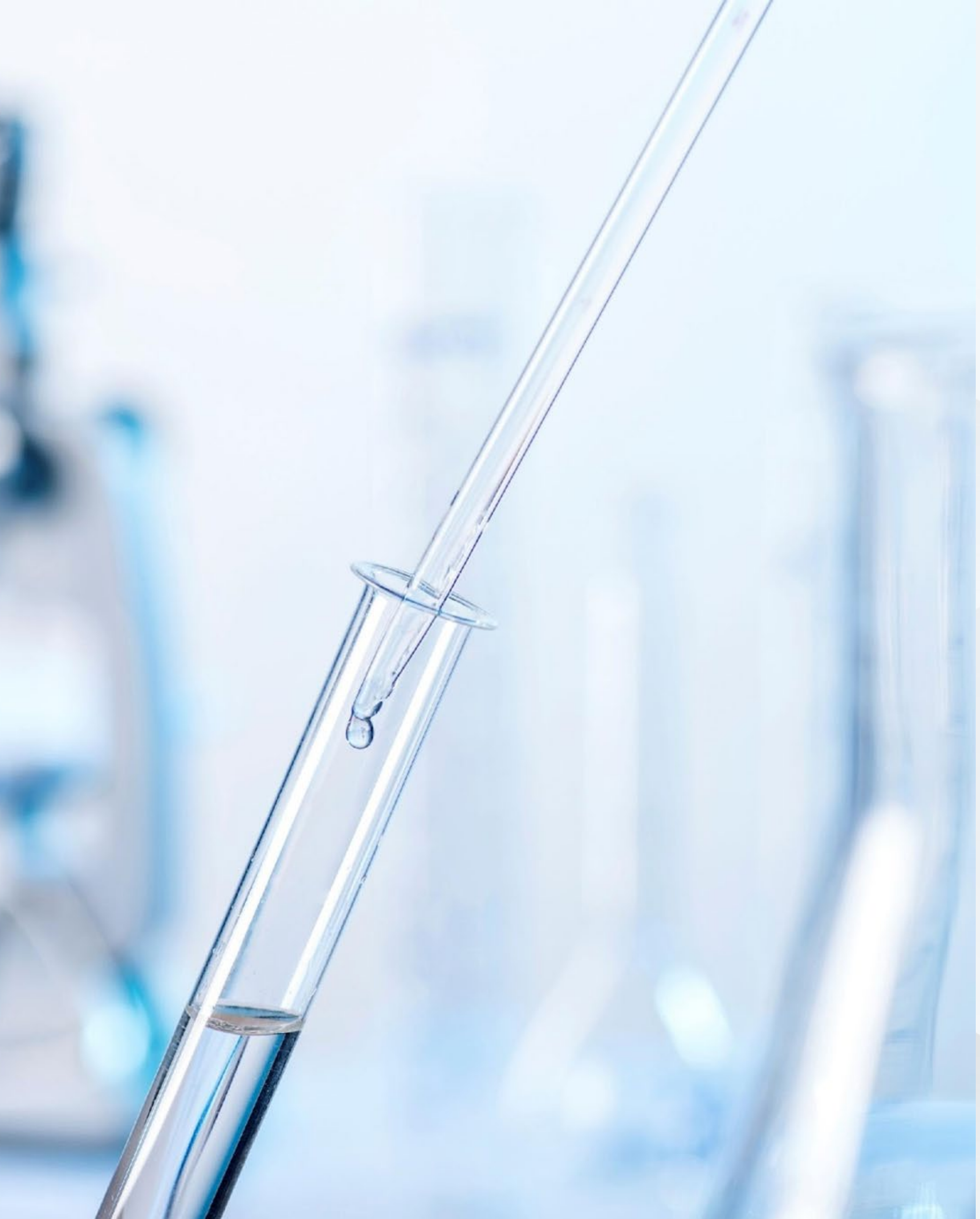

10 Biomarkers That Elevate Your Practice: Beyond the Basics of Functional Lab Testing

THE LYONS' SHARE

www.thelyonsshare.org

Intro to Dr. Megan Lyons

- **Owner, The Lyons' Share Wellness**
  - >12 years in practice
  - >15,000 client sessions completed
  - 5.0 client satisfaction rating (out of 5!)
- **Education**
  - Doctor of Clinical Nutrition (DCN)
  - Functional Medicine Certified Practitioner (IFMCP)
  - Harvard University: BA, economics
  - Kellogg School of Management: MBA
  - Master of Science, Holistic Nutrition
  - Certified Nutrition Specialist (CNS)
  - Licensed Dietitian Nutritionist (LDN)
  - Board Certified in Holistic Nutrition®
  - Board Certified Clinical Nutritionist (CNCB)
- **Learn more:**
  - @thelyonsshare Instagram
  - Wellness Your Way Podcast

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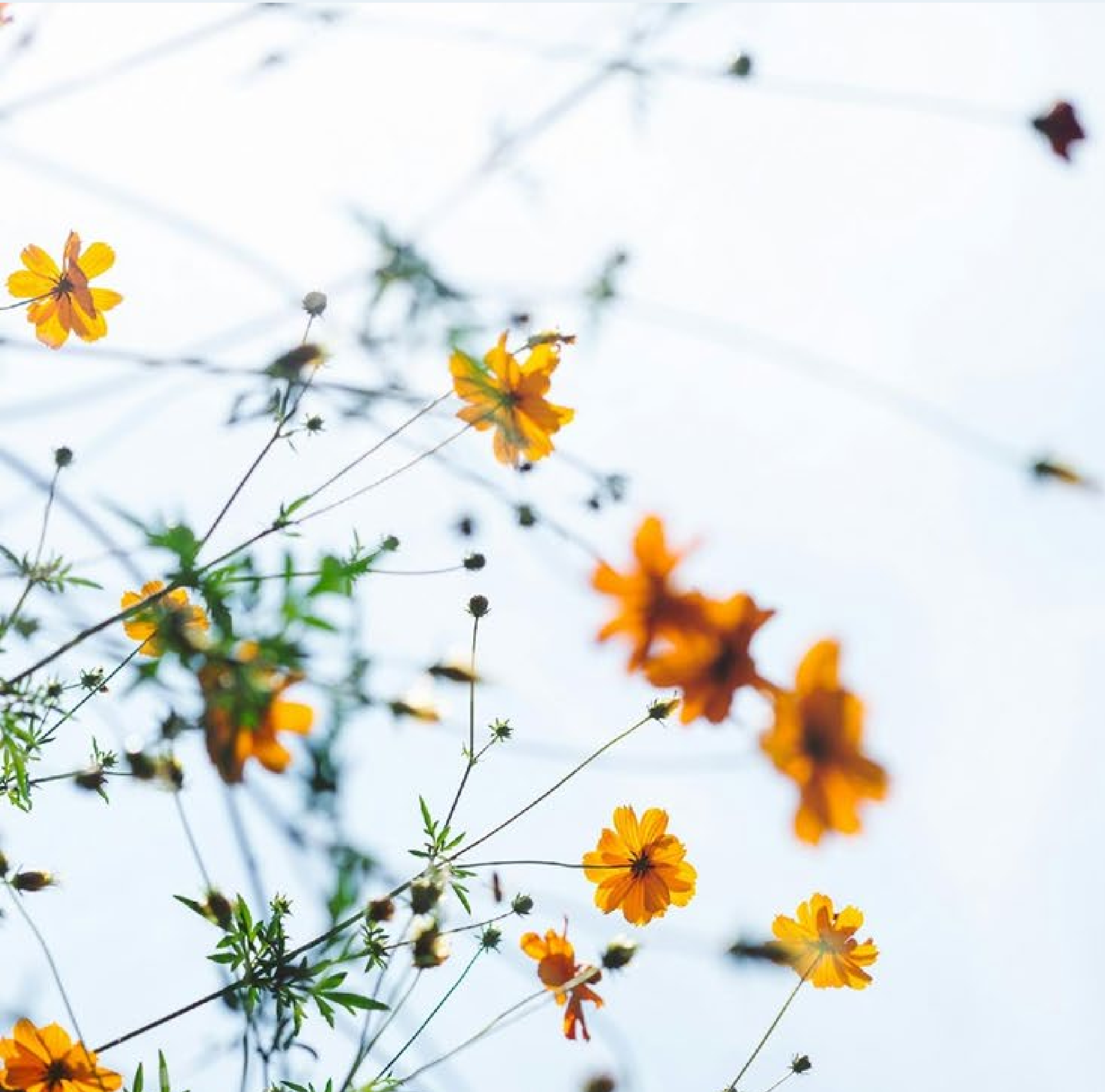
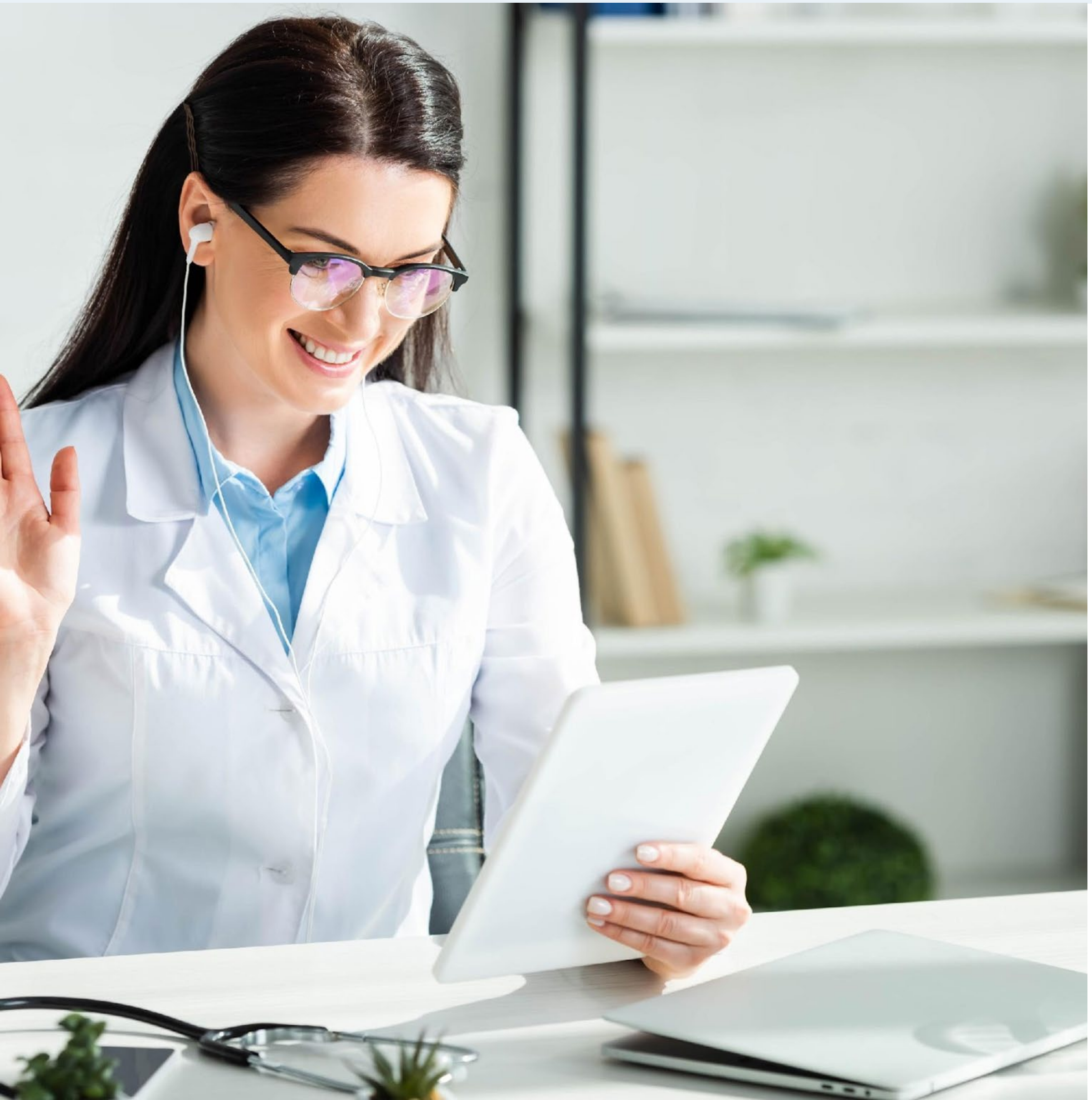
Collective Deep Breath



- Take a deep breath
- Let’s be present together for this time

What We Will Cover



1. The Case for Going Deeper
2. Metabolic Indicators
3. Hidden Cardiovascular Drivers
4. Longevity and Resilience Levers
5. Wrap up & Questions

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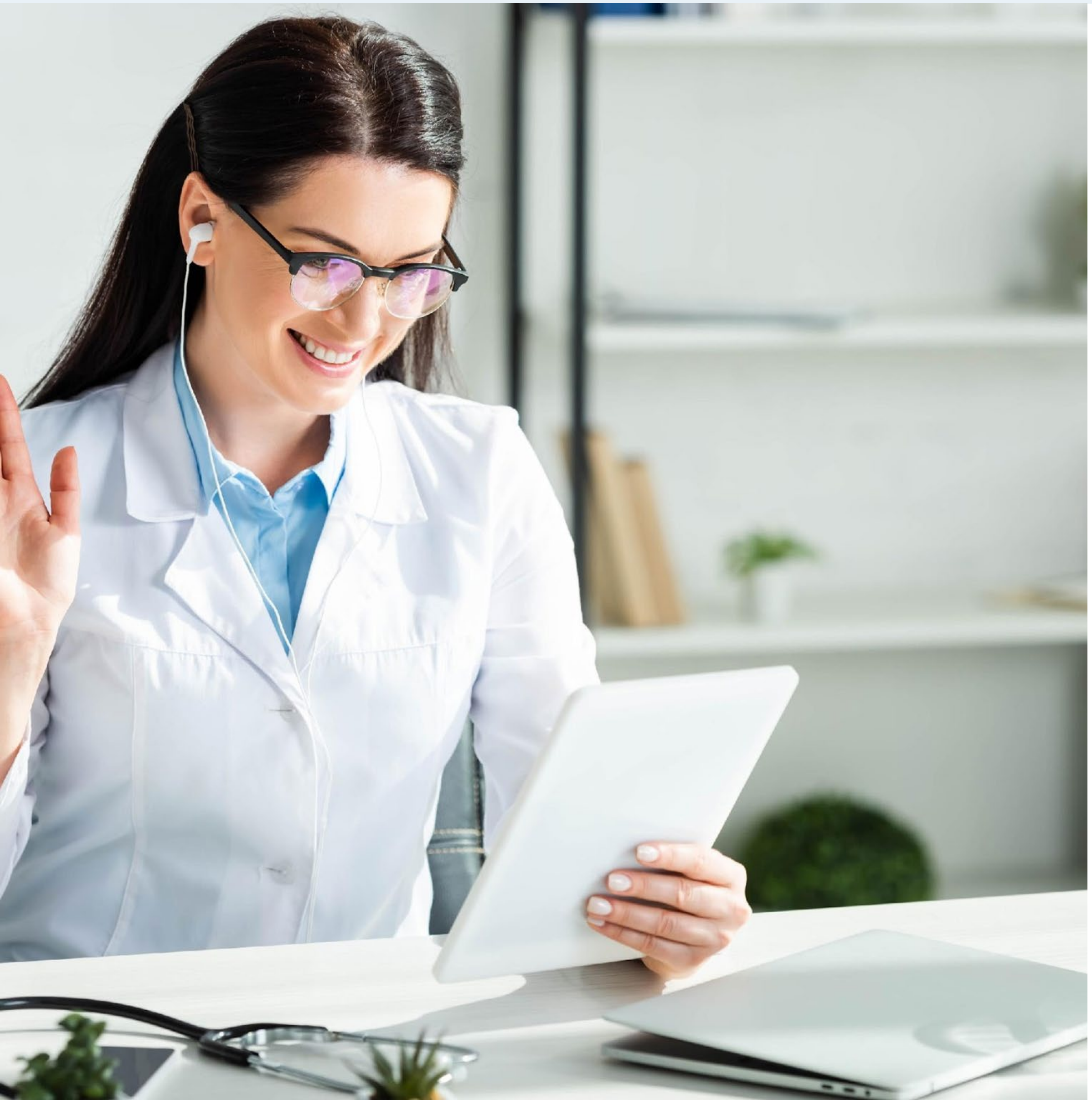

1. **The Case for Going Deeper**
2. Metabolic Indicators
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Why This Talk Matters Now

- “Normal” labs and lab ranges detect disease, not dysfunction
- Clients are more metabolically complex than ever
- Our clinical edge as BCHNs comes from seeing patterns before pathology
- When clients are not satisfied with what they’re getting elsewhere, we shine

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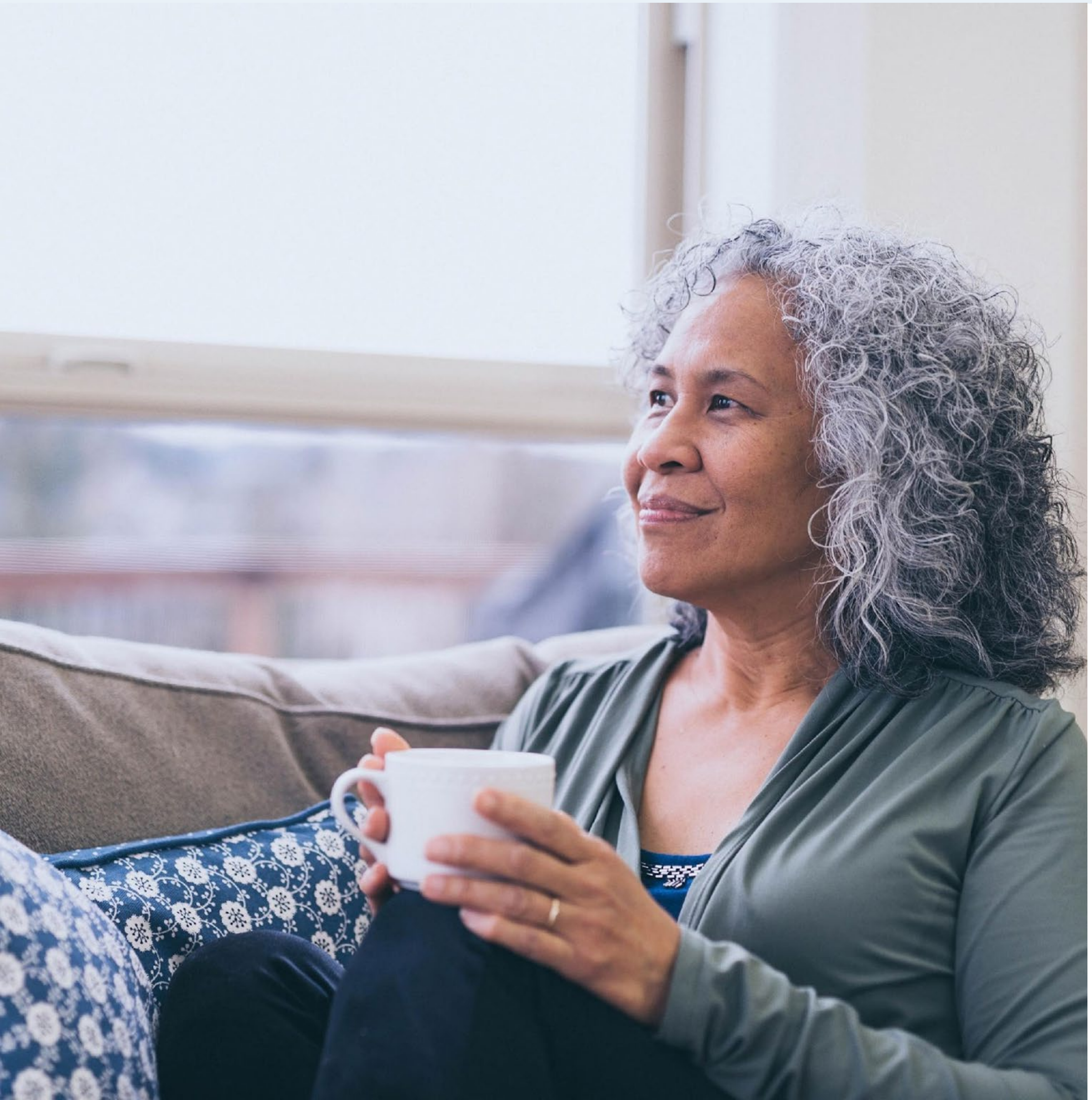
The Gap in Testing



- Reality check: most practices run the same labs:
  - CBC
  - CMP
  - Basic lipid panel
- If we're "lucky," we may get:
  - Vitamin D
  - Fasting insulin or A1c
  - TSH ± free T4
- Yet clients still report:
  - Resistant weight gain
  - Persistent fatigue
  - "Something is off" feeling

The question: What are we not measuring?

The Gap in Interpretation

- Conventional Model: Detect and treat disease once it crosses a threshold.
- Functional Model: Identify physiologic "drift" before disease develops.
    - Small deviations and trends reveal large patterns
    - Compensation often precedes technically abnormal labs
- *Constant reminder: normal ≠ optimal*
- Our clinical advantage comes from seeing this nuance

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Three Root Drivers of Dysfunction

Metabolic Blockers

Hormonal signals that drive weight resistance & insulin dysfunction

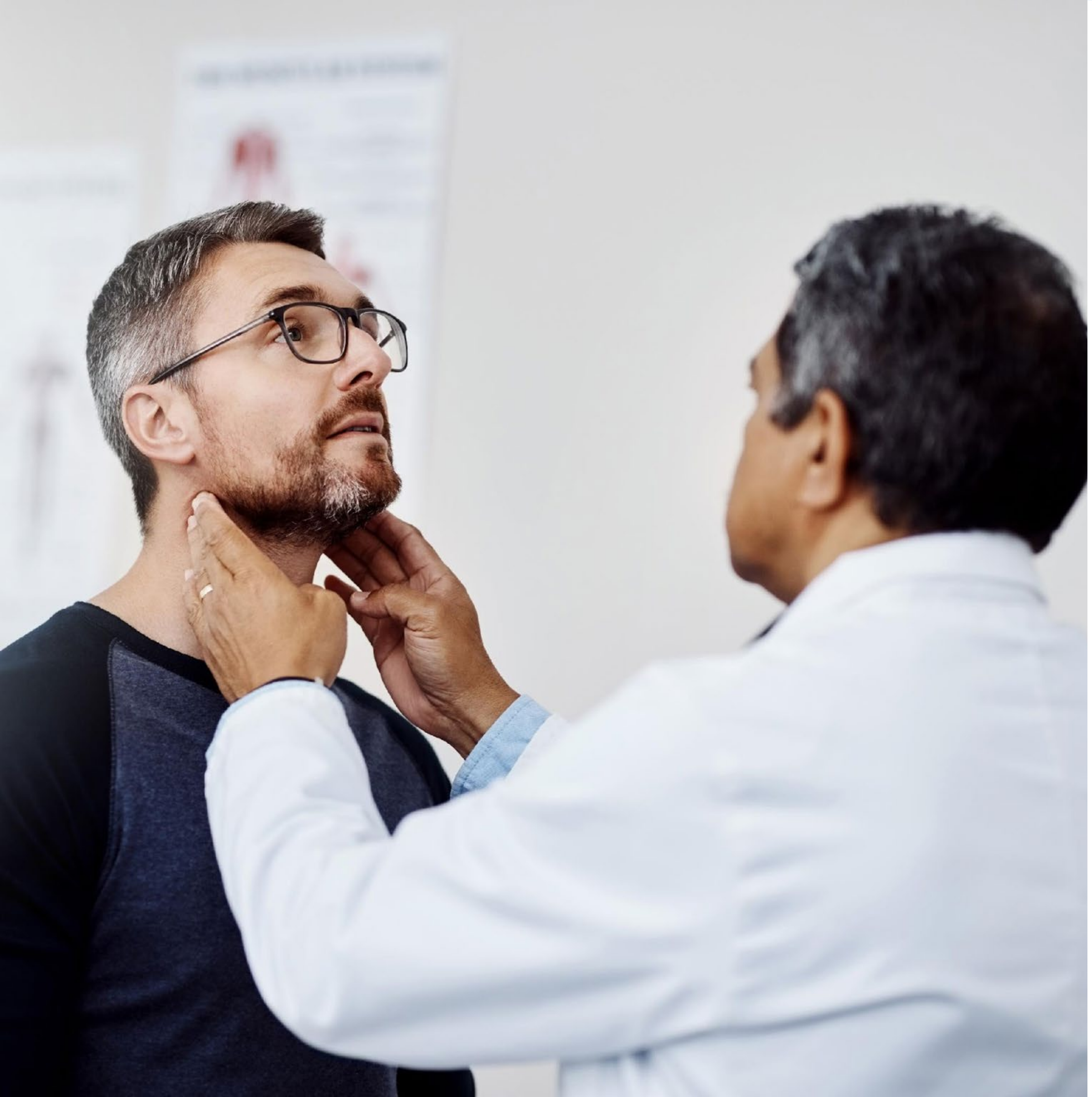
Hidden Cardiovascular Risk

Markers that outperform traditional lipids

Resilience & Longevity Signals

Indicators of cellular stress, adrenal reserve, and long - term disease vulnerability

The Differentiation Factor as BCHNs



Advanced biomarkers allow you to:

- Detect dysfunction earlier
- Personalize nutrition & lifestyle strategies
- Increase client buy -in with objective data
- Differentiate your practice in a saturated market

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Why Standard Panels Miss Root Causes

- Most dysfunction is compensatory before it is pathological
- The body maintains “normal” ranges on basic lab markers through compensation but starts to drift on more detailed markers
  - Insulin rises before glucose changes
  - Inflammation rises before lipids shift
  - Oxidative stress rises before structural damage
- If we only test end -stage markers, we intervene late, when it’s more difficult to make change

The Problem with Downstream Markers

Conventional labs measure downstream reflections, not upstream drivers.

Examples:

LDL-C = cholesterol content → ApoB = number of atherogenic particles
A1c = 3-month glucose average → Leptin & adiponectin = energy signaling dysfunction
TSH = pituitary signal → DHEA-S = systemic adaptive reserve

Upstream markers can guide intervention more precisely if used accurately

When to Go Beyond the Basics

- It is easy to run ALL the labs ALL the time, and while this is exciting, we still need clinical judgment
- Consider advanced biomarkers when you see:
  - Weight resistance despite caloric compliance
  - “Normal lipids” but strong family CVD history (or abnormal lipids with optimal diet and lifestyle)
  - Fatigue with unremarkable thyroid labs
  - High stress without patient recognition
  - Clients doing “everything right” but plateaued

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Overview of The 10 Biomarkers That Elevate Your Practice

- Metabolic Signaling
  - Leptin
  - Adiponectin
  - Uric Acid
- Hidden Cardiovascular Risk
  - ApoB
  - Lipoprotein(a)
  - Oxidized LDL
- Resilience & Longevity Signals
  - 8-OHdG
  - DHEA-S
  - ApoE Genotype
  - MTHFR Variants

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Leptin: The Master Regulator of Energy Signaling

- We think of leptin as a satiety hormone, which it is, but we can use it clinically as a metabolic status signal
- Leptin [1]:
  - Signals energy sufficiency to the hypothalamus
  - Regulates appetite and thermogenesis
  - Modulates insulin sensitivity
  - Influences reproductive and thyroid axis
  - Regulates immune and inflammatory pathways
- I think of it as a major signal of: energy availability, inflammation, and neuroendocrine control

Two Clinical Extremes: Low vs. High Leptin

Low Leptin

- Energy deficiency / low body fat
- Hypothalamic suppression
- Amenorrhea, sex hormone suppression
- Thyroid downregulation
- Reduced thermogenesis
- Impaired glycemic regulation (even with normal insulin) via hypothalamic signaling deficits

High Leptin (Leptin Resistance)

- Chronic overnutrition
- Hypothalamic inflammation
- Persistent hunger despite energy sufficiency
- Insulin resistance via inflammatory pathways
- Reduced metabolic rate
- Sympathetic overactivation & hypertension risk

Leptin reflects *nutritional history*, not just current intake [1].

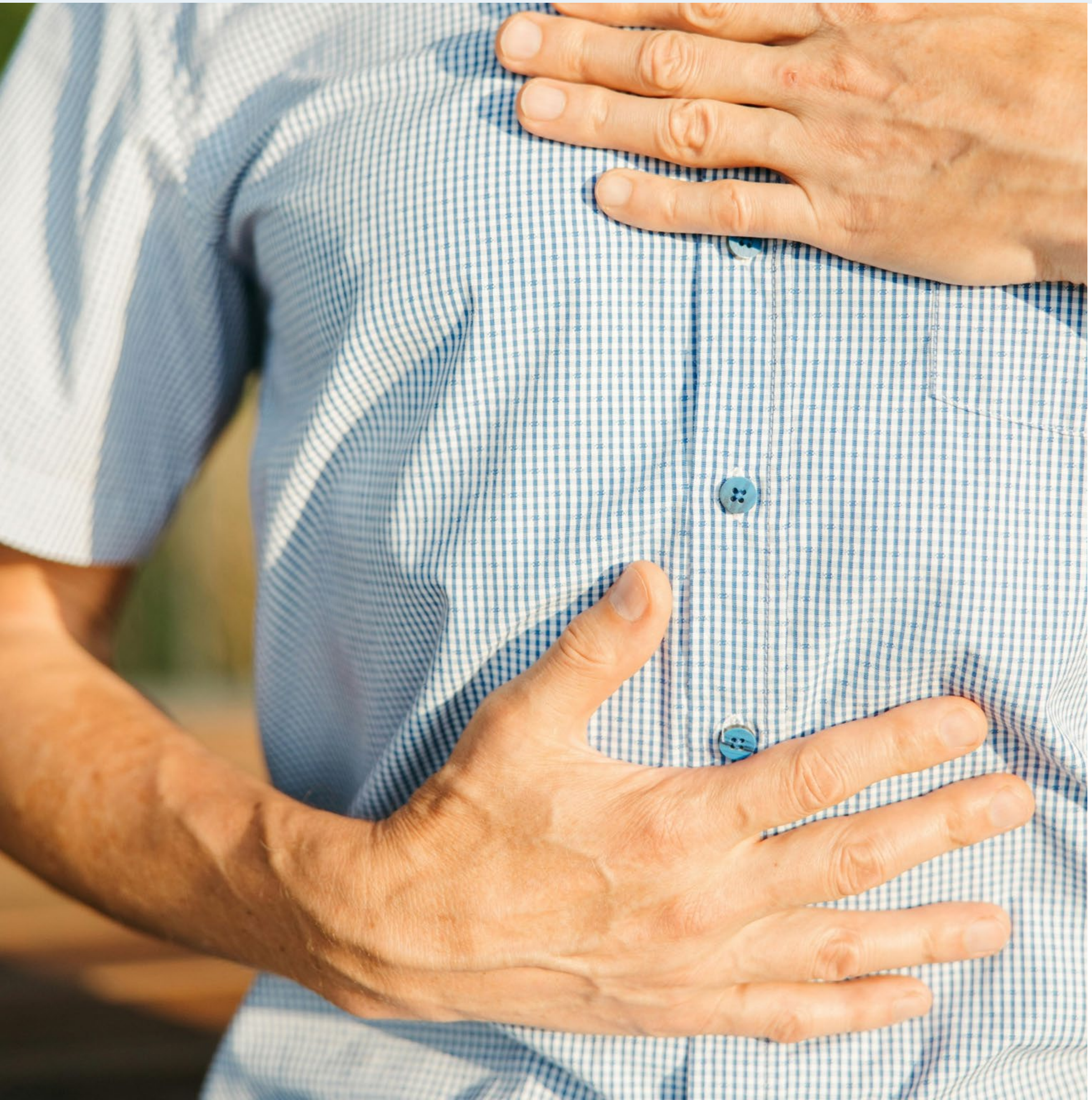
Optimal Levels Are Multifactorial

	Men	Premenopausal Women	Menopausal Women
Possible energy deficit / low body fat	<2 ng/mL	<4 ng/mL	<3 ng/mL
Generally metabolically healthy	2-8 ng/mL	4-19 ng/mL	3-12 ng/mL
Consider leptin resistance	9-20 ng/mL	20-30 ng/mL	13-25 ng/mL
Strong suspicion of leptin resistance	>20 ng/mL	>30 ng/mL	>25 ng/mL

Leptin resistance must also be interpreted in the context of body fat. We expect those with higher body fat to have higher leptin.

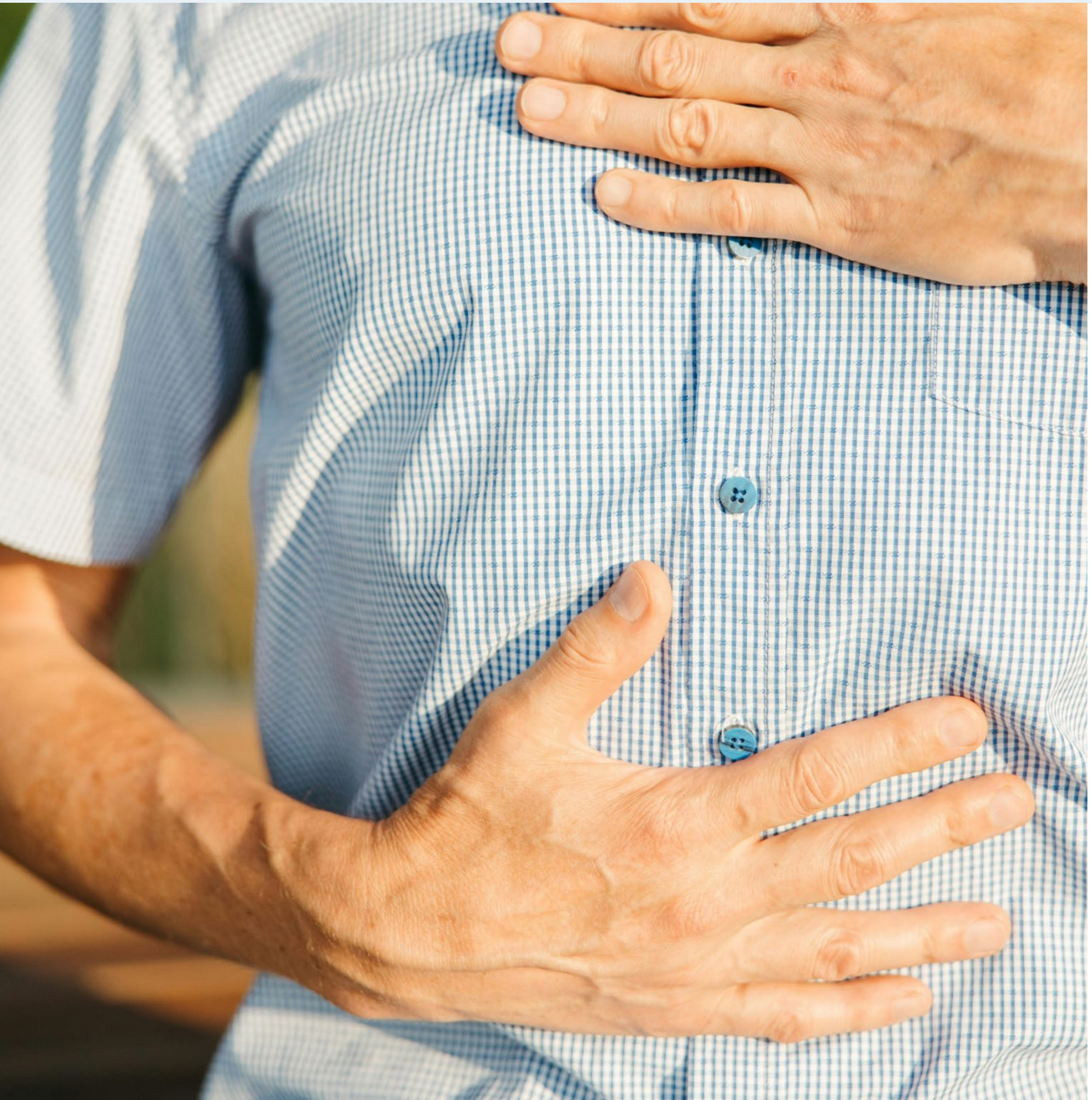
Note: these levels are Dr. Lyons' optimal ranges based on a multitude of research. Each lab will have different optimal ranges and conclusive research is yet to emerge.

Leptin Resistance: The Hidden Driver



- Chronic elevation of leptin -> impaired signaling (much like insulin resistance)
- Leptin resistance is associated with [2]:
  - Obesity
  - Type 2 diabetes
  - Hypertension
  - Cardiovascular inflammation
- Mechanisms of development:
  - Hypothalamic inflammation
  - High-fat + high-sugar dietary patterns
  - Low protein intake
  - Hyperinsulinemia synergy
  - Lack of breaks between meals
  - Hypercaloric diets

How Leptin Changes Clinical Strategy



- Insulin and A1c primarily reflect glucose handling (downstream markers of glycemic control)
- Leptin reflects long -term energy sufficiency and hypothalamic signaling (earlier neuroendocrine signal)
- Someone with normal glucose, A1c, and insulin, but high leptin may already have:
  - Hypothalamic inflammation
  - Reduced satiety signaling
  - Altered metabolic rate
  - Increased sympathetic tone
  - Increased cardiovascular risk
- Leptin may reflect decades of dietary history. In one Guatemalan study, leptin mediated 34.9% of the pathway between early -life nutrition and fasting glucose in women [3]

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Leptin: A Clinical Decision Framework

If Leptin is HIGH (Suspect Resistance)

Ask:

- Is there chronic overnutrition?
- Ultra-processed intake?
- Sleep deprivation?
- Hyperinsulinemia?

Clinical priorities:

- Reduce inflammatory load
- Increase protein intake
- Improve sleep
- Stabilize insulin
- Consider strategic fasting (case-dependent)

Note: aggressive calorie restriction may cause reduced metabolic rate, increased hunger signaling, increased stress hormones, and weight loss "plateau." Focusing on dietary *quality* is key here.

If Leptin is LOW (Energy Deficiency Signal)

Ask:

- Is intake adequate?
- Overtraining?
- Amenorrhea?
- Chronic stress?

Clinical priorities:

- Increase caloric intake
- Reintroduce carbohydrates strategically
- Reduce training load
- Support thyroid & reproductive recovery
- Avoid aggressive restriction

Note: aggressive calorie restriction may cause further thyroid and hypothalamic suppression, worsening fatigue

Leptin + GLP-1: The Emerging Connection

- Both influence overlapping neural circuits that regulate:
  - Appetite
  - Energy expenditure
  - Glycemic control
  - Neuroinflammation
- Key Distinction
  - Leptin = long-term energy sufficiency signal
  - GLP-1 = short-term satiety and glucose regulator
- GLP-1 agonists improve satiety and glycemic control, but do **not** inherently correct the root causes of leptin resistance:
  - Chronic inflammatory diet patterns
  - Hyperinsulinemia
  - Sleep deprivation
  - Ultra-processed food exposure
  - Sedentary behavior
- If those drivers remain when GLP-1 is discontinued:
  - Appetite signaling may revert
  - Leptin resistance may persist
  - Weight regain risk increases
- Understanding leptin physiology may help explain variability in GLP-1 response and durability

Adiponectin: Leptin's Metabolic Counterbalance

- Adiponectin [4]:
  - Enhances insulin sensitivity (AMPK activation)
  - Promotes fatty acid oxidation
  - Suppresses hepatic gluconeogenesis
  - Reduces vascular inflammation
  - Improves endothelial function
- Unlike leptin, adiponectin decreases as adiposity increases
- Low adiponectin is associated with:
  - Type 2 diabetes
  - Metabolic syndrome
  - Atherosclerosis

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The Leptin: Adiponectin Ratio (LAR)

- Helps determine energy sufficiency vs metabolic flexibility
  - Leptin reflects energy storage
  - Adiponectin reflects metabolic efficiency
- Higher LAR (≥ 1 for men, ≥2.5 for women) is associated with:
  - Insulin resistance
  - Cardiometabolic risk
  - Endothelial dysfunction
- Emerging research suggests LAR may outperform HOMA-IR in predicting metabolic syndrome[5]

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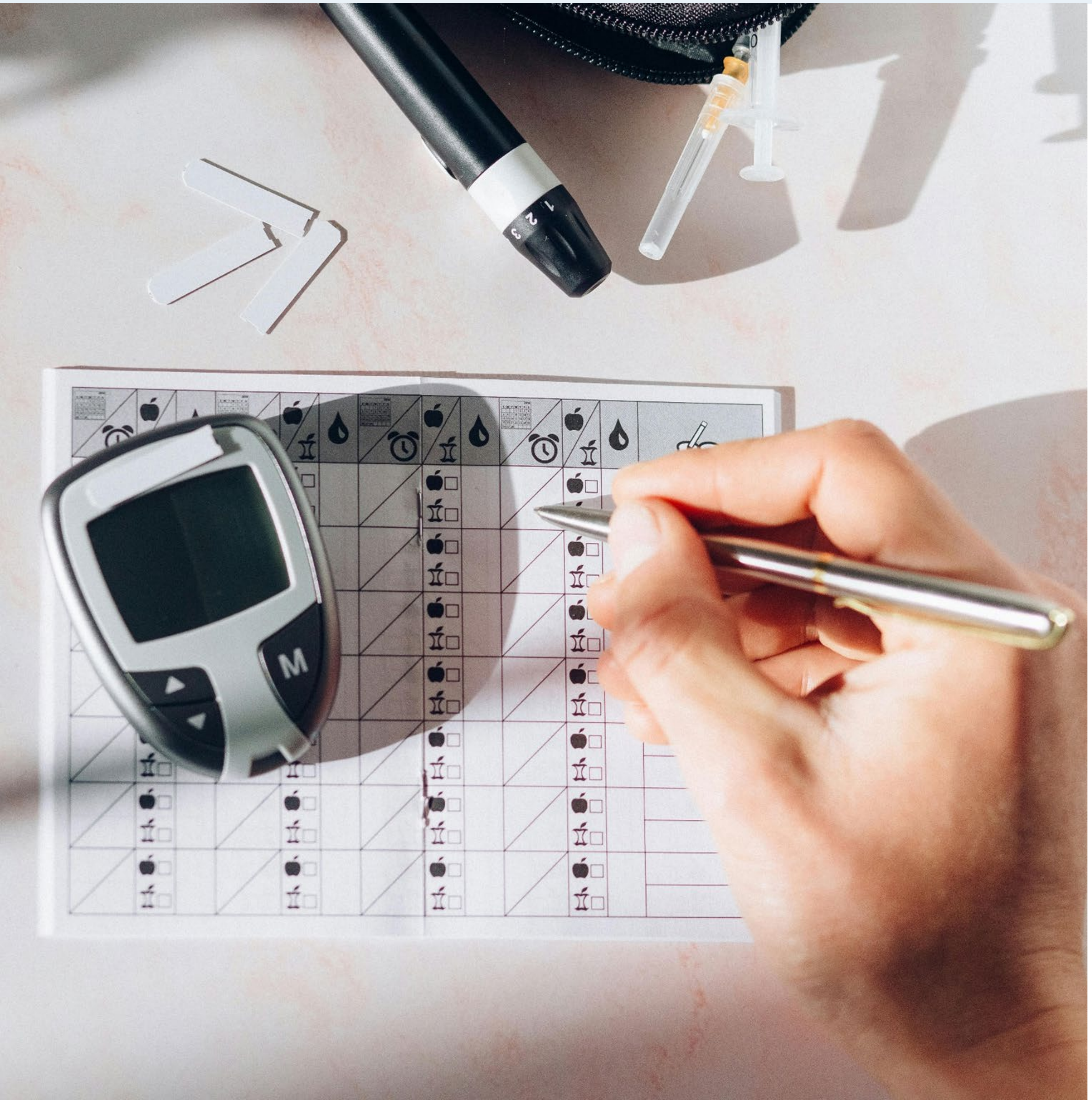
Clinical Application: Adiponectin

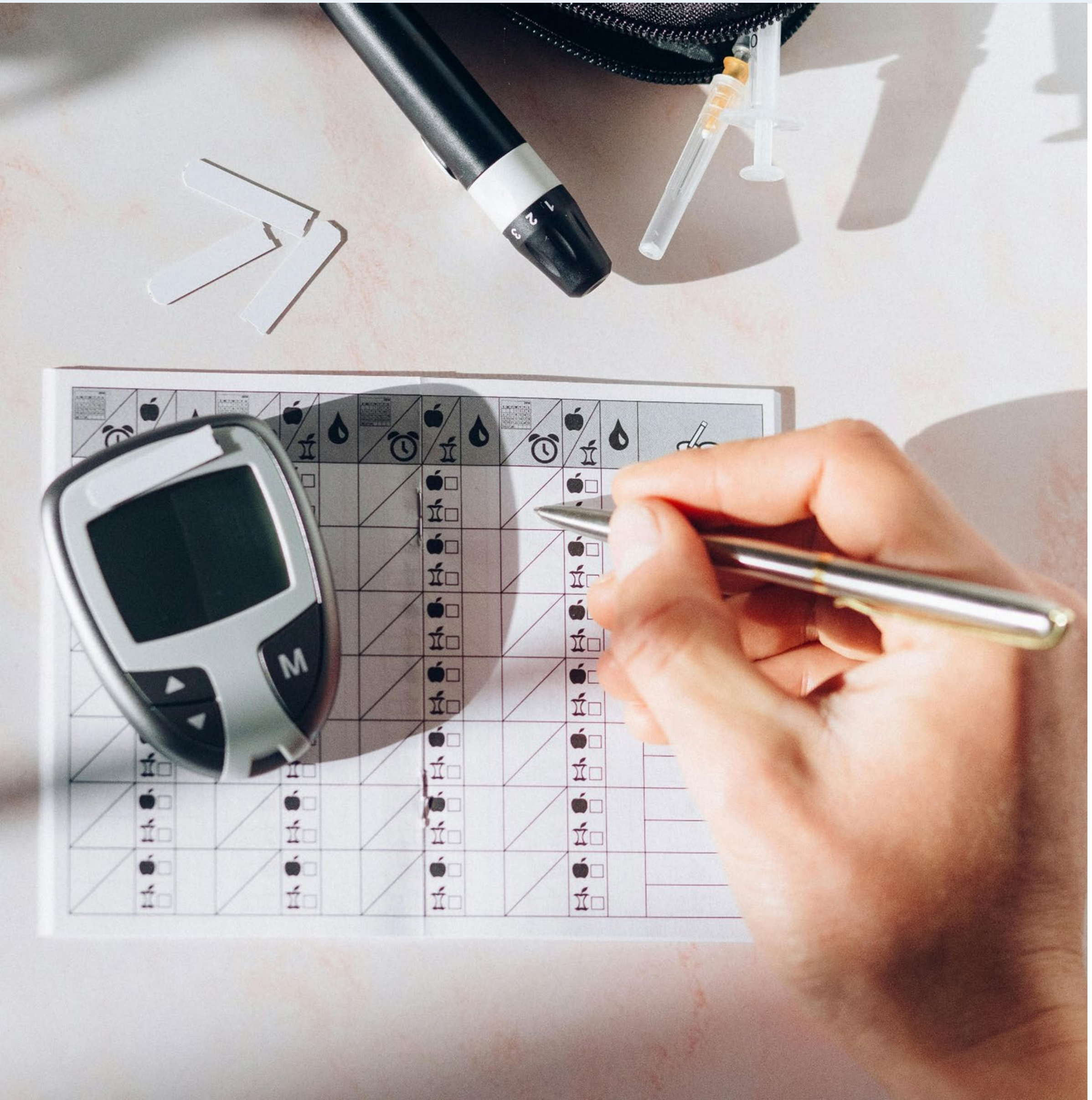
- Low adiponectin suggests:
  - Visceral adiposity
  - Hepatic insulin resistance
  - Low-grade inflammation
  - Reduced fatty acid oxidation
- Strategies That Increase Adiponectin
  - Weight loss (especially visceral fat reduction)
  - Increased physical activity
  - Higher dietary fiber intake
  - Omega -3 fatty acids
  - Mediterranean -style dietary patterns
  - Adequate sleep
  - Protein adequacy and reduced refined carbohydrate intake also correlate positively
- When to Run Adiponectin
  - Fasting insulin is borderline or elevated
  - A1c is normal but weight is resistant
  - PCOS presentation
  - Family history of type 2 diabetes
  - Central adiposity despite “healthy diet”

Uric Acid: More Than a Gout Marker



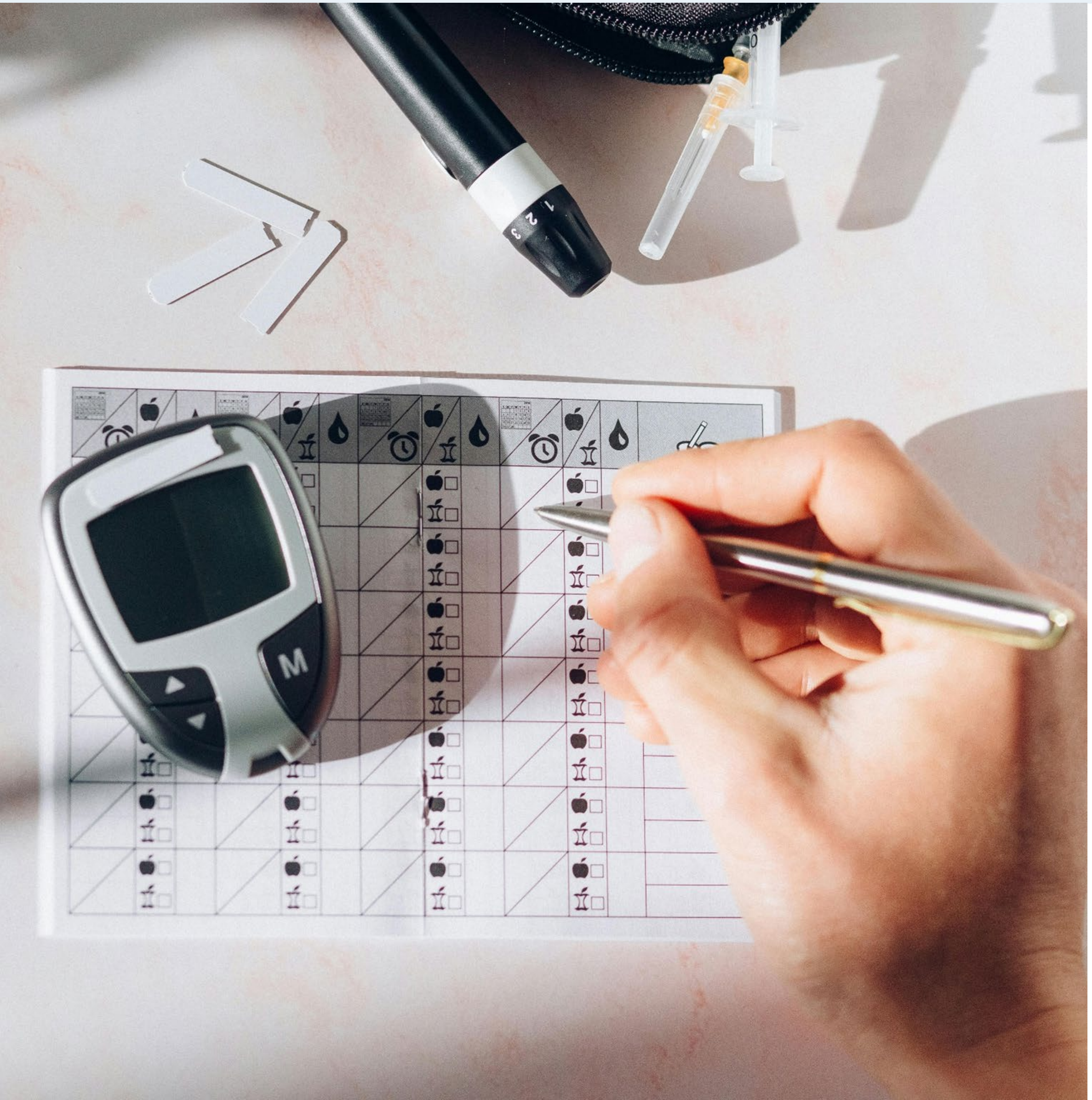
- Uric acid is a metabolic stress signal
- Produced from purine metabolism, but significantly influenced by:
  - Fructose metabolism
  - ATP depletion
  - Insulin resistance
  - Mitochondrial dysfunction
- Elevated uric acid is associated with [6]:
  - Hypertension
  - Metabolic syndrome
  - Nonalcoholic fatty liver disease
  - Type 2 diabetes
  - Cardiovascular disease
- Uric acid often rises before overt metabolic disease

Fructose, ATP Depletion & Metabolic Shift



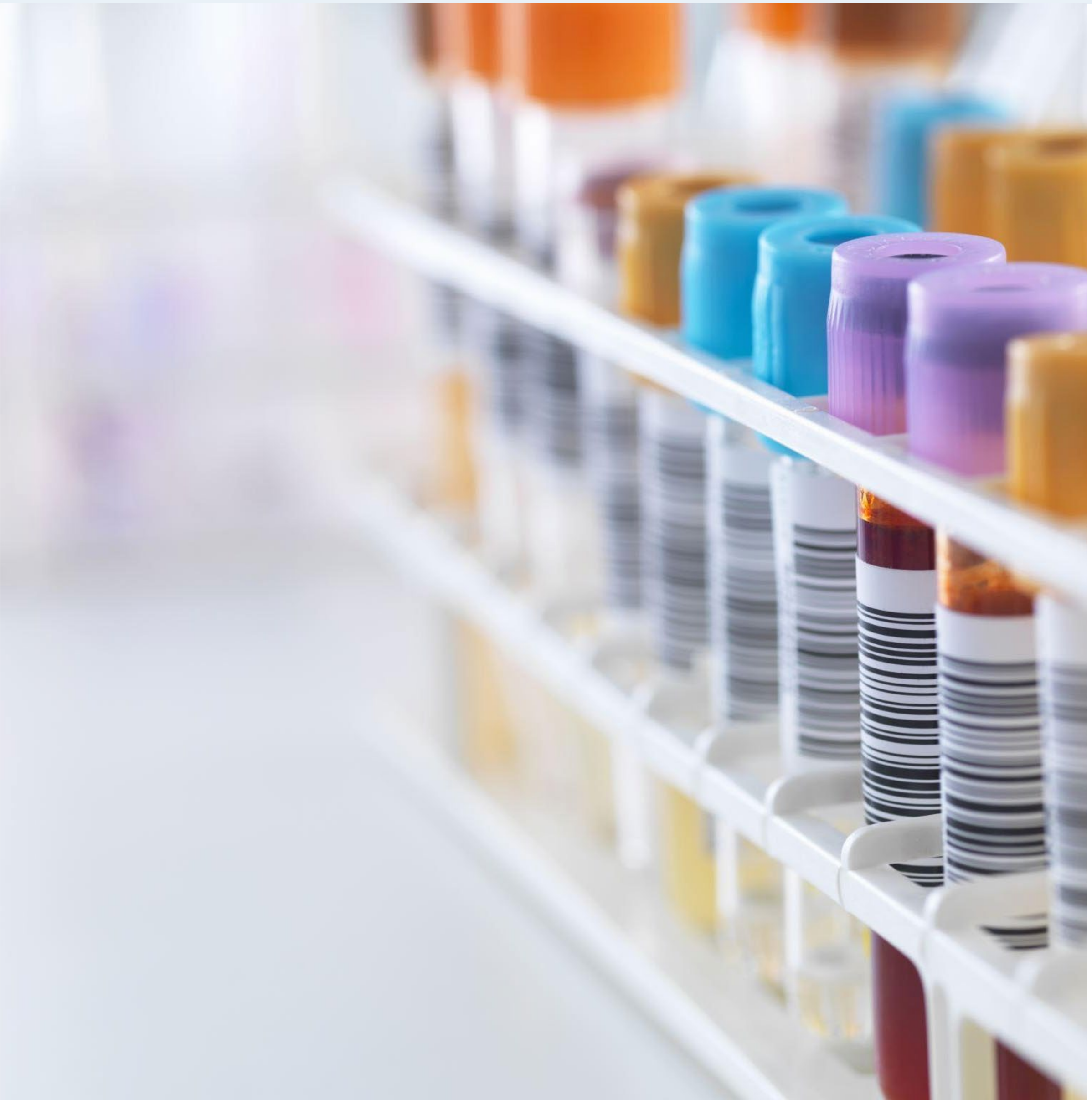
- Fructose uniquely increases uric acid production
  - Fructose ▯ rapid hepatic phosphorylation ▯ ATP depletion▯ AMP degradation▯ Uric acid generation
- Consequences:
  - Mitochondrial oxidative stress
  - Increased hepatic fat accumulation
  - Impaired nitric oxide production
  - Endothelial dysfunction
- High fructose intake → hyperuricemia → hypertension & fatty liver[7]

Connection Between Uric Acid & Insulin Resistance



- Elevated uric acid:
  - Reduces nitric oxide availability
  - Promotes endothelial dysfunction
  - Activates inflammatory pathways
  - Correlates with visceral adiposity
- Uric acid can rise **before** fasting glucose and A1c. "High-normal" may still signal metabolic dysfunction.
- Practical Ranges (Fasting)
  - Conventional upper limit:
    - ~7.0 mg/dL (men)
    - ~6.0 mg/dL (women)
  - Functional consideration:
    - 5.5–6.0 mg/dL → consider metabolic risk
    - 6.5 mg/dL → strong suspicion of metabolic stress

Clinical Application: Uric Acid



- When to consider running:
  - Resistant hypertension
  - Central adiposity
  - Elevated triglycerides
  - Suspected fatty liver
  - High fructose intake history

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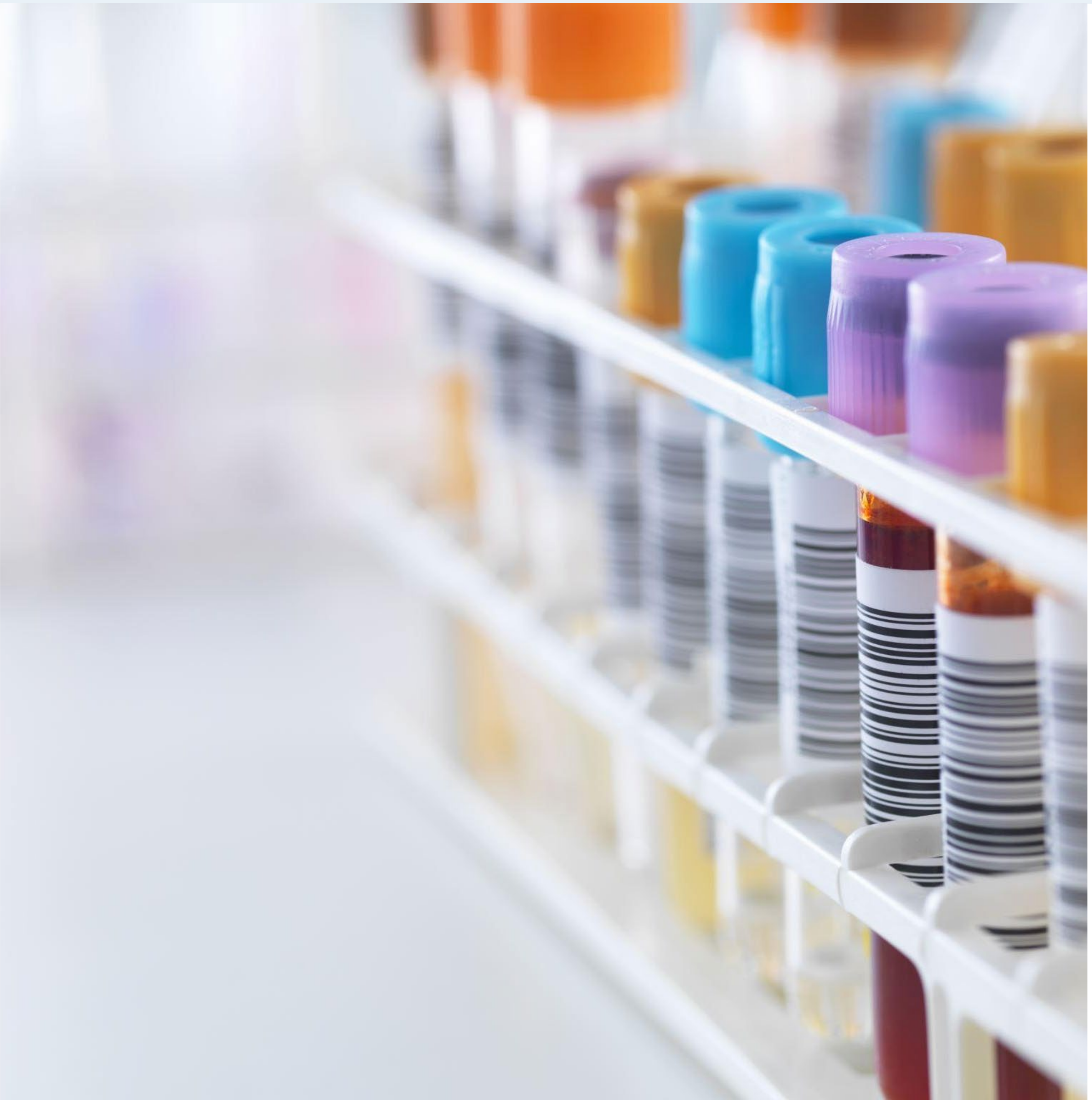
Clinical Application: Uric Acid



- Dietary:
  - Reduce added fructose (especially liquid sources)
  - Reduce ultra -processed intake
  - Moderate alcohol (especially beer)
  - Increase fiber intake
- Lifestyle:
  - Improve insulin sensitivity
  - Increase physical activity
  - Improve sleep
- Consider:
  - Vitamin C (shown to reduce uric acid modestly), tart cherry juice
  - Weight loss if indicated

Cholesterol vs. Lipoproteins: The Foundational Distinction

- Cholesterol is a molecule that helps make hormones and build cell membranes
- Because cholesterol cannot travel freely in blood, it is packaged into lipoproteins:
  - LDL → delivers cholesterol to tissues
  - HDL → participates in reverse transport
  - VLDL/IDL → triglyceride-rich precursor particles
- LDL-C measures how much cholesterol is inside LDL particles.
- However, atherosclerosis risk correlates more strongly with atherogenic particle number than with cholesterol content alone, so we need better markers

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ApoB: A Direct Measure of Atherogenic Particle Number

- Only some lipoproteins are atherogenic
- Every atherogenic lipoprotein particle carries one ApoB100 molecule
    - VLDL
    - LDL
    - Lp(a)
- Because there is one ApoB per particle, ApoB ≈ total number of atherogenic particles
- Atherosclerosis risk tracks with atherogenic particle number

Why LDL-C Isn't Enough

- LDL-C measures cholesterol mass.
- ApoB measures atherogenic particle count.
- Two patients can have identical LDL-C, but:
  - Patient A → fewer cholesterol-rich particles
  - Patient B → many cholesterol-poor particles
- Patient B has higher ApoB and higher risk of atherosclerosis
- Higher ApoB increases:
  - Arterial entry events
  - Retention probability
  - Cumulative plaque burden
- LDL-C can underestimate risk when particles are small and numerous

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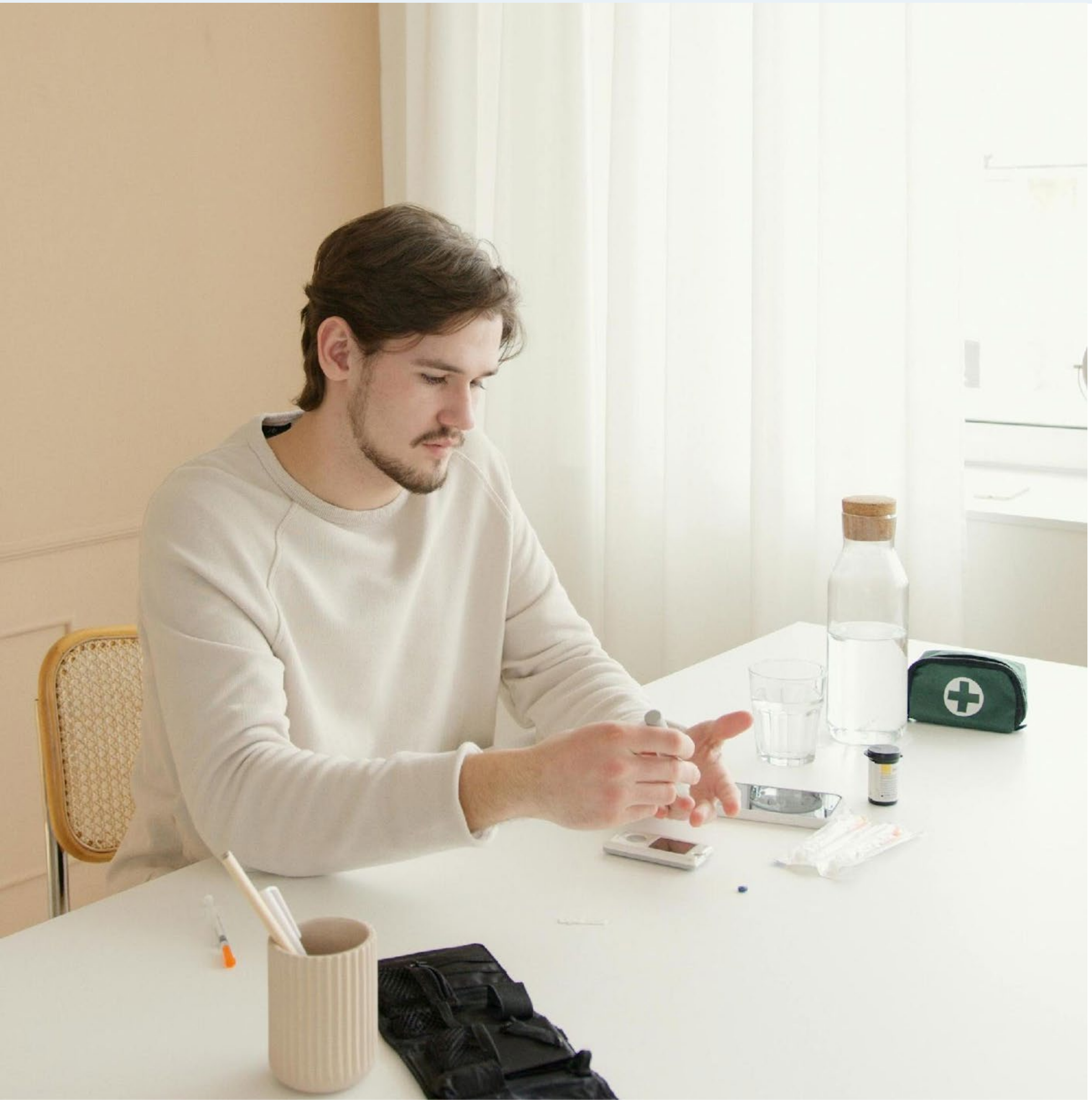
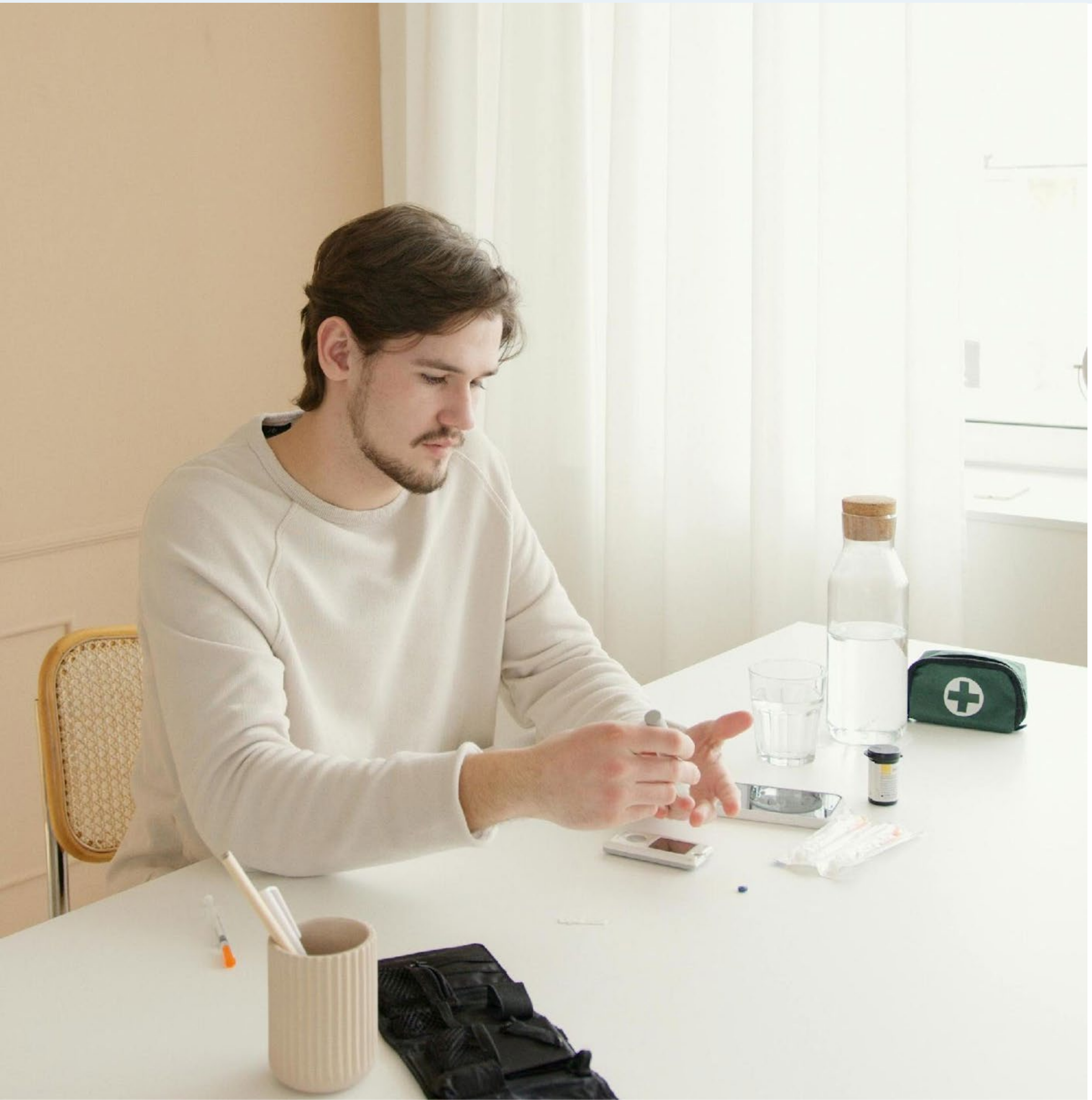
What Drives Elevated ApoB?



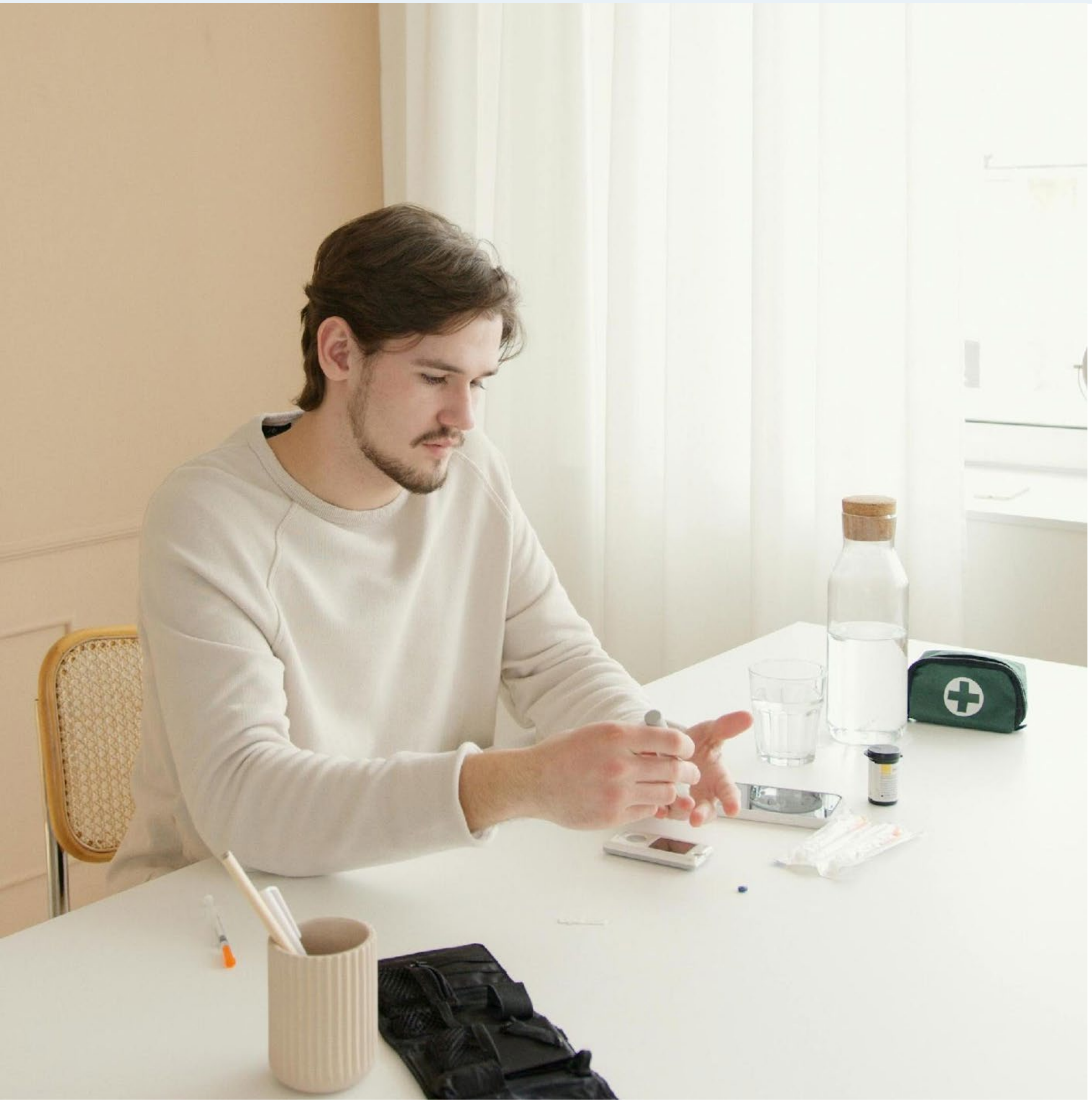
- Elevated ApoB reflects [8]:
  - Hepatic overproduction of VLDL
  - Insulin resistance
  - Hypertriglyceridemia
  - Genetic LDL receptor dysfunction
  - Elevated Lp(a)
- Insulin resistance increases VLDL production → increases ApoB → increases LDL particle burden

Practical ApoB Guidelines



- Primary prevention targets (general guidance):
  - < 80 mg/dL → favorable
  - 80–90 mg/dL → moderate risk
  - > 90 mg/dL → elevated risk
  - > 100 mg/dL → high risk
- Lower targets may be appropriate in:
  - Diabetes
  - Established ASCVD
- Interpret in context:
  - Family history
  - hs-CRP
  - Lp(a)
  - Triglycerides

Clinical Application: ApoB



- If ApoB is elevated, shift focus to:
  - Insulin sensitivity
  - Hepatic triglyceride production
  - Soluble fiber intake
  - Omega -3 fatty acids
  - Physical activity
  - Weight reduction if indicated

Lp(a): The Genetic Risk Amplifier (and Why It's Different)

- Lp(a) is a largely **genetic**, **ApoB-containing**, causal **risk factor** for ASCVD that also has **pro-inflammatory** and **pro-thrombotic** properties, and is strongly linked to calcific aortic valve stenosis[9]
- Lp(a) is an LDL-like particle with apo(a) attached to ApoB100
- Levels are largely genetically determined (LPA gene; minimal lifestyle impact)
- Elevated Lp(a) is an independent, causal risk factor for:
  - ASCVD (MI, stroke)
  - Calcific aortic valve stenosis

What makes Lp(a) High Risk?

- Lp(a) contributes to risk via:
  - Atherogenicity (it is an ApoB particle → arterial wall entry/retention)
  - Inflammatory cargo (Lp(a) often carries oxidized phospholipids)
  - Thrombotic biology (apo(a) has plasminogen-like features → may promote thrombosis)

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How to Test and Interpret Lp(a)

- Measure at least once in adulthood (especially with family history / premature ASCVD)[10]
- Common “high -risk” cutpoints used in guidelines/consensus:
  - $\geq$50 mg/dL ($\approx$ $\geq$125 nmol/L, assay dependent)

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Clinical Interpretation: Lp(a)

- Lp(a) is mostly genetic; our job is to manage the *residual risk* it creates
- Because lifestyle usually won't "fix" Lp(a), the clinical play is risk mitigation:
  - Aggressively control ApoB / LDL-C and other risk factors (BP, insulin resistance, inflammation, smoking)
  - Consider cardiology collaboration for higher-risk patients
- Be aware: PCSK9 inhibitors lower Lp(a) modestly; dedicated Lp(a)-lowering drugs are in development

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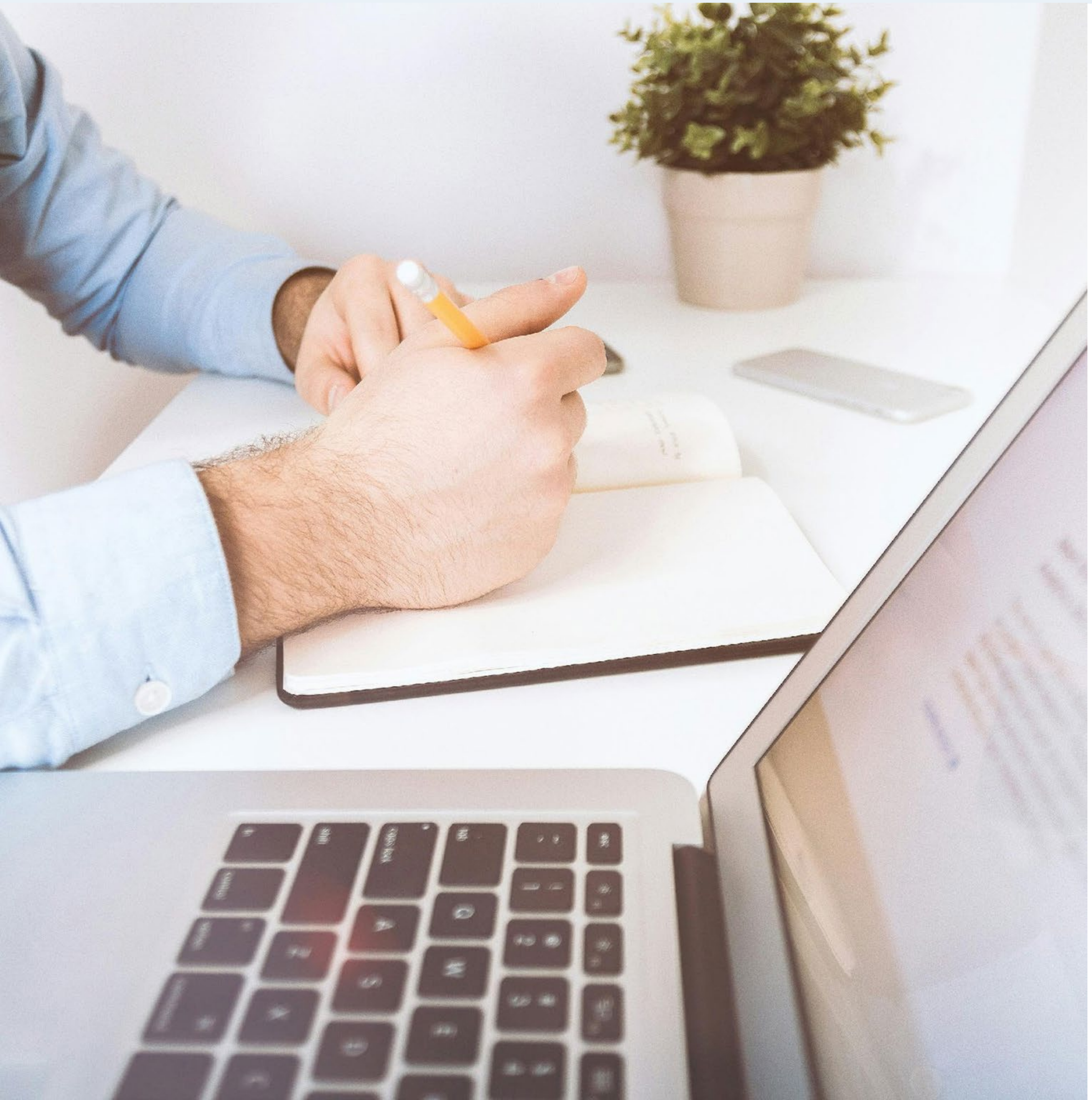
Oxidized LDL: When LDL Becomes “Damaged”



- OxLDL = LDL that has been modified by oxidative processes
- This makes it more likely to:
  - Trigger endothelial dysfunction
  - Promote foam cell formation and plaque progression
  - Reflect higher oxidative/inflammatory burden
- OxLDL is often elevated in chronic inflammatory states and is associated with higher CVD risk in those populations [11]

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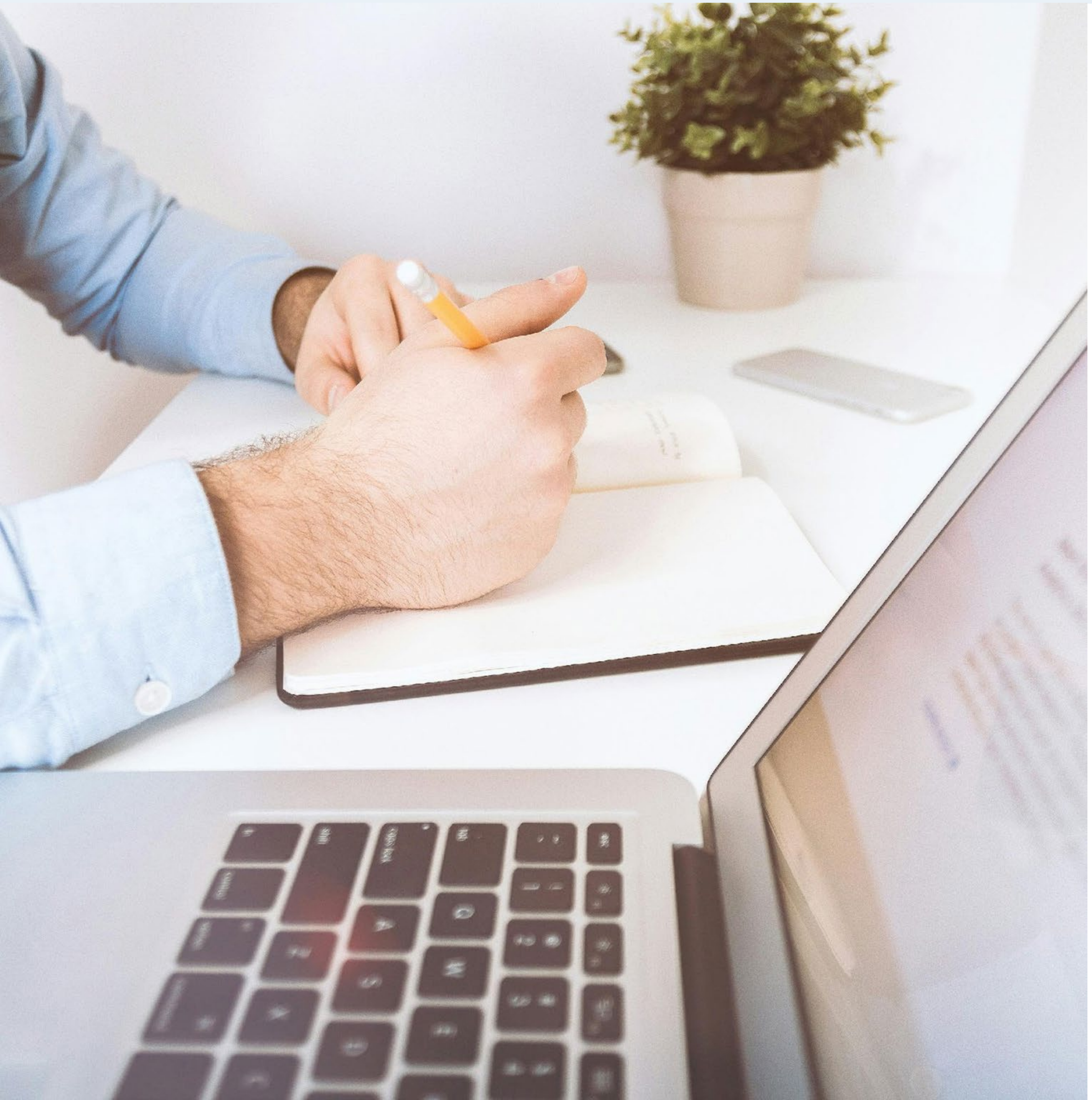
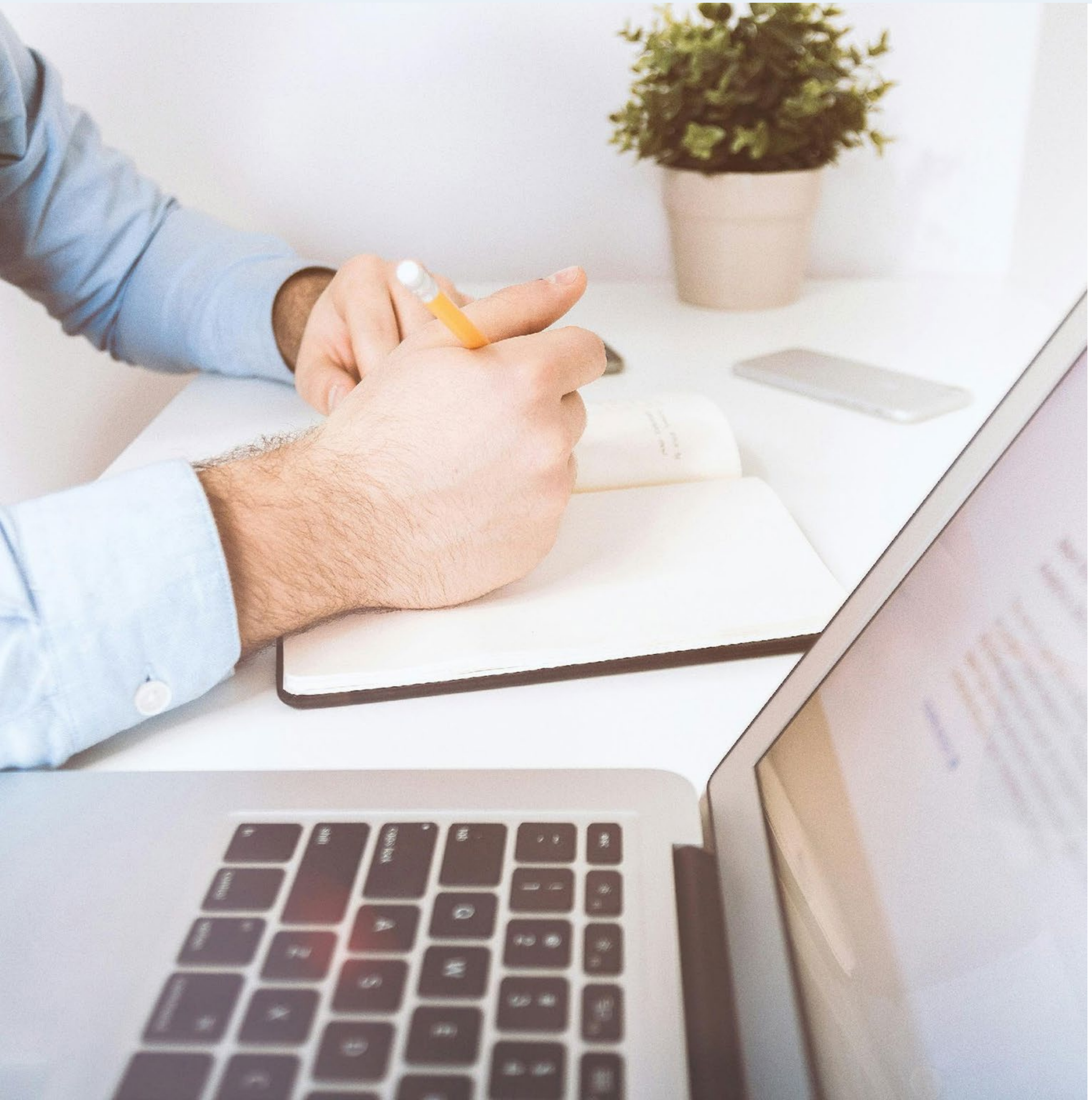
What Drives High OxLDL



- OxLDL tends to rise with:
  - Higher oxidative stress + inflammation (metabolic syndrome, smoking, poor sleep)
  - Higher postprandial oxidative load (ultra-processed foods, repeated glucose spikes)
  - Lower antioxidant/phytonutrient intake
  - Poor fat quality (low omega-3, high oxidized oils)
- OxLDL is often a “diet/lifestyle responsiveness” marker and is far more modifiable than Lp(a), so I like to focus here

Diet Strategies That Consistently Lower OxLDL



- Mediterranean -style patterns have RCT -level evidence for lowering oxLDL, especially when emphasizing extra virgin olive oil or nuts [12]
- Actionable levers:
  - Extra virgin olive oil (polyphenol -rich; swap in for refined fats)
  - Nuts most days (walnuts/almonds/pistachios; improves lipid oxidation markers)
  - Fruits + vegetables ↑ (higher intakes correlate with oxLDL reductions in dietary interventions)
  - Fiber (especially soluble): oats, beans, lentils, chia/ flax; improves postprandial biology (supports lower oxidative load)
- Avoid/ limit:
  - Repeated refined carb/ sugar spikes (postprandial oxidative stress)
  - Ultra-processed foods (lower antioxidant density + higher oxidative burden)
  - Reused/ high-heat industrial oils (oxidized lipids)

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Key Lifestyle & Behavior Strategies to Lower LDL

- Consistent exercise lowers oxLDL
- Short sleep increases oxidative stress biology; prioritize 7 –9h and treat sleep apnea when suspected
- Smoking/vaping: direct oxidative injury → oxLDL rises
- Stress recovery: chronic sympathetic tone increases oxidative signaling; build in daily downshifts

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Clinical Application: OxLDL

- Focusing on OxLDL as a “damage marker” helps clients get out of the mentality of “just lower cholesterol”
- If oxLDL is high, focus on:
  - Fat quality upgrade: EVOO + nuts + omega -3-rich fish
  - Antioxidant density: ≥6 servings colorful plants/ day
  - Glucose stability: protein + fiber at every meal; reduce liquid sugar
  - Training consistency: 150 min/ week + 2x resistance
  - Sleep triage: screen for apnea if snoring/ fatigue/ HTN

Cardiovascular Pattern Recognition

High ApoB, Normal Lp(a), Normal OxLDL

Pattern: Metabolic Overproduction

- Likely drivers:
  - Insulin resistance
  - Hepatic VLDL overproduction
  - Hypertriglyceridemia
- Primary focus:
  - Improve insulin sensitivity
  - Reduce hepatic triglyceride production
  - Weight optimization
  - Fiber + omega -3 intake

Normal ApoB, High Lp(a), Normal OxLDL

Pattern: Genetic Structural Risk

- Likely drivers:
  - LPA genotype
  - Elevated lifelong exposure
- Primary focus:
  - Aggressive ApoB optimization
  - Blood pressure control
  - Inflammation reduction
  - Risk mitigation strategy

Normal ApoB, Normal Lp(a), High OxLDL

Pattern: Oxidative Stress Dominance

- Likely drivers:
  - Poor fat quality
  - Postprandial glucose spikes
  - Low phytonutrient intake
  - Smoking / poor sleep
- Primary focus:
  - Mediterranean -style pattern
  - EVOO, nuts, plants
  - Glucose stabilization
  - Exercise + sleep

Cardiovascular Pattern Matrix

Modifiable Burden (OxLDL + ApoB) (low → high)

Genetic Risk: Lp(a) (low → high)

Low Lp(a) + High ApoB ± High OxLDL
Metabolic/lifestyle-driven particle burden

Likely drivers:

- Insulin resistance
- Hepatic VLDL overproduction
- Hypertriglyceridemia
- Central adiposity
- Ultra-processed food exposure

Primary focus:

- Improve insulin sensitivity
- Reduce refined carbohydrates
- Increase soluble fiber
- Weight reduction if indicated
- Omega-3 fatty acids
- Resistance + aerobic training

High Lp(a) + High ApoB + High OxLDL
Genetic substrate + particle burden + oxidative damage
Highest concern pattern

Likely drivers:

- LPA genotype
- Insulin resistance
- Poor fat quality
- Chronic inflammation
- Sleep deprivation / stress

Primary focus:

- Aggressive ApoB reduction
- Mediterranean-style pattern (EVOO, nuts, plants)
- Glucose stabilization
- Reduce oxidative load
- Exercise prescription
- Blood pressure optimization
- Close monitoring including cardiology referral

Low Lp(a) + Normal ApoB + Low OxLDL
Favorable cardiovascular pattern

Likely drivers:

- Adequate insulin sensitivity
- Low inflammatory load
- Good fat quality
- Adequate sleep and activity

Primary focus:

- Maintain Mediterranean-style dietary pattern
- Continue fiber + omega-3 intake
- Preserve metabolic flexibility
- Monitor over time

High Lp(a) + Normal ApoB + Low OxLDL
Genetic structural risk, well-managed modifiable factors

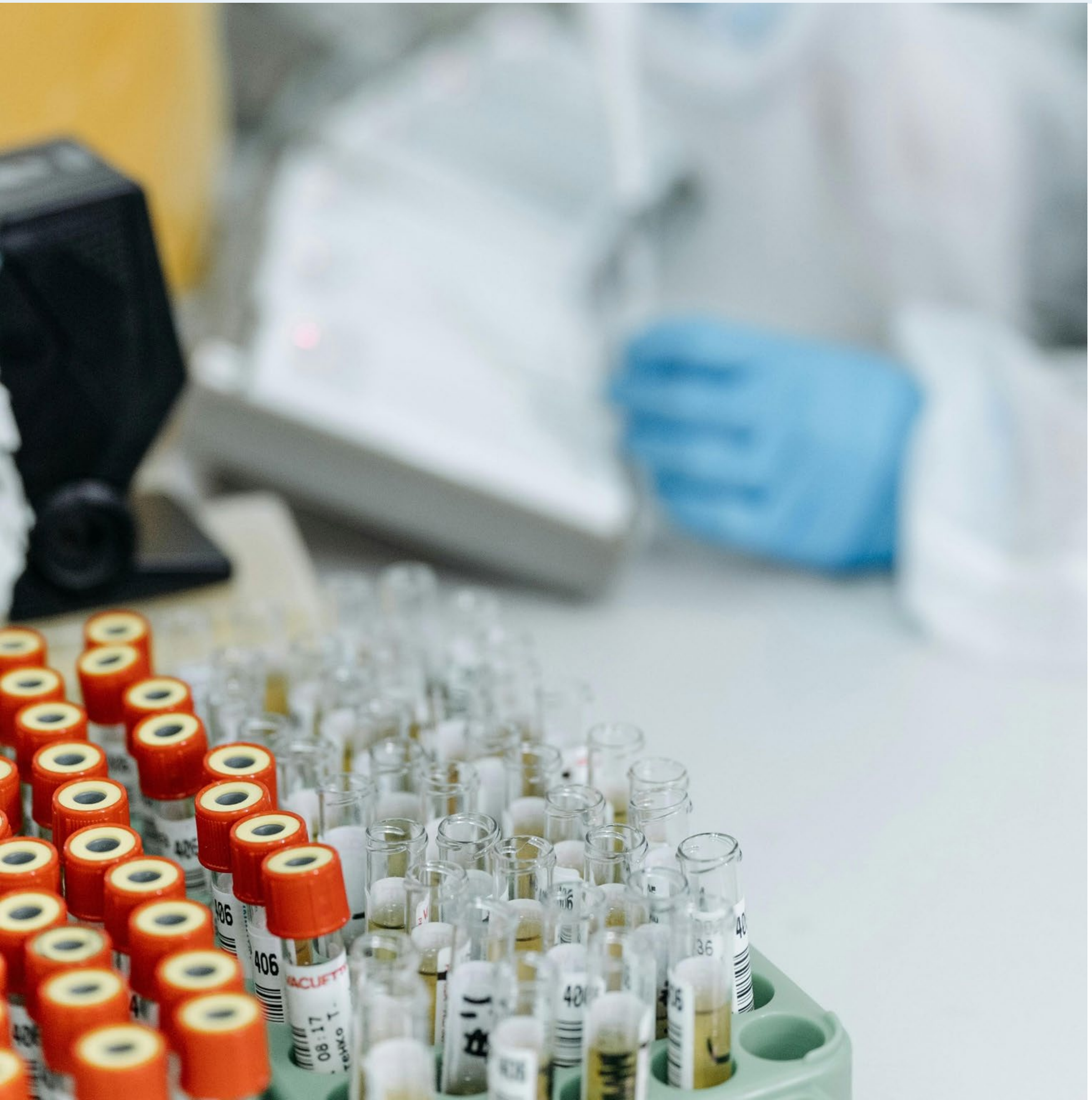
Likely drivers:

- LPA genotype
- Lifelong elevated exposure
- Possibly family history of premature ASCVD

Primary focus:

- Aggressively optimize ApoB (even if “normal”)
- Tight blood pressure control
- Glycemic stability
- Anti-inflammatory dietary pattern
- Regular exercise
- Consider cardiology collaboration if risk profile warrants

8-OHdG: A Marker of Oxidative DNA Damage



- 8-OHdG is formed when reactive oxygen species (ROS) damage guanine in DNA [13]
- It reflects:
  - Oxidative stress burden
  - DNA repair activity
  - Mitochondrial stress
  - Cumulative cellular wear
- Measured in:
  - Urine (most common)
  - Serum (less common)
- Elevated levels are associated with:
  - Cardiovascular disease
  - Neurodegenerative disease
  - Diabetes
  - Chronic fatigue states
- Distinction:
  - OxLDL = lipid oxidation
  - 8-OHdG = DNA oxidation

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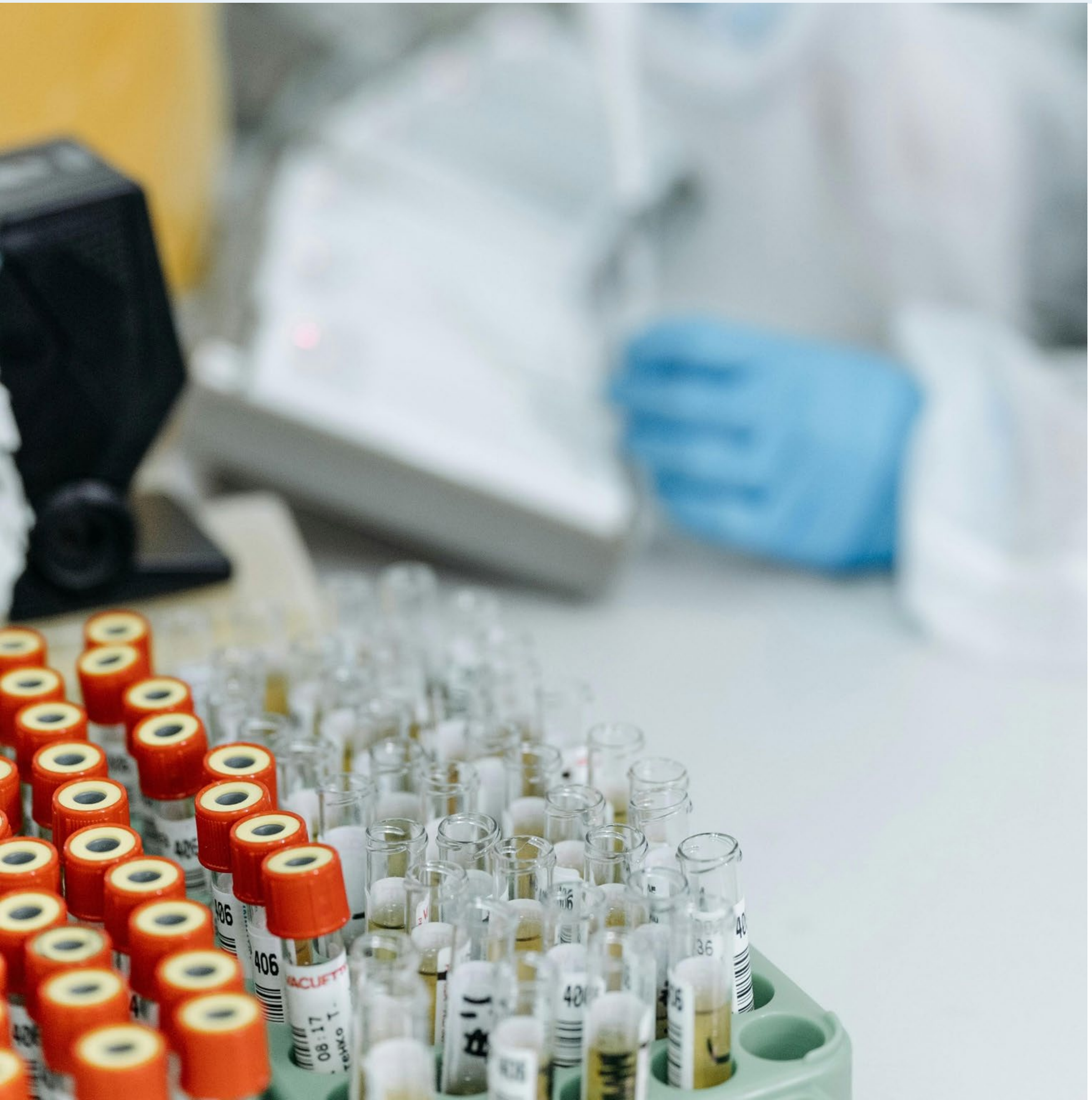
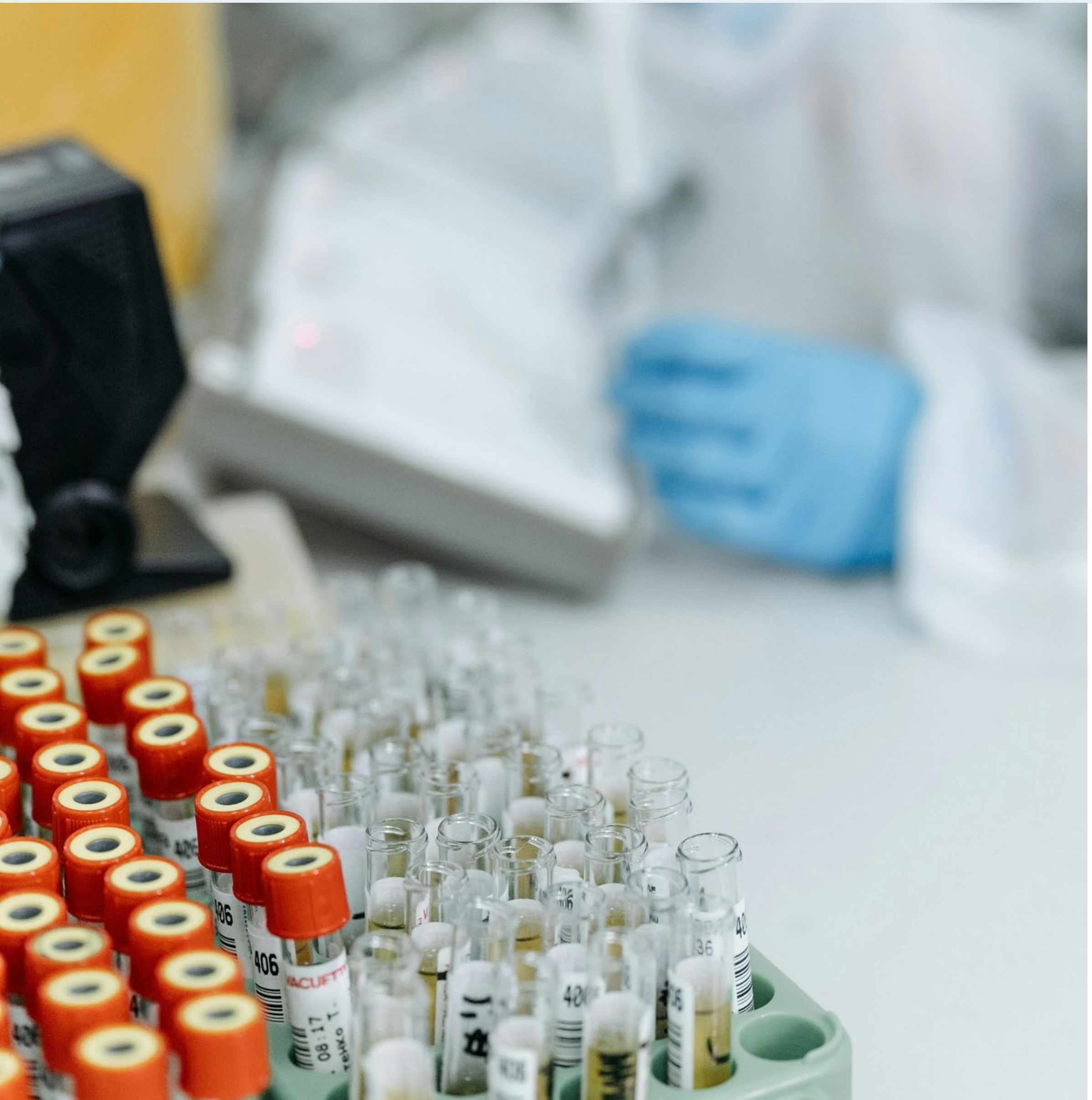
What Drives Elevated 8-OHdG?



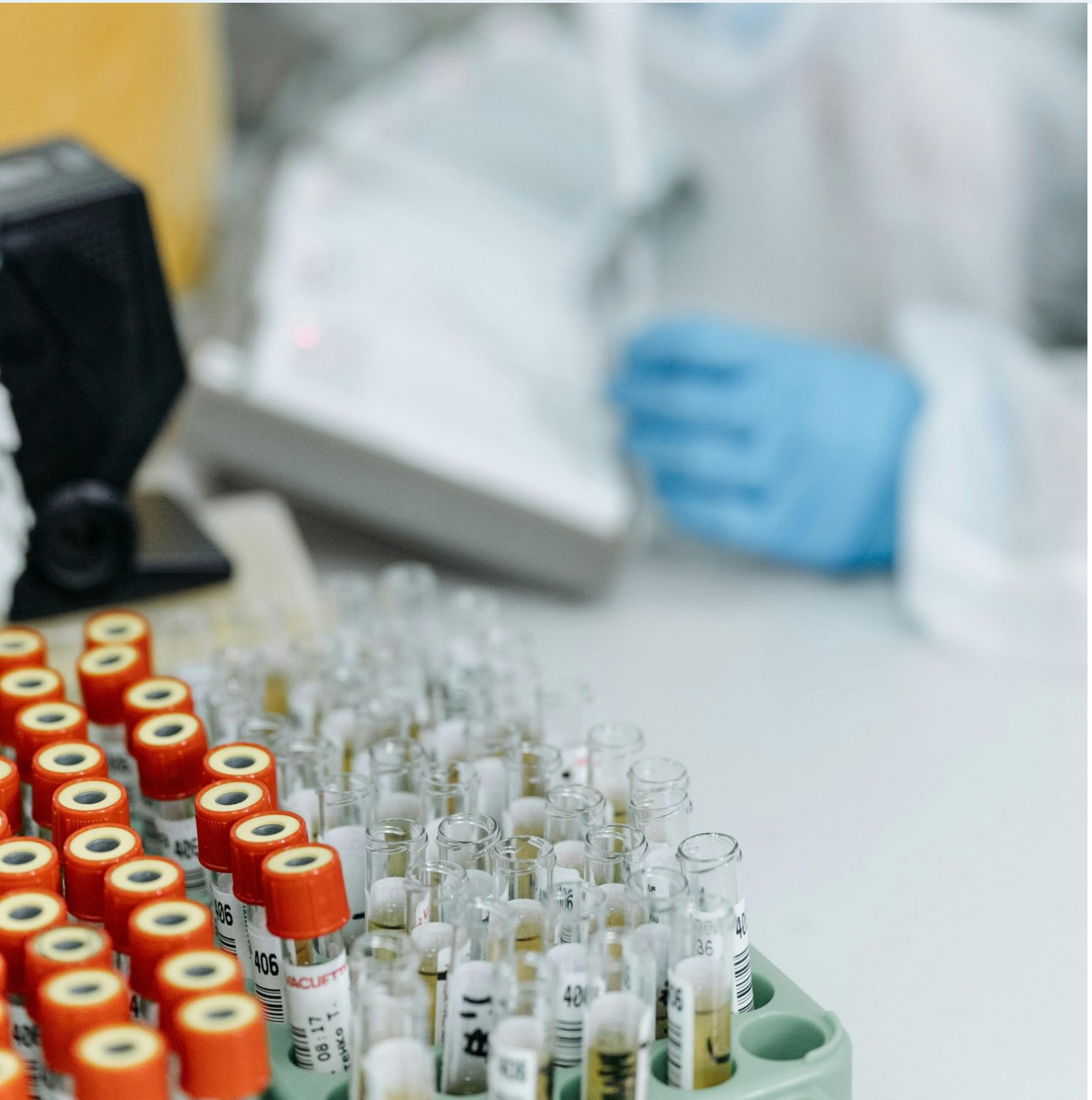
- **Metabolic Drivers**
  - Hyperglycemia
  - Insulin resistance
  - Mitochondrial overload
- **Lifestyle Drivers**
  - Smoking
  - Poor sleep
  - Overtraining
  - Chronic psychological stress
- **Environmental Drivers**
  - Air pollution
  - Heavy metals
  - Persistent organic pollutants
- **Nutritional Gaps** [14]
  - Low antioxidant intake
  - Low polyphenol intake
  - Poor omega-3 status

Clinical Interpretation: 8-OHdG



- 8-OHdG is a stress-load (or allostatic load) marker showing how much oxidative wear is occurring at the DNA level
- Patterns to consider:
  - High 8-OHdG + High OxLDL
    - Likely central adiposity, insulin resistance, borderline trigylcerides
    - Eats “healthy-ish” but lots of restaurant meals
    - Sporadic sleep and exercise
  - High 8-OHdG + Low DHEA-S
    - High-achieving, chronically stressed
    - Possibly overtraining
    - Fatigue, brain fog, menstrual irregularities
  - High 8-OHdG + Normal lipids
    - Environmental factor (smoking, air pollution, frequent travel, high occupational load)
    - Poor sleep
    - Low phytonutrient intake

Clinical Interpretation: 8 -OHdG



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    - Poor sleep
    - Low phytonutrient intake
- Reference ranges vary by lab
  - Upper quartile of range → investigate drivers
  - Persistently elevated → intervene
- Context:
  - Exercise 24–48h prior can transiently elevate
  - Acute illness elevates

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Clinical Strategy: Lowering 8 -OHdG

- Nutrition
  - Increase polyphenol -rich foods (berries, pomegranate, green tea, cocoa)
  - Mediterranean -style dietary pattern
  - Increase cruciferous vegetables
  - Adequate protein for glutathione production
  - Omega -3 fatty acids
- Lifestyle
  - Optimize sleep (7 –9h)
  - Periodize exercise (avoid chronic overreaching)
  - Stress reduction practices
  - Avoid smoking and secondhand smoke
- Environmental
  - Air filtration if urban exposure
  - Reduce ultra -processed food intake
  - Assess heavy metal exposure if indicated

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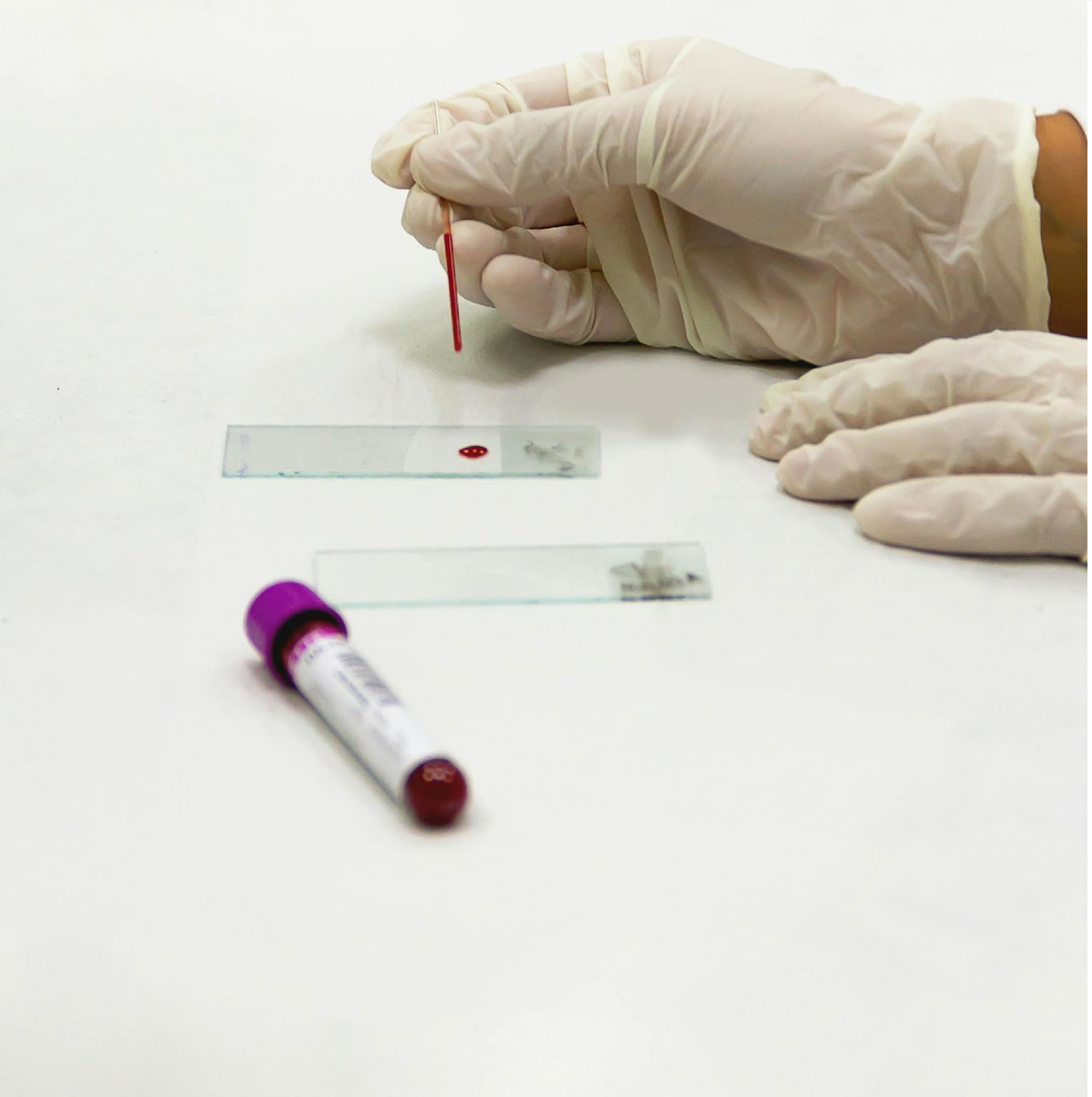
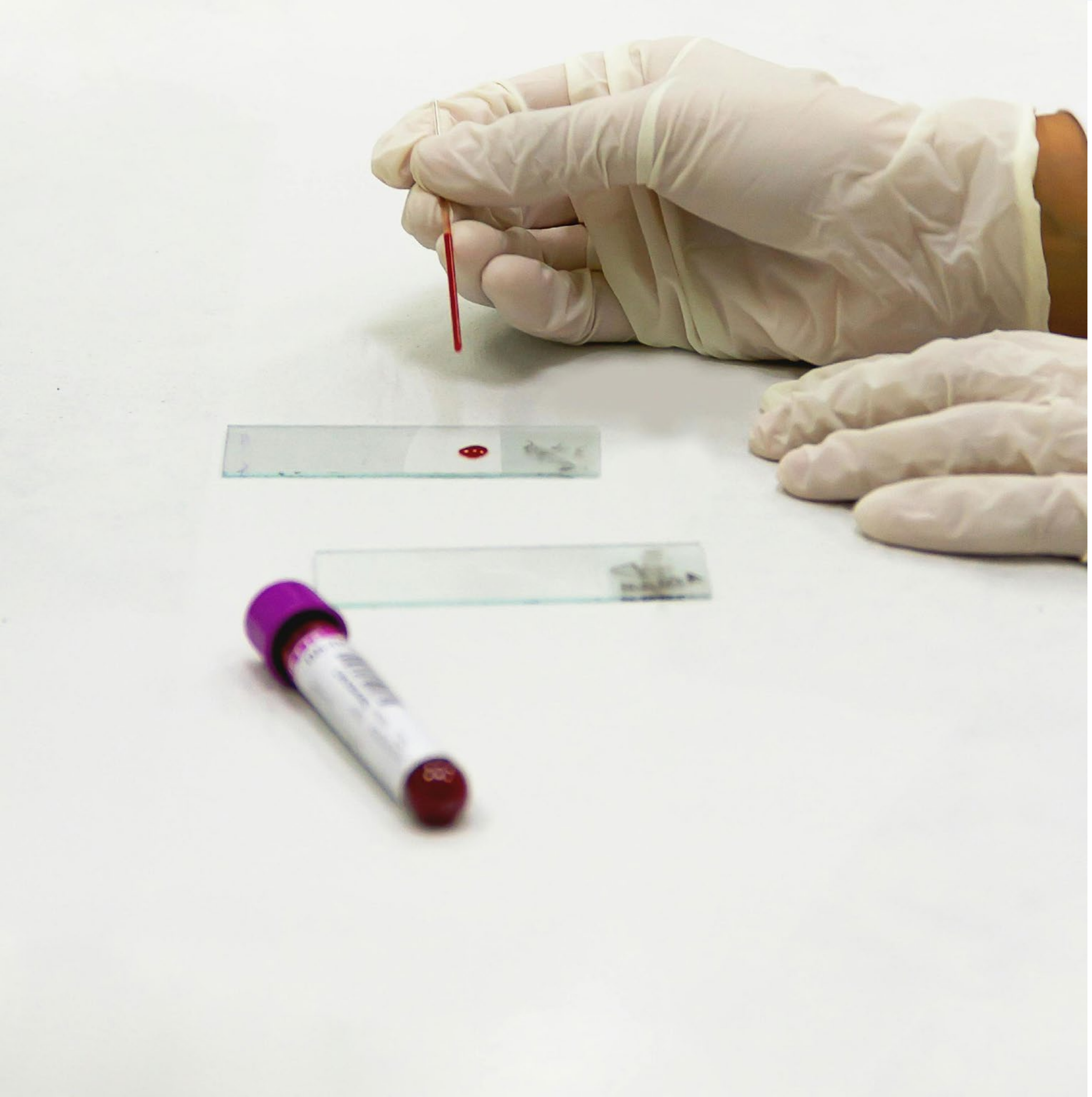
DHEA-S: A Marker of Adaptive Reserve



- DHEA-S (dehydroepiandrosterone sulfate)[15]:
  - Produced primarily by the adrenal cortex
  - Serves as a precursor to androgens and estrogens
  - Counterbalances cortisol
  - Modulates immune and inflammatory activity
- DHEA-S naturally declines with age, but a rapid decline is not inevitable
- It reflects:
  - Stress buffering capacity
  - Anabolic reserve
  - Long-term resilience

Why DHEA-S Matters Clinically



- Low DHEA-S is associated with:
  - Chronic stress exposure
  - Burnout physiology
  - Increased inflammatory tone
  - Reduced immune competence
  - Frailty and aging trajectory / catabolic dominance

Why DHEA -S Matters Clinically

High DHEA-S follows two pathologies:

- **Adaptive / Early Stress Activation:** The "high performer" phenotype
  - High output, high training volume
  - Mild sleep restriction
  - Strong drive
  - Still compensating effectively
- Often paired with:
  - Normal to elevated cortisol curve
  - Normal or mildly elevated 8 -OHdG
  - High performance but early warning signs

- **Hyperandrogenic Pathology (Especially in Women):** The "PCOS" phenotype
  - PCOS
  - Adrenal hyperandrogenism
  - Exogenous supplementation
  - Rare adrenal pathology (if very high)
- Often paired with:
  - High fasting insulin
  - High testosterone and androgens

Clinical Interpretation: DHEA-S

Pattern Recognition:

Low DHEA-S + High Cortisol → Catabolic dominance

Low DHEA-S + High 8-OHdG → Reduced repair capacity

Low DHEA-S + Low Leptin → Energy deficiency phenotype

First ask:

- Is caloric intake adequate?
- Is training load excessive?
- Is sleep fragmented?
- Is stress chronic and unbuffered?

Primary focus:

- Restore energy availability
- Periodize training
- Improve sleep quality
- Stress modulation practices
- Adequate protein intake

Then, consider DHEA supplementation if in your scope.

ApoE: A Lipid Transport & Brain Risk Gene

- Apolipoprotein E (ApoE) is [16]:
  - A lipid transport protein
  - Expressed in liver and brain
  - Involved in cholesterol trafficking and neuronal repair
- Three common isoforms:
  - ε2
  - ε3
  - ε4
- Each person inherits two copies.
- ApoE influences:
  - Lipid metabolism
  - Inflammatory signaling
  - Alzheimer's disease risk
  - Cardiovascular risk (modestly)

ApoE Genotypes: What We Know

- ApoE3/E3 (Most Common)
  - Neutral baseline risk
- ApoE2
  - Often lower LDL -C
  - May increase triglycerides in some
  - Slightly protective for Alzheimer’s
- ApoE4
  - Higher lifetime Alzheimer’s risk
  - Increased sensitivity to metabolic stress
  - Often higher LDL -C response to saturated fat
  - Increased neuroinflammatory response
  - Important: ApoE4 is a risk factor, not a destiny marker.

ApoE4: Mechanistic Insights

- ApoE4 is associated with:
  - Reduced lipid transport efficiency in brain
  - Increased oxidative stress
  - Increased neuroinflammation
  - Impaired amyloid clearance
- Metabolic dysfunction amplifies this risk
- Insulin resistance + ApoE4 = higher cognitive vulnerability [17]

Clinical Application: ApoE

- When ApoE4 is present, our primary focus is to:
  - Optimize insulin sensitivity
  - Avoid chronic hyperglycemia
  - Emphasize Mediterranean -style dietary pattern
  - Increase omega -3 intake (especially DHA)
  - Exercise consistently (especially aerobic)
  - Prioritize sleep

MTHFR: What It Is (and What It Isn't)

- MTHFR encodes an enzyme that helps convert folate into 5 -MTHF, supporting methylation (including homocysteine → methionine)
- Two common variants:
  - C677T (bigger impact on enzyme activity, especially TT)
  - A1298C (usually milder impact)
- Key clinical point: common MTHFR variants are not a diagnosis and do not require panic
- If you want a *clinically actionable* marker, focus on fasting homocysteine (plus B-vitamin status and potentially MMA) more than genotype

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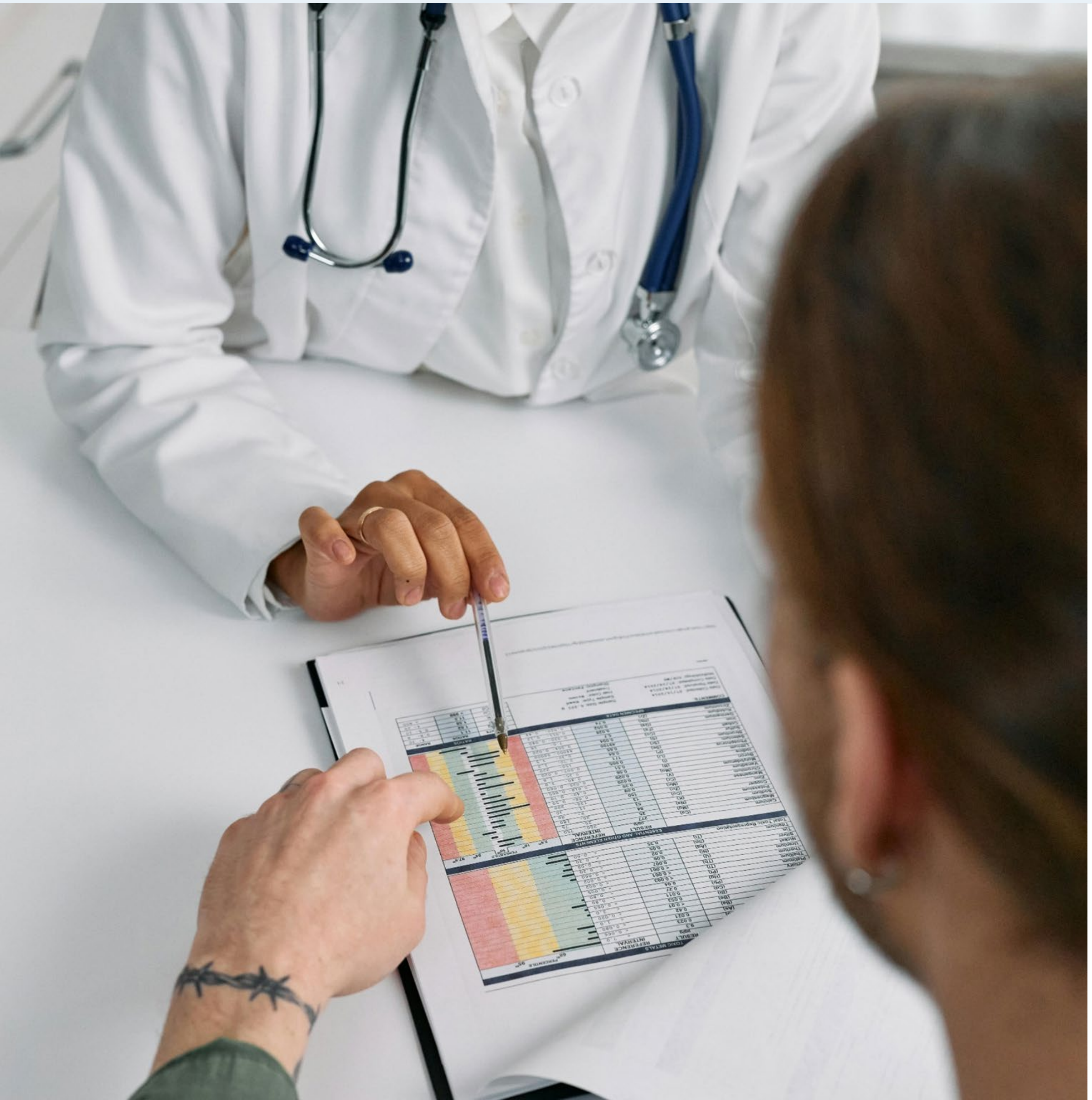
Important Clinician’s Rule: Treat the Phenotype, Not the SNP



- Do NOT tell clients “everything is harder with MTHFR.”
- Most of the time, we can improve phenotype by focusing on:
  - Inadequate folate/B -vitamin intake or absorption
  - Higher demand (pregnancy, stress, inflammation)
  - Kidney/thyroid issues, meds, alcohol, smoking
  - Overall cardiometabolic dysfunction

Important Clinician's Rule: Treat the Phenotype, Not the SNP

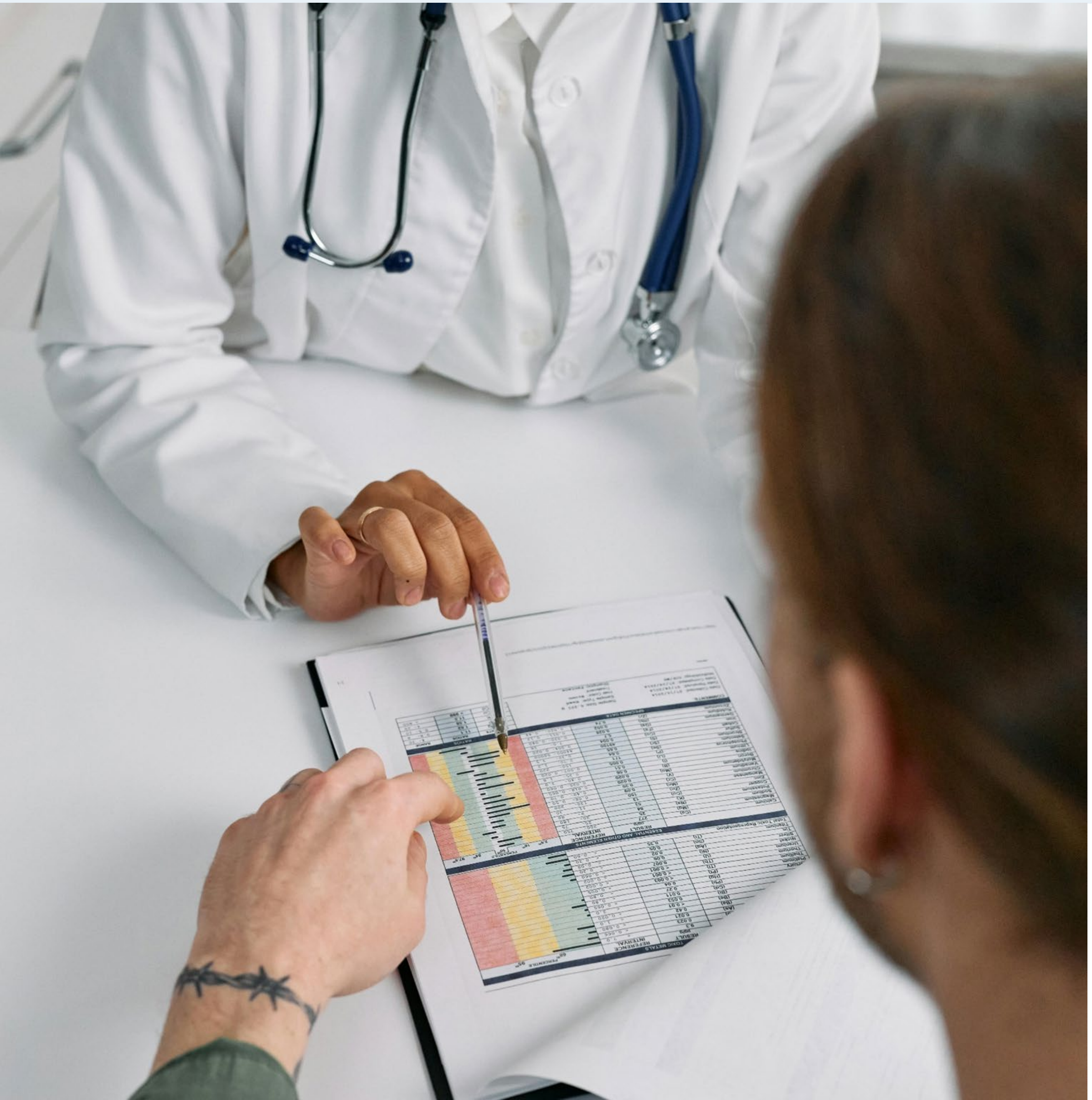
Step 1: Measure fasting homocysteine (and basics):

- B12 (± MMA), folate (prefer RBC folate if available), optional B6 and riboflavin
- Consider adding creatinine/eGFR, TSH, hs-CRP

Step 2: If homocysteine is elevated (I consider >10 elevated):

- Folate repletion
  - Food-first: leafy greens, legumes, asparagus, broccoli
  - Consider 5-MTHF (especially if folate intake is low or conversion is suspected to be limited). Supplemental L-MTHF lowers total homocysteine more than folic acid in most
- B12 adequacy
  - Ensure B12 is sufficient before high-dose folate (avoid "masking" issues)
- B6 support (transsulfuration pathway)
- Riboflavin (B2) (MTHFR is a flavin-dependent enzyme)

Emerging Data on Riboflavin, MTHFR, and Blood Pressure



- If genotype shows C677T TT and BP is elevated or borderline:
  - Riboflavin supplementation has been shown to lower blood pressure in hypertensive patients with MTHFR 677TT [18]
- Practical clinician takeaway:
  - 677TT + hypertension is one of the few places where genotype can clearly guide a nutrition intervention

Beyond Folate/B12

Additional interventions that help methylation demand:

Diet & lifestyle

- Protein adequacy (methionine cycle substrate balance)
- Choline/betaine -rich foods (eggs, seafood, beets) support an alternate remethylation route (BHMT)
- Reduce alcohol, improve sleep, manage stress (all raise demand / worsen processing)
- Address gut absorption issues if suspected

Clinical guardrails

- Avoid mega -dosing methyl donors without a phenotype reason (anxiety/insomnia can worsen in some)
- Recheck homocysteine trend after 8 –12 weeks of intervention

Overview of The 10 Biomarkers That Elevate Your Practice

Metabolic Signaling

- Leptin
- Adiponectin
- Uric Acid

Is energy sensing and insulin signaling working?

Hidden Cardiovascular Risk

- ApoB
- Lipoprotein(a)
- Oxidized LDL

How many particles, how damaged, and how much genetic amplification?

Resilience & Longevity Signals

- 8-OHdG
- DHEA-S
- ApoE Genotype
- MTHFR Variants

How well is this person adapting and repairing?

From Marker to Mechanism to Intervention

Marker	What it Reflects	What We Can Adjust
Leptin	Energy sufficiency & satiety signaling	Restriction vs refeeding; inflammatory load
Adiponectin	Insulin sensitivity & metabolic flexibility	Fiber, omegas, exercise, visceral fat reduction
Uric acid	Fructose load & mitochondrial stress	Reduce added sugars, improve insulin sensitivity
ApoB	Atherogenic particle number	Insulin sensitivity, fat quality
Lp(a)	Genetic structural risk	Aggressive ApoB optimization, BP control
OxLDL	Oxidative lipid damage	Fat quality, antioxidants, sleep
8-OHdG	Oxidative DNA damage	Polyphenols, sleep, stress load
DHEA-S	Adaptive reserve	Recovery, caloric adequacy, training load
ApoE	Brain lipid transport & inflammatory response	Metabolic health, omega -3, aerobic exercise
MTHFR	Methylation efficiency	Folate, B12, B6, riboflavin, choline

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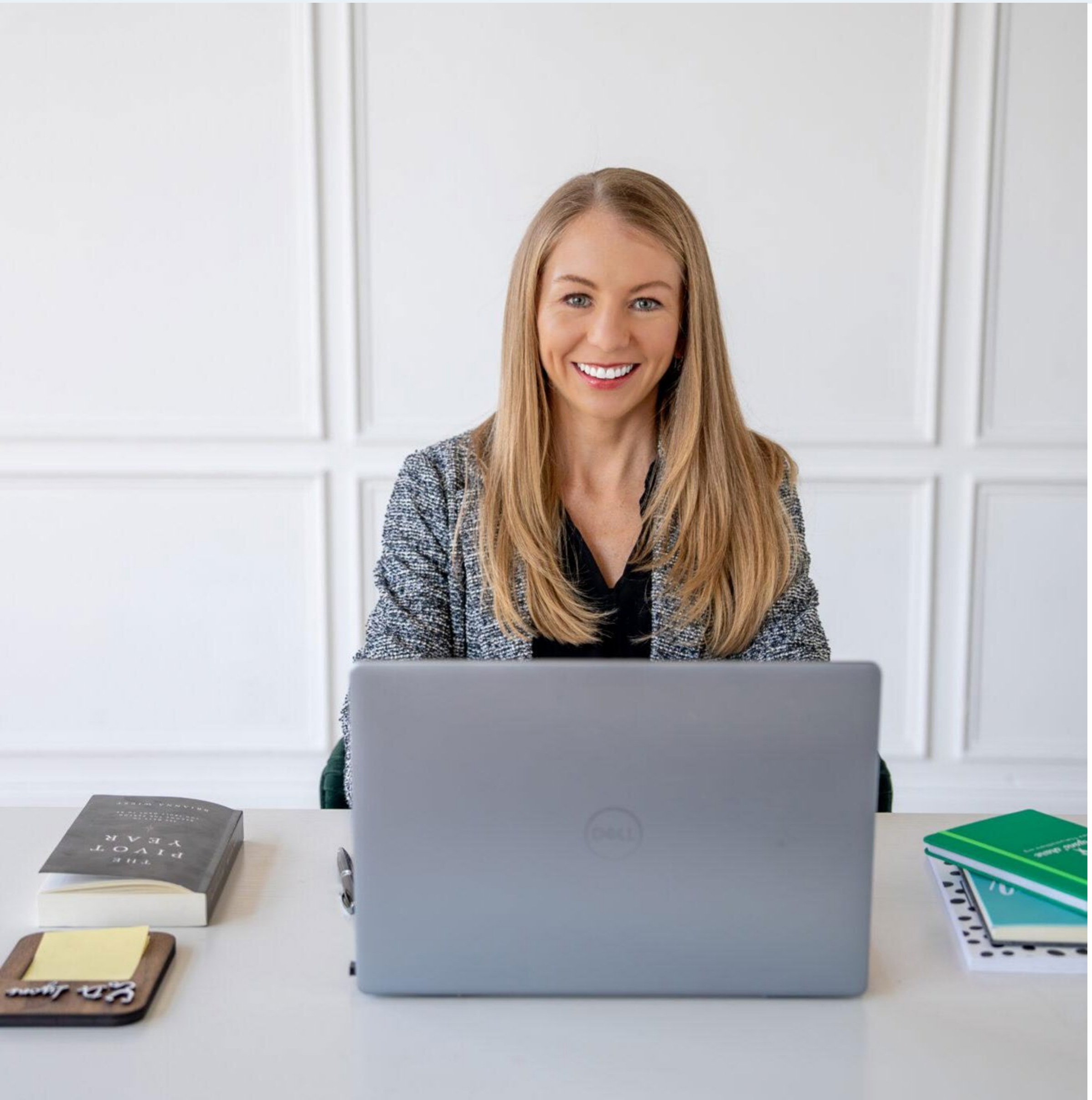
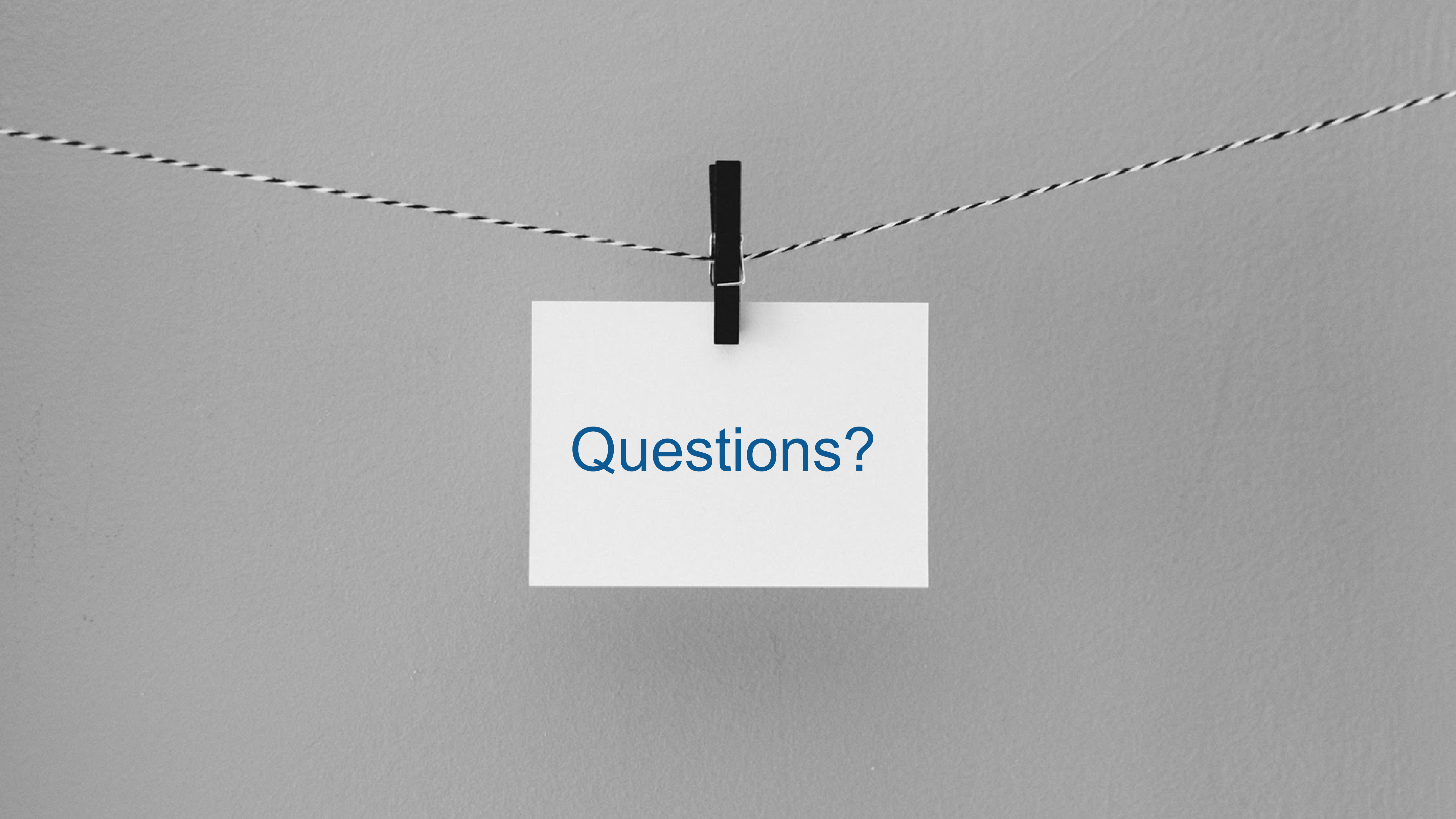
The Clinical Algorithm

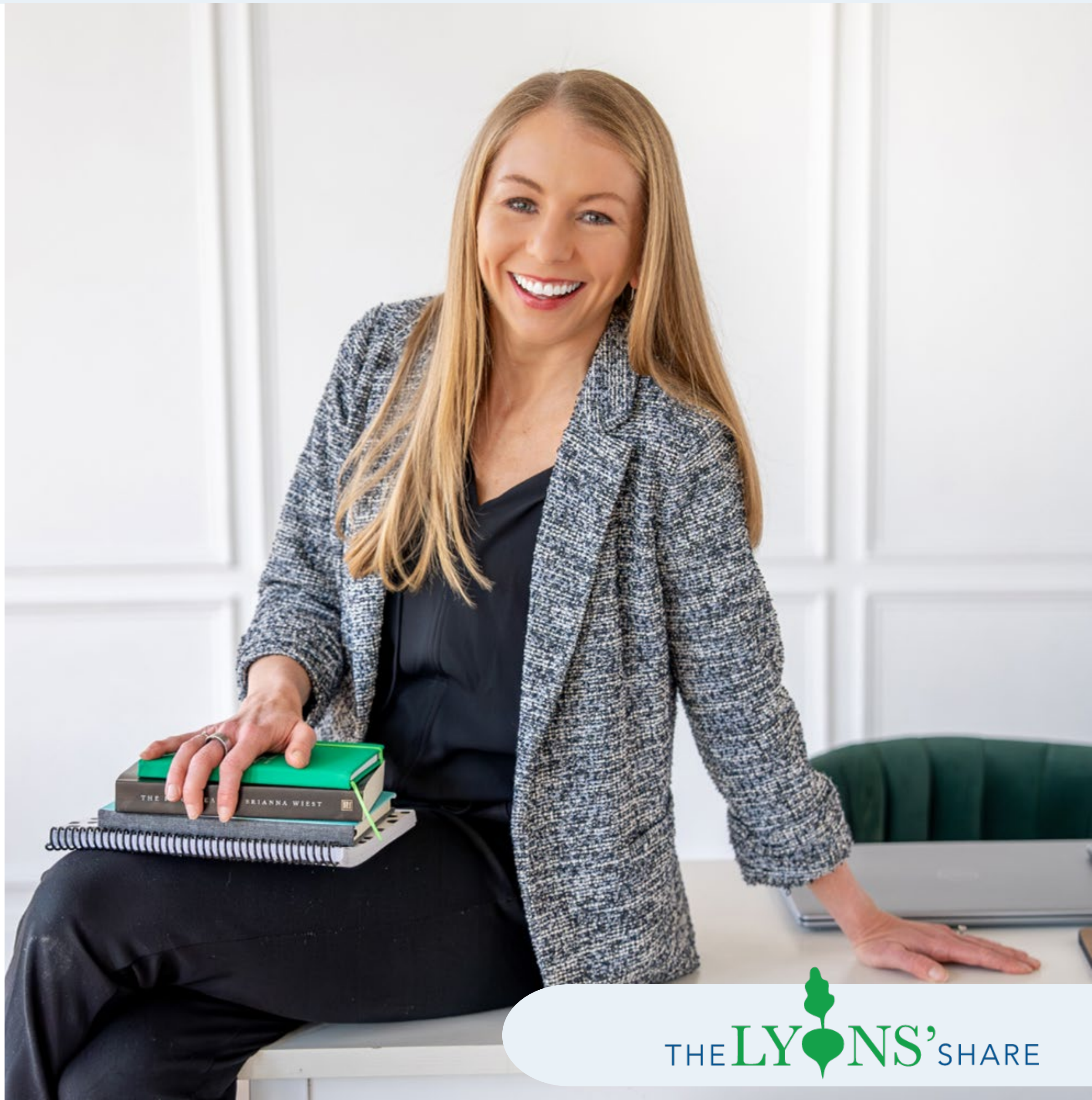


- When a client is stuck:
  - Confirm basics (sleep, protein, fiber, movement) FIRST!
  - Identify the dominant driver:
    - Energy dysregulation?
    - Particle burden?
    - Oxidative load?
    - Low resilience?
  - Target upstream physiology
  - Re-test strategically


Questions?

If I can help further…

- www.TheLyonsShare.org
- @thelyonsshare Instagram
- Wellness Your Way with Dr. Megan Lyons podcast



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