Evidence-Based Prescribing of Food Supplements

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Disclosures and Affiliations

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Overview of Presentation

Topics:

1. Evidence-Based Prescribing
2. Magnesium
3. Curcumin (Turmeric extract)
4. N-acetyl cysteine

Evidence-Based Prescribing

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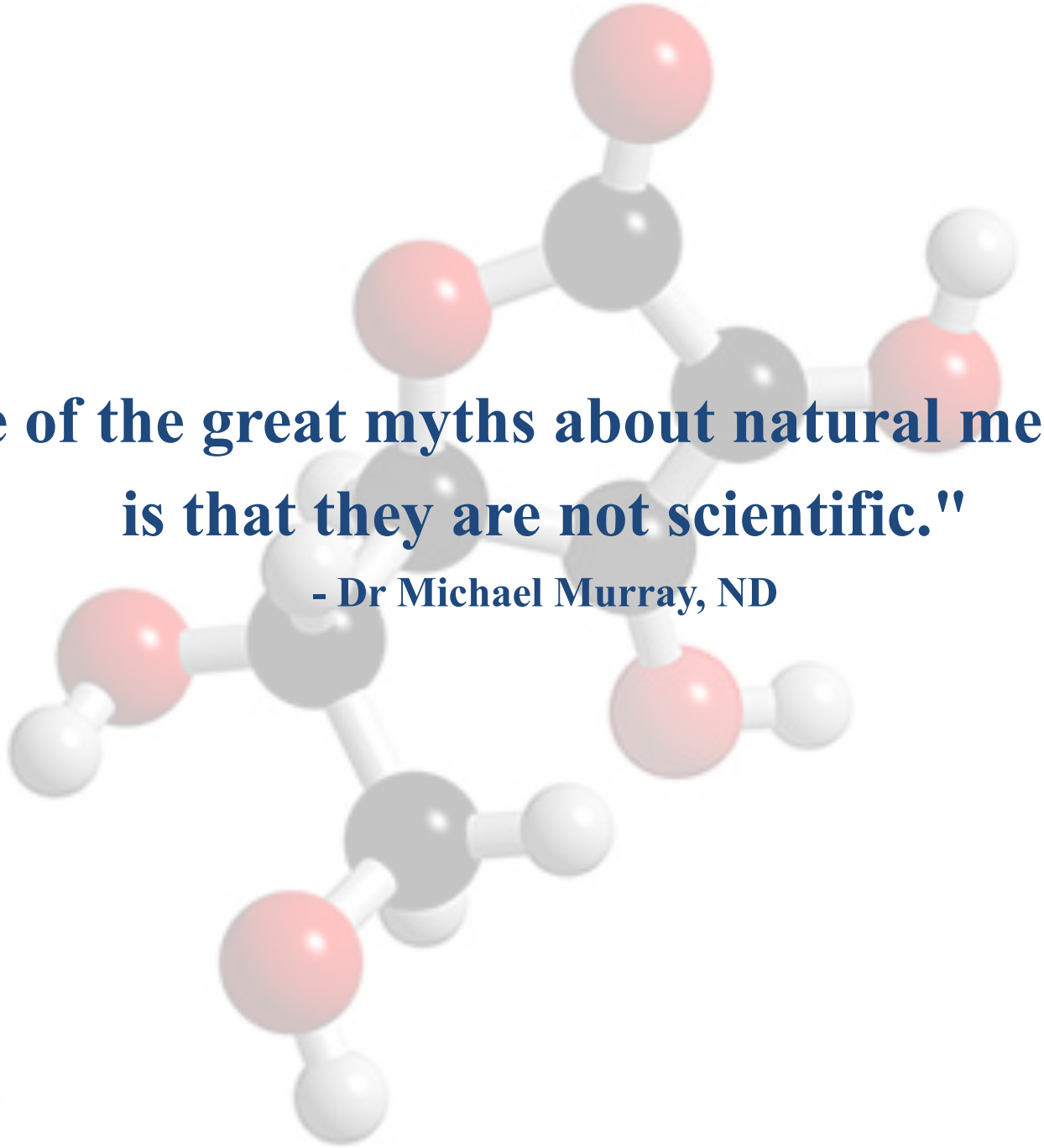

"One of the great myths about natural medicines is that they are not scientific."

- Dr Michael Murray, ND

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Rationale Use of Food Supplements

Deficiency

- Clinical signs and symptoms, dietary records or biochemical tests provide evidence of a nutritional deficiency.

Sub-clinical deficiency

- No overt clinical symptoms or classical biochemical evidence of deficiency, but the person may benefit from an increased intake of certain nutrients or food sources. May be marginal deficiency (narrower reference range) or secondary clinical or biochemical indicators.

Indications not associated with deficiency

- Symptoms, metabolic dysfunction or disease unrelated to nutritional deficiency, but clinical evidence indicates that nutritional supplementation can provide health benefits (possible pharmacological or physicochemical effects).

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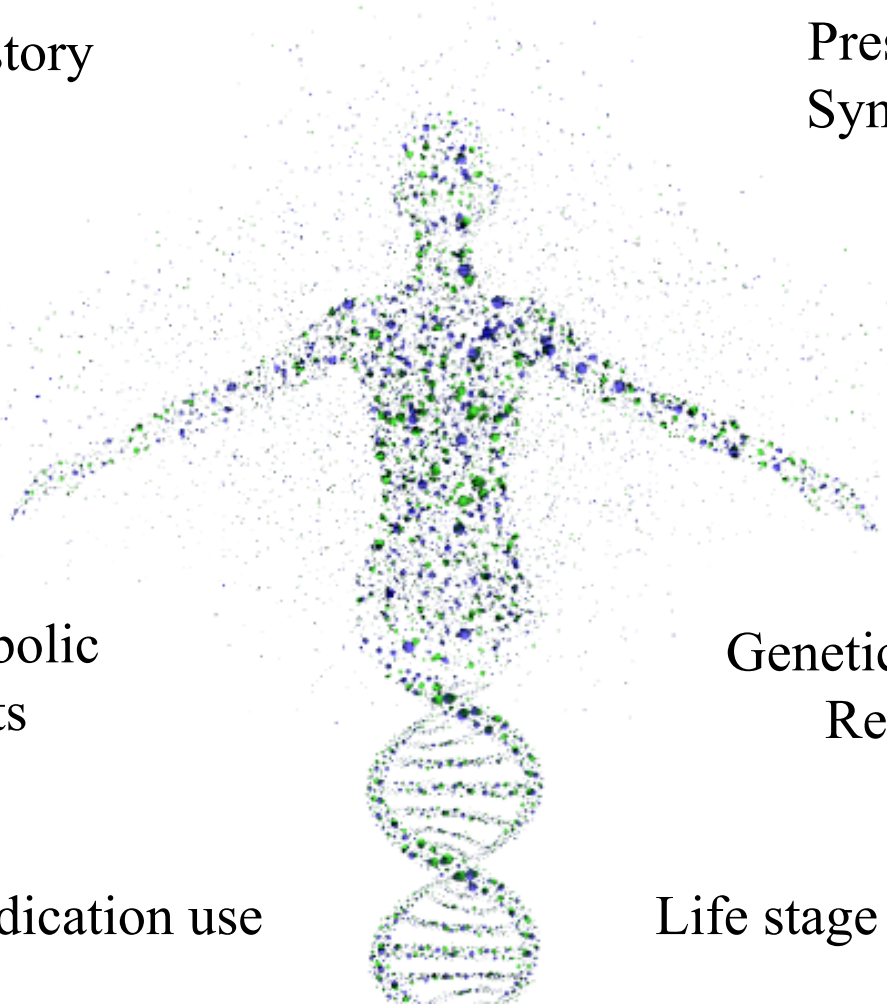
Personalised Nutritional Therapy

Deficiency

Dietary History

Presenting Symptoms



Pharmacological Effects

Functional Status

Increased Metabolic Requirements

Genetic/ Physiological Requirements

Medication use

Life stage

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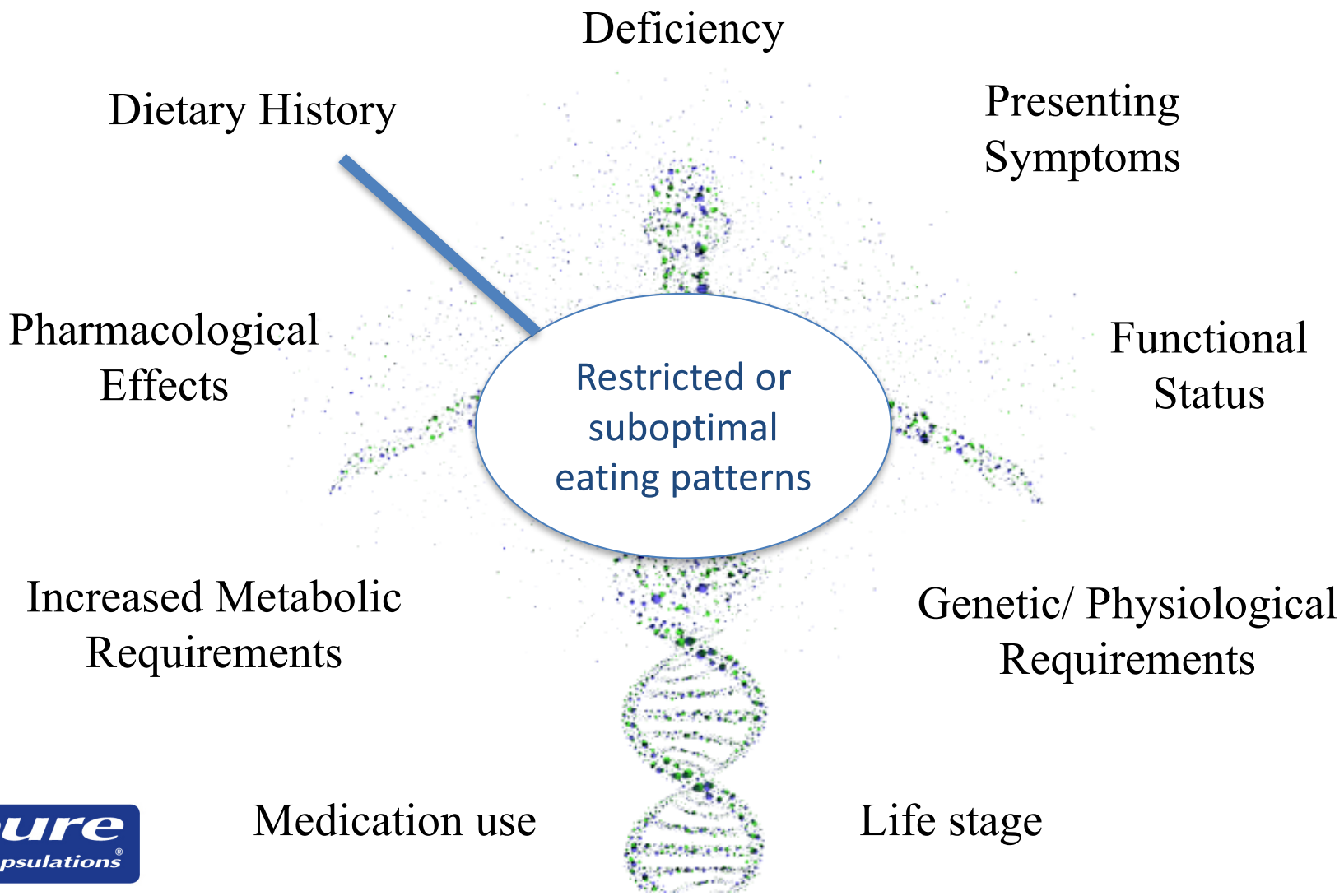
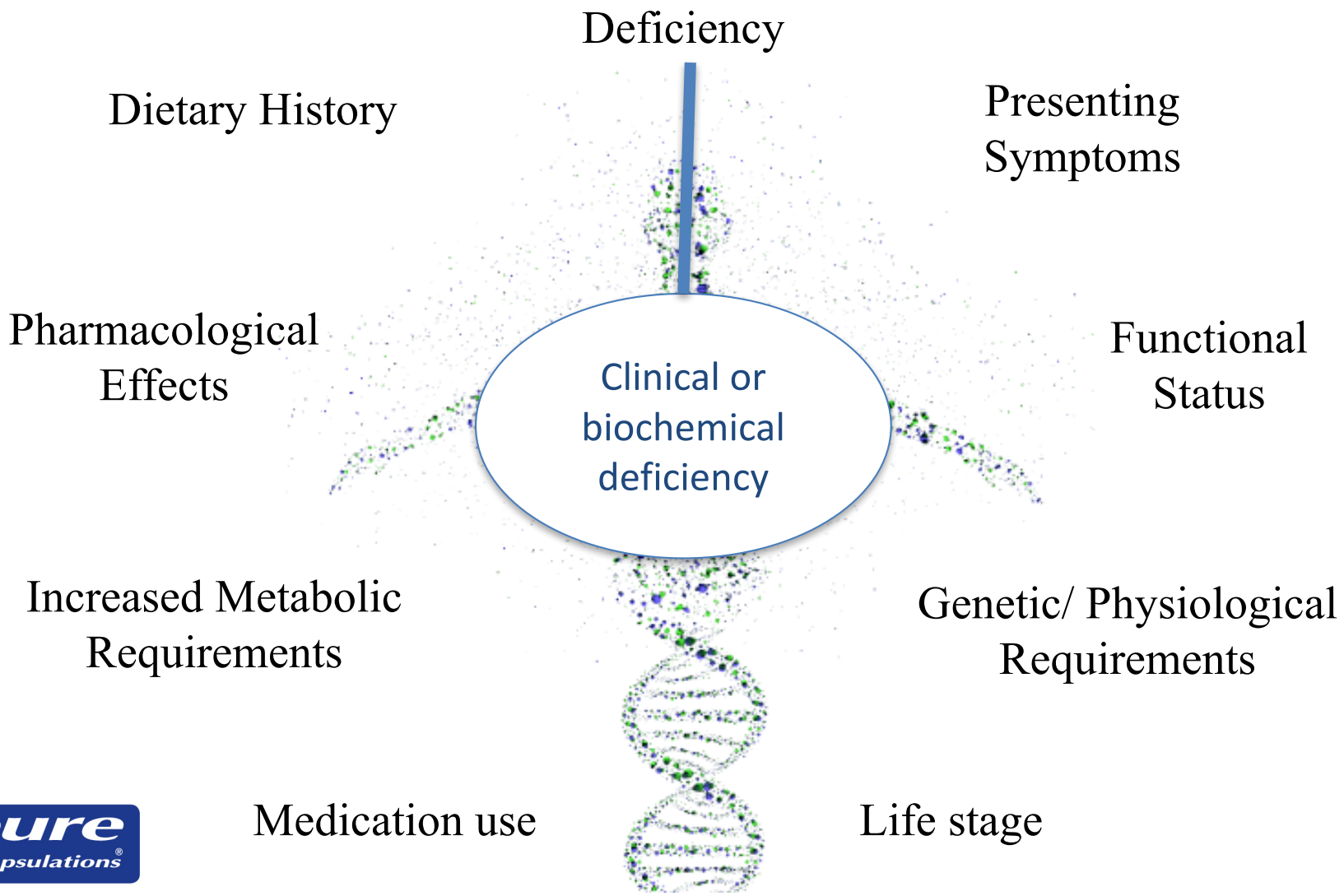


Personalised Nutritional Therapy



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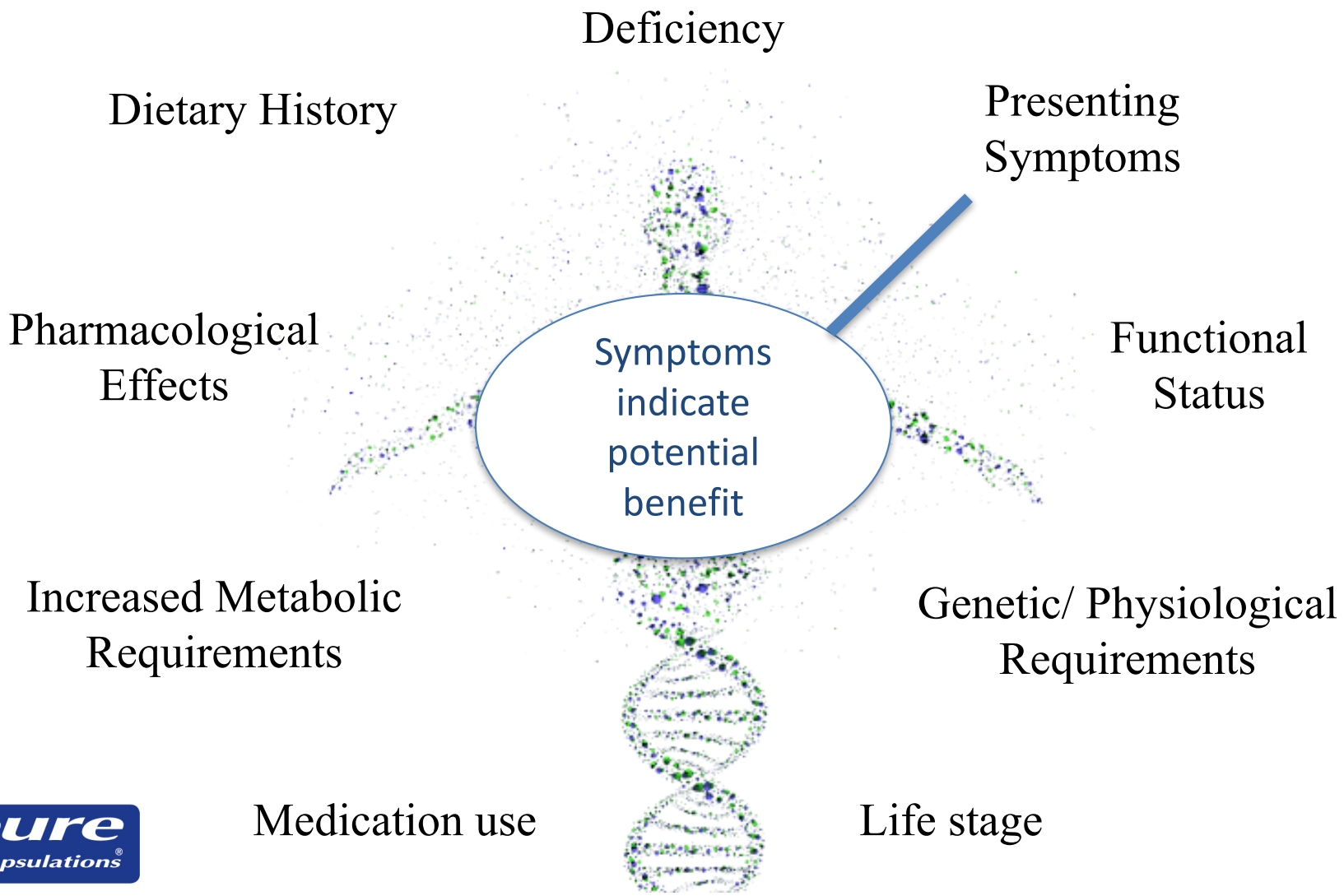

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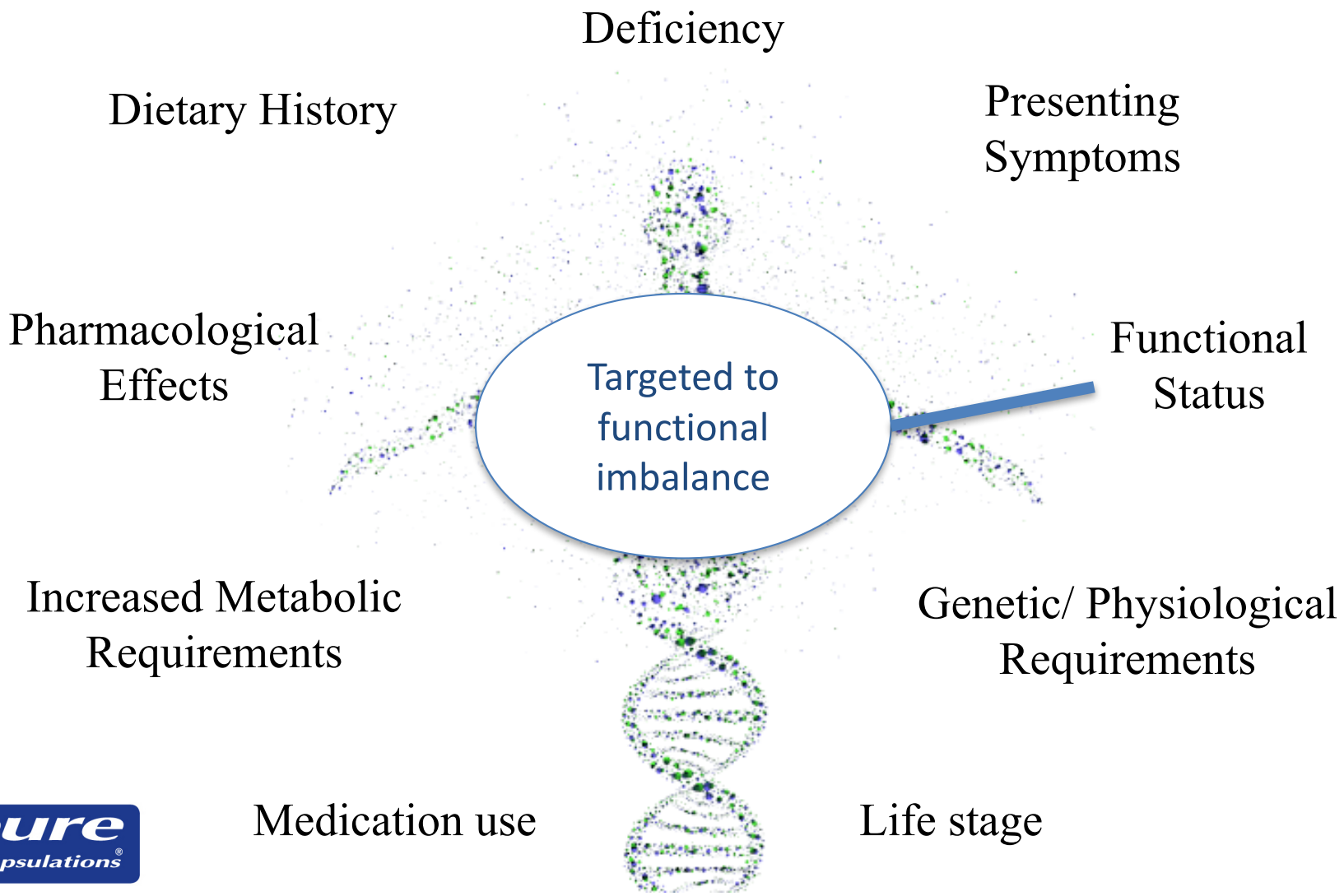

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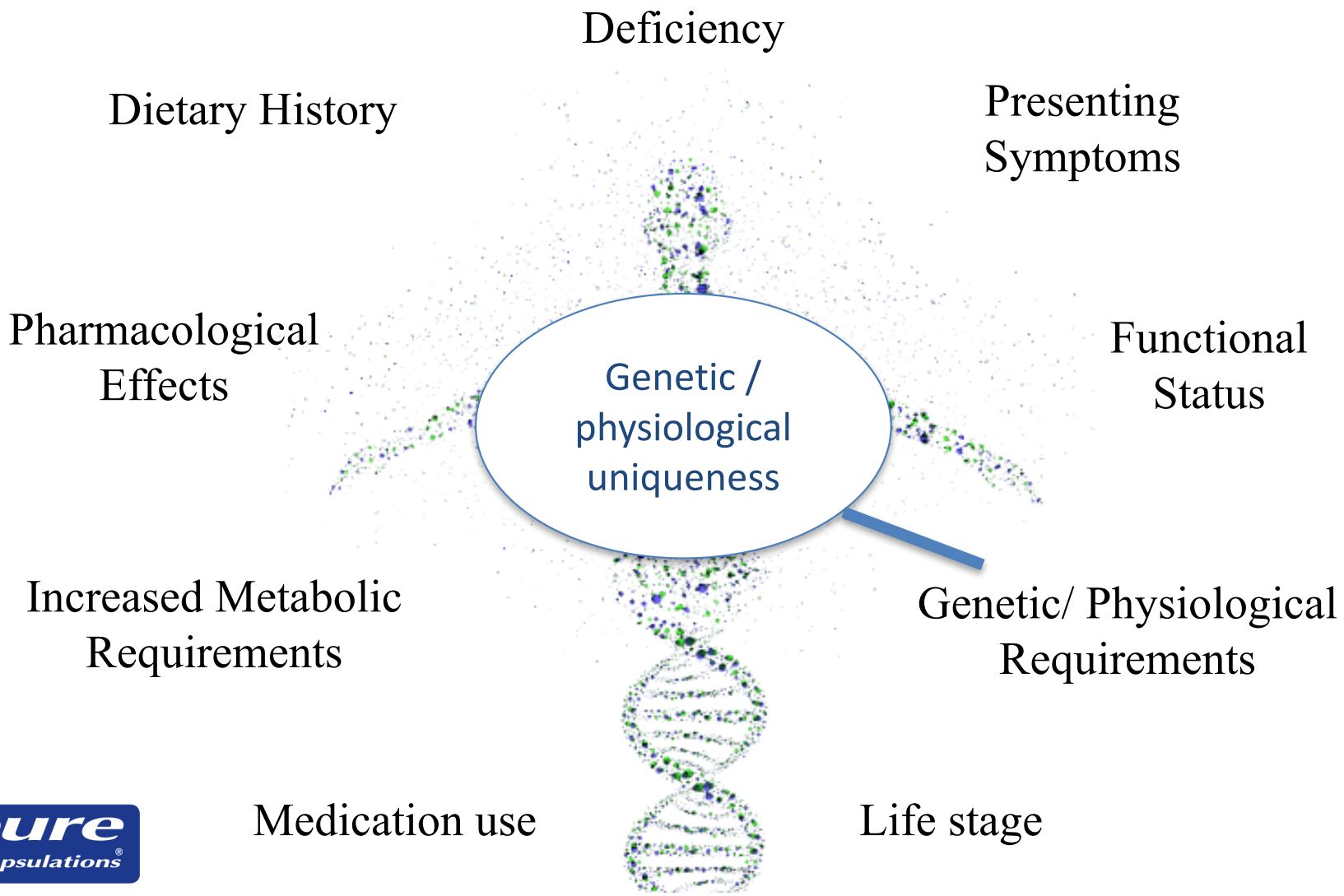

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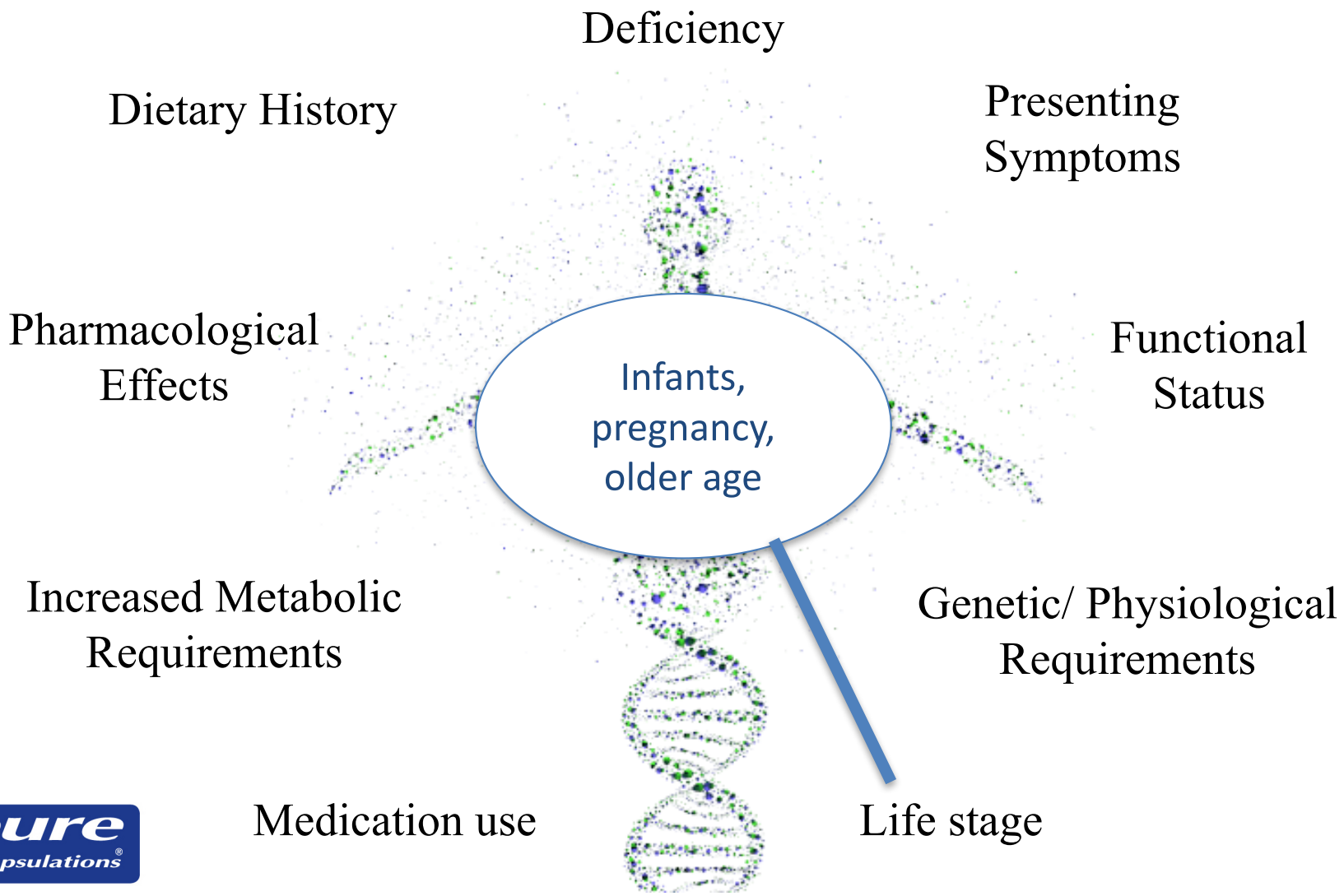

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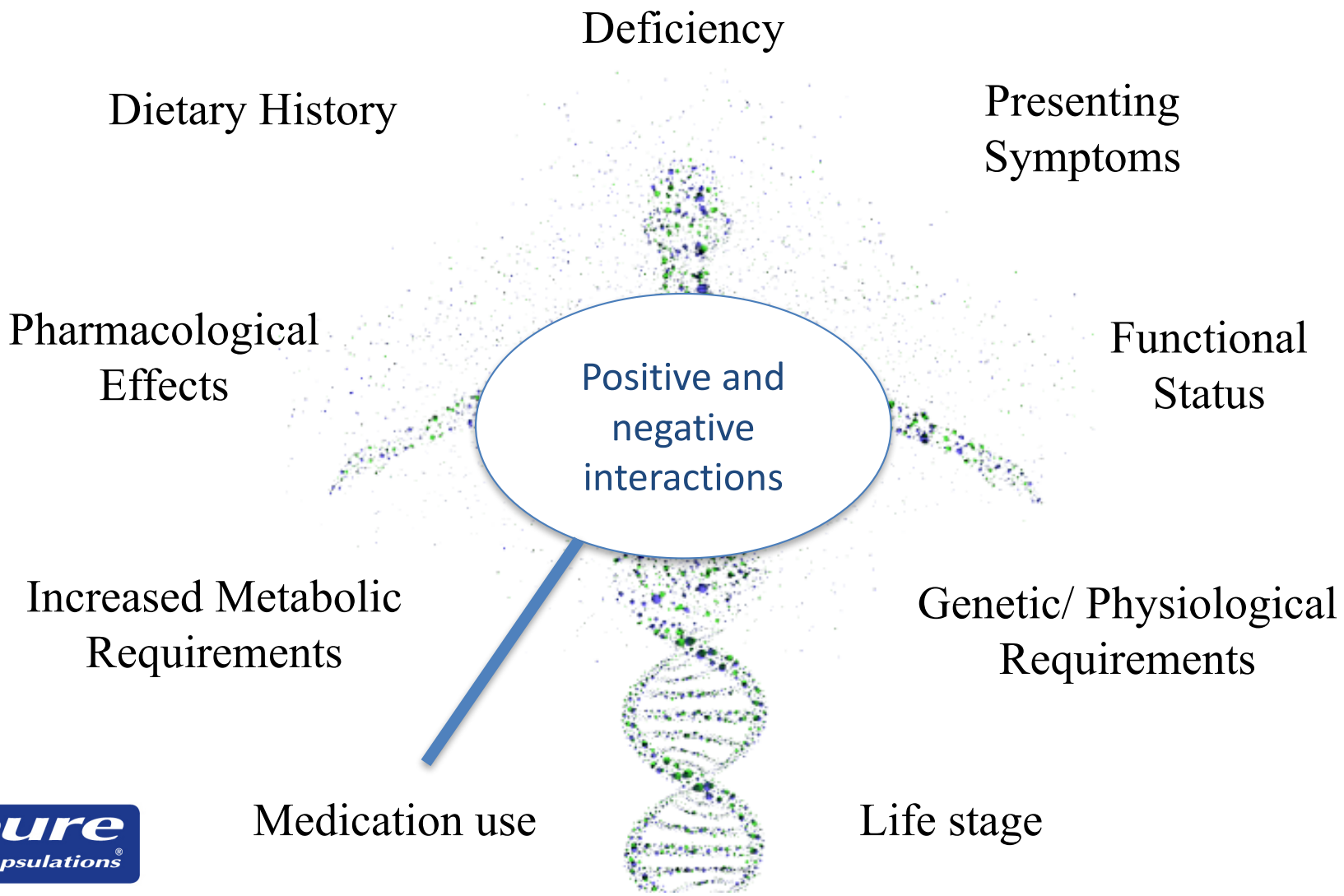

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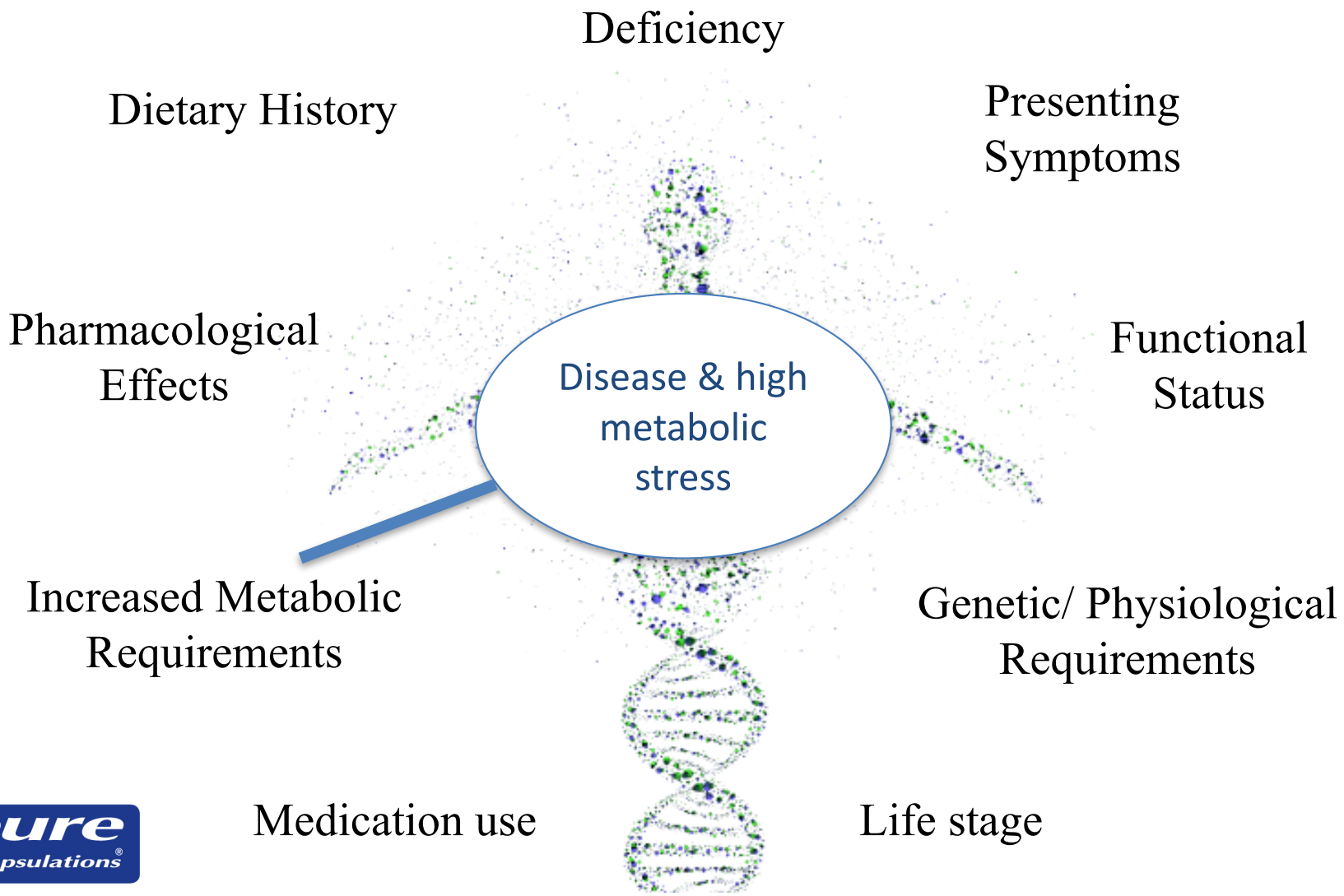

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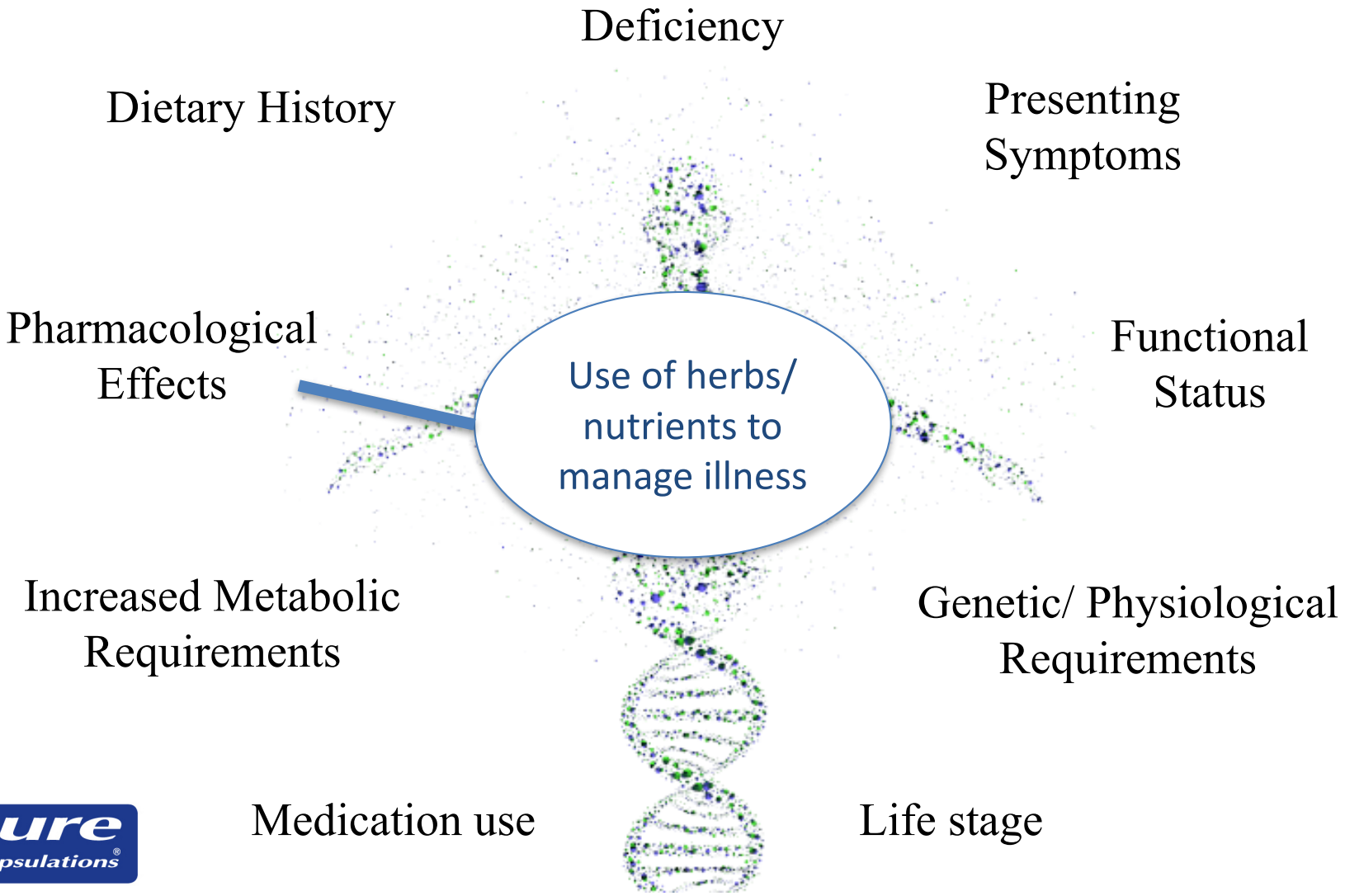

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FUNCTIONAL MEDICINE MATRIX

Retelling the Patient's Story

Antecedents

•Born 2 mths premature -2lbs (0.9kg) - in hospital 6 mths, no breast-feeding.
•Brother only 10 months older.
•Mother suffered with depression.
•Mother smoked 3-4 cigarettes a day throughout her life - incl. during pregnancy.
•Father had eating disorder, binged on sugar and carbs. Dx with LADA aged 44y, injects insulin.
•Sketchy info on grandparents, but some suggestion of Hx of CVD.
•Maternal grandmother had a 'wheat allergy'.

Triggering Events

•Repeated concussions
•Mother died of emphysema aged 74y in 2003.
•Wife died of bowel cancer in 2004 after a long illness.
•Estranged from father and brother for last 5-10 years, minimal contact from sister.
•Hospitalised for 1 week 2013 following dizzy & fainting spell playing golf

Mediators/Perpetuators

•Middle child.
Initially raised by maternal grandmother due to stress of his birth on parents & mother's depression.
•Father was controlling, emotionally & physically abusive till he left home.
•Brother - MI 2017.
•LGI
•Fatigue

Physiology and Function: Organizing the Patient's Clinical Imbalances

Assimilation

•Nutritionally deficient - protein, EFAs, phytonutrients
•Severe bloating after wheat
•Reflux - occasional PPI use
•GI tract "not comfortable"
•Dysbiosis

Defense & Repair

•Never ill/No immune response
•Dyslipidemia
•Low-grade inflammation

Mental

•Good cognitive function

Emotional

•Depression, deep sadness, rejection, vulnerability, loner
•Early retirement

Structural Integrity

•OA - fingers, L big toe
•Severe pain from L big toe

Energy

•Low energy
•Increasing fatigue
•Dizzy & faint after hard exercise
•Never feels the cold
•Poor sleep
•↓stamina

Spiritual

Communication

•Severe SAD as soon as the clocks go back
•Depression/apathy - neurotransmitters?

Biotransformation & Elimination

•Long-term constipation - 1 x bwl mvt 5/6 days
•Dehydrated, dark & infrequent urination

Transport

•Family Hx CVD
•Q re abnormal P wave
•Dizzy & faint episodes after exertion

Name: Mr L Date: CC:

Prescription: Mr L

PE Curcumin

PE Betaine HCl w pepsin 520 mg

BioTech Vitamin D3

PE Digestive Enzymes Ultra

PE Zinc

PE ProFlora 50B

Nuzest Good Green Stuff

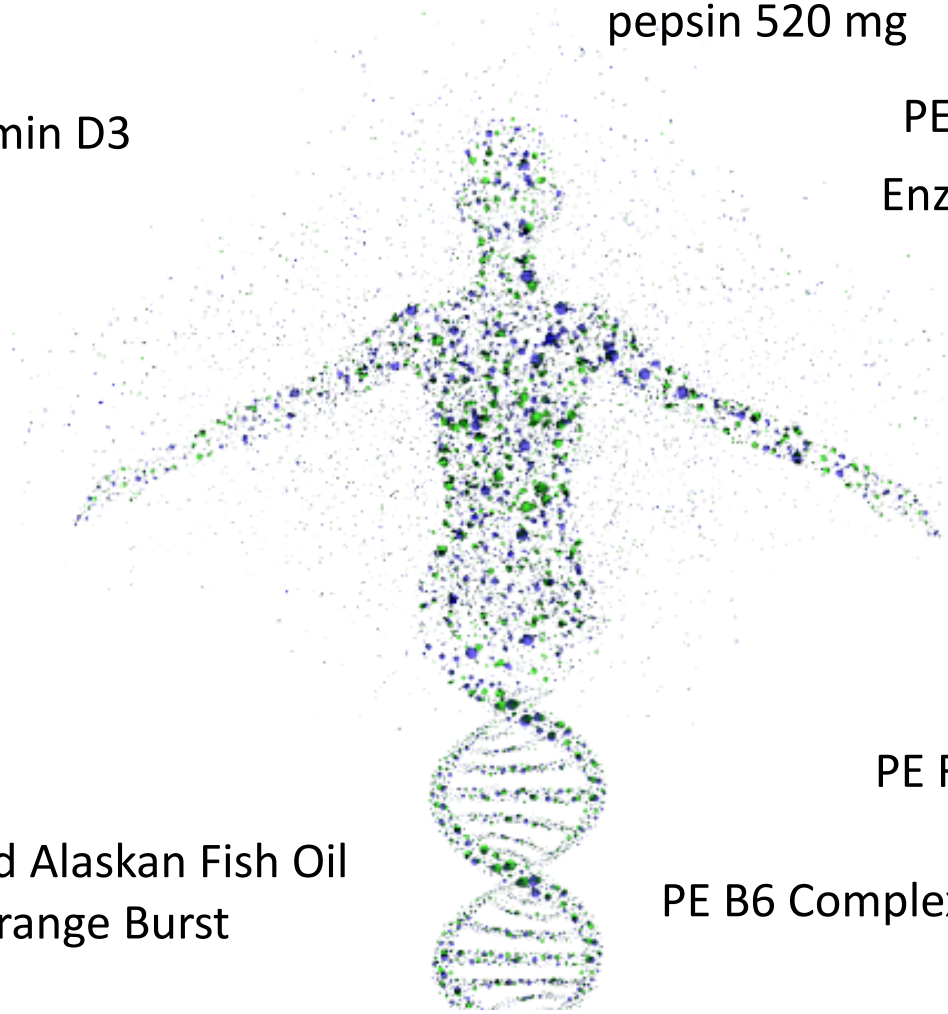
Nuzest Clean Lean Protein

PE Magnesium Powder

PE Folate

WF Wild Alaskan Fish Oil Orange Burst

PE B6 Complex



PE = Pure Encapsulations
WF = Wiley's Finest

THE INSTITUTE FOR FUNCTIONAL MEDICINE®

FUNCTIONAL MEDICINE MATRIX

Retelling the Patient's Story

Antecedents

•One month premature, home birth, 4.2lb (1.9kg), no hospitalisation, mix of breast milk and formula. Usual childhood illnesses.
•Mother had TB 2 x preceding pregnancy.
•Father died of liver cancer at 36 yo.
•Maternal grandmother died @ 50 yo from cancer (female).

Triggering Events

•Father died of liver cancer @ 36 yo, 1974, age 10
•Tonsillectomy 1975, age 11.
•Prescribed birth control pill at age 15 for menorrhagia.
•Four children - 1989 (CS), 1992, 1994, 2004 (CS).
•Divorce 1999.
•Separation 2003/4.
•Gall stones Dx 2004.
•4th child Dx with T1D in 2010.
•Something 'snapped' in R knee, 2013, no Dx, no investigation, loss of full flexion.

Mediators/Perpetuators

•Frequent antibiotics through childhood, allergic to penicillin.
•BCP from age 15 to 33.
•Controlling & abusive stepfather - breakdown of relationship with mother.
•Chronically sleep-deprived - emotional trauma & mgt of son with T1D.
•LGI
•Exhaustion
• HPATG axis

Physiology and Function: Organizing the Patient's Clinical Imbalances

Assimilation

•Gall stones age 40, no Tx
•Difficulty digesting fat
•Bloating & flatulence after eating
•Protein absorption?

Defense & Repair

•Hayfever and occasional eczema
•Dyslipidemia
•Low-grade inflammation

Mental

•No cognitive issues, just exhausted from lack of sleep
•Home schools 13 yo son

Emotional

•Deeply long-term stressed, survival stress, anxiety

Structural Integrity

•Occasional eczema
•Displaced pelvis from 4th 10.5lb (4.76kg) child
•Lumber discs displaced
•Numbness down right leg, walks with a limp
•Frequent pain in right hip
•Right knee, possibly ligament damage
•Hands very stiff, finger joints beginning to swell
•Headaches
•Sarcopenia

Energy

•TATT due to lack of sleep
•Mitochondrial dysfunction

Spiritual

•Strong sense of community
•Connection to the Universe
•Intuitive & open hearted

Communication

•Menorrhagia
•Ovulation pain
•Occasional menstrual pain
•HPATG axis

Biotransformation & Elimination

•Daily bwl mvts, only disturbed during menstruation
•Gall stones, Tx with diet

Transport

•Sluggish lymphatics, fluid retention

Name: Ms A _____ Date: _____ CC: _____

Prescription: Ms A

PE Curcumin

PE NAC 600 mg

BioTech Vitamin D3

PE Alpha Lipoic Acid 400 mg

PE Zinc

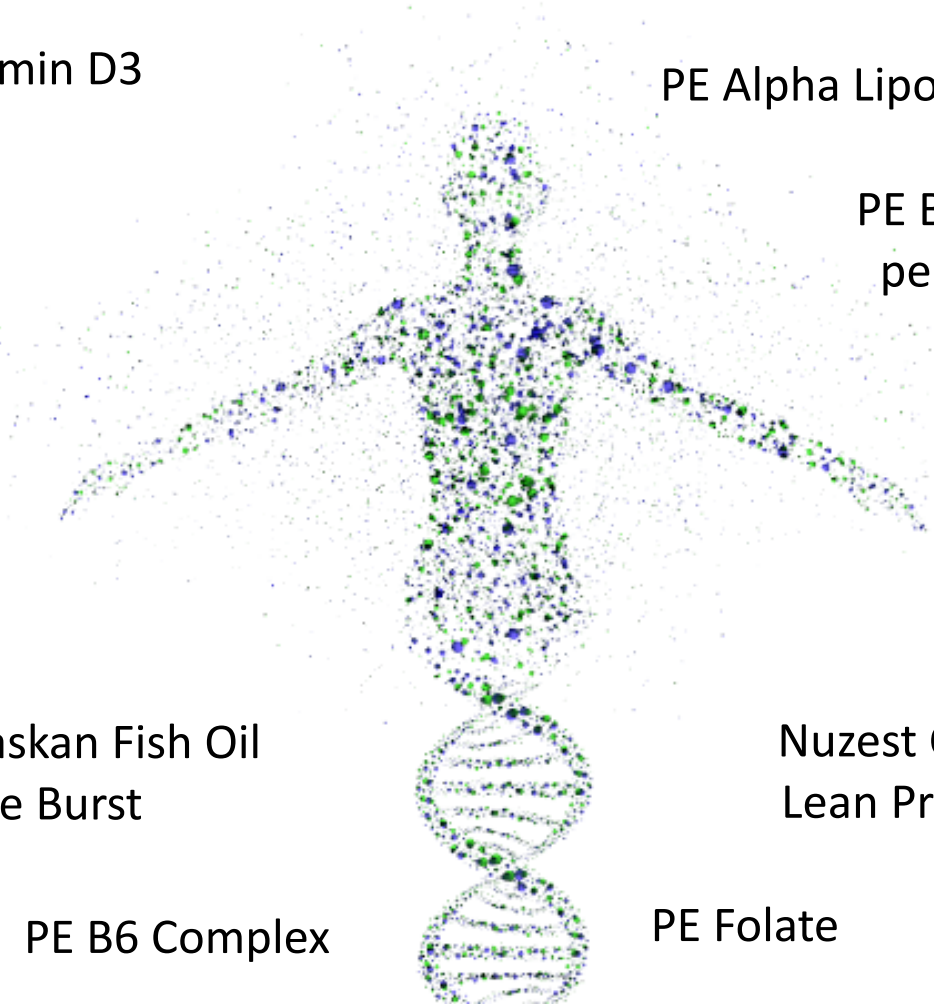
PE Betaine HCl w pepsin 520 mg

Nuzest Good Green Stuff

PE Digestive Enzymes Ultra

PE Magnesium Powder

PE ProFlora 50B



WF Wild Alaskan Fish Oil Orange Burst

Nuzest Clean Lean Protein

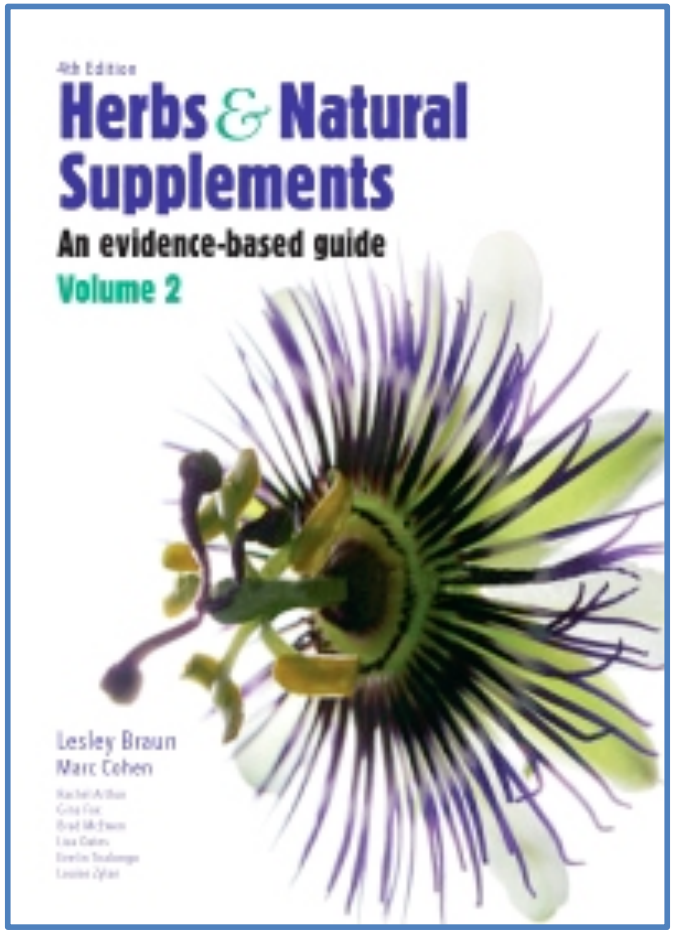
PE B6 Complex

PE Folate

PE = Pure Encapsulations
WF = Wiley's Finest

Evidence-Based Information Resources

- Natural Medicines Professional Database. https://naturalmedicines.therapeuticresearch.com
- Braun & Cohen. Herbs and Natural Supplements, 4th Edition. Elsevier. 2015.
- Pizzorno & Murray. Textbook of Natural Medicine, 4th Edition. 2012.
- Gaby, AR. Nutritional Medicine. 2011



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Key Areas to Investigate

- ✓ Established clinical uses
- ✓ Deficiency signs and symptoms
- ✓ Dosage range
- ✓ Treatment duration
- ✓ Adverse reactions
- ✓ Significant interactions
- ✓ Contraindications & precautions

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Evaluating Common Marketing Themes

Absorption

- Claims should be substantiated by human clinical evidence unique to that product or ingredient, but many are not. Improved absorption should translate to better clinical effects, but better absorption does not always mean better efficacy.

Delivery

- Delivery forms such as sublingual, liquids, sprays, or trans-dermal delivery do not necessarily mean better absorption and/ or greater clinical benefit.

Natural

- Claims that a product is more 'natural' and therefore effective or safe may be unsubstantiated. Nutrients in food supplements are often equally (e.g. vitamin c) or better absorbed (e.g. vitamin B12) than foods and have well documented data of efficacy and safety.

Synergy

- Synergy (additive effects) has very rarely been truly demonstrated and may be implied when it cannot be proven or is improbable. Synergy may be used to justify doses unlikely to be effective.

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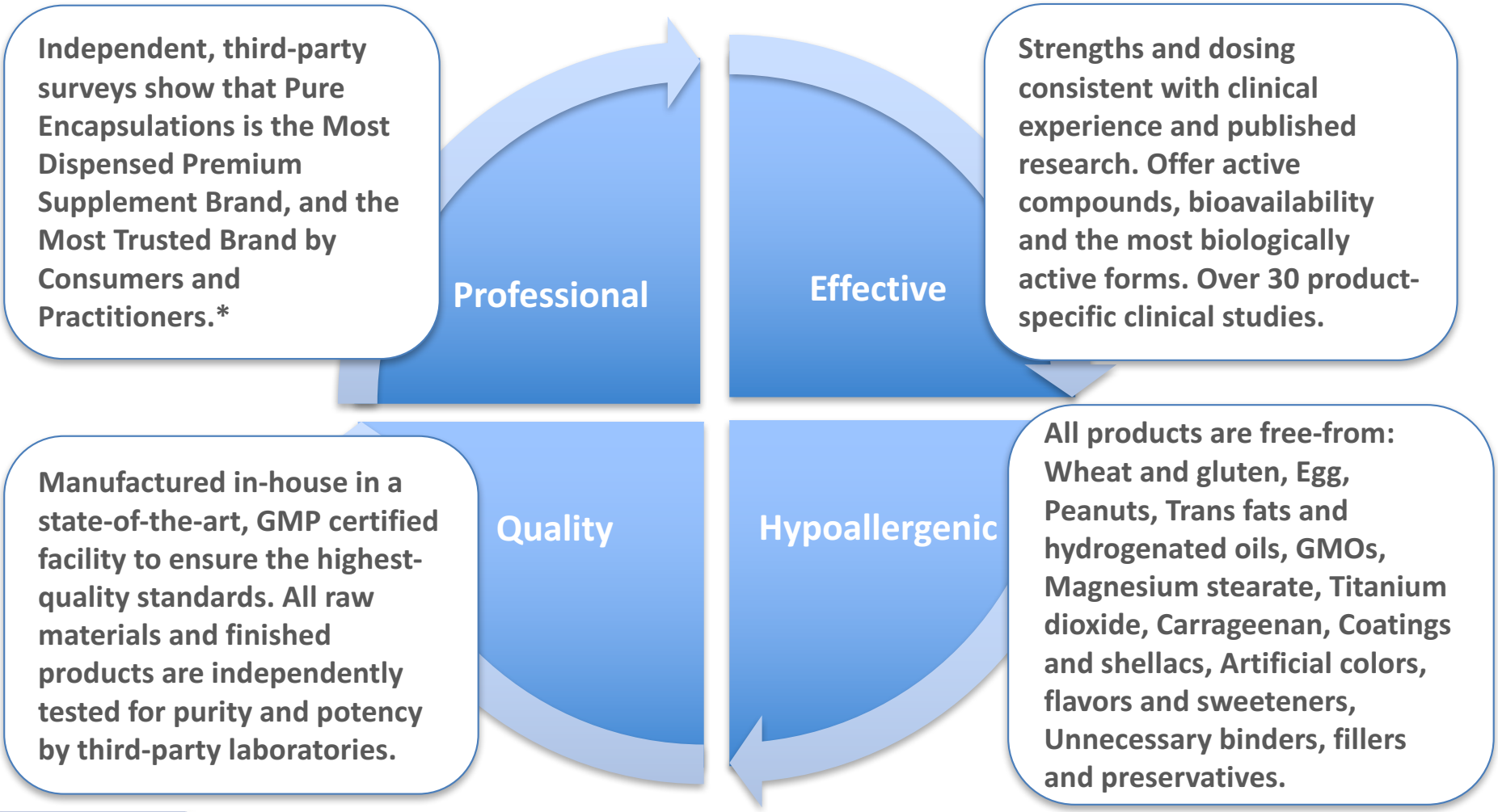
Hypoallergenic, Research-Based Food Supplements



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at pure-encapsulations.co.uk

Magnesium

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Clinical Symptoms and Signs of Magnesium Deficiency

Clinical signs of overt magnesium deficiency are usually totally absent (chronic latent intracellular deficit), but classical deficiency symptoms include:

- Neuromuscular: weakness; tremor; muscle fasciculation; dysphagia; positive Chvostek's sign (facial twitching as a reaction to facial nerve tapping); positive Trousseau's sign (application of a pressure cuff to transiently occlude the brachial artery resulting in spasm of muscles of the hand and forearm)
- Cardiac: arrhythmias and ECG changes
- Central nervous system: depression, agitation, psychosis, nystagmus, and seizures

However, deficiency is very common (56 to 68% of adults do not meet daily intake requirements) and associated with a myriad of clinical presentations that may reflect a deficiency state.

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Scientifica (Cairo). 2017;2017:4179326.

Clinical Symptoms Associated with Magnesium Deficiency

A number of common clinical presentations have been associated with a higher prevalence of magnesium deficiency and also respond well to treatment with magnesium, including:

- Pre-diabetes/ type 2 diabetes mellitus
- Depression
- Fibromyalgia
- Chronic Fatigue Syndrome
- Poor physical fitness
- Migraine headaches
- Hypertension
- Insomnia

Laboratory Assessment of Magnesium Status

The most commonly used test is the total serum magnesium concentration (SMC), but this laboratory marker has limited clinical benefit as it does not accurately reflect intracellular or total body magnesium status.

Low serum magnesium levels < 0.7 mmol/L (1.8 mg/dL, 1.5 mEq/L) are indicative of deficiency, although symptoms occur when serum magnesium is < 0.5 mmol/L (1.2 mg/dL, 1.0 mEq/L)

Given that sub-optimal intake of magnesium is wide-spread, deficiency is very common (especially in certain clinical presentations – see previous), and increasing intake with supplements and/ or food is safe, cheap and likely to benefit, laboratory assessment may not be necessary.

Clin Kidney J. 2012 Feb;5(Suppl 1):i3-i14.

Uses Based on Clinical Trials

Hypertension: 360–600 mg/day.

Migraine: 600 mg daily

Migraine prophylaxis in children: 9 mg/kg/day

PMS fluid retention symptoms: 200 mg daily

PMS mood swings: 360 mg daily

Coronary artery disease: 365 mg daily

T1DM: 300 mg daily

T2DM: 300 mg daily

T2DM, with hyperlipidemia: 600 mg daily

ADHD: 6 mg/kg/day ± 0.6–0.8 mg/kg/day vitamin B_6.

ASD: 6 mg/kg/day ± 0.6–0.8 mg/kg/day vitamin B_6

Kidney stone prevention: 400–500 mg/day

Nocturnal leg cramps: 300 mg daily

Paediatric asthma: 200–300 mg daily

Osteoporosis prevention: 250 mg daily

Hot flushes in breast cancer therapy: 250 mg to 500 mg daily

Physical/ muscle performance in older age: 300 mg daily

Depression: 250 mg to 450 mg daily

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PMS; premenstrual syndrome, T1DM; type 1 diabetes mellitus, T2DM; type 2 diabetes mellitus, ADHD; attention deficit hyperactivity disorder, ASD; autistic spectrum disorder.

Magnesium Supplement Bioavailability

Bioavailability studies have typically compared just a few types of magnesium and mostly used single-dose response in urinary magnesium excretion as a marker of bioavailability, which is not very accurate. These are the studies to date:

- Lindberg et al (1990) demonstrated greater bioavailability from magnesium citrate versus magnesium oxide.
- Muhlbauer et al (1991) found magnesium aspartate superior to oxide.
- Schuette et al (1993 & 1994) did not find a difference between magnesium glycinate and magnesium oxide.
- Firoz & Graber (2001) revealed a relatively poor bioavailability of magnesium oxide when compared to magnesium chloride, lactate, and aspartate.
- Walker et al (2003) found magnesium citrate to be superior to glycinate and oxide.
- Schecter et al (2012) found that magnesium oxide was superior to magnesium citrate both in terms of bioavailability and health benefits.

Magnesium Supplement Bioavailability

There is not sufficient evidence to suggest one form of magnesium is superior to another in terms of bioavailability.

Clinical studies have generally found that a variety of forms are able to correct deficiency and are clinically effective (oxide, citrate, orotate, glycinate, etc.).

It is unlikely that any difference in absorption between various types of magnesium is clinically meaningful.

However, it is likely that the ligand (in particular citrate, glycine, orotate or taurate) offers additional therapeutic benefits related to these molecules.

Dose for Magnesium Supplements

In the United Kingdom, the average daily magnesium intake for adult men and women are estimated to be 308 mg and 229 mg respectively. Thus, most people are not meeting the recommended daily intake of 375 mg.

While it is not clear what dietary intake of magnesium is optimal, it is apparent that modern diets do not supply a sufficient amount to prevent disease.

It has been estimated that pre-agricultural and pre-industrial intakes of magnesium were approximately 600 mg per day.

One study found that at least 300 mg per day, in addition to usual diet, is required to acutely increase plasma levels.

Clinical studies typically use between 200 mg to 600 mg daily in divided doses for at least 3-months.

Potential Adverse Effects of Magnesium

The most common adverse effects of oral magnesium supplements are diarrhoea (18.6%) and gastric irritation (4.7%).

Typically, doses magnesium preparations supplying above 350 mg/day (elemental) may be associated with adverse effects.

Dividing total daily supplemental amounts over 2–3 separate doses may help to reduce this risk.

Hypermagnesemia is rare and usually iatrogenic (e.g. magnesium enemas, magnesium-based laxative and antacid use [e.g. epsom salts, citrimag, milk of magnesia]) and related to renal disease or severe constipation.

Herbs and Natural Supplements, 3rd Edition. 2014.

Magnesium (powder)

Serving size: 1 scoop

Servings per container: 63

	Amount Per Serving
Magnesium (as citrate)	250 mg

Directions: 1 scoop 1–2 times per day, in divided doses, with meals, mixed with 220 ml of water.

Ingredients: Magnesium citrate.

Magnesium (powder)

Health Benefits and Product Features:

- ✓ convenient, additive-free, no-taste powder
- ✓ providing magnesium as bioavailable magnesium citrate
- ✓ professional-strength of 250 mg magnesium per scoop
- ✓ contributes to normal functioning of the nervous system
- ✓ contributes to the reduction of tiredness and fatigue

Turmeric

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Introducing the Golden Spice

More than 100 human clinical trials of turmeric have been completed, and as many as 100 clinical trials are under way.

Turmeric powder contains 3-5% curcuminoids (curcumin, demethoxycurcumin, bisdemethoxycurcumin) and extracts typically provide 85-95% total curcuminoids.

Turmeric is chemically diverse: to date approximately 235 compounds have been identified in this spice. Each curcuminoid has important biological effects (all are “active”). Curcumin-free turmeric is active and clinically effective.

Uses Based on Clinical Trials

Metabolic syndrome: 1000 mg of extract daily

Cognitive health: 90 mg of curcumin (Theracurmin®) twice daily

Depression: 500 mg to 1000 mg of extract daily

Osteoarthritis: 1000 mg to 1500 mg of extract daily

Rheumatoid arthritis (adjuvant): 500 mg of extract daily

Ulcerative colitis (maintenance): 1000 mg of extract twice daily

Colorectal neoplasia (prevention): 2000 mg to 4000 mg of extract daily

Type-2 diabetes: 300mg to 1500mg of extract daily

Bronchial asthma (adjuvant): 500 mg of extract daily

Wellness: 80 mg of curcuminoids daily

Laboratory Assessment of Inflammatory Status

Turmeric extracts have been shown to lower inflammatory biomarkers across a number of clinical studies in meta-analysis:

- ✓ Tumor necrosis factor-α (TNF-α)
- ✓ Interleukin-6 (IL-6)
- ✓ C-reactive protein (CRP)

Pharmacol Res. 2016 May;107:234-242.
Pharmacol Res. 2016 Sep;111:394-404.
Phytother Res. 2014 May;28(5):633-42.

Turmeric Bioavailability

Poor absorption and bioavailability of the curcuminoids is a major focus of commercial turmeric products, but this may be more marketing than science.

The general presumptions are:

a) curcumin is poorly absorbed, therefore

b) turmeric is not effective, consequently

c) absorption enhancers are required for turmeric to be effective

Turmeric Bioavailability

Clinical studies have shown that turmeric or turmeric extracts are clinically effective without bioavailability enhancers. i.e. turmeric and/ or curcumin is clinically effective despite low absorption.

Explanations for this “turmeric paradox” include: 1) Curcumin may be at low concentrations or not detectable in blood after ingestion because it has been metabolized into more biologically active compounds. 2) Gastrointestinal effects may explain systemic effects.

Caution: Bioavailability “enhancers’” may displace extract and result in low turmeric per capsule and/ or have potential adverse effect e.g. polysorbate-80 and povidone. Bioavailability may be overstated or unproven.

Dose for Turmeric Supplements

Extract standardized to 95% curcumin: 100 mg to 2000 mg per day in divided doses.

Powdered turmeric: 1.5 to 3 g (1/2 to 1 teaspoon) per day.

No studies have yet assessed whether consumption with or without food improves absorption or efficacy.

Traditionally, turmeric is heated with cows milk and taken in the evening to improve clinical effects. Interestingly, an increased capacity of heated milk proteins to bind curcumin has been shown. And the circadian clock modulates anti-cancer properties of curcumin.

Potential Adverse Effects of Turmeric

Turmeric, turmeric extract and curcumin have a long established safety record.

Studies on the toxicity and anti-inflammatory properties of curcumin have included in vitro, animal, and human studies.

A phase 1 human trial with 25 subjects using up to 8000 mg of curcumin per day for 3 months found no toxicity from curcumin.

Five other human trials using 1125-2500 mg of curcumin per day have also found it to be safe.

J Altern Complement Med. 2003 Feb;9(1):161-8.

Curcumin

Serving size: 2 capsules

Servings per container: 30

	Amount Per Serving
Turmeric (*Curcuma longa*) root extract (providing 95% total curcuminoids [475mg] as Curcumin 75-81%, Demethoxycurcumin 15 – 19%, Bisdemethoxycurcumin 2.2 – 6.5%).	500 mg

Directions: 2 capsules, 1–3 times daily, with meals.

Curcumin 500 with Bioperine®

Serving size: 1 capsule

Servings per container: 60

	Amount Per Serving
Turmeric (*Curcuma longa*) root extract (providing 95% total curcuminoids [475mg] as Curcumin 75-81%, Demethoxycurcumin 15 – 19%, Bisdemethoxycurcumin 2.2 – 6.5%).	500 mg
Bioperine® black pepper (piper nigrum) fruit extract (standardised to contain 95% piperine)	5 mg

Directions: 1 capsule, 1–3 times daily, with meals.

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Curcumin

Health Benefits and Product Features:

- ✓ Curcumin C3 Complex® is a high-quality, clinically-studied turmeric extract
- ✓ high-potency turmeric extract standardised to curcuminoids
- ✓ provides a guaranteed amount of curcumin in each capsule
- ✓ features the full-spectrum of curcuminoids including curcumin, demethoxycurcumin, and bisdemethoxycurcumin
- ✓ free-from synthetic and chemical additives common in curcumin products

N-acetyl cysteine

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N-acetyl cysteine

N-acetylcysteine (NAC) has been used as an antioxidant precursor to glutathione (γ-glutamylcysteinylglycine; GSH) for more than 30 years.

Glutathione is the primary endogenous antioxidant. Glutathione neutralizes reactive oxygen and nitrogen species from the cell through both direct and indirect scavenging. As the most abundant and ubiquitous antioxidant, it is responsible for maintaining the oxidative balance in the cell.

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J Psychiatry Neurosci. 2011 Mar;36(2):78-86

Uses Based on Clinical Trials

Autism: 600 mg to 1200 mg daily

Alzheimer's disease: 600 mg (+ other nutrients)

Cocaine, cannabis, marijuana, & smoking addiction: 1200 mg to 2400 mg daily

Bipolar disorder: 2000 mg daily

Depression: 2000 mg daily

Trichotillomania: 1200- 2400 mg daily

Obsessive-compulsive disorder: 3000 mg daily

Schizophrenia: 2000 mg daily

Anxiety: 1200 mg to 2400 mg daily

Attention deficit hyperactivity disorder: 2400 mg to 4800 mg daily

Non-alcoholic steatohepatitis: 1000 mg daily

Colon cancer (prevention): 800 mg daily

Colds & influenza: 600 mg daily

Chronic bronchitis: 600 mg daily

Lead detoxification: 200 mg to 800 mg daily

Laboratory Assessment of Oxidative Stress

N-acetylcysteine plays a key role in glutahione synthesis, thus assesment of redox balance may be a useful indicator for supplementation.

Possible assessments include:

- ✓ Glutathione (GSH)
- ✓ Glutathione Peroxidase (GPX)
- ✓ Total Antioxidant Capacity (TAC)
- ✓ Lipid Peroxides
- ✓ F2 -isoprostanes

Dose for NAC

The precise dose of NAC remains to be definitively established.

Clinical studies typically range from 600-2400 mg in divided doses.

Potential Adverse Effects of NAC

NAC is safe and well tolerated with a low incidence of serious adverse events.

Oral administration of NAC at doses up to 8000 mg per day is not known to cause clinically significant adverse reactions.

Rarely, gastrointestinal symptoms symptoms (mild abdominal pain or discomfort, nausea, vomiting and heartburn) or neurological symptoms (headaches) may occur.

Curr Opin Pharmacol. 2007 Aug;7(4):355-9.

J Psychiatry Neurosci. 2011 Mar;36(2):78-86

NAC (n-acetyl-l-cysteine) 600 mg

Serving size: 1 capsule

Servings per container: 90

	Amount Per Serving
N-Acetyl-L-Cysteine (free-form)	600 mg

Directions: 1 capsule, 1–3 times daily, between meals.

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NAC (n-acetyl-l-cysteine) 600 mg

Health Benefits and Product Features:

- ✓ provides free-form NAC (n-acetyl-l-cysteine)
- ✓ professional strength of 600mg per capsule
- ✓ NAC is a sulphur containing amino acid involved in glutathione synthesis

References

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Magnesium

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Clinical Symptoms Associated with Magnesium Deficiency

References:

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