Interpretive Guide for Fatty Acids

Metametrix Clinical Laboratory

Name		*Potential Responses*	*Metabolic Association*
Omega-3 Polyunsaturated			
Alpha Linolenic	L	Add flax and/or fish oil	Essential fatty acid
Eicosapentaenoic	L	Add fish oil	Eicosanoid substrate
Docosapentaenoic	L		Nerve membrane function
Docosahexaenoic	L		Neurological development
Omega-6 Polyunsaturated			
Linoleic	L	Add corn or black currant oil	Essential fatty acid
Gamma Linolenic	L	Add evening primrose oil	Eicosanoid precursor
Eicosadienoic			
Dihomogamma Linolenic	L	Add black currant oil	Eicosanoid substrate
Arachidonic	H	Reduce red meats	Eicosanoid substrate
Docosadienoic			
Docosatetraenoic	H	Weight control	Increase in adipose tissue
Omega-9 Polyunsaturated			
Mead (plasma only)	H	Add corn or black	Essential fatty acid status
Monounsaturated			
Myristoleic			
Palmitoleic			
Vaccenic			
Oleic	H	See comments	Membrane fluidity
11-Eicosenoic			
Erucic	L	Add peanut oils	Nerve membrane function
Nervonic	L	Add fish or canola oil	Neurological development
Saturated Even-Numbered			
Capric Acid	H	Assure B3 adequacy	
Lauric	H		Peroxisomal oxidation
Myristic	H		
Palmitic	H	Reduce sat. fats; add niacin	Cholesterogenic
Stearic	H	Reduce sat. fats; add niacin	Elevated triglycerides
Arachidic	H	Check eicosanoid ratios	Δ6 desaturase inhibition Nerve membrane function
Behenic	H	Consider rape or mustard seed oils	
Lignoceric	H		
Hexacosanoic	H		
Saturated Odd-Numbered			
Pentadecanoic	H	Add B12 and/or carnitine	
Heptadecanoic	H		
Nonadecanoic	H		Propionate accumulation
Heneicosanoic	H		Omega oxidation
Tricosanoic	H		
Trans Isomers from Hydrogenated Oils			
Palmitelaidic	H	Eliminate hydrogenated oils	Eicosanoid interference
Total C18 Trans Isomers	H		
Calculated Ratios			
LA/DGLA	H	Add black currant oil	Δ6 desaturase, Zn deficiency
EPA/DGLA	H	Add black currant oil	Eicosanoid imbalance
	L	Add fish oil	
AA/EPA (Omega-6/Omega-3)	H	Add fish oil	
Stearic/Oleic (RBC only)	L	See Comments	Cancer Marker
Triene/Tetraene Ratio (plasma only)	H	Add corn or black currant oil	Essential fatty acid status

Table 1: Signs and Symptoms Associated with Fatty Acid Abnormalities		
SIGNS & SYMPTOMS	FATTY ACID ASSOCIATION	ACTION
Emaciation, weakness, disorentation	Caloric deprivation	Add food balanced in fat, protein, and carbohydrate.
Reduced growth, renal dysplasia, reproductive deficiency, scaly skin	Classic essential fatty acid deficiency	Add good quality fats and oils
Eczema-like skin eruptions, loss of hair, liver degradation, behavorial disturbances, kidney degeneration, increased thirst, frequent infections, poor wound healing, sterility, miscarriage, arthralgia, cardiovascular disease, growth retardation	Linoleic acid insufficiency	Add corn or safflower oils
Growth retardation, weakness, impairment of vision, learning disability, poor coordination, tingling in arms/legs, behavorial changes, mental disturbances, low metabolic rate, high blood pressure, immune dysfunction	Alpha or gamma linolenic acid insufficiency	Add flax, primrose, or black currant oil
Depression, anxiety, learning, behavorial and visual development, cardiovascular disease risk	Long chain PUFA-dependent neuromembrane function, imbalanced prostanoids	Add fish oils
Cancer	Low stearic/oleic ratio, loss of prostanoid cell controls (RBC only)	Add omega 3 PUFAs Use omega 6 PUFAs with caution
Vitamin B12 and/or carnitine deficiencies	Increased odd numbered FAs	Add vitamin B12 and carnitine
Myelinated nerve degeneration	Increased very long chain FAs	Add high-erucate rape oil, mustard seed oils
Fatty liver	Saturated and omega 9 family accumulation in hepatic cells	Restrict alcohol consumption, and increase lecithin and methionine intake
Accelerated aging	High polyunsaturated acid intake without increased antioxidants	Increase vitamins E and C and the minerals Se, Mn, and Zn
Obesity	Various imbalances resulting from using processed oils (high elaidic with low GLA)	Re-establish proper fat-to-protein balance using foods like nuts, seeds, and fresh whole grains.

Polyunsaturated Omega-3

Alpha Linolenic Acid
One of the most common essential fatty acid deficiencies is that of alpha linolenic acid (18:3n3), abbreviated as ALA or LNA. It is found in flax, hemp, rape (canola) seed, soybean, walnut, and dark green leaves and must be supplied by such foods. Because of the central importance of this fatty acid and its counterpart, GLA, see the table of clinical associations with dietary insufficiencies (Table 1).

Eicosapentaenoic Acid
Deficiency of eicosapentaenoic acid (20:5n3) is likely the most prevalent fatty acid abnormality affecting the health of individuals in western societies. Low levels in plasma or especially in erythrocytes are indicative of insufficiency. Arthritis, heart disease, and general aging result from direct or indirect effects of unchecked inflammatory response.

Eicosapentaenoic acid (EPA) is anti-inflammatory and should balance the levels of pro-inflammatory arachidonic acid. Although EPA can be produced from the essential fatty acid, ALA, dietary intakes of this fatty acid are generally poor. The conversion also requires the action of the $\Delta 6$ desaturase enzyme that may be low due to inadequate Zn, Mg, or vitamins B_3, B_6, and C. Such an enzyme impairment would be indicated if EPA is low and ALA is normal or high. High levels of saturated, monounsaturated, trans fatty acids, and cholesterol also slow the conversion of ALA to EPA (as well as GLA to DGLA).

Docosapentaenoic Acid
Docosahexaenoic Acid
The growth and development of the central nervous system is particularly dependent upon the presence of an adequate amount of the very long chain, highly unsaturated fatty acids, docosapentaenoic (22:5n3) and docosahexaenoic acids (22:6n3) (1,2). Attention deficit hyperactivity disorder (3) and failures in the development of the visual system in

EFA deficiencies are two examples of this dependency. Docosahexaenoic acid (DHA) is an important member of the very long chain fatty acids (C22 to C26) that characteristically occur in glycosphingolipids, particularly in the brain. Since this fatty acid is so important in early development, it is worth noting that the levels in breast milk are correlated with the mother's intake of fish oils (4), which are rich sources of both of these fatty acids. DHA intake may also help to lower blood pressure (5).

Polyunsaturated Omega-6

Linoleic Acid
Linoleic acid (18:2n6) is by far the most abundant polyunsaturated fatty acid in most human tissues. Linoleic acid (LA) is an essential fatty acid, and low levels indicate dietary insufficiency, which can lead to a variety of symptoms (see Table 1). Some of these symptoms result from lack of LA in membranes, where it plays a role in structural integrity. Most, however, are from failure to produce eicosanoids, which are cell regulators. LA is the starting point for this pathway. Normal neonatal status of this fatty acid is marginal, if not insufficient (6). Since dietary sources (especially corn oil) are abundant, however, LA may be found above normal. Excessive LA can contribute to inflammation. Supplementation with LA has been shown to increase body weight and essential fatty acid status in patients with cystic fibrosis (7).

Gamma Linolenic Acid
Gamma linolenic acid (18:3n6), abbreviated GLA, is the precursor of DGLA, an anti-inflammatory fatty acid, and it's also the precursor of arachidonic acid, a pro-inflammatory fatty acid. It is found in hemp, borage, black currant, and evening primrose oils. It can be produced in human tissues by the action of desaturase enzymes on LA. See Table 1 for clinical associations. GLA corrects most of the biological effects of zinc deficiency (8), highlighting the zinc requirement of the Δ5 desaturase enzyme.

Eicosadienoic Acid
Eicosadienoic acid (20:2n6) is the elongation product of GLA and the direct precursor of DGLA. Levels of this fatty acid reflect levels of other polyunsaturated omega-6 fatty acids. Plasma levels are significantly lower than those present in erythrocytes, which indicates that the conversion of linoleic to eicosadienoic acid occurs at a higher rate than the conversion of eicosadienoic acid to DGLA.

Dihomogamma-linolenic Acid
Low levels of dihomogamma-linolenic acid (20:3n6) result from diets low in both essential fatty acids, LA, and dihomogamma-linolenic acid (DGLA). DGLA is also anti-inflammatory, so an insufficiency of this fatty acid impairs a wide range of cellular functions and tissue responses. When testing reveals low levels of DGLA, supplementation with black currant or evening primrose oils should be considered, but if a history of tumor formation is known, always consider ALA sources (black currant) as well (9).

Arachidonic Acid
Because of the prevalence of corn and corn oil products in feed for cattle and hogs, diets high in these red meats are rich in arachidonic acid (20:4n6). Arachidonic acid (AA) is a 20-carbon or fatty acid that serves as the principal pro-inflammatory fatty acid. Its synthesis is inhibited by non-steroidal anti-inflammatory drugs (NSAIDs). High AA promotes gallstone formation by stimulating mucin production in the gallbladder mucosa (10).

Docosadienoic Acid
Docosatetraenoic Acid
Docosadienoic acid (22:2n6) is a very long-chain fatty acid (VLCFA). It is the elongation product of DGLA. Elevated levels of docosadienoic acid should appear only under conditions of dietary adequacy of LA and DGLA, together with stimulation of elongation. The latter is one effect of insulin resistance. Metametrix is currently researching the additional clinical relevance of docosadienoic acid.

When omega-6 dietary fatty acids are consumed in abundance, there is an accumulation of desaturation and elongation intermediates. Diets high in fat and simple sugars contribute to obesity and to the accumulation of docosatetraenoic acid (22:4n6).

Polyunsaturated Omega-9

Mead Acid (plasma only)
Mead acid (20:3n9) is a marker for overall, essential fatty acid status. It is produced in human tissues from oleic acid and, therefore, is not considered essential. The essential fatty acids, linoleic and alpha linolenic, prevent Mead acid formation in individuals with good dietary fat intake. When essential fatty acids are depleted, higher levels of Mead acid are detected. During essential fatty acid deficiency, Mead acid serves as a structural component in cell membranes as a substitute for the normal polyunsaturated fatty acids derived from essential precursors. It cannot substitute, however, in the critical role of precursor to eicosanoid cell regulators. Mead acid formulation may also be stimulated by high intake of omega 3 fatty acids.

Monounsaturated

Myristoleic Acid
The medium-chain unsaturated myristoleic acid (14:1n5) accumulates in adipose tissue with the consumption of milk products, which are rich sources of the fatty acid. Myristoleic acid is particularly good at increasing cell membrane fluidity because of its short chain length and unsaturated status. Diets high in saturated fat lead to low membrane fluidity. Therefore, increased membrane fluidity is generally a favorable health consequence. However, high levels of myristoleic acid may raise concern when found in cancer patients because of the tumor-promoting effect of high membrane fluidity.

Palmitoleic Acid
Palmitoleic acid (16:1n7) is the desaturation product of palmitic acid. Since palmitic acid is predominant in human tissues where desaturase enzyme activity is present, one might expect relatively high levels of palmitoleic acid. Such levels are not found in healthy humans. Palmitoleic acid formation is increased only when intake of essential fatty acids is low. Thus, high palmitoleic acid is a marker of essential fatty acid deficiency.

Vaccenic Acid
Oleic Acid
Vaccenic acid (18:1n7) is a positional isomer of oleic acid – they have the same number of carbon molecules but the double bond is shifted. Vaccenic acid also plays a role in maintaining membrane fluidity.

Oleic acid (18:1n9) is present in the fat of all foods and is also produced from essential fatty acids in normal human liver cells and fat cells. Oleic acid makes up 15% of the fatty acids in the membranes of red blood cells and, because of the presence of one double bond in the center of the molecule, helps maintain critical membrane fluidity. Low levels of oleic acid have an impact on this function and can be corrected by increasing dietary intake (olive oil). For erythrocyte abnormalities, read about the stearic/ oleic ratio below.

11-Eicosenoic Acid
11-Eicosenoic acid (20:1n11) is the elongation product of oleic acid. Metametrix is currently researching its clinical relevance.

Erucic Acid
Since erucic acid (22:1n9) is one of the components responsible for the favorable response of individuals with adrenoleukodystrophy to preparations containing rape and mustard seed oils (Lorenzo's Oil), low levels may occur with this disease, and increased consumption of erucic acid may offset the metabolic effects of the disease.

Nervonic Acid
Nervonic acid (24:1n9) has the longest carbon chain of all monounsaturated fatty acids. It is found in highest concentrations in nerve membranes, particularly in the myelin sheath. Factors like high carbohydrate diets that inhibit fatty acid synthesis cause low levels, and conditions like insulinemia stimulate fatty acid synthesis resulting in higher levels.

Saturated Even Numbered

Capric Acid
Lauric Acid
Myristic Acid
Capric (10:0), lauric (12:0), and myristic (14:0) acids, the medium chain fatty acids (MCFAs), are present in small amounts in plant oils and butter. The MCFAs are virtually nonexistent in meats because animals oxidize them very rapidly from plants consumed, and do not accumulate in the tissues. Various "medium chain triglyceride" products have become available for lipid digestive disorders and have found use in athletic training. They contain MCFAs that are assimilated rapidly without the normal bile acid dispersal requirement. In human tissues, capric, lauric, and myristic acids are oxidized by peroxisomal oxidative pathways to a larger extent than the longer chain fatty acids. Elevated levels could indicate general suppression of peroxisomal oxidation which utilizes riboflavin-derived cofactors.

Palmitic Acid
The liver can convert fatty acids into cholesterol. Although any fatty acid can enter this pathway, palmitic acid (16:0) is the most stimulatory one known. Palmitic acid is high in palm kernel and coconut oils. High levels can lead to increased serum cholesterol and increased risk of atherosclerosis, cardiovascular disease, and stroke. In contrast to saturated fatty acids, unsaturated fatty acids cause either no reaction or actually lower serum cholesterol (as in the case of EPA).

Stearic Acid
Stearic acid (18:0) is a saturated fatty acid that is two carbon atoms longer than palmitic acid. Diets high in saturated fat contribute to elevated levels of stearic acid in the body. High levels in plasma occur with high serum triglycerides, which is a risk factor in atherosclerotic vascular disease. (See palmitic acid above.)

Arachidic Acid
Arachidic acid (20:0), the elongation product of stearic acid, can be utilized as an energy source to build membranes. Its accumulation can interfere with essential fatty acid metabolism, as it inhibits the Δ6 desaturase enzyme needed to produce DGLA, EPA, and AA. Similar effects occur with other long chain, saturated fatty acids.

Behenic Acid
Lignoceric Acid
Hexacosanoic Acid
Accumulation of certain very long chain fatty acids (VLCFAs) is associated with degenerative diseases of the central nervous system like adrenoleukodystrophy. There are a number of genetic disorders involving accumulation of sphingolipids, usually due to the lack of enzymes necessary for the turnover of membrane VLCFAs, which include behenic (22:0), lignoceric (24:0), and hexacosanoic (26:0) acids as well as the unsaturated members of the C22-24 classes, particularly nervonic acid.

The common lifestyle of low physical exertion and high fat diet sets a metabolic pattern that can lead to increasing levels of VLCFAs in plasma and erythrocyte membranes. The effect is mediated by hormonal responses, mainly norepinephrine and insulin, and is exacerbated by drugs that modulate energy metabolism such as the antianginal drug, trimetazidine (11).

Saturated Odd Chain

Pentadecanoic Acid
Heptadecanoic Acid
Nonadecanoic Acid
Heneicosanoic Acid
Tricosanoic Acid
Fatty acids with odd numbers of carbon atoms are produced primarily by initiating the synthetic series with the three carbon compound, propionic acid. Vitamin B_{12} is required for the conversion of propionate into succinate for oxidation in the central energy pathways. Deficiency of vitamin B_{12} results in accumulation of propionate and subsequent buildup of the odd numbered fatty acids, pentadecanoic (15:0), heptadecanoic (17:0), nonadecanoic (19:0), heneicosanoic (21:0), and tricosanoic (23:0) acids.

The bacteria in the gut of ruminants (grazing animals like cows and sheep) produce large amounts of propionate, which is absorbed and enters the metabolism of the animal. High intake of animal and dairy products favor high levels of these fatty acids. Alternatively, it is possible that the bacteria in the human gut could produce sufficient amounts of propionate to lead to elevation in the odd-carbon fatty acids. This would only occur under conditions of significant gut dysbiosis.

Carnitine is required for fatty acid oxidation. In carnitine insufficiency, fatty acids are oxidized via an omega oxidation pathway that creates odd chain units. Therefore, odd chain fatty acid accumulation may indicate carnitine deficiency and the need for carnitine supplementation (12).

Trans Isomers from Hydrogenerated Oils

Palmitelaidic Acid
Total C18 *Trans* Isomers
The *trans* fatty acids are prevalent in most diets because of the widespread use of hydrogenated oils used by manufacturers of margarines, bakery products, and peanut butters.

Palmitelaidic acid (16:1:7t) is the shorter and less abundant member of the trans fats, because oils used in hydrogenation contain very little of its precursor, palmitoleic acid.

The total C18 *trans* isomers include elaidic acid, petroselaidic, and trans-vaccenic acids. The presence of these eighteen-carbon long trans fatty acids in human tissue can disrupt or impair cell membrane function. A patient with high levels of total C18 *trans* isomers should be told to avoid hydrogenated oils.

These fatty acids contain one double bond and thus are included in the unsaturated category. Because of the geometry of the trans bond, however, they behave like saturated fats on the one hand, leading to elevated cholesterol levels (13). On the other hand they mimic unsaturated fats that bind to desaturase enzymes and antagonize the normal production of necessary products. The net effect is to raise plasma LDL cholesterol and lower HDL. It is now the consensus among experts in lipid nutrition that foods containing hydrogenated oils are to be avoided. These fatty acids are also produced by the bacteria in the gut of ruminant animals which is the reason that beef and milk contain small amounts (13%) of elaidic acid. Moderate use of these foods is unlikely to provide *trans* fatty acids at levels that are of concern.

Calculated ratios

LA/DGLA Ratio
The ratio of LA to DGLA increases when the Δ6 desaturase enzyme is inhibited by zinc and magnesium deficiency, elevated insulin, or dietary excess of saturated, monoenoic, or *trans* fatty acid. Under these conditions, the enzyme cannot convert the substrate (LA) to its product (DGLA) fast enough. The production of all desaturation products is affected, including GLA, EPA and AA. These longer chain polyunsaturated fatty acids, then must be supplied from the diet or supplements.

EPA/DGLA Ratio
The balance of 20-carbon or eicosanoic fatty acids is critical for proper supply of the prostanoid and leukotriene 1-, 2-, and 3-series local hormones that control a host of cellular functions and responses. The EPA/DGLA ratio will be low when DGLA is elevated relative to EPA, indicating a need for EPA sources like fish oils. When the ratio is high, sources of DGLA (black currant or evening primrose oil) are indicated.

AA/EPA (Omega-6/Omega-3) Ratio
AA and EPA are the most critical fatty acids for maintaining the ratio of the omega-6 and omega-3 classes because they compete for enzymes that make cell regulators. A high ratio indicates an overabundance of the pro-inflammatory, omega-6 fatty acid, AA. An overabundance of AA is quite common in Western high meat and corn oil diets and can result in an imbalance in the AA/EPA ratio. This is one of the indicators that extra omega-3 fatty acids, including EPA of fish oils, would be beneficial.

Stearic/Oleic Ratio (RBC only)
The stearic acid/oleic acid ratio from red blood cells is a marker for the presence of malignant tissue, particularly with prostate cancer (14). In tumors, the net result of changes in fatty acid metabolism is low stearic acid and high oleic acid, causing a profound shift in the ratio of stearic to oleic acids (15). One likely outcome of this shift is increased fluidity of the tumor cell membrane, resulting in more rapid movement of nutrients and waste products and allowing for faster metabolic rate. The stearic/oleic ratio is used to monitor the effectiveness of cancer therapy (16). Values below 1.1 are associated with malignancy.

Triene/Tetraene Ratio (plasma only)
The Triene/Tetraene (T/T) ratio is another marker for essential fatty acid status. It is calculated as the ratio of Mead acid to arachidonic acid. This ratio, combined with measurements of the essential fatty acids and Mead acid, gives a more complete picture of the degree and nature of fatty acid deficiency. An elevated ratio shows a relative excess of triene (3 double bonds) compared to tetraene (4 double bonds), which results from essential fatty acid deficiency.

Resources

Information on the clinical effects of fatty acids, lipoproteins and glycolipids is rapidly expanding. The following sources are recommended for further study.

Erasmus (17): Excellent general review of structure and function of dietary and physiological fats.

Horrobin (18): Symposium proceedings emphasizing clinical uses of evening primrose oil.

Murray et. al. (19) : A brief comprehensive review of the metabolism of fatty acids and related compounds.

Contributing authors to Annual Reviews (20): In depth reviews with extensive references.

Recommended Review Articles:

Fenton WS, Hibbeln J, Knable M. Essential fatty acids, lipid membrane abnormalities, and the diagnosis and treatment of schizophrenia. Biological Psychiatry. 47(1):8-21, 2000 Jan 1.

Leaf A, Kang JX, Xiao YF, Billman GE, Voskuyl RA. The antiarrhythmic and anticonvulsant effects of dietary N-3 fatty acids. Journal of Membrane Biology. 172(1):1-11, 1999 Nov 1.

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Valenzuela A, Morgado N. Trans fatty acid isomers in human health and in the food industry. Biological Research. 32(4):273-87, 1999.

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13. Abbey M, Nestel PJ. Plasma cholesterol ester transfer protein activity is increased when trans-elaidic acid is substituted for cis-oleic acid in the diet. *Atherosclerosis*, 106:99-107 (1994).
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15. Wood CB, Habib NA, Thompson A, Bradpiece H, Smadja C, Hershman M, Barker W, Apostolov K. Increase of oleic acid in erythrocytes associated with malignancies, *Br Med J*, 291: 163 (1985).
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