CME AUDIENCE HANDOUT · INTEGRATIVE MEDICAL ACADEMY

# Live Long & Prosper

*The Top 10 Biomarkers That Matter*

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> *A companion reference document — clinical evidence, Monday-morning applications, and full AMA-format citations for every biomarker covered in tonight's presentation.*

# Contents

CME ACTIVITY

# Learning Objectives

At the conclusion of this presentation, participants will be able to:

**01** Define a biomarker and explain its role in predicting disease trajectory.

**02** Identify the top 10 biomarkers that predict disease trajectory and longevity risk.

**03** Compare traditional biomarkers versus emerging evidence-based alternatives.

**04** Apply biomarker data clinically — articulate what changes Monday morning.

**05** Redefine what a truly healthy patient looks like using objective biomarker criteria.

**HOW TO USE THIS HANDOUT**

Each biomarker is presented on a single page with its clinical evidence, a Monday-morning application, and full AMA-format references. The countdown (#10 → #1) mirrors the order of presentation and builds from downstream structural markers toward the upstream origin.

FRAMING

# Modern Medicine's Fatal Flaw

> "*We built a system that waits for disease to appear… then tries to manage it.*"

Modern medicine is structured around the diagnosis of disease after damage has been done — not the prediction of disease while it is still reversible. A1C is diagnosed after β-cell loss. LDL-C is measured after plaque has formed. Creatinine rises only after nephrons have been lost. BMI categorizes mass, not biology.

The standard of care was designed to *catch* disease, not to *prevent* it. Those are two different jobs. The biomarkers that follow sit closer to the origin of disease than what is traditionally ordered — revealing risk on a 10–20 year upstream runway.

## UPSTREAM VS. DOWNSTREAM

| DOWNSTREAM (TRADITIONAL) | VS | UPSTREAM (EVIDENCE-BASED) |
|---|---|---|
| A1C — rises only after β-cell compensation fails | *vs.* | **Fasting Insulin — 10–20 years earlier** |
| BMI — mass divided by height, no biology | *vs.* | **Waist-to-Hip Ratio — where fat actually lives** |
| Creatinine — confounded by muscle mass | *vs.* | **Cystatin C — cleaner GFR signal, earlier** |
| LDL-C — estimates cholesterol content | *vs.* | **ApoB — counts atherogenic particles** |

**TONIGHT'S FRAME**

**We work upstream.** The goal is not to replace standard labs — it is to add the measurements that reveal risk *before* the standard labs catch up.

# 10 LEVEL 03 · STRUCTURAL RISK

# ApoB — *Total Atherogenic Particle Burden*

> "*ApoB counts the bullets. LDL-C only measures the caliber.*"

## CLINICAL EVIDENCE

- **Mechanism** — every atherogenic particle (LDL, VLDL, IDL, Lp(a)) carries exactly one ApoB molecule. ApoB provides a direct particle count; LDL-C only estimates cholesterol content.
- **Richardson 2021** — Mendelian randomization: genetically higher ApoB → shortened lifespan (~1–2 years lost per SD increase), independent of LDL when modeled together.
- **Johannesen 2024 (JACC)** — Excess ApoB particles linked to cardiovascular events and all-cause mortality, even when traditional lipids appear acceptable.
- **Wilkins 2016 (JACC)** — Discordance between ApoB and LDL-C predicts coronary artery calcification — revealing hidden risk when LDL-C appears "normal."
- **Marston 2022 (JAMA Cardiol)** — MI risk is driven by ApoB particle number, not cholesterol content; LDL-C misses risk when particle count is high.
- **Martin 2024 (Commun Biol)** — ApoB causally reduces healthspan and carries an Alzheimer's signal; head-to-head, ApoB remains significant while LDL drops out.
- **Soffer 2024 NLA Consensus** — ApoB formally endorsed as the most accurate cardiovascular risk biomarker in clinical practice.
- **Sniderman 2011 (meta-analysis)** — Foundational work: ApoB is the strongest predictor of CV risk among standard lipid markers.

### MONDAY MORNING

Add ApoB to every baseline lipid panel. When LDL-C is "normal" but ApoB is elevated, that is discordance — treat the particle burden, not the cholesterol number. Target ApoB < 80 mg/dL for primary prevention; < 60 mg/dL for secondary prevention.

## REFERENCES


1. Richardson TG, Sanderson E, Palmer TM, et al. Effects of apolipoprotein B on lifespan and risks of major diseases including type 2 diabetes: a Mendelian randomisation analysis using outcomes in first-degree relatives. *EBioMedicine.* 2021;64:103186.
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LEVEL 03 · STRUCTURAL RISK

# 9 Waist-to-Hip Ratio — *Where Fat Lives Matters*

> "*BMI fades when real risk shows up. WHR is where biology lives.*"

## CLINICAL EVIDENCE

- **Mechanism** — BMI is a ratio of mass to height with no biological information. WHR reflects fat distribution. Central (visceral) fat is metabolically active, drives inflammation and insulin resistance, and deposits ectopically into liver, pancreas, and heart.
- **Jayedi 2020 (BMJ)** — Central fatness shows a direct, linear mortality association independent of BMI.
- **Czernichow 2011 (Obes Rev)** — Abdominal adiposity predicts CV mortality; BMI loses statistical significance after adjustment for WHR.
- **Khan 2023 (JAMA Netw Open)** — WHR demonstrates the strongest all-cause and cause-specific mortality association of anthropometric measures tested.
- **Harris / Paré (JAMA 2023)** — WHR shows the most consistent and potentially causal relationship with mortality via Mendelian randomization.
- **Åberg 2023 (Commun Med)** — WHR superior to BMI for organ-specific disease prediction.
- **The obesity paradox** — higher BMI can appear *protective* in large cohorts, while higher WHR consistently predicts death. BMI can point in the wrong direction.

### MONDAY MORNING

Stop documenting BMI alone. Measure and record WHR at every adult physical — waist at the iliac crest, hips at the widest point. Target men < 0.90, women < 0.85. Track the ratio over time; it responds to intervention within weeks.

## REFERENCES


1. Jayedi A, Soltani S, Zargar MS, Khan TA, Shab-Bidar S. Central fatness and risk of all cause mortality: systematic review and dose-response meta-analysis of 72 prospective cohort studies. *BMJ*. 2020;370:m3324.
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LEVEL 02 · ROOT PHYSIOLOGY

# 8 Fasting Insulin — *The Early Warning A1C Misses*

> *"A1C diagnoses the fire. Fasting insulin detects the smoke."*

## CLINICAL EVIDENCE

- **Timeline** — insulin resistance develops 10–20 years before diabetes is diagnosable. By the time A1C crosses 5.7%, the pancreas has been compensating for a decade. A1C is a confirmation of late failure, not an early warning.
- **Lawlor 2007 (PLoS Med)** — Fasting insulin predicted future CVD in a British cohort; A1C and glucose did *not*, after adjustment.
- **Lin 2024** — Higher HOMA-IR → increased all-cause and cardiovascular mortality even in non-diabetic populations.
- **Rooney 2023** — HOMA-IR identifies cardiometabolic risk even when A1C indicates only prediabetes.
- **Liao 2025 (NHANES)** — Insulin-based indices strongly predict all-cause mortality.
- **Saravia 2015** — Fasting insulin correlates more strongly with metabolic syndrome clustering than A1C.
- **Downstream effects** — hyperinsulinemia drives atherosclerosis, fatty liver, and cognitive decline before glucose ever rises.

### MONDAY MORNING

Add fasting insulin to every metabolic workup — with fasting glucose on the same draw so HOMA-IR can be calculated. Optimal fasting insulin is < 5 µIU/mL. Any value above 8–10 in a non-diabetic patient is hyperinsulinemia and deserves intervention, regardless of A1C.

## REFERENCES


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LEVEL 05 · SYSTEM PERFORMANCE

# Muscle Strength — *Grip & Lower Body*

> "*A weak handshake predicts death. Weak legs predict dependence.*"

## CLINICAL EVIDENCE — GRIP STRENGTH

- **García-Hermoso 2018 (Arch PMR, n=1.9M)** — High grip strength → 31% lower all-cause mortality (HR 0.69).
- **Leong 2015 (PURE, Lancet)** — Grip strength predicts all-cause death, CV death, and CV events across seventeen countries globally.
- **Wu 2017 (JAMDA, n>3M)** — Each 5-kg decrease in grip strength → 16% higher all-cause mortality.

## CLINICAL EVIDENCE — LOWER EXTREMITY

- **Guralnik 1995 (NEJM)** — Lower-extremity function predicts disability, nursing home admission, and death.
- **LaMonte 2026 (JAMA Netw Open, n=5,472 women)** — Chair-stand test: HR 0.63 for all-cause mortality.
- **Núñez-Cortés 2025 (n=43,605)** — Grip strength wins overall; chair-stand test is more relevant in older women.
- **Summary** — grip strength tells you who is aging badly. Lower-extremity strength tells you who is about to lose their life in motion. Test both.

### MONDAY MORNING

Buy a Jamar dynamometer (~$200). Measure grip strength at every adult physical — male cutoff < 26 kg dominant hand, female < 16 kg indicates sarcopenia risk. Add a 30-second chair-stand test for patients over 60 (< 12 repetitions is flagged). Document both as vital signs.

## REFERENCES


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LEVEL 03 · STRUCTURAL RISK

# 6 The Glycocalyx — *Where Vascular Disease Begins*

> "*It's not just a marker. It's part of the mechanism.*"

## CLINICAL EVIDENCE

- **Mechanism** — the endothelial glycocalyx is a gel-like protective layer of proteoglycans and glycoproteins lining every blood vessel. Loss → ↑ permeability → plaque formation → impaired $O_2$ delivery.
- **Dane 2015 (Circulation)** — Reduced glycocalyx (↑ perfused boundary region / PBR) → impaired microvascular perfusion and increased cardiovascular risk.
- **Lee 2019 (Diabetes Care)** — Diabetics show significantly increased PBR correlating with microvascular complications.
- **Broekhuizen 2009 (JACC)** — Reduced glycocalyx integrity → higher CV risk and endothelial dysfunction.
- **What damages it** — LDL particles damage it. Hyperglycemia strips it. Inflammation degrades it.
- **Measurement** — measurable in clinic today via sublingual **GlycoCheck** imaging (PBR).
- **Sits upstream of** — atherosclerosis · insulin resistance · hypertension · microvascular dysfunction · organ hypoxia.

### MONDAY MORNING

Consider GlycoCheck as part of baseline vascular assessment in high-risk patients (diabetes, hypertension, metabolic syndrome). Target upstream glycocalyx restoration via glycemic control, ApoB reduction, anti-inflammatory intervention, and sulodexide where appropriate.

## REFERENCES


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# 5

LEVEL 02 · ROOT PHYSIOLOGY

# hs-CRP — *Systemic Inflammatory Burden*

> "*Risk exists even with normal LDL and normal A1C. CANTOS proved inflammation causes disease.*"

## CLINICAL EVIDENCE

- **Physiology** — liver-produced, IL-6 driven; reflects chronic low-grade inflammation. A global signal, not a diagnosis — powerful as a screening tool.
- **Ridker 2000 (NEJM)** — hs-CRP independently predicts CV events in apparently healthy individuals.
- **ERFC 2010 (Lancet, ~160,000)** — CRP associated with CAD, stroke, vascular, and all-cause mortality.
- **JUPITER 2008 (NEJM)** — Normal LDL + elevated hs-CRP → significant CV risk; reducing CRP lowered events.
- **CANTOS 2017 (NEJM)** — Lowering inflammation *without* changing LDL reduced cardiovascular events. The landmark causal trial.
- **Li 2017 (NHANES)** — Higher hs-CRP → increased all-cause mortality independent of traditional risk factors.
- **Mechanism** — endothelial dysfunction + IL-6 cytokine activation + plaque instability + insulin resistance.

### MONDAY MORNING

Add hs-CRP to every baseline panel. Target < 1.0 mg/L. 1–3 mg/L is average risk; above 3 mg/L is elevated and warrants investigation. Repeat after resolution of any acute illness — hs-CRP is a chronic signal, and acute infection will transiently invalidate it.

## REFERENCES


1. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med.* 2000;342(12):836-843.
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# 4

LEVEL 02 + 04 · ROOT + ORGAN DAMAGE

# GGT & Cystatin C — *Hidden in Plain Sight*

> *"The most powerful predictors of death are already in your lab panel. You're just not looking at them right."*

## GGT — OXIDATIVE STRESS SENSOR

- **Reframe** — traditionally viewed as a "liver enzyme"; actually tracks oxidative stress and glutathione metabolism. Rises early in the metabolic cascade — predicting diabetes, hypertension, and metabolic syndrome.
- **Ho 2022 (UK Biobank, n=293,000)** — Normal-range GGT → all-cause mortality HR 1.31, CV mortality HR 1.43, liver mortality HR 3.25.
- **Position as** — "not a liver enzyme — a metabolic stress sensor."

## CYSTATIN C — THE BETTER KIDNEY MARKER

- **Advantage** — less affected by muscle mass than creatinine; detects GFR dysfunction earlier; more linear mortality curve.
- **ARDS Cohort 2020** — Highest cystatin C quartile → ~2.5x higher mortality when creatinine showed no AKI.
- **NHANES 2025** — Higher cystatin C → increased all-cause and cardiovascular mortality. Cleaner signal, less noise than creatinine.
- **Position as** — "Creatinine tells you when the kidneys are failing. Cystatin C tells you when the system is starting to fail."

### MONDAY MORNING

Read GGT on every CMP — target ideally < 20 U/L (men) and < 15 U/L (women), even within "normal" reference range. Add cystatin C (with cystatin-based eGFR) to renal assessment in elderly, sarcopenic, and high-risk patients. When cystatin-C and creatinine-based eGFR disagree, trust cystatin C.

## REFERENCES


1. Ho FK, Ferguson LD, Celis-Morales CA, et al. Association of gamma-glutamyltransferase levels with total mortality, liver-related and cardiovascular outcomes: a prospective cohort study in the UK Biobank. *EClinicalMedicine.* 2022.
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# 3

LEVEL 04 · ORGAN DAMAGE

# FibroScan — *Cumulative Metabolic Injury*

> "*It's not fat in the liver that kills you. It's fibrosis.*"

## LIVER STIFFNESS → EVENT RATE AT 2 YEARS

| STIFFNESS (KPA) | CLINICAL INTERPRETATION |
|---|---|
| **< 10 kPa** | ~2.6% event rate — baseline risk |
| **10–20 kPa** | Moderate risk — rising steeply |
| **≥ 40 kPa** | 34% event rate at 2 years |

## CLINICAL EVIDENCE

- **Bril 2026 (JAMA Netw Open, NHANES)** — Liver stiffness independently predicts all-cause mortality; HR 1.06 per kPa — every kPa adds risk.
- **Braude 2022** — Progressive fibrosis in NAFLD strongly associated with all-cause and liver-related mortality.
- **Loomba 2023 (Gut)** — Liver stiffness ≥ 16.6 kPa → progression to cirrhosis.
- **JAMA 2024** — FibroScan-based scoring accurate for liver events; viable biopsy alternative.

### MONDAY MORNING

Integrate FibroScan into the evaluation of any patient with metabolic syndrome, type 2 diabetes, elevated ALT/AST, or elevated GGT. Thresholds: < 7 kPa (normal), 7–10 kPa (monitor), 10–14 kPa (intervene aggressively), > 14 kPa (refer and intensify). Re-scan at 6–12 months — fibrosis regresses measurably with intervention.

## REFERENCES


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LEVEL 05 · SYSTEM PERFORMANCE

# 2 $VO_2$ Max — *The Integrated Survival Metric*

> *"$VO_2$ max is the single best measure of how well your body can stay alive under stress."*

## THE HEADLINE NUMBERS

- **~12–13% mortality reduction** per +1 MET increase (Myers NEJM 2002; Kodama JAMA 2009).
- **~80% lower mortality** in elite versus low-fitness (Mandsager JAMA Netw Open 2018).
- **No ceiling** — no identifiable upper limit where additional fitness stops helping (Mandsager 2018).

## CLINICAL EVIDENCE

- **Integrated measurement** — $VO_2$ max reflects mitochondrial density, stroke volume, capillary density, and oxygen extraction operating simultaneously under load.
- **Blair 1989 (JAMA, Cooper Clinic)** — Higher CRF → lower all-cause mortality independent of traditional risk factors. Foundational study.
- **Harber 2017 (Circulation lineage)** — CRF often outperforms hypertension, smoking, and diabetes as a mortality predictor.
- **No drug has this profile** — no pharmacologic intervention carries a 12% per-unit mortality reduction with no upper limit and essentially zero contraindications.

### MONDAY MORNING

Estimate or measure $VO_2$ max on every adult patient — CPET if available, or validated estimation (Åstrand–Rhyming, 1-mile walk test, or wearable-derived). Target: reach or exceed the 75th percentile for age/sex. Prescribe zone 2 training 3–4 hours/week plus one weekly $VO_2$ max interval session. Track every 6 months.

## REFERENCES


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# 1

LEVEL 01 · ORIGIN

# ACE Score — *The Origin Story*

> *"Some of the strongest predictors of early death aren't found in the lab — they're found in childhood."*

## THE HEADLINE NUMBERS

- **~20 years** shorter lifespan with ≥ 6 ACEs (60.6 yrs vs 79.1 yrs).
- **~45% higher mortality** risk with ≥ 4 ACEs.
- **Each ACE adds ~10%** incremental premature mortality risk — graded, dose-response relationship.

## CLINICAL EVIDENCE

- **Mechanism** — ACEs → HPA axis dysregulation → chronic cortisol → systemic inflammation → insulin resistance → accelerated aging. This is biological, measurable, and upstream of every biomarker on this list.
- **Brown 2009 (Am J Prev Med)** — ≥ 6 ACEs → 20-year lifespan delta. One of the largest life expectancy differences in the epidemiologic literature.
- **CDC-Kaiser ACE Study (Felitti 1998)** — Foundational longitudinal cohort (n > 46,000) establishing the graded dose-response relationship.
- **Hughes 2017 (Lancet Public Health)** — Systematic review and meta-analysis confirming effect of multiple ACEs on health across populations; OR ~1.64 for all-cause mortality.
- **Reframe** — ACE is not a "psychosocial" factor. It is a biologic risk factor established early in life that shapes every downstream system.

### MONDAY MORNING

Integrate the ACE questionnaire into adult intake — normalize it alongside any other screening tool. A score ≥ 4 should trigger the same level of clinical attention as a significantly abnormal biomarker: trauma-informed care referral, nervous-system regulation support (somatic work, breathwork, EMDR where indicated), and heightened surveillance for downstream metabolic and cardiovascular disease. Document it. Treat it.

## REFERENCES


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SYNTHESIS

# The Complete Picture

None of these biomarkers live in isolation. Read from the top of the cascade — the origin — and follow the progression downward to the integrated outcome.

**#1**

### ACE Score

Programs stress response, inflammation set point, and health behavior.

▼

**#8 · #5 · #4**

### Fasting Insulin · hs-CRP · GGT

Root physiology — metabolic dysfunction, inflammation, and oxidative stress.

▼

**#10 · #9 · #6**

### ApoB · WHR · Glycocalyx

Structural risk — atherogenic burden, visceral fat, and endothelial injury.

▼

**#3 · #4**

### FibroScan · Cystatin C

Organ damage — cumulative fibrosis and early renal or vascular failure.

▼

**#7 · #2**

### Muscle Strength · $VO_2$ Max

Integrated system performance — functional reserve and total capacity to tolerate stress.

*Disease is not an event. It is a progression. Most medicine measures the bottom.*
**Longevity lives at the top.**

CLOSING THOUGHT

> *"The future of medicine isn't treating disease.*
> *It's measuring it before it exists."*

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