions**
  - Plasma Lipid abnormalities
  - Presence or increased risk for Cardiovascular Disease



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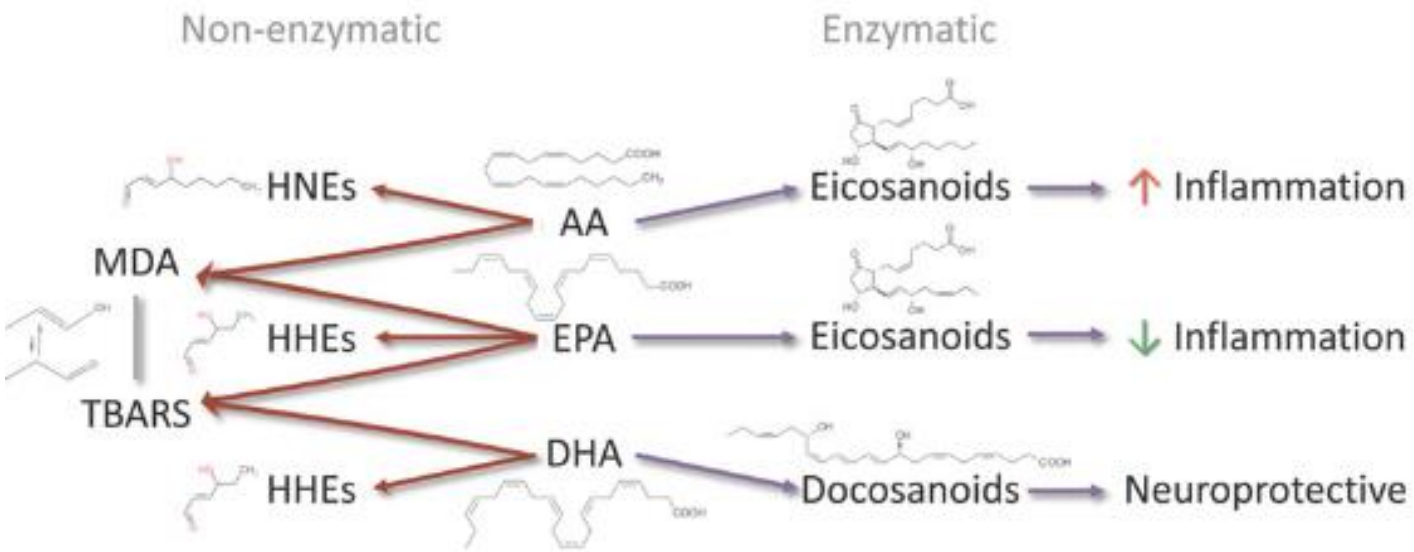

Non-enzymatic lipid peroxidation products of AA, EPA and DHA.

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http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4171779/pdf/acps0130-0163.pdf

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Review

Effects of oxidative stress on fatty acid- and one-carbon-metabolism in psychiatric and cardiovascular disease comorbidity

Summations

- Oxidative stress and its effects on fatty acid and 1-carbon cycle metabolism may underlie co-occurrence of cardiovascular and psychiatric disorders.
- During oxidative stress, fatty acids shorten in chain length and decrease in unsaturation and peroxidation, while the 1-carbon cycle shifts from the methylation to the transsulfuration pathway.
- While these changes initially may enhance oxidative stress resistance, persisting chronically, they may cause damage.

Results: Oxidative stress, mainly generated in mitochondria, is implicated in both psychiatric and cardiovascular pathophysiology. Oxidative stress affects the intrinsically linked FA and 1-C cycle metabolism: FAs decrease in chain length and unsaturation (particularly omega-3 polyunsaturated FAs), and lipid peroxidation

Nijmegen, the Netherlands and "Donders Institute for Brain, Cognition and Behavior, Radboud University, Nijmegen, the Netherlands

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4171779/pdf/acps0130-0163.pdf

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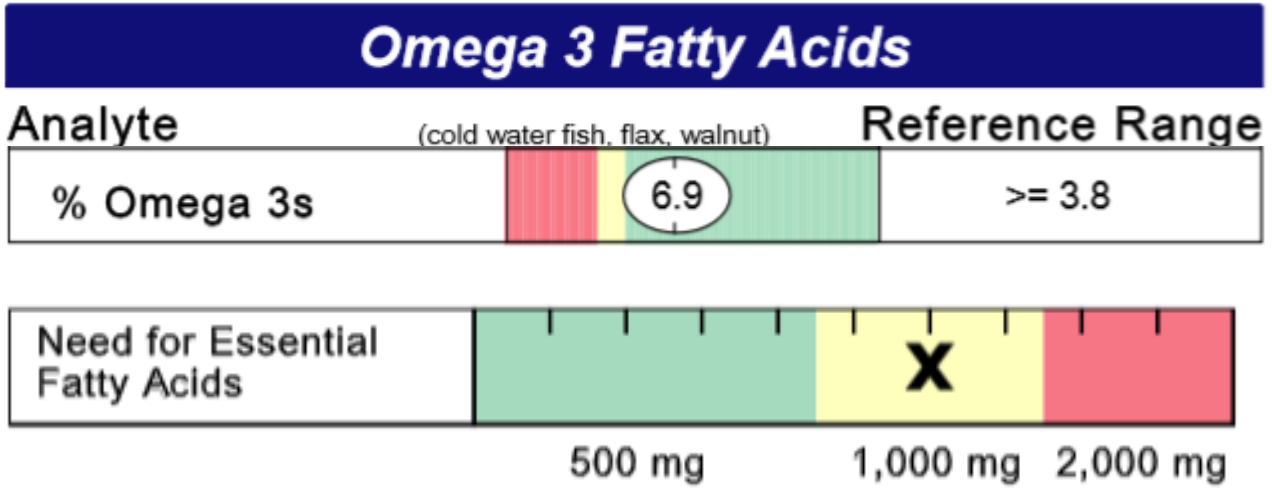
APOE3/3 Health Implications:

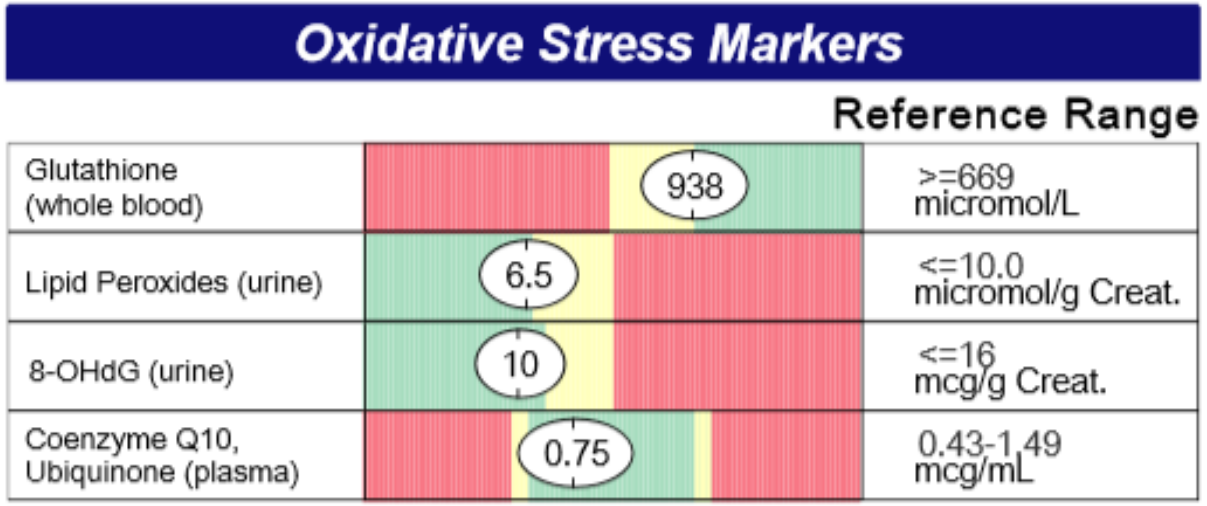
- Moderate tendency toward elevated total- and LDL cholesterol, and lower HDL-C

APOE3/3

Clinical Management Considerations:

- Dietary Fiber
- Fish Oils
- Exercise
- Avoid smoking
- Dietary fat restriction





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Tumor Necrosis Factor - alpha (TNF-α)

TNF-α is a pro-inflammatory cytokine that plays an important role in host defense against infection.

- Excessive release of the cytokine increases inflammation and oxidative stress

Consider testing in

- Patients with **inflammatory conditions**
- Presence or increased risk for Cardiovascular Disease

- TNF-α 308 -/- G/G
  - Baseline “normal” TNF-α production
- TNF-α 308 -/+ G/A
  - Moderately increased TNF-α production
- TNF-α 308 +/+ A/A
  - Substantially increased TNF-α production

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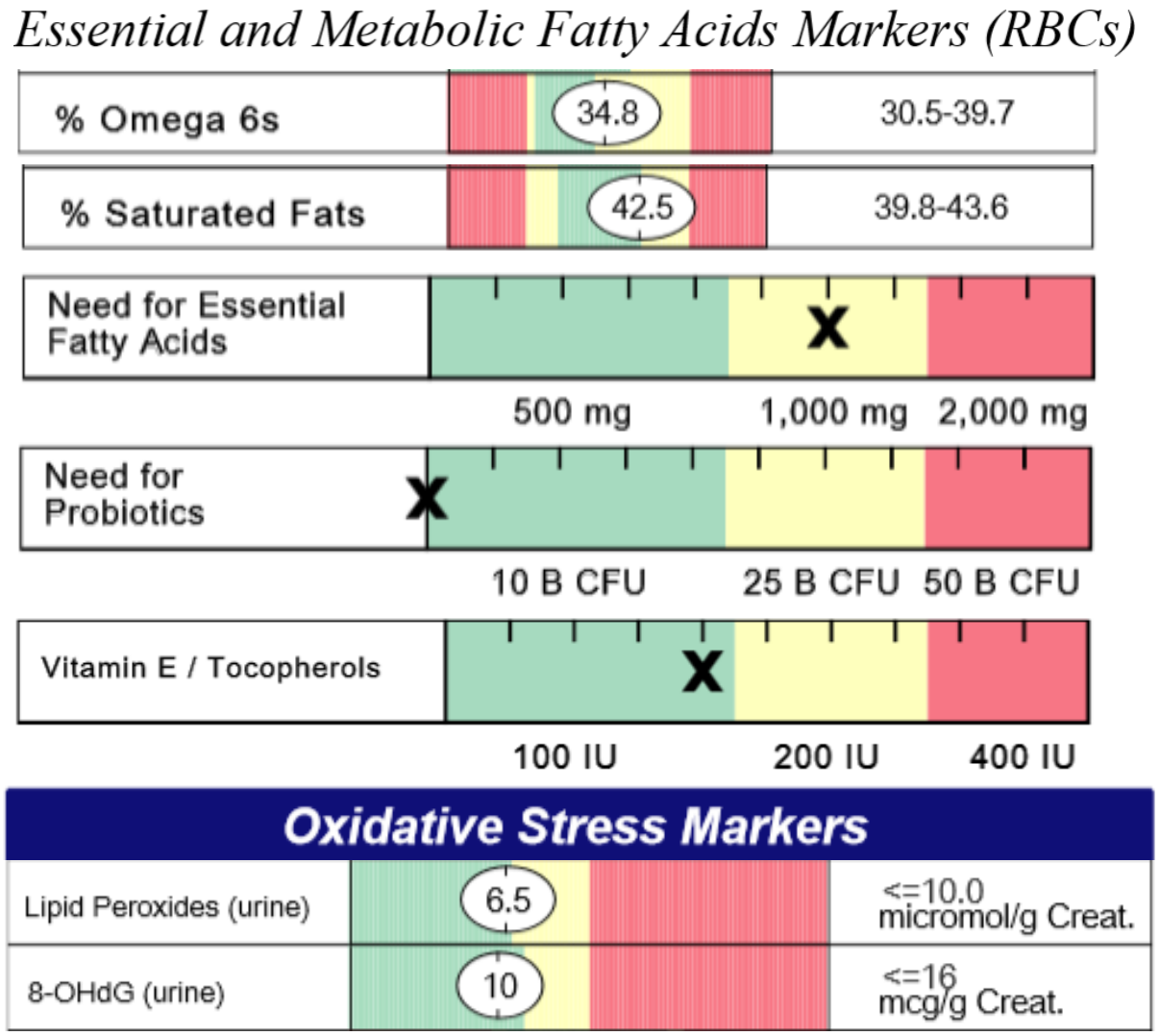
Tumor Necrosis Factor - alpha (TNF-α)

Clinical Management Considerations

- TNF-α 308 -/- G/G
  - No particular treatment indicated
  - Maintain a healthy lifestyle to minimize inflammation
- TNF-α 308 -/+ & TNF-α 308 +/+
  - Weight loss (abdominal fat)
  - Improve insulin sensitivity and stress maintenance
  - Decrease saturated fat and/or omega-6 fatty acids
  - Vitamin E, fish oils, NAC, green tea, and lactobacillus



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Neuroimmunomodulation. 2014;21(2-3):95-101. doi: 10.1159/000356535. Epub 2014 Feb 14.

Chronic low-grade inflammation in metabolic disorders: relevance for behavioral symptoms.

Lasselin J[1], Capuron L.

Author information

Abstract

The ability of cytokines to influence cerebral functions and to induce the development of behavioral alterations is well established in conditions of acute or chronic high-grade activation of the innate immune system. Recent evidence suggests that the release of these immune mediators during chronic low-grade endogenous inflammatory processes may also contribute to the development of behavioral alterations. Metabolic disorders, including obesity, type 2 diabetes and the metabolic syndrome, represent examples of those conditions which are both characterized by a chronic low-grade inflammatory state and an increased prevalence of behavioral disorders. In metabolic disorders, the increased production of acute-phase proteins and cytokines (e.g. C-reactive protein, interleukin-6 and tumor necrosis factor-α), but at relatively low levels, may promote and contribute to the development of behavioral symptoms, including depressive symptoms, cognitive impairment, fatigue, sleep problems and pain. This hypothesis is supported by a growing literature referring both to experimental and clinical findings that will be reviewed here.

. . . **the increased production of acute-phase proteins** (e.g. C-reactive protein and tumor necrosis factor-α) . . **at relatively low levels, may promote and contribute to the development of behavioral symptoms, including . . . fatigue**, sleep problems . . .

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Outcomes

Case Study

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Risk Reduction!

Life Optimization!

Before	Lab Marker	After
207	Cholesterol	**161**
505	Triglycerides	**181**
6.8%	HbA1C%	**5.8%**
38.5	Body Mass Index (BMI)	**35.8**
51inches	Waist Circ.	**46 inches**

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53yr old male

Cardiovascular Risk

Analyte		Reference Range
Omega 6s / Omega 3s	5.6	3.4-10.7
AA / EPA (20:4 n6 / 20:5 n3)	46	12-125
Omega 3 Index	4.3	>= 4.0

Oxidative Stress Markers

		Reference Range
Glutathione (whole blood)	938	>=669 micromol/L
Lipid Peroxides (urine)	6.5	<=10.0 micromol/g Creat.
8-OHdG (urine)	10	<=16 mcg/g Creat.
Coenzyme Q10, Ubiquinone (plasma)	0.75	0.43-1.49 mcg/mL

Supplements	Daily Recommended Intake (DRI)	Patient's Daily Recommendations	Provider Daily Recommendations
Antioxidants			
Vitamin A / Carotenoids	2,333 IU	5,000 IU	
Vitamin C	75 mg	250 mg	
Tocopherols	22 IU	200 IU	
id		50 mg	
		90 mg	
ns			
1	1.1 mg	25 mg	
B2	1.1 mg	50 mg	
	14 mg	20 mg	
- B6	1.3 mg	25 mg	
	30 mcg	100 mcg	
Folic Acid - B9	400 mcg	800 mcg	
Cobalamin - B12	2.4 mcg	500 mcg	
	320 mg	600 mg	
	1.8 mg	3.0 mg	
	45 mcg	150 mcg	
	8 mg	10 mg	
ds			
	500 mg	2,000 mg	
		25 billion CFU	
Pancreatic Enzymes		5,000 IU	
Other Vitamins			
Vitamin D	600 IU	4,000 IU	

This is HOW I KNOW what he really needs?

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Manufacturing Facility: Model Site

National Pilot Program

July-September, 2014

20 Participants

Risk Marker	% Population	% Improvement
Cholesterol	62.5%	14.4%
LDL	68.8%	17.8%
Triglycerides	56.3%	39.5%
HbA1C%	50.0%	5.7%
hsCRP	37.5%	24.0%
Diastolic BP	47.1%	10.4%
Waist Circ.	35.3%	5.5%

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Today's Presenter

Jamie Wright DO, MS

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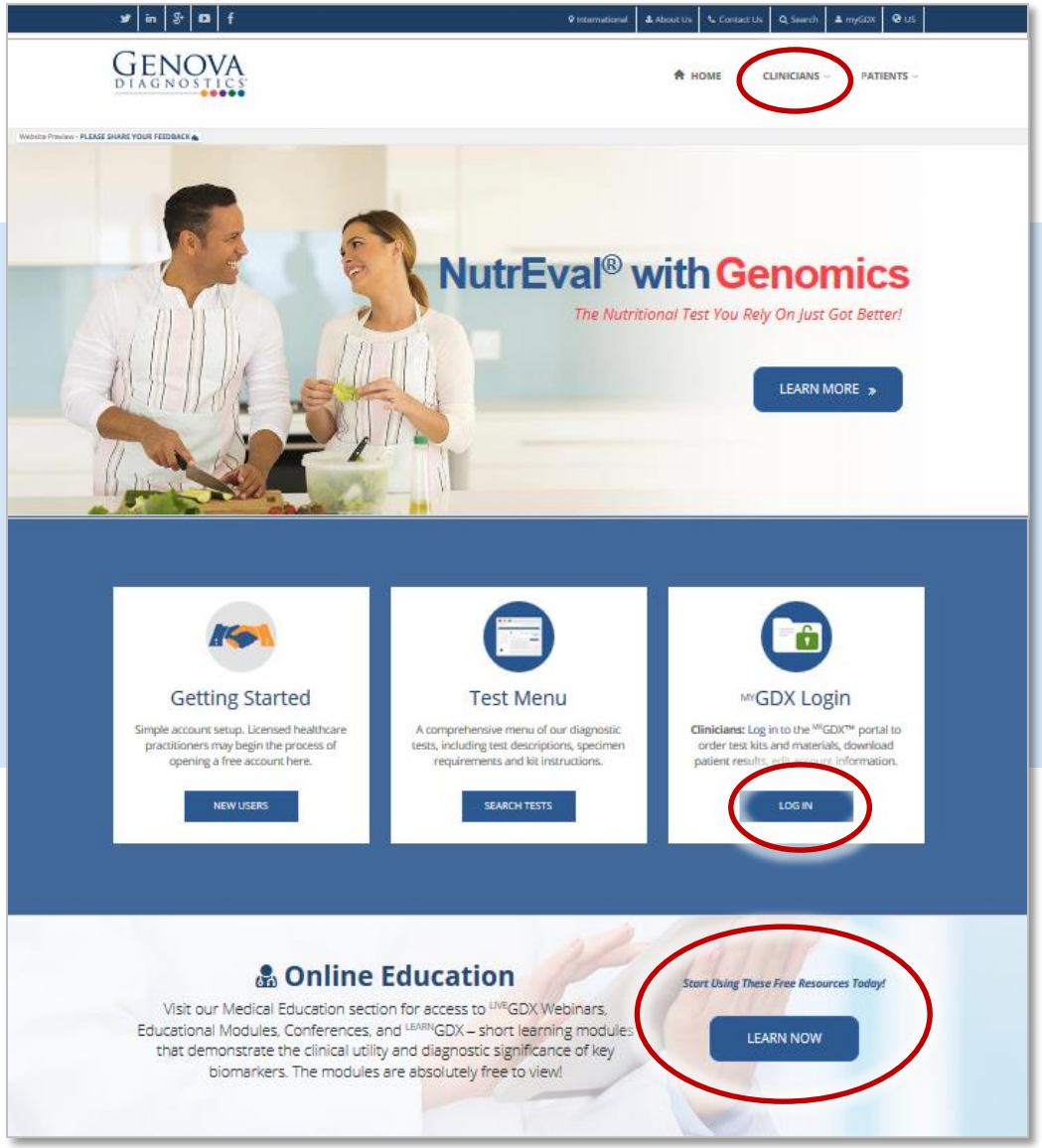

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Additional Questions?

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We look forward to hearing from you!

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Sick, Tired and on Fire: Nutrition and Inflammation

Jamie Wright, DO, MS

Genova Diagnostics LiveGDX

24 February 2016

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