Fatty Acids

Making Clinical Sense of Lab Reports

Deanna Minich, PhD, FACN, CNS, IFMCP

Food & Spirit, LLC

Warren Brown, ND

Clinical Science Liaison

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Deanna Minich, PhD

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This webinar is for informational and educational purposes only.

The contents of this webinar are for informational purposes only and are not intended to be a substitute for professional medical advice, diagnosis, or treatment.

Objectives for This Presentation

- Understand the interrelationships of fatty acids
- Understand how to take away basic clinical pearls from fatty acid laboratory tests
- Review tests and clinical signs to assess fatty acid balance
- Learn how to connect the dots to fat-soluble nutrients, and some basic nutrition physical exam findings

- M.S.
  - Oxidative stress, lipids, and carotenoids
- Ph.D.
  - Essential fatty acid absorption and metabolism
    - www.direct-ms.org/pdf/NutritionFats/EFA%20metabolism.pdf

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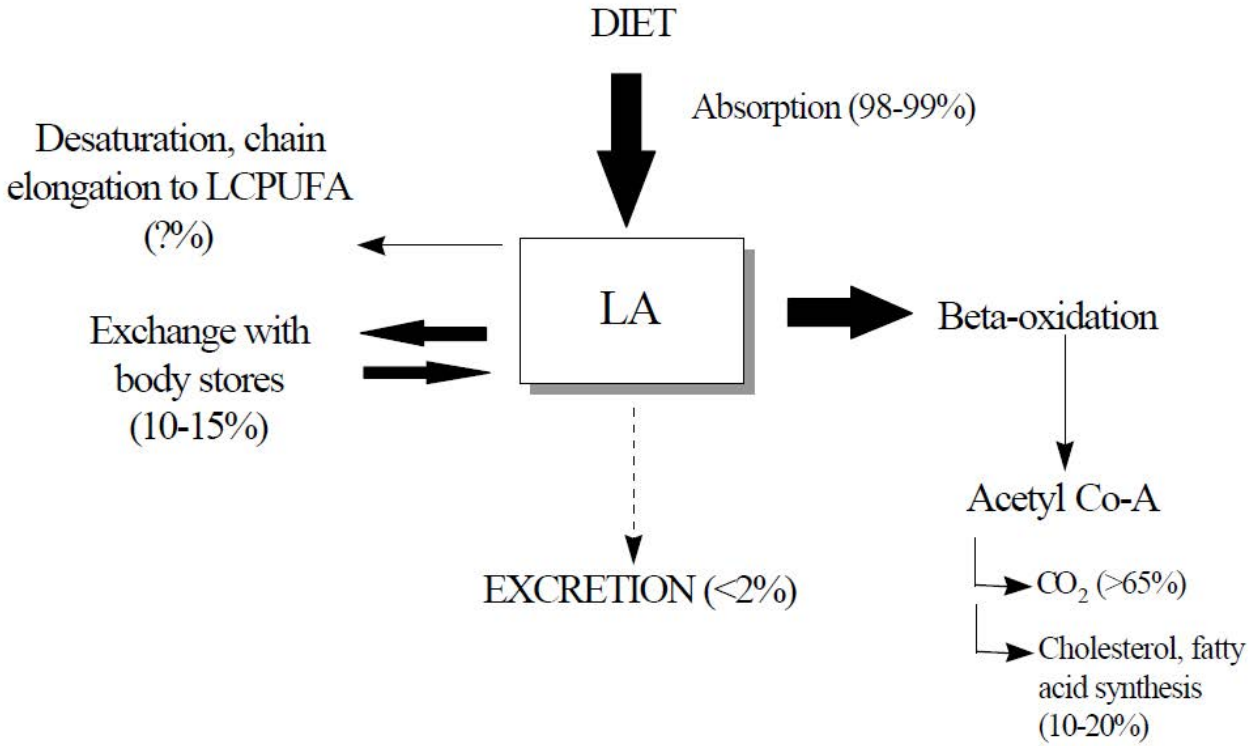
What to Consider in Conjunction With a Lab

- Look at the larger picture of all the fatty acids
- Decide whether you need adjunctive labs or even SNPs
- Assess findings together with nutrition physical exam observations

What to Consider When You are Looking at a Fatty Acid Lab

- Know that you are looking into a “black box”
- Difficult to know from a lab whether a patient is experiencing issues with absorption, excretion, metabolism, or desaturation/elongation unless you look at the deeper clues



Graphic from Deanna Minich, PhD, Dissertation: http://www.direct-ms.org/pdf/NutritionFats/EFA%20metabolism.pdf

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Let’s Start With The Basics…

What are FATS (aka FATTY ACIDS)?

- Organic compounds that are made up of carbon, hydrogen, and oxygen
- Most concentrated source of energy in foods
- Belong to a group of substances called lipids
- Come in liquid or solid form
- All fats are combinations of saturated and unsaturated fatty acids
- Can be called very saturated or very unsaturated depending on their proportions

What Do Fatty Acids Do?

- Supply ENERGY (kcals) to the body (infants)
- Raw materials that help in the control of blood pressure, blood clotting, inflammation, and other body functions
- Storage & insulation
- Healthy skin, hair and nails
- Fat helps in the absorption, and transport through the bloodstream of the fat-soluble vitamins A, D, E, and K
- Behavior/mood

Three Critical Takeaways

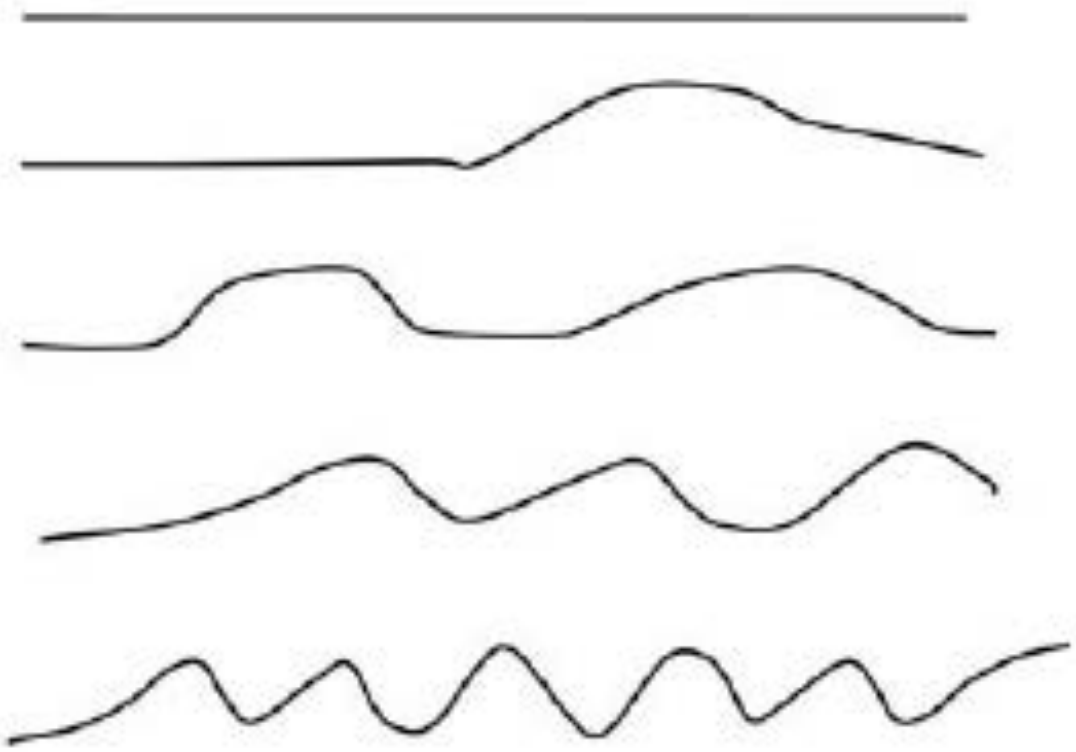
1. Too much fat in whatever form can lead to disease
2. Too little fat in whatever form can lead to disease
3. The kind of fat and the balance of various fats are the critical features that determine how fat contributes to disease

Nutrition Physical Exam Findings: Fatty Acid Imbalance

- Dry skin
- Dry, unmanageable hair
- Dry eyes
- Dandruff
- Alligator skin
- “Chicken skin” on back of arms
- Cracked skin on heels or fingertips
- Patches of pale skin on cheeks
- Brittle, easily frayed nails
- Weakness
- Fatigue
- Irritability
- Attention deficit
- Allergies
- Lowered immunity
- Learning problems
- Poor wound healing
- Frequent infections
- Excessive thirst
- Frequent urination
- Hyperactivity

Chemical Structure:

From Solid (Saturated) to Fluid (Unsaturated)



Saturated fat

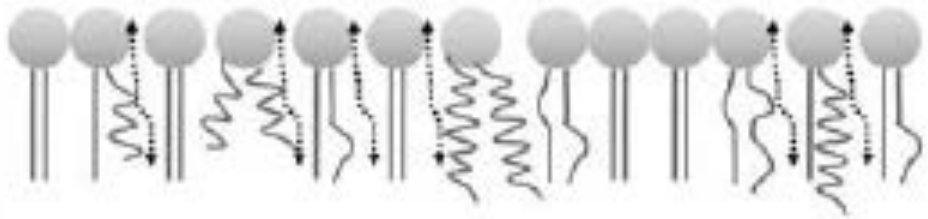
Monounsaturated fat (e.g., olive oil)

Polyunsaturated, omega-6 fat (e.g., corn oil)

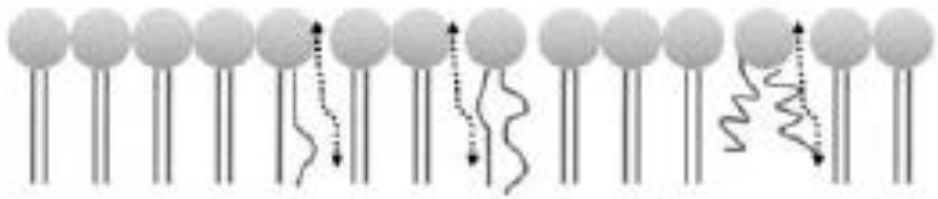
Polyunsaturated, omega-3 fat (e.g., flaxseed oil)

Highly unsaturated, flowing omega-3 fat (e.g., fish oil)

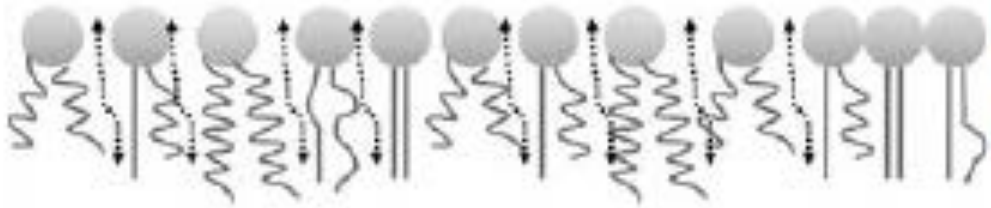
Structure Determines Function:
The Proper Balance is Required for Cell Membranes



Healthy cell membrane with mixture of fats allowing for adequate flow of substances in and out of cell



Too many rigid saturated fats in the cell membrance leading to less flow



Too many flowing unsaturated fats in the cell membrance leading to too much flow

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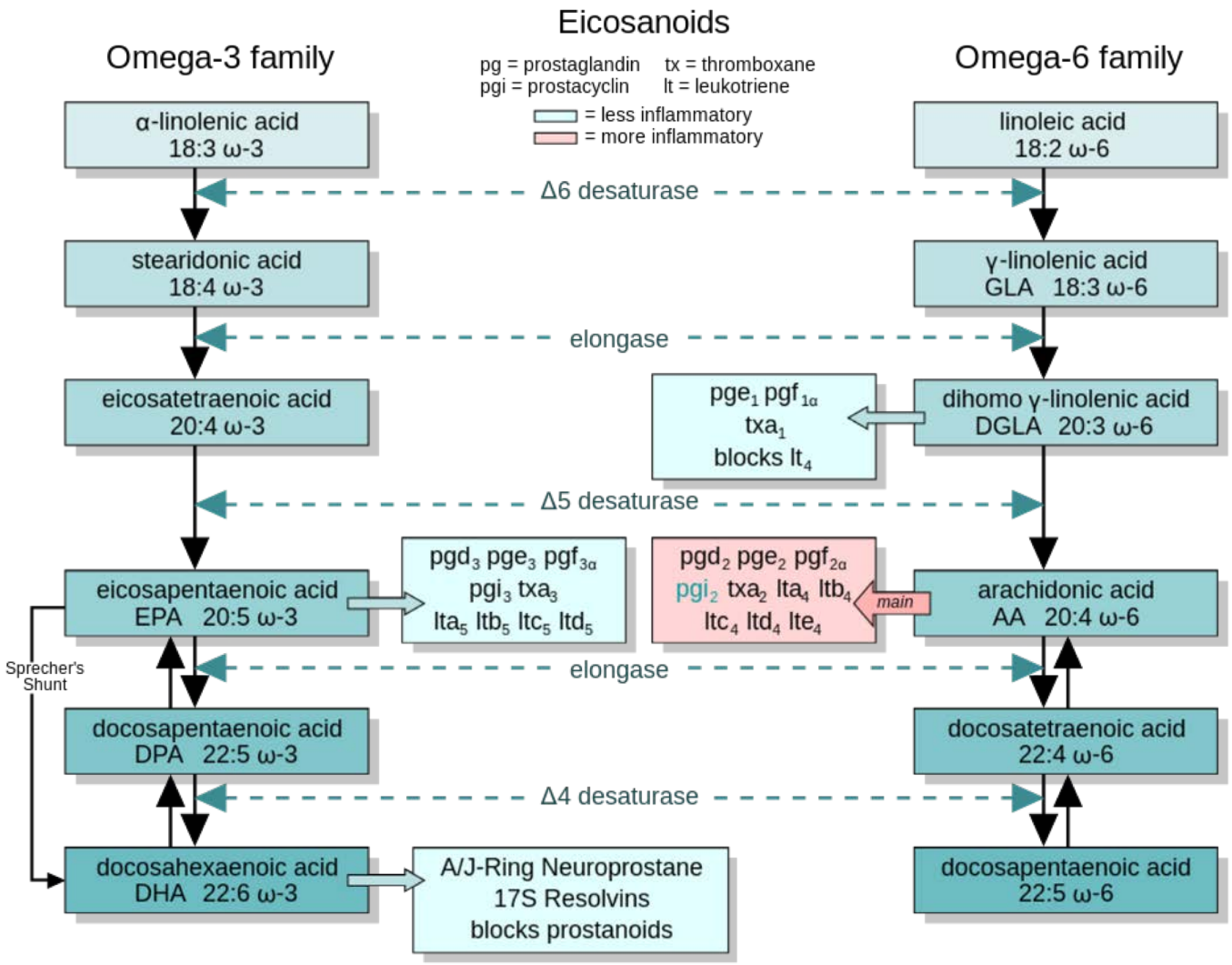
Fatty Acid Families

- Essential Fatty Acids (EFAs)
  - Linoleic Acid (Omega-6) from vegetable oils
  - ALA (Omega-3) from flax seed/oil
  - EPA & DHA (Omega-3)

- Non-essential Fatty Acids
  - Saturated fatty acids (SFAs)
  - Monounsaturated fatty acids (MUFAs)
  - Polyunsaturated fatty acids (PUFAs)
  - Trans-fatty acids (TFAs)

Essential Fatty Acid Families



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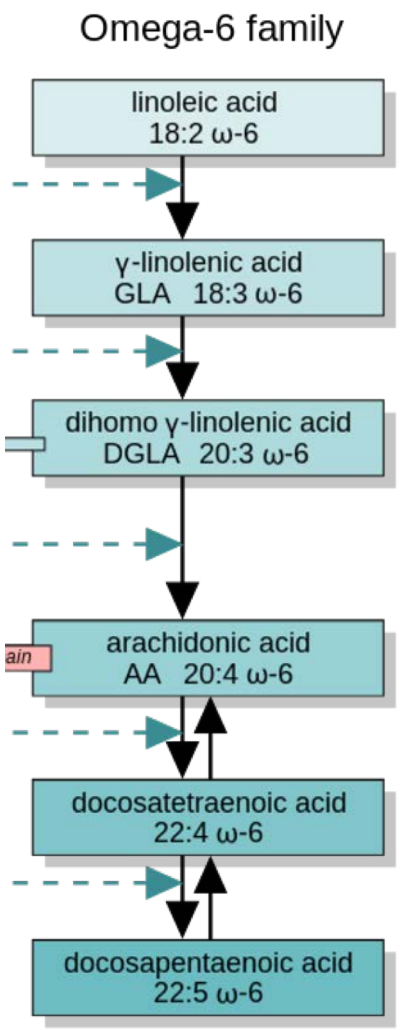
Omega-6 Essential Fats: GLA and DGLA

- Overall cell membrane composition
- Role in inflammatory processes/pain
- Skin
- Cardiovascular health
- Metabolic syndrome
- Autoimmune disease



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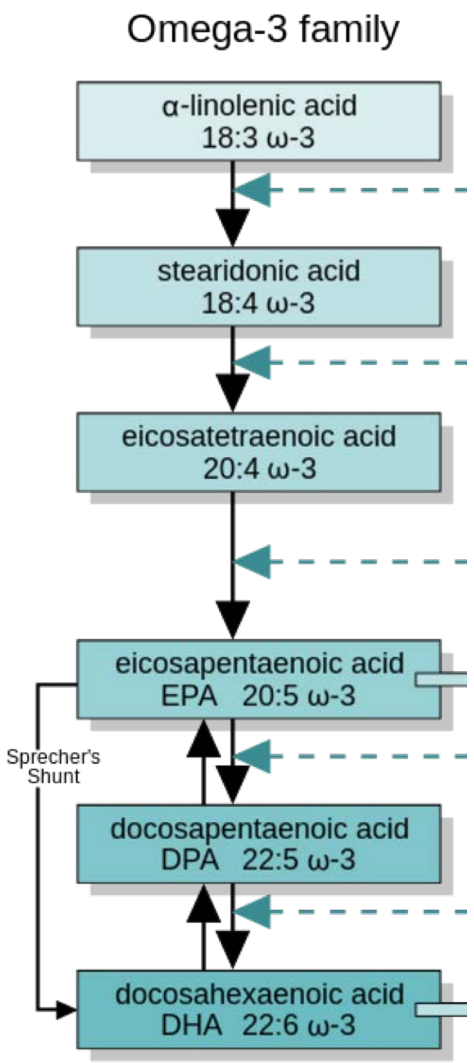
Omega-3 Essential Fats

- Overall cell membrane composition
- Role in inflammatory processes/pain
- Cardiovascular health
- Brain health
- Nerve health



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The Balance Between the Two

- "Studies indicate that a high intake of ω-6 fatty acids shifts the physiologic state to one that is prothrombotic and proaggregatory, characterized by increases in blood viscosity, vasospasm, and vasoconstriction, and decreases in bleeding time."

- "ω -3 fatty acids, however, have anti-inflammatory, antithrombotic, antiarrhythmic, hypolipidemic, and vasodilatory properties."

GENOVA DIAGNOSTICS

Simopoulos, AP. *Curr Sports Med Rep*. 2007;6(4):230-6.

An Increase in the Omega-6/Omega-3 Fatty Acid Ratio Increases the Risk for Obesity

- "In the past three decades, total fat and saturated fat intake as a percentage of total calories has continuously decreased in Western diets, while the **intake of omega-6 fatty acid increased and the omega-3 fatty acid decreased**, resulting in a large increase in the omega-6/omega-3 ratio from 1:1 during evolution to **20:1** today or even higher."

GENOVA DIAGNOSTICS

Simopoulos AP. *Nutrients*. 2016;8(3):128-145.

An Increase in the Omega-6/Omega-3 Fatty Acid Ratio Increases the Risk for Obesity

- "Experimental studies have suggested that omega-6 and omega-3 fatty acids elicit **divergent effects on body fat gain** through mechanisms of adipogenesis, browning of adipose tissue, lipid homeostasis, brain-gut-adipose tissue axis, and most importantly systemic inflammation."

- "Prospective studies clearly show **an increase in the risk of obesity as the level of omega-6 fatty acids and the omega-6/omega-3 ratio** increase in red blood cell (RBC) membrane phospholipids, whereas high omega-3 RBC membrane phospholipids decrease the risk of obesity."

GENOVA DIAGNOSTICS

Simopoulos AP. *Nutrients*. 2016;8(3):128-145.

Look to the Ratio

- “In the secondary prevention of cardiovascular disease, a ratio of 4/1 was associated with a 70% decrease in total mortality.”
- “A ratio of 2.5/1 reduced rectal cell proliferation in patients with colorectal cancer whereas a ratio of 4/1 with the same amount of omega-3 PUFA had no effect.”
- “The lower omega-6/omega-3 ratio in women with breast cancer was associated with decreased risk.”
- “A ratio of 2-3/1 suppressed inflammation in patients with rheumatoid arthritis.”
- “A ratio of 5/1 had a beneficial effect on patients with asthma, whereas a ratio of 10/1 had adverse consequences.”
- “These studies indicate that the optimal ratio may vary with the disease under consideration.”

GENOVA DIAGNOSTICS

Simopoulos AP. *Biomed Pharmacother.* 2002;56(8):365-79.

A Qualitative Rather Than a Quantitative Assessment of Nutrients

nutrients MDPI

Concept Paper

Utilizing Dietary Micronutrient Ratios in Nutritional Research May be More Informative than Focusing on Single Nutrients

Owen J. Kelly [1,*], Jennifer C. Gilman [1] and Jasminka Z. Ilich [2]

1 Abbott Nutrition, 2900 Easton Square Place, 01C13A/ES1, Columbus, OH 43219, USA; jennifer.gilman@abbott.com

2 Department of Nutrition, Food and Exercise Sciences, Florida State University, Tallahassee, FL 32306, USA; jilichernst@fsu.edu

* Correspondence: drojkelly@gmail.com

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Abstract: The 2015 US dietary guidelines advise the importance of good dietary patterns for health, which includes all nutrients. Micronutrients are rarely, if ever, consumed separately, they are not tissue specific in their actions and at the molecular level they are multitaskers. Metabolism functions within a seemingly random cellular milieu however ratios are important, for example, the ratio of adenosine triphosphate to adenosine monophosphate, or oxidized to reduced glutathione. Health status is determined by simple ratios, such as the waist hip ratio, or ratio of fat mass to lean mass. Some nutrient ratios exist and remain controversial such as the omega-6/omega-3 fatty acid ratio and the sodium/potassium ratio. Therefore, examining ratios of micronutrients may convey more information about how diet and health outcomes are related. Summarized micronutrient intake data, from food only, from the National Health and Nutrition Examination Survey, were used to generate initial ratios. Overall, in this preliminary analysis dietary ratios of micronutrients showed some differences between intakes and recommendations. Principles outlined here could be used in nutritional epidemiology and in basic nutritional research, rather than focusing on individual nutrient intakes. This paper presents the concept of micronutrient ratios to encourage change in the way nutrients are regarded.

GENOVA DIAGNOSTICS

Kelly OJ, et al. *Nutrients*. 2018;10(1):1-24.

Two Tests to Choose From

- Fatty Acids Profile – Bloodspot
- Fatty Acids Profile – Plasma

Bloodspot Fatty Acids

NUTRITIONAL

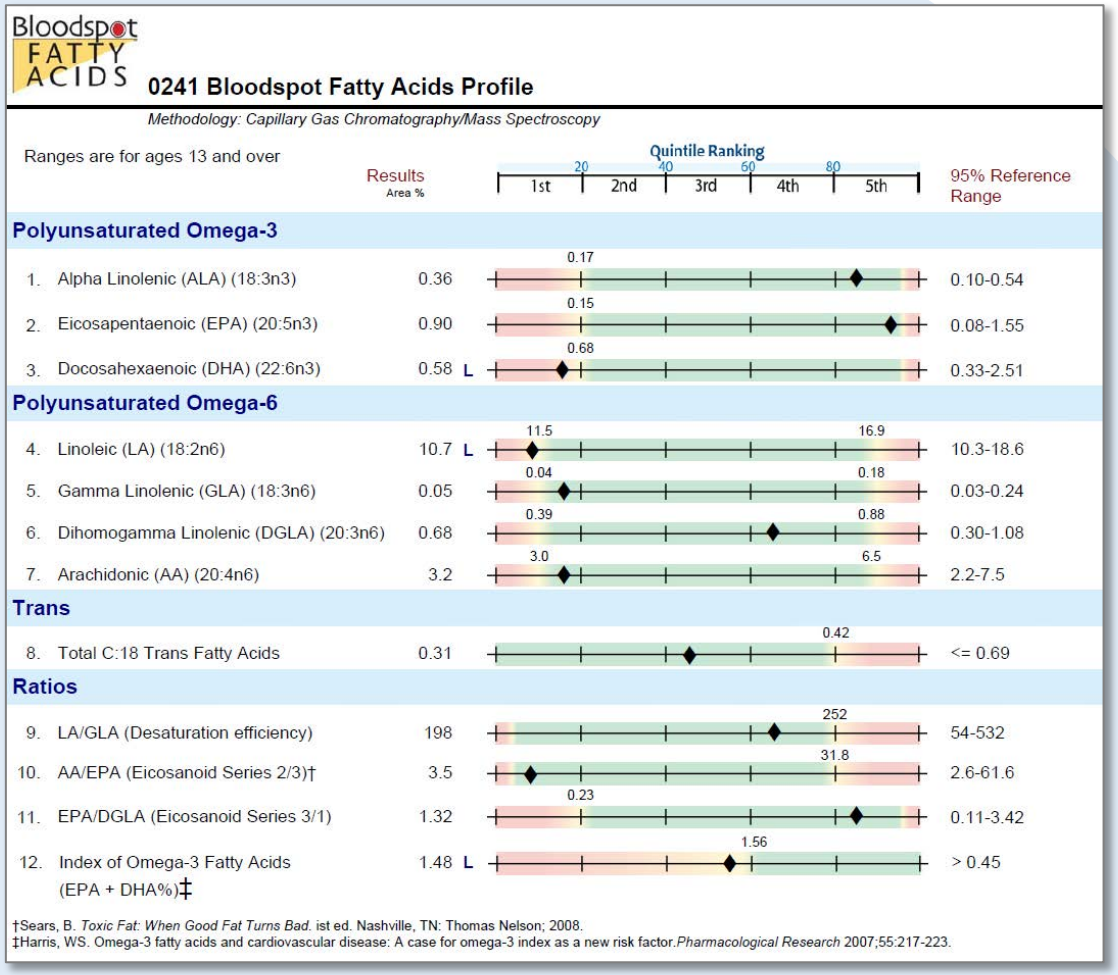
Fatty Acids Profile - Plasma

NUTRITIONAL

Fatty Acids Profile – Bloodspot

- Quick checking in on omega-3 index/status
- Helpful for omega-3 supplementation
- Convenient for the patient

AA (Arachidonic Acid)
ALA (Alpha-Linolenic Acid)
DGLA (Dihomogamma Linolenic Acid)
DHA (Docosahexaenoic Acid)
EPA (Eicosapentaenoic Acid)
GLA (Gamma Linolenic Acid)
LA (Linoleic Acid)
Total C:18 Trans-Isomers



Bloodspot FATTY ACIDS

0241 Bloodspot Fatty Acids Profile

Methodology: Capillary Gas Chromatography/Mass Spectroscopy

Ranges are for ages 13 and over

	Results Area %		Quintile Ranking (1st / 2nd / 3rd / 4th / 5th; 20, 40, 60, 80)	95% Reference Range
Polyunsaturated Omega-3				
1. Alpha Linolenic (ALA) (18:3n3)	0.36		0.17	0.10-0.54
2. Eicosapentaenoic (EPA) (20:5n3)	0.90		0.15	0.08-1.55
3. Docosahexaenoic (DHA) (22:6n3)	0.58	L	0.68	0.33-2.51
Polyunsaturated Omega-6				
4. Linoleic (LA) (18:2n6)	10.7	L	11.5, 16.9	10.3-18.6
5. Gamma Linolenic (GLA) (18:3n6)	0.05		0.04, 0.18	0.03-0.24
6. Dihomogamma Linolenic (DGLA) (20:3n6)	0.68		0.39, 0.88	0.30-1.08
7. Arachidonic (AA) (20:4n6)	3.2		3.0, 6.5	2.2-7.5
Trans				
8. Total C:18 Trans Fatty Acids	0.31		0.42	<= 0.69
Ratios				
9. LA/GLA (Desaturation efficiency)	198		252	54-532
10. AA/EPA (Eicosanoid Series 2/3)†	3.5		31.8	2.6-61.6
11. EPA/DGLA (Eicosanoid Series 3/1)	1.32		0.23	0.11-3.42
12. Index of Omega-3 Fatty Acids (EPA + DHA%)‡	1.48	L	1.56	> 0.45

†Sears, B. *Toxic Fat: When Good Fat Turns Bad.* ist ed. Nashville, TN: Thomas Nelson; 2008.
‡Harris, WS. Omega-3 fatty acids and cardiovascular disease: A case for omega-3 index as a new risk factor.*Pharmacological Research* 2007;55:217-223.

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Fatty Acids Profile – Plasma

- More thorough
- A broader array of fatty acids

0040 Fatty Acids Profile - Plasma

Methodology: Capillary Gas Chromatography/Mass Spectrometry

Ranges are for ages 13 and over

	Results µmol/L		Quintile Ranking (1st–4th)
Polyunsaturated Omega-3			
1. Alpha Linolenic (18:3n3)	26		20
2. Eicosapentaenoic (20:5n3)	25		17
3. Docosapentaenoic (22:5n3)	16		16
4. Docosahexaenoic (22:6n3)	66		59
Polyunsaturated Omega-6			
5. Linoleic (18:2n6)	1121		930
6. Gamma Linolenic (18:3n6)	8		7
7. Eicosadienoic (20:2n6)	4.9	L	6.4
8. Dihomogamma Linolenic (20:3n6)	45		34
9. Arachidonic (20:4n6)	452	H	201
10. Docosadienoic (22:2n6)	<0.23		
11. Docosatetraenoic (22:4n6)	2.4	L	3.7
Polyunsaturated Omega-9			
12. Mead (20:3n9)	2.2		

0040 Fatty Acids Profile - Plasma

Methodology: Capillary Gas Chromatography/Mass Spectrometry

Ranges are for ages 13 and over

	Results µmol/L		Quintile Ranking (1st–4th)
Monounsaturated			
13. Myristoleic (14:1n5)	2.4		1.2
14. Palmitoleic (16:1n7)	51		40
15. Vaccenic (18:1n7)	60		48
16. Oleic (18:1n9)	563		555
17. 11-Eicosenoic (20:1n9)	5.0		4.6
18. Nervonic (24:1n9)	1.4		1.1
Saturated			
19. Capric (10:0)	1.8		1.4
20. Lauric (12:0)	8.0		3.3
21. Myristic (14:0)	37		20
22. Palmitic (16:0)	857		792
23. Stearic (18:0)	369		294
24. Arachidic (20:0)	2.2		1.5
25. Behenic (22:0)	1.3		0.8
26. Lignoceric (24:0)	0.98		0.84
27. Hexacosanoic (26:0)	<0.27		0.36

0040 Fatty Acids Profile - Plasma

Methodology: Capillary Gas Chromatography/Mass Spectrometry

Ranges are for ages 13 and over

	Results µmol/L		Quintile Ranking (1st–5th)	95% Reference Range
Odd Chain				
28. Pentadecanoic (15:0)	7.1		14.5	<= 20.6
29. Heptadecanoic (17:0)	11.1		19.3	<= 24.4
30. Nonadecanoic (19:0)	1.06		1.51	<= 1.89
31. Heneicosanoic (21:0)	<0.38		0.50	<= 0.74
32. Tricosanoic (23:0)	0.38		0.62	<= 0.78
Trans				
33. Palmitelaidic (16:1n7t)	<0.4		0.4	<= 1.8
34. Total C:18 Trans	49	H	42	<= 59
Ratios				
35. LA/DGLA	22		30	11-46
36. EPA/DGLA	0.29		0.24	0.07-5.98
37. AA/EPA	18.1		20	1-57
38. Triene/Tetraene	0.005		0.016	<= 0.023

UC* = Unable to Calculate

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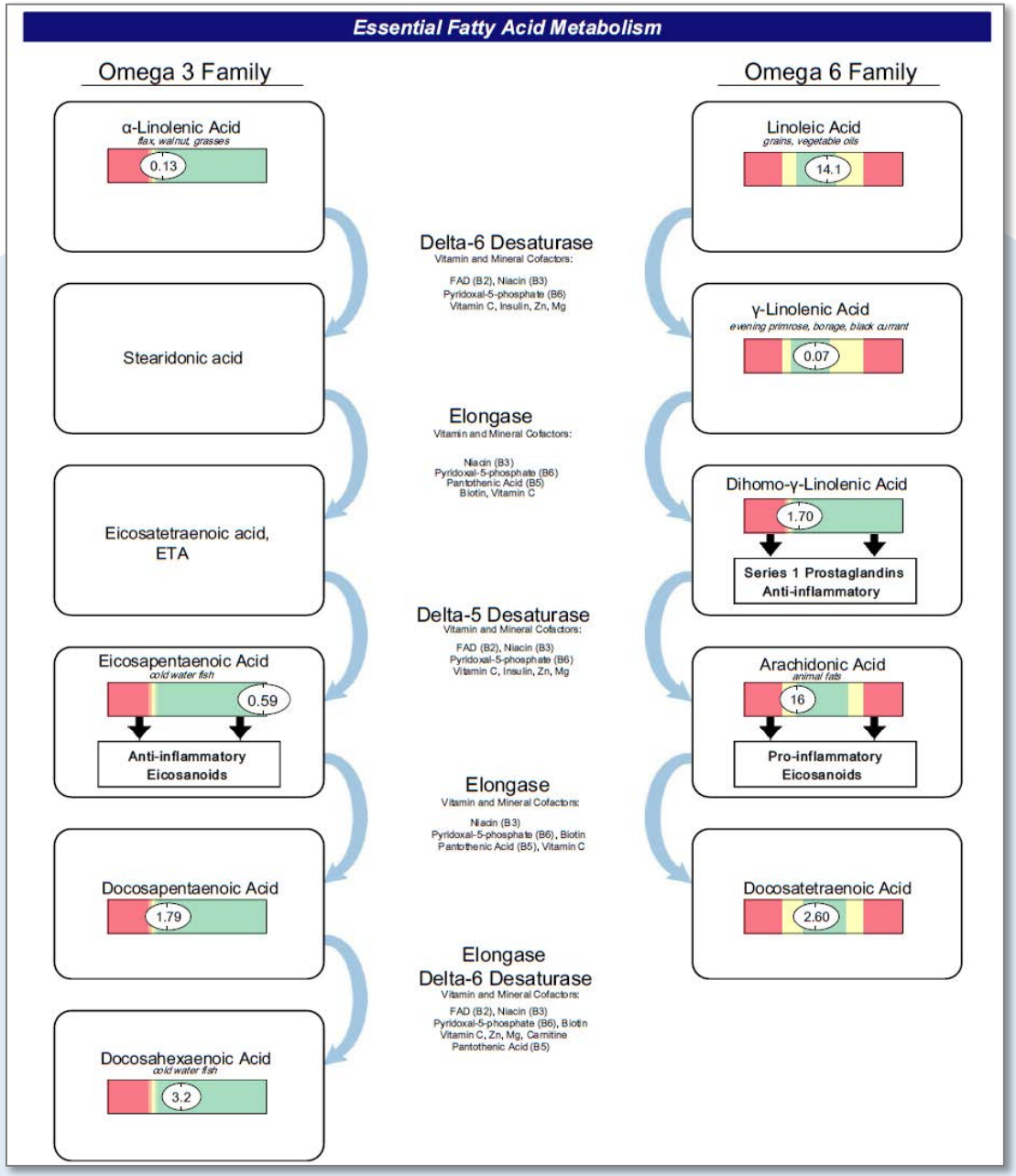
Nutrients for the EFA Conversions



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Omega-3 and Omega-6 Fatty Acid Desaturation

- Low amounts of omega-6 and omega-3 fatty acid needed to achieve maximal enzyme activity (saturation)
- Δ-6 desaturase requires as little as 1% dietary energy or less from LA plus ALA for maximum activity
- Omega-6 and omega-3 fatty acids compete for the enzyme and influence each other's metabolism

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Innis SM. *Mil Med*. 2014;179(11):82-7.

What Might You See On Some Reports? What Do You Do About It?

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Clinical Evidence of Essential Fatty Acid Deficiency

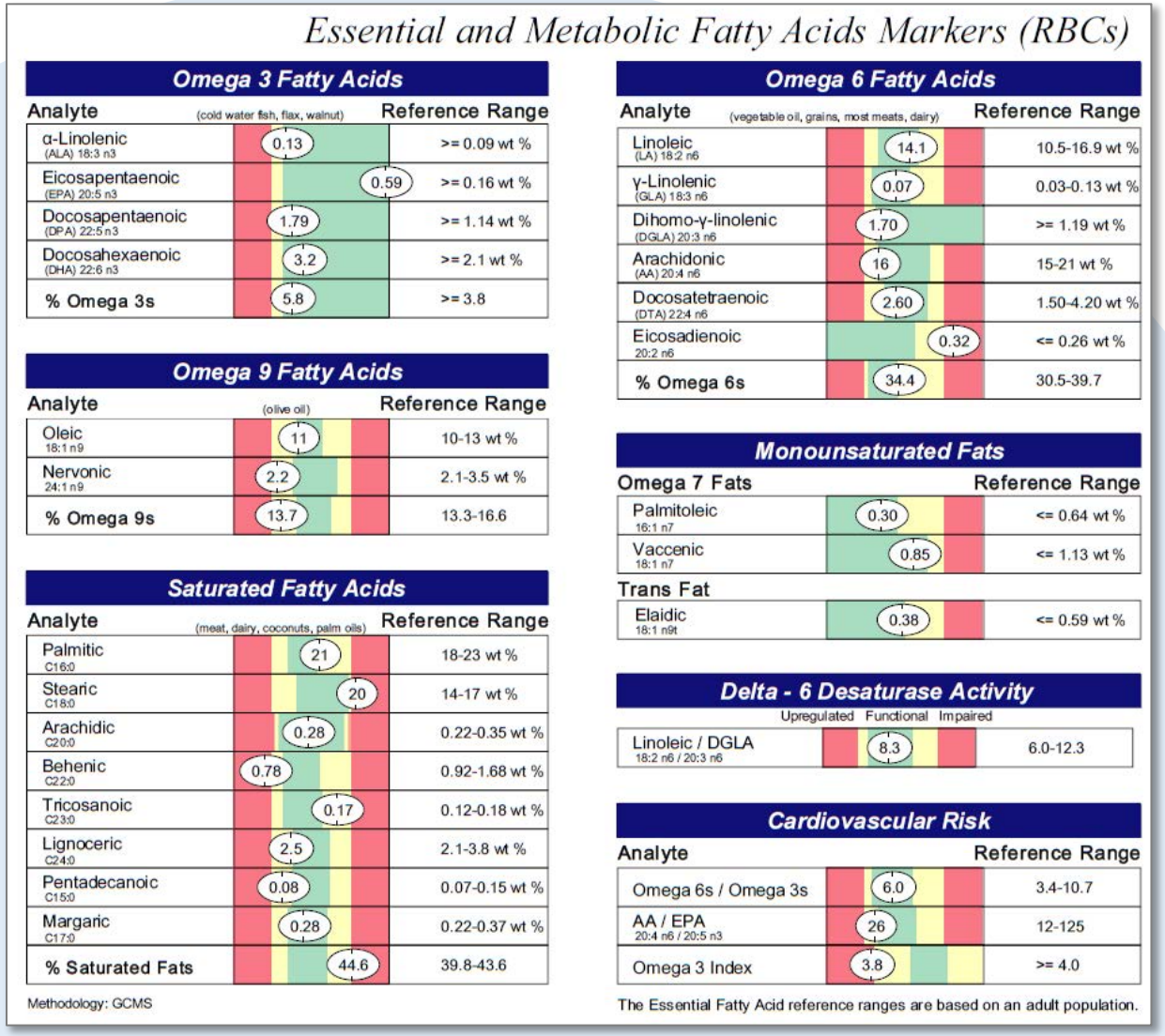
Essential fatty acids must be obtained from the diet

Consider insufficiency

Look to omega-3 AND omega-6

The 6 Top Features to Focus on Clinically

- Omega-3 Index – ensure that it is around 8%
- Linoleic/DGLA – to assess D6D
- AA/EPA – indicator of active metabolites
- Saturated fat percentage – especially for those on a high saturated fat diet
- Omega 6s/Omega 3s – balanced ratios
- Trans fats as a marker of processed food consumption



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Mead Acid and the Triene: Tetraene Ratio

"the MEADplus children were on average more symptomatic than MEADminus children. In the MEADplus group, food allergy presented with skin symptoms in 100% (vs. 70% in the MEADminus group, $p < 0.001$) and with vomiting or diarrhea in 70% (vs. 44% in the MEADminus group, $p < 0.05$)."

Polyunsaturated Omega-3				
1. Alpha Linolenic (18:3n3)	3	L	20	13 - 80
2. Eicosapentaenoic (20:5n3)	7		17	5 - 210
3. Docosapentaenoic (22:5n3)	4	L	16	11 - 50
4. Docosahexaenoic (22:6n3)	19	L	59	31 - 213
Polyunsaturated Omega-6				
5. Linoleic (18:2n6)	297	L	930 - 1,669	821 - 2,032
6. Gamma Linolenic (18:3n6)	35		7 - 33	5 - 46
7. Eicosadienoic (20:2n6)	3.6	L	6.4 - 15.3	5.2 - 22.5
8. Dihomogamma Linolenic (20:3n6)	21	L	34 - 102	27 - 140
9. Arachidonic (20:4n6)	147	L	201 - 451	158 - 521
10. Docosadienoic (22:2n6)	1.1		0.9	<= 2.0
11. Docosatetraenoic (22:4n6)	3.9		3.7 - 13.8	2.6 - 18.1
Polyunsaturated Omega-9				
12. Mead (20:3n9)	5.4		5.3	<= 8.3

Odd Chain				
28. Pentadecanoic (15:0)	3.4		14.5	<= 20.6
29. Heptadecanoic (17:0)	4.9		19.3	<= 24.4
30. Nonadecanoic (19:0)	<0.86		1.51	<= 1.89
31. Heneicosanoic (21:0)	<0.38		0.50	<= 0.74
32. Tricosanoic (23:0)	<0.37		0.62	<= 0.78
Trans				
33. Palmitelaidic (16:1n7t)	<0.4		0.4	<= 1.8
34. Total C:18 Trans	5		42	<= 59
Ratios				
35. LA/DGLA	14		30	11 - 46
36. EPA/DGLA	0.33		0.24	0.07 - 5.98
37. AA/EPA	21		20	1 - 57
38. Triene/Tetraene	0.037	H	0.016	<= 0.023

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Paassilta M, et al. *Lipids Health Dis*. 2014;13:180-5.

The Omega-3 Index

- “In 2004, the 'ω-3 index' was described as the sum of eicosapentaenoic acid (EPA, 20 : 5 n-3) and docosahexaenoic acid (DHA, 22 : 6 n-3) in red blood cells (RBCs) as an index of coronary heart disease mortality.”
- Mean omega-3-I in the U.S. (4.3%)
- American women had a significantly higher omega-3-I than men (4.8% vs. 3.8%, $p < 0.001$).
- Ideal is 8% for cardiovascular health.
- “…we estimate that risk for fatal CHD would have been reduced by about 30% moving from an Omega-3 Index of 4%-8%.”

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Fielding BA. *Curr Opin Clin Nutr Metab Care*. 2017;20(5):360-365.
Thuppal SV, et al. *Nutrients.* 2017;9(9):930-41.
Harris WS, et al. *Atherosclerosis.* 2017;262:51-54.

Low Omega-3 Index

Cardiovascular Risk		
Analyte		**Reference Range**
Omega 6s / Omega 3s	6.4	3.4-10.7
AA / EPA 20:4 n6 / 20:5 n3	42	12-125
Omega 3 Index	3.8	>= 4.0

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

- Use the omega-6/omega-3 ratio as a general measure alongside inflammatory markers, especially for those with IL-6 and TNF-a SNPs
- Omega-3 index is a well-established marker of omega-3 levels and can help in determination of extent of omega-3 supplementation
- Retest in 120 days

Omega-3 Index and Specialized Pro-Resolving Lipid Mediators

- "A doubling of the omega-3 index correlated with increases of 2.3-fold in 18-hydroxy-eicosapentaenoic acid (HEPE; $P < .0001$), 1.7-fold in 15-HEPE ($P = .03$), 1.9-fold in 5-HEPE ($P = .04$), and 3.6-fold in 4-hydroxy-docosahexaenoic acid ($P < .001$)."

- "Among subjects with symptomatic PAD who took oral fish oil supplements for 1 month, observed changes in the omega-3 index were strongly associated with increases in downstream mediators in the biochemical pathways of resolution."

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Schaller MS, et al. *J Clin Lipidol*. 2017;11(5):1289-1295.

Robust ALA with Low/Normal DHA

Omega 3 Fatty Acids		
Analyte	(cold water fish, flax, walnut)	**Reference Range**
α-Linolenic (ALA) 18:3 n3	0.32	>= 0.09 wt %
Eicosapentaenoic (EPA) 20:5 n3	0.46	>= 0.16 wt %
Docosapentaenoic (DPA) 22:5 n3	2.12	>= 1.14 wt %
Docosahexaenoic (DHA) 22:6 n3	2.5	>= 2.1 wt %
% Omega 3s	5.4	>= 3.8

- May indicate increased need for DHA
- May indicate impaired elongation/desaturation
- Conversion from ALA to DHA is nominal (5-15%, slightly higher in women due to estrogen)
- Some retroconversion of DHA to EPA can occur

GENOVA DIAGNOSTICS

Conquer, JA et al. *J Nutr.* 1996 Dec;126(12):3032-9.

What If Supplementation With Omega-3s Is Required?

- **Toxin-free:** No heavy metals, no microbiological contamination, no rancidity, no plastic, dark bottle
- **Pharmaceutical grade** – no oxygen exposure processing – no peroxidation or peroxidation end-products
- **Antioxidants** – to protect and stabilize fatty acids from peroxidation

Can Adults Adequately Convert Alpha-linolenic Acid (18:3n-3) to Eicosapentaenoic Acid (20:5n-3) and Docosahexaenoic Acid (22:6n-3)?

- "The use of ALA labelled with radioisotopes suggested that with a background diet high in saturated fat conversion to long-chain metabolites is approximately 6% for EPA and 3.8% for DHA."
- "With a diet rich in n-6 PUFA, conversion is reduced by 40 to 50%."
- "It is thus reasonable to observe an n-6/n-3 PUFA ratio not exceeding 4-6."

GENOVA DIAGNOSTICS

Gerster H. *Int J Vitam Nutr Res*. 1998;68(3):159-73.

EPA vs. DHA

- DHA and EPA have some differences depending on population
- Findings of benefits with DHA supplementation lean toward anti-inflammatory effects, memory, cognitive function, attention, etc.
- EPA was also seen to have an impact in these areas but more so with mood/behavior/depression
- One study pointed out that the effects of EPA and DHA may be less consistent on expression of pro-inflammatory genes than on anti-inflammatory
  - EPA benefited CVD risk reduction without adversely affecting LDL-C. In contrast, DHA decreased postprandial TG, but raised LDL-C

EPA Supplementation to Adults

- **Coronary Artery Disease**: Ethyl eicosapentaenoic acid (EPA) 0.6 grams three times daily has been used
- **Depression:** Ethyl eicosapentaenoic acid (ethyl-EPA) 0.5-1 gram twice daily has been used – in some case eicosapentaenoic acid is taken in combination with docosahexaenoic acid; the combination formulations containing at least 60% eicosapentaenoic acid seem to work best
- **Hypertriglyceridemia**: Ethyl eicosapentaenoic acid (Vascepa, formerly ARM101, Amarin) 4 grams daily in two divided doses, taken as an adjunct to dieting and possibly statin treatment, has been used

GENOVA DIAGNOSTICS

Natural Medicines. (1995-2018). DHA Monograph. Retrieved from https://naturalmedicines.therapeuticresearch.com

Forms of EPA

- Ethyl ester vs. triglyceride

DHA Supplementation to Adults

- **Age-related Macular Degeneration (AMD):** A combination of DHA 280 mg, lutein 12 mg, and zeaxanthin 0.6 mg, taken daily for one year, has been used
- **Atrial Fibrillation:** Taking 2 grams of a combination of DHA plus EPA in a 2:1 ratio starting 7 days before cardiac surgery and continuing until hospital discharge has been used – these patients also received vitamin C 1 gram daily plus vitamin E 400 IU daily starting 2 days prior to surgery and continuing until discharge
- **Dementia:** DHA 0.72 grams daily for one year has been used
- **Hyperlipidemia:** DHA 1.25 to 4 grams daily for 6 to 7 weeks has been used

GENOVA DIAGNOSTICS

Natural Medicines. (1995-2018). DHA Monograph. Retrieved from https://naturalmedicines.therapeuticresearch.com

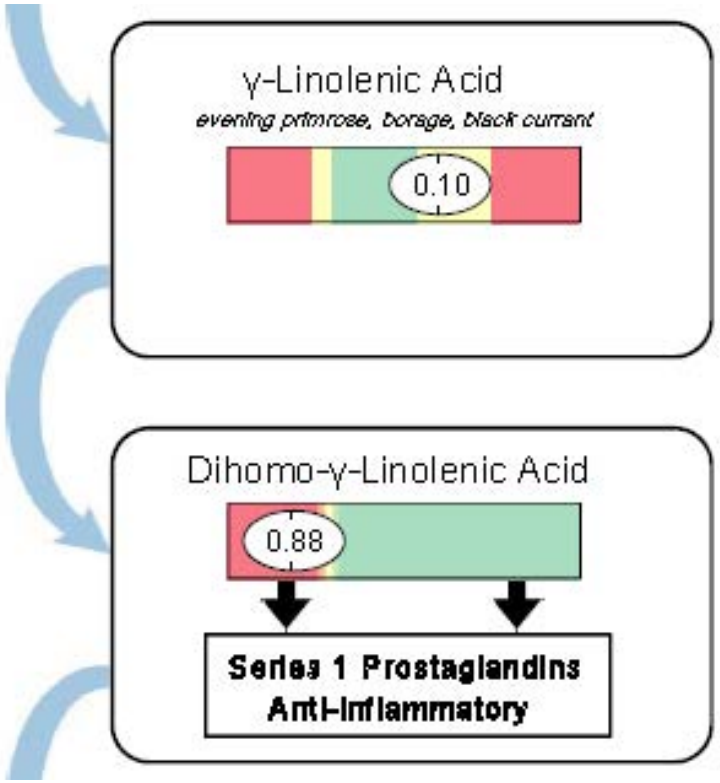
Deficient DGLA (Impairment at Elongase Enzyme)

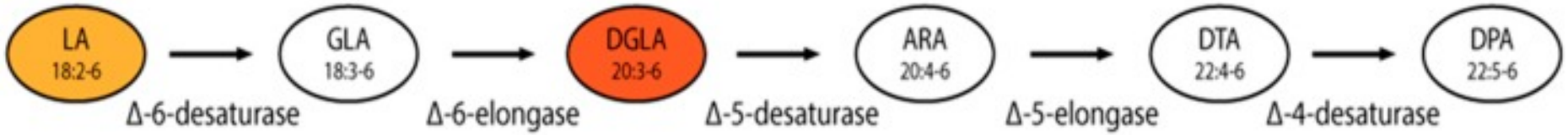
Omega 6 Fatty Acids		
Analyte (vegetable oil, grains, most meats, dairy)		**Reference Range**
Linoleic (LA) 18:2 n6	13.0	10.5-16.9 wt %
γ-Linolenic (GLA) 18:3 n6	0.10	0.03-0.13 wt %
Dihomo-γ-linolenic (DGLA) 20:3 n6	0.88	>= 1.19 wt %
Arachidonic (AA) 20:4 n6	15	15-21 wt %
Docosatetraenoic (DTA) 22:4 n6	1.64	1.50-4.20 wt %
Eicosadienoic 20:2 n6	0.20	<= 0.26 wt %
% Omega 6s	31.2	30.5-39.7

Elongase

Vitamin and Mineral Cofactors:

Niacin (B3)
Pyridoxal-5-phosphate (B6)
Pantothenic Acid (B5)
Biotin, Vitamin C





GENOVA DIAGNOSTICS

Knez M, et al. *Nutrients*. 2017;9(8):825-36.

Deficient GLA/DGLA (Low/Normal GLA with Low DGLA)

Omega 6 Fatty Acids		
Analyte (vegetable oil, grains, most meats, dairy)		**Reference Range**
Linoleic (LA) 18:2 n6	15.7	10.5-16.9 wt %
γ-Linolenic (GLA) 18:3 n6	0.05	0.03-0.13 wt %
Dihomo-γ-linolenic (DGLA) 20:3 n6	1.00	>= 1.19 wt %
Arachidonic (AA) 20:4 n6	15	15-21 wt %
Docosatetraenoic (DTA) 22:4 n6	1.84	1.50-4.20 wt %
Eicosadienoic 20:2 n6	0.30	<= 0.26 wt %
% Omega 6s	34.0	30.5-39.7

- High LA – reduce corn and seed oils in the diet
- Issue with desaturase conversion to GLA; consider nutrient supplementation
- GLA repletion with EPO
- DGLA repletion with black currant oil

Therapeutic Doses for Supplementation in Adults

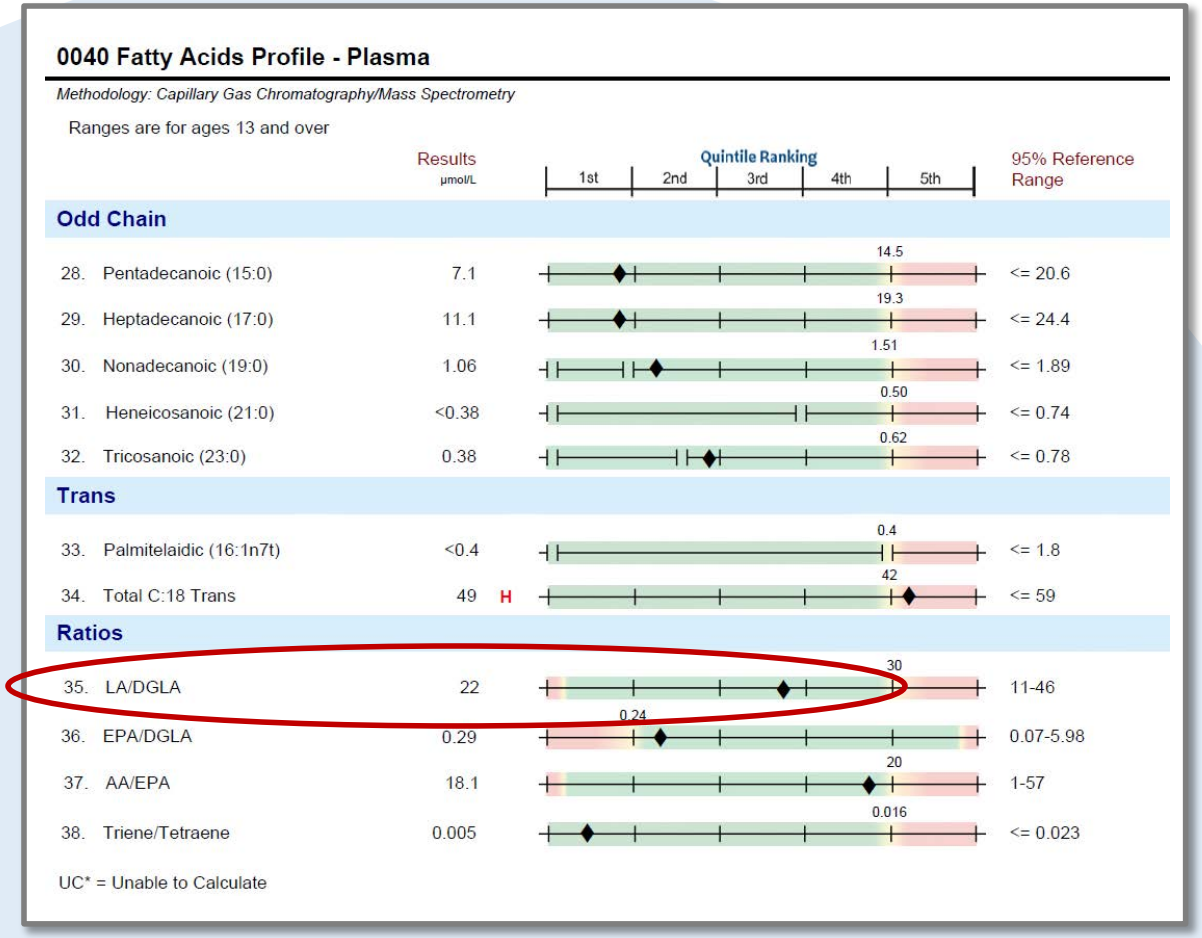
- **GLA: Evening Primrose Oil (EPO)**
  - **Atopic Dermatitis**: Evening primrose 2-3 grams twice daily for 3 weeks to 5 months has been used
  - **Rheumatoid Arthritis**: Evening primrose (Efamol) 6 grams daily for 12 months has been used
  - **Hyperlipidemia**: Evening primrose 1.5-2 grams twice daily for 4 weeks to 3 months, has been used
- **DGLA: Black Currant Oil (BCO)**
  - **General**: "As a dietary supplement, black currant is available in 500mg and 1,000mg capsules that typically contain black currant seed oil, vegetable glycerin, and gelatin. Based on some herbal textbooks, no toxicity concerns or issues have been reported with black currant consumed as food or ingested in 500 mg tablets three times a day."
  - **Immunomodulation**: 750mg of black currant seed oil has been used for two months

GENOVA DIAGNOSTICS

Natural Medicines. (1995-2018). DHA Monograph. Retrieved from https://naturalmedicines.therapeuticresearch.com

LA:DGLA as an Indicator of Zn Status

- The LA:DGLA ratio (linoleic acid:dihomo-γ-linolenic acid ratio) may be a useful additional indicator for assessing Zn status more precisely
- "Similarly, in situations when EFA deficiency is of dietary origin, there is an increased attempt to synthetize more linoleic acid, so Δ6 desaturase activity is increased. However, when EFA deficiency is metabolic (as in Zn deficiency) Δ6 activity is inhibited. Finally, increased Δ6 desaturase activity will not necessarily lead to the elevated metabolizing of linoleic acid and its conversion to DGLA."



0040 Fatty Acids Profile - Plasma

Methodology: Capillary Gas Chromatography/Mass Spectrometry

Ranges are for ages 13 and over

	Results µmol/L		Quintile Ranking (1st, 2nd, 3rd, 4th, 5th)	95% Reference Range
Odd Chain				
28. Pentadecanoic (15:0)	7.1		14.5	<= 20.6
29. Heptadecanoic (17:0)	11.1		19.3	<= 24.4
30. Nonadecanoic (19:0)	1.06		1.51	<= 1.89
31. Heneicosanoic (21:0)	<0.38		0.50	<= 0.74
32. Tricosanoic (23:0)	0.38		0.62	<= 0.78
Trans				
33. Palmitelaidic (16:1n7t)	<0.4		0.4	<= 1.8
34. Total C:18 Trans	49	H	42	<= 59
Ratios				
35. LA/DGLA	22		30	11-46
36. EPA/DGLA	0.29		0.24	0.07-5.98
37. AA/EPA	18.1		20	1-57
38. Triene/Tetraene	0.005		0.016	<= 0.023

UC* = Unable to Calculate

GENOVA DIAGNOSTICS

Knez M, et al. *Nutrients.* 2017;9(8):825-36.

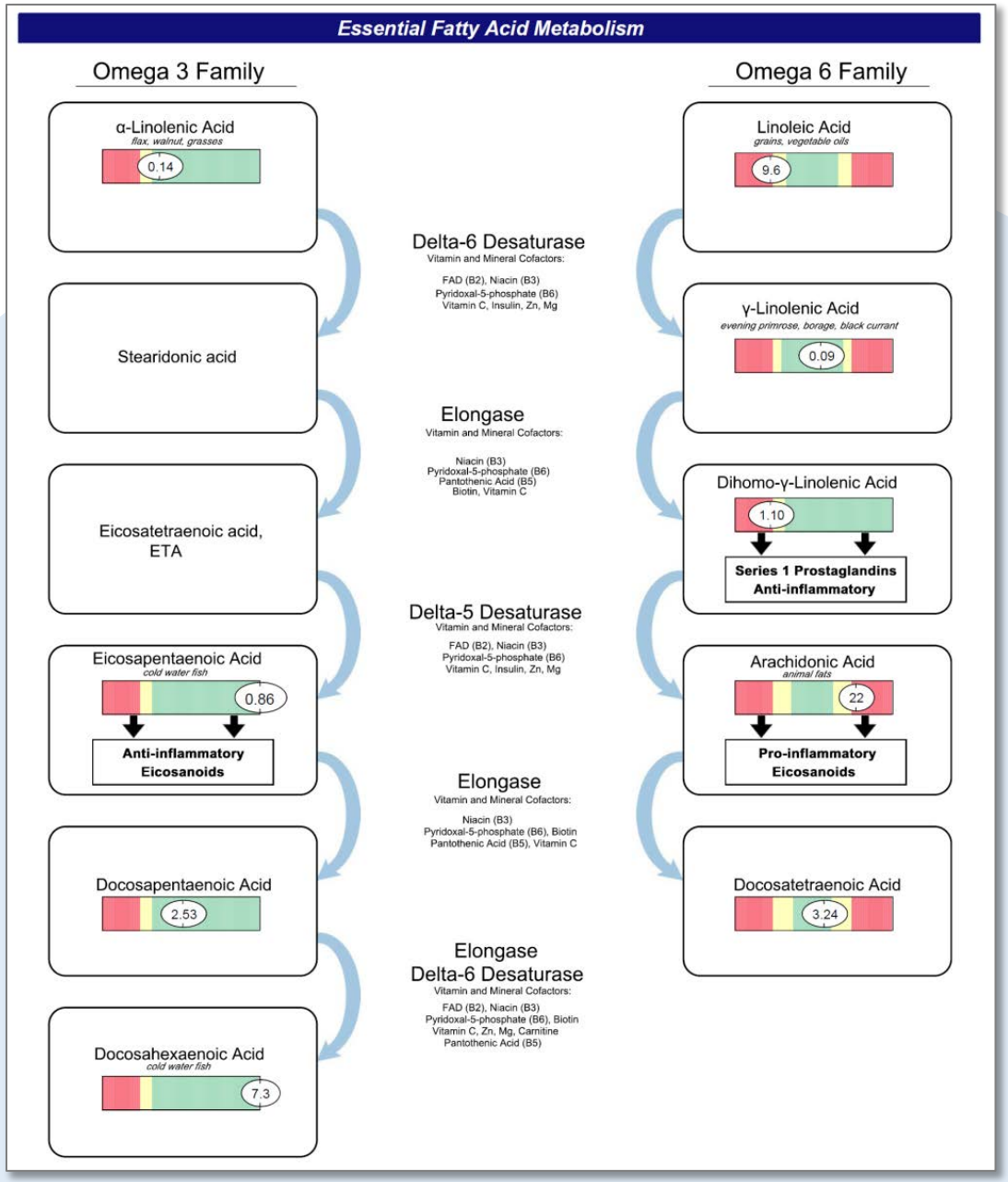
Why is zinc important for EFAs?

- Zn may have a role in the absorption of linoleic acid. Lower levels of Zn produce lower levels of linoleic acid
- Zn deficiency reduces the availability of linoleic acid metabolites γ-linolenic and arachidonic acid
- Zn deficiency decreases the mobilization of DGLA from tissue stores
- Zn is needed in the formation of GLA and in the mobilization of DGLA
- EFA supplementation worsens the effect of Zn deficiency
- Zn deficiency decreases the esterification of essential fatty acids into phospholipids
- During Zn deficiency, linoleic acid accumulates in tissues when EFA supplements are administered
- Zn deficiency results in a higher concentration of linoleic and a lower concentration of arachidonic acid in tissue phospholipids
- Zn-deficient subjects have an increased β-oxidation of linoleic acid, resulting in decreased amounts of linoleic acid available to be metabolized into arachidonic acid
- The most important EFA functions are carried out by molecules downstream of GLA
- In animals exposed to diets deficient in essential fatty acids, the characteristic symptoms develop much more rapidly if the diets are also deficient in Zn
- The inhibition of the desaturases by Zn deficiency is so strong that it causes a more rapid decline in tissue arachidonic acid and docosahexaenoic acid than does the direct dietary deficiency of all the omega 6 or omega 3 polyunsaturated fatty acids
- Enzymes involved in prostaglandin synthesis are also Zn-dependent, and defects in prostaglandin synthesis are observed under Zn deficiency

GENOVA DIAGNOSTICS

Knez M, et al. *Nutrients*. 2017;9(8):825-36.

Nutrients for the EFA Conversions



GENOVA DIAGNOSTICS

Which Nutritional and Lifestyle Factors Alter Desaturase and Elongase enzymes?

- Genetic factors (SNPs)
- Obesity surgery
  - *"...the estimated activity of **elongase** (18:1 n-7/16:1 n-7) **increased significantly after obesity surgery** in all lipid fractions (all P<4 × 10−7) and the increase in the estimated activity of D5D in triglycerides was associated with higher weight loss"*
- Weight gain
  - *"**palmitic acid, stearoyl-CoA-desaturase and Δ6-desaturase indices were associated with abdominal obesity**;... Linoleic acid, α-linolenic acid, docohexaenoic acid, and Δ5-desaturase were inversely associated with abdominal obesity... abdominal obesity was more common among individuals with relatively high proportions of palmitic acid, whilst the contrary was true for linoleic acid."*
- One mouse study showed curcumin increases levels of enzymes for fatty acid synthesis
  - *"**curcumin enhances the synthesis of DHA** from its precursor, α-linolenic acid (C18:3 n-3; ALA) and **elevates levels of enzymes involved in the synthesis of DHA such as FADS2 and elongase 2** in both liver and brain tissues."*

Mathias RA, et al. *Curr Nutr Rep*. 2014;3(2):139-148.
Vernekar M, et al. *Meta Gene*. 2017;11:152-6.
Walle P, et al. *Nutr Diabetes*. 2017;7(9):e285.
Alsharari ZD, et al. *PloS One.* 2017: e0170684.
Wu A, et al. *Biochim Biophys Acta*. 2015;1852(5):951-61.

Which Nutritional and Lifestyle Factors Alter Desaturase and Elongase enzymes?

- Mg
  - "Mechanistically, Mg deficiency was accompanied by enhanced desaturase and elongase mRNA expression in maternal livers along with higher circulating insulin and glucose concentrations ($P < 0.05$) and increased mRNA expression of Srebf1 and Chrebp, regulators of fatty acid synthesis ($P < 0.05$)."
- Vitamin B6
  - "…relative mRNA expressions of Δ5 and Δ6 desaturases were 40-50% lower in vitamin B-6-restricted cells."
- Vitamin A
  - "Treatment of VA-deficient rats with all-trans-retinoic acid lowered the level of expression of D5D mRNA toward that of VA-sufficient rats."
- Note that higher expression of enzymes do not always correspond to higher activity.

Gupta M, et al. *Mol Med*. 2014;20:332-40.

Zhao M, et al. *Am J Physiol Endocrinol Metab*. 2013;304(4):E342-51.

Zolfaghari R, et al. *Arch Biochem Biophys*. 2001;391(1):8-15.

Drąg J, et al. *Genes Nutr*. 2017;12:2-10.

High Trans Fat Markers

Monounsaturated Fats		
Omega 7 Fats		**Reference Range**
Palmitoleic 16:1 n7	0.25	<= 0.64 wt %
Vaccenic 18:1 n7	0.81	<= 1.13 wt %
Trans Fat		
Elaidic 18:1 n9t	0.45	<= 0.59 wt %

- A marker of processed food consumption
- Correlate with inflammatory markers like hs-CRP

Trans Fats

- Unsaturated fatty acids with at least one unsaturated, non-conjugated double bond in the *trans* (rather than the typical *cis*) configuration:
  - Elaidic acid [C18:1 t9], vaccenic acid [C18:1 t11], palmitelaidic acid [C16:1 t9], and linoelaidic acid [C18:2 t9, 12]
    - *"Plasma elaidic acid levels are associated with higher risk of all-cause and CVD mortality, and palmitelaidic acid levels are associated with higher cancer mortality in later life." https://www.ncbi.nlm.nih.gov/pubmed/28915883*
- Humans do not inherently make trans-fatty acids (TFAs)
- TFAs occur in fat from ruminant animal meat, milk, and dairy fat and artificially in industrially hardened vegetable oils.
- Also as part of partially hydrogenated vegetable oils through consumption of margarine and industrially processed foods such as cakes, candies, cookies, chocolate, mayonnaise, potato chips, French fries and other deep-fat fried foods, and fast food.
- Use trans fatty acid levels as marker for inflammatory diet
- One study showed how levels declined in American population after implementation of regulations .
    - *These nationally representative data for the adult US population show that TFA concentrations were 54% lower in NHANES 2009-2010 than in NHANES 1999-2000.*
    - *"The results indicate an overall reduction in TFA concentrations in the US population and provide a valuable baseline to evaluate the impact of the recent regulation categorizing TFAs as food additives."*
- Specific trans fatty acids may be associated with specific disease outcomes such as breast cancer, CVD mortality and cancer mortality.
  - An increased risk of breast cancer was associated with increasing levels of the trans-monounsaturated fatty acids palmitoleic acid and elaidic acid (highest quintile vs. lowest: odds ratio = 1.75, 95% confidence interval: 1.08, 2.83; p-trend = 0.018).
  - "A high serum level of trans-monounsaturated fatty acids, presumably reflecting a high intake of industrially processed foods, is probably one factor contributing to increased risk of invasive breast cancer in women."

Vesper H, et al. *Am J Clin Nutr*. 2017;105(5):1063-1069.
Chajes V, et al. *Am J Epidemiol*. 2008;167(11):1312-20.
Penke, M et al. *Lipids Health Dis.* 2017 Aug 4;16(1):147.
Mazidi M, et al. *J Nutr Metab*. 2017;2017:1-6.

Trans Fats and Inflammation

"A high level of TFAs appears to be a contributor to an unfavourable inflammatory profile. Because serum TFAs concentrations are affected by dietary TFA intake, these data suggest a possible contribution of TFAs intake modulation in the prevention of inflammation-related chronic diseases."

"After adjustment for age and sex, mean serum TFAs rose with the increasing quarters of hs-CRP and fibrinogen (both $p < 0.001$)."

GENOVA DIAGNOSTICS

Mazidi M, et al. *J Nutr Metab*. 2017;2017:1-6.

Why You Need to Look at Levels of C16:0 (Palmitic Acid)

- High palmitic acid is associated with higher levels of resistin, increased diabetes risk
  - "Even- and odd-chain saturated fatty acids were differentially associated with adipokines. Higher levels of even-chain saturated fatty acids (14:0 myristic, 16:0 palmitic, and 18:0 stearic acids) were associated with higher levels of resistin (P for trend = 0.048) and lower levels of adiponectin (P for trend = 0.003). By contrast, odd-chain saturated fatty acids (15:0 pentadecanoic and 17:0 heptadecanoic acids) showed inverse associations with leptin and PAI-1 (P for trend = 0.048 and 0.02, respectively)."

GENOVA DIAGNOSTICS

Mazidi M, et al. *J Nutr Metab*. 2017;2017:1-6.

High Palmitic; Trans Fat; Deficient GLA/DGLA

Polyunsaturated Omega-3				
1. Alpha Linolenic (18:3n3)	12	L	20	13 - 80
2. Eicosapentaenoic (20:5n3)	26		17	5 - 210
3. Docosapentaenoic (22:5n3)	17		16	11 - 50
4. Docosahexaenoic (22:6n3)	18	L	59	31 - 213
Polyunsaturated Omega-6				
5. Linoleic (18:2n6)	392	L	930 – 1,669	821 - 2,032
6. Gamma Linolenic (18:3n6)	30		7 – 33	5 - 46
7. Eicosadienoic (20:2n6)	30.1	H	6.4 – 15.3	5.2 - 22.5
8. Dihomogamma Linolenic (20:3n6)	44		34 – 102	27 - 140
9. Arachidonic (20:4n6)	174		201 – 451	158 - 521
10. Docosadienoic (22:2n6)	1.9		0.9	<= 2.0
11. Docosatetraenoic (22:4n6)	9.8		3.7 – 13.8	2.6 - 18.1
Polyunsaturated Omega-9				
12. Mead (20:3n9)	1.0		5.3	<= 8.3

Monounsaturated				
13. Myristoleic (14:1n5)	33.4	H	1.2 – 6.1	0.8 - 9.7
14. Palmitoleic (16:1n7)	>256	H	40 – 155	30 - 256
15. Vaccenic (18:1n7)	105		48 – 93	40 - 122
16. Oleic (18:1n9)	1,284		555 – 1,182	466 - 1,470
17. 11-Eicosenoic (20:1n9)	4.6		4.6 – 10.3	3.7 - 18.1
18. Nervonic (24:1n9)	1.1		1.1 – 2.2	1.1 - 2.7
Saturated				
19. Capric (10:0)	4.5		1.4 – 4.0	0.8 - 6.2
20. Lauric (12:0)	182.7	H	3.3 – 14.5	2.2 - 27.3
21. Myristic (14:0)	199	H	20 – 87	15 - 139
22. Palmitic (16:0)	2,465		792 – 1,794	667 - 2,526
23. Stearic (18:0)	288		294 – 511	250 - 629
24. Arachidic (20:0)	1.4		1.5 – 3.2	1.3 - 4.7
25. Behenic (22:0)	0.6		0.8 – 2.0	0.6 - 2.9
26. Lignoceric (24:0)	0.53	L	0.84 – 1.66	0.63 - 2.45
27. Hexacosanoic (26:0)	<0.27		0.36	<= 0.43

- High animal fats
- Possibly high inflammation/increase omega-3s
- High palmitoleic acid suggests EFA deficiency
- Reduce saturated fats

GENOVA DIAGNOSTICS

Who Is at Risk for Low Fat-soluble Vitamins?

- Gastric surgery
- Cystic fibrosis
- Chronic pancreatitis
- Biliary issues
- Genetic defects in bile production
- Intestinal failure/IBD
- Renal function
- Late stage liver disease
- Demographic factors - age, season, hospitalization, poor nutritional status

Fat Soluble Vitamin Panel

Polyunsaturated Omega-3		
1. Alpha Linolenic (18:3n3)	23	20
2. Eicosapentaenoic (20:5n3)	13	17
3. Docosapentaenoic (22:5n3)	15	16
4. Docosahexaenoic (22:6n3)	55	59
Polyunsaturated Omega-6		
5. Linoleic (18:2n6)	1,051	930
6. Gamma Linolenic (18:3n6)	9	7
7. Eicosadienoic (20:2n6)	7.2	6.4
8. Dihomogamma Linolenic (20:3n6)	37	34
9. Arachidonic (20:4n6)	248	201
10. Docosadienoic (22:2n6)	0.6	
11. Docosatetraenoic (22:4n6)	6.5	3.7
Polyunsaturated Omega-9		
12. Mead (20:3n9)	0.9	<= 8.3
Monounsaturated		
13. Myristoleic (14:1n5)	1.1	1.2
14. Palmitoleic (16:1n7)	49	40
15. Vaccenic (18:1n7)	75	48
16. Oleic (18:1n9)	816	555
17. 11-Eicosenoic (20:1n9)	6.4	4.6
18. Nervonic (24:1n9)	1.1	1.1

Coenzyme Q10 Plus Vitamins Profile - Serum

Methodology: High Performance Liquid Chromatography

Ranges: Ages 13 and over.

		Results mg/L		Ranges
1.	Coenzyme Q10	0.87	0.64 – 2.16	0.48 - 3.04
2.	alpha-Tocopherol	11.5	9.8 – 25.1	6.8 - 31.7
3.	gamma-Tocopherol	0.93	0.26 – 2.06	0.06 - 2.99
4.	Vitamin A (Retinol)	0.48	0.36 – 0.74	0.29 - 1.05
5.	β-Carotene	0.31	0.15 – 1.70	0.10 - 2.71

Vitamin D Profile - Serum

Methodology: LC/Tandem Mass Spectrometry

		Results ng/mL		Reference Range
8.	25-Hydroxyvitamin D	21.6	L	30.0 - 100.0
9.	25-Hydroxyvitamin D2	<0.1		
10.	25-Hydroxyvitamin D3	21.5		

30 50 80 100

GENOVA DIAGNOSTICS

Fat-Soluble Vitamins

- Fat malabsorption also results in a deficit of fat-soluble vitamins A and E, with consequent clinical manifestations, such as weight loss, abdominal discomfort and abdominal swelling sensation.
- Research on fat-soluble vitamins as indicators of fat absorption has offered conclusions.
  - For example, vitamin E is transported exclusively by lipoproteins and requires chylomicrons to be brought into circulation from the gut making it an indicator of the gut's ability to absorb fat (Borel et al., 1997)

GENOVA DIAGNOSTICS

Pezzilli R. *World J Gastroenterol*. 2009;15(14):1673-6.

When overall fatty acids and fat-soluble vitamins are low, look to digestion and absorption markers.

High Mead/High triene:tetraene; Low Oleic; Low Capric/lauric; Low GLA/DGLA

Polyunsaturated Omega-3				
1. Alpha Linolenic (18:3n3)	3	L	20	13 - 80
2. Eicosapentaenoic (20:5n3)	7		17	5 - 210
3. Docosapentaenoic (22:5n3)	4	L	16	11 - 50
4. Docosahexaenoic (22:6n3)	19	L	59	31 - 213
Polyunsaturated Omega-6				
5. Linoleic (18:2n6)	297	L	930 - 1,669	821 - 2,032
6. Gamma Linolenic (18:3n6)	35		7 - 33	5 - 46
7. Eicosadienoic (20:2n6)	3.6	L	6.4 - 15.3	5.2 - 22.5
8. Dihomogamma Linolenic (20:3n6)	21	L	34 - 102	27 - 140
9. Arachidonic (20:4n6)	147	L	201 - 451	158 - 521
10. Docosadienoic (22:2n6)	1.1		0.9	<= 2.0
11. Docosatetraenoic (22:4n6)	3.9		3.7 - 13.8	2.6 - 18.1
Polyunsaturated Omega-9				
12. Mead (20:3n9)	5.4		5.3	<= 8.3

Monounsaturated				
13. Myristoleic (14:1n5)	<0.8	L	1.2 - 6.1	0.8 - 9.7
14. Palmitoleic (16:1n7)	31		40 - 155	30 - 256
15. Vaccenic (18:1n7)	33	L	48 - 93	40 - 122
16. Oleic (18:1n9)	343	L	555 - 1,182	466 - 1,470
17. 11-Eicosenoic (20:1n9)	1.5	L	4.6 - 10.3	3.7 - 18.1
18. Nervonic (24:1n9)	<1.1	L	1.1 - 2.2	1.1 - 2.7
Saturated				
19. Capric (10:0)	1.9		1.4 - 4.0	0.8 - 6.2
20. Lauric (12:0)	<1.0	L	3.3 - 14.5	2.2 - 27.3
21. Myristic (14:0)	8	L	20 - 87	15 - 139
22. Palmitic (16:0)	369	L	792 - 1,794	667 - 2,526
23. Stearic (18:0)	159	L	294 - 511	250 - 629
24. Arachidic (20:0)	0.6	L	1.5 - 3.2	1.3 - 4.7
25. Behenic (22:0)	<0.6	L	0.8 - 2.0	0.6 - 2.9
26. Lignoceric (24:0)	0.23	L	0.84 - 1.66	0.63 - 2.45
27. Hexacosanoic (26:0)	<0.27		0.36	<= 0.43
Odd Chain				
28. Pentadecanoic (15:0)	3.4		14.5	<= 20.6
29. Heptadecanoic (17:0)	4.9		19.3	<= 24.4
30. Nonadecanoic (19:0)	<0.86		1.51	<= 1.89
31. Heneicosanoic (21:0)	<0.38		0.50	<= 0.74
32. Tricosanoic (23:0)	<0.37		0.62	<= 0.78
Trans				
33. Palmitelaidic (16:1n7t)	<0.4		0.4	<= 1.8
34. Total C:18 Trans	5		42	<= 59
Ratios				
35. LA/DGLA	14		30	11 - 46
36. EPA/DGLA	0.33		0.24	0.07 - 5.98
37. AA/EPA	21		20	1 - 57
38. Triene/Tetraene	0.037	H	0.016	<= 0.023

- Most fats are low
- Discuss incorporating more dietary fats
- Low EFAs overall

Functional Medicine: DIGIN

Digestion/Absorption

Intestinal Permeability

Gut Microbiota

Immune Regulation

Nervous System – Gut Feelings

Physical Exam Findings
Questionnaires
Laboratory Tests

Fat Digestion

Enzymes: Fat Digestion

- Lipase is secreted in the stomach and is particularly sensitive to acid inactivation and has a short half life
- Increased fecal fats on the GI Effects can identify impaired fat digestion
- Low PE1 can indicate impaired secretion of digestive enzymes

Nutrients

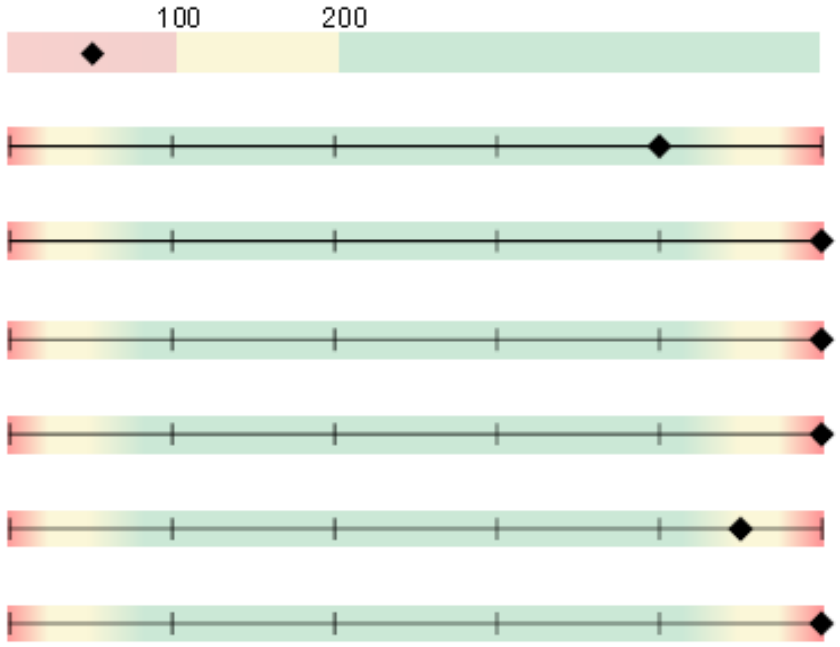
- Impaired digestion of fats can lead to decreased fatty acids and fat soluble vitamins
  - Need to check essential fatty acids ALA and LA, as well as EPA and DHA
  - Need to check fat soluble vitamins

GENOVA DIAGNOSTICS

Pezzilli R. *World J Gastroenterol*. 2009;15(14):1673-6.
Degnan PH, et al. *Cell Metab*. 2014;20(5):769-78

GI Effects Comprehensive: High Fecal Fats / Low PE-1

Digestion and Absorption			
Pancreatic Elastase 1 †	52	L	>200 mcg/g
Products of Protein Breakdown (Total*) (Valerate, Isobutyrate, Isovalerate)	6.5		1.8-9.9 micromol/g
Fecal Fat (Total*)	112.2	H	3.2-38.6 mg/g
Triglycerides	8.3	H	0.3-2.8 mg/g
Long-Chain Fatty Acids	81.8	H	1.2-29.1 mg/g
Cholesterol	4.6		0.4-4.8 mg/g
Phospholipids	17.5	H	0.2-6.9 mg/g



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Markers of Digestion/Absorption

- Pancreatic Elastase 1
- Chymotrypsin
- Putrefactive SCFAs
- Meat & Vegetable Fibers

- Triglycerides
- LCFAs
- Cholesterol
- Phospholipids
- Fecal Fat

Functional Medicine 5R Protocol

- Remove
- Replace
- Reinoculate
- Repair
- Rebalance

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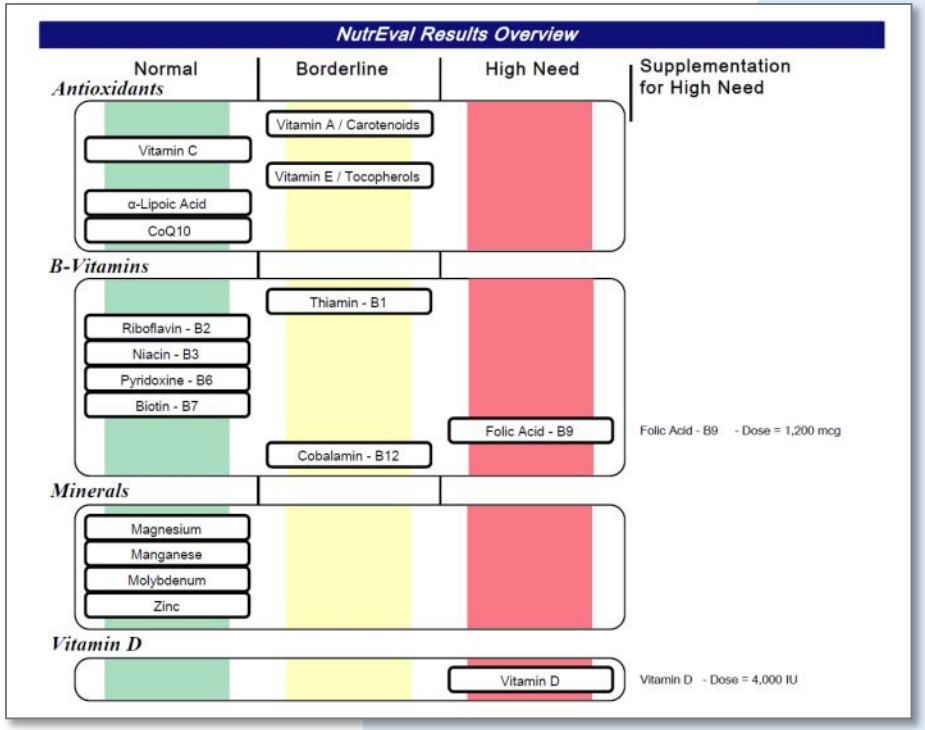
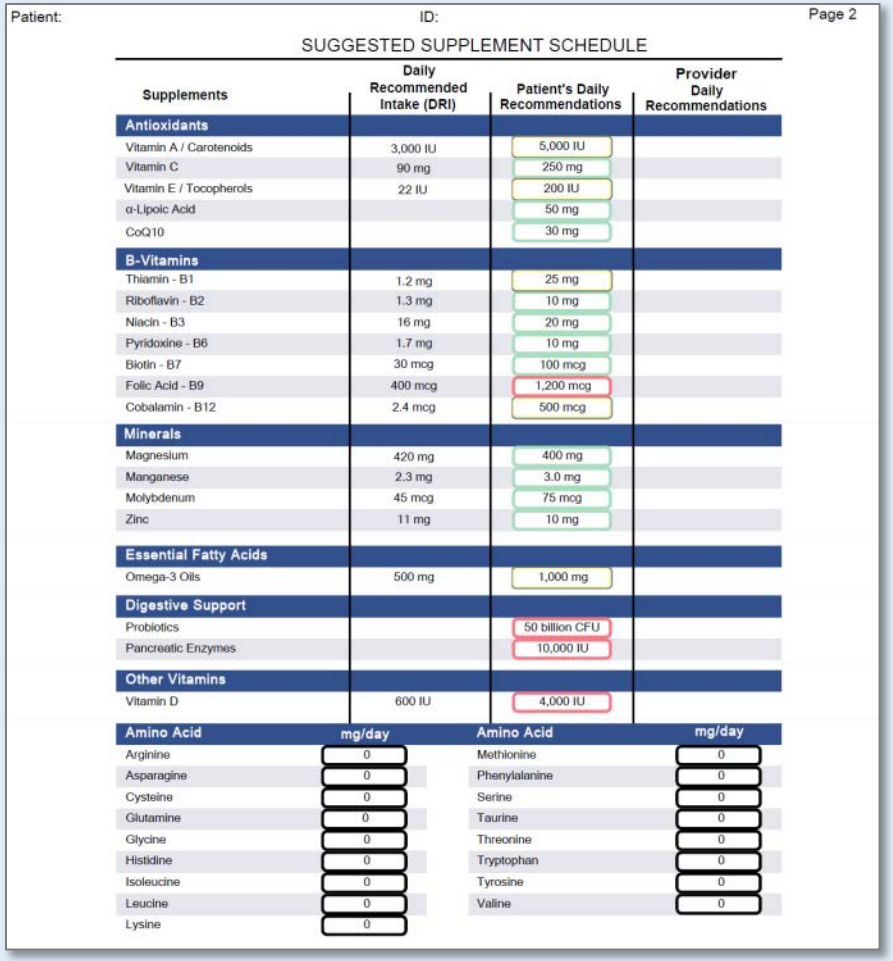
Couple Digestive Tests with Nutrient Tests for a Complete Picture of Gut Health





Patient: ID: Page 2

SUGGESTED SUPPLEMENT SCHEDULE

Supplements	Daily Recommended Intake (DRI)	Patient's Daily Recommendations	Provider Daily Recommendations
Antioxidants			
Vitamin A / Carotenoids	3,000 IU	5,000 IU	
Vitamin C	90 mg	250 mg	
Vitamin E / Tocopherols	22 IU	200 IU	
α-Lipoic Acid		50 mg	
CoQ10		30 mg	
B-Vitamins			
Thiamin - B1	1.2 mg	25 mg	
Riboflavin - B2	1.3 mg	10 mg	
Niacin - B3	16 mg	20 mg	
Pyridoxine - B6	1.7 mg	10 mg	
Biotin - B7	30 mcg	100 mcg	
Folic Acid - B9	400 mcg	1,200 mcg	
Cobalamin - B12	2.4 mcg	500 mcg	
Minerals			
Magnesium	420 mg	400 mg	
Manganese	2.3 mg	3.0 mg	
Molybdenum	45 mcg	75 mcg	
Zinc	11 mg	10 mg	
Essential Fatty Acids			
Omega-3 Oils	500 mg	1,000 mg	
Digestive Support			
Probiotics		50 billion CFU	
Pancreatic Enzymes		10,000 IU	
Other Vitamins			
Vitamin D	600 IU	4,000 IU	

Amino Acid	mg/day	Amino Acid	mg/day
Arginine	0	Methionine	0
Asparagine	0	Phenylalanine	0
Cysteine	0	Serine	0
Glutamine	0	Taurine	0
Glycine	0	Threonine	0
Histidine	0	Tryptophan	0
Isoleucine	0	Tyrosine	0
Leucine	0	Valine	0
Lysine	0		

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Moderator:
Warren Brown, ND

Presenter:
Deanna Minich, PhD

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Additional Questions?

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