IMA 2026

EMERGING TRENDS IN MEDICINE

LIVE LONG & PROPER – BIOMARKERS THAT MATTER

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INDEPENDENT™ MEDICAL ALLIANCE

Live Long & Prosper

The Top 10 Biomarkers That Matter

CME Presentation

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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

MODERN MEDICINE'S FATAL FLAW

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

- Standard labs: CBC, CMP, lipid panel
- Diagnose disease after damage is done
- Treat the outcome, not the origin
- A1C after diabetes develops — too late

- BMI instead of fat distribution
- Creatinine instead of Cystatin C
- LDL-C instead of ApoB particle count
- Miss the 10–20 year upstream runway

Tonight, we work upstream.

LEVEL 03 — STRUCTURAL RISK

ApoB

10

Total atherogenic particle burden.

10

LEVEL 03 — STRUCTURAL RISK

ApoB — Total Atherogenic Particle Burden

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

- One ApoB molecule per atherogenic particle (LDL, VLDL, IDL, Lp(a))
- Richardson 2021: Higher ApoB → shorter lifespan (Mendelian randomization)
- Johannesen 2024: Excess ApoB particles linked to CV events and mortality
- ApoB/LDL discordance: normal LDL-C can coexist with lethal ApoB burden
- Wilkins 2016 (JACC): ApoB reveals hidden risk when LDL-C appears 'normal'
- Martin 2024: ApoB predicts healthspan and carries Alzheimer's signal
- Soffer 2024 NLA Consensus: ApoB endorsed as the most accurate CV risk biomarker in clinical practice
- The patient who 'shouldn't have had a heart attack' has ApoB discordance

ApoB predicts cardiovascular events better than LDL-C. Discordance analysis reveals hidden risk that standard lipid panels miss entirely.

Richardson TG, et al. 2021 | Johannesen CDL, et al. 2024 | Wilkins JT, et al. JACC 2016;67:2130 | Soffer DE, et al. NLA Consensus 2024

LEVEL 03 — STRUCTURAL RISK

Waist-to-Hip Ratio

9

Where fat lives matters more than how much.

Waist-to-Hip Ratio — Where Fat Lives Matters

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

- WHR = fat distribution (biology + risk). BMI = mass/height — no biology
- Normal BMI can coexist with high mortality risk if fat is centralized
- Jayedi 2020 (BMJ): Central fatness → direct, linear mortality association independent of BMI
- Czernichow 2011 (Obes Rev): Abdominal adiposity predicts CV mortality; BMI loses significance after adjustment
- Khan 2023 (JAMA Netw Open): WHR shows strongest all-cause + cause-specific mortality association
- Paré et al. / Harris JAMA 2023: WHR most consistent and potentially causal mortality relationship
- Åberg 2023 (Commun Med): WHR superior to BMI for organ-specific disease prediction
- The obesity paradox: Higher BMI can appear PROTECTIVE — while higher WHR consistently predicts death

Higher BMI may be associated with lower mortality. Higher WHR is associated with increased mortality. BMI can literally point you in the wrong direction.

Jayedi A, et al. BMJ 2020;370:m3324 | Czernichow S, et al. Obes Rev 2011 | Khan I, et al. JAMA Netw Open 2023 | Åberg F, et al. Commun Med 2023

LEVEL 02 — ROOT PHYSIOLOGY

Fasting Insulin

8

The early warning A1C will never give you.

8

LEVEL 02 — ROOT PHYSIOLOGY

Fasting Insulin — The Early Warning A1C Misses

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

- Insulin resistance develops 10–20 years before diabetes is diagnosable
- Normal A1C + normal glucose + severely elevated insulin = already in trouble
- Lawlor 2007 (PLoS Med): Fasting insulin predicted future CVD. A1C and glucose did NOT after adjustment
- Lin 2024: Higher HOMA-IR → ↑ all-cause + CV mortality even in non-diabetics
- Rooney 2023: HOMA-IR identifies cardiometabolic risk even when A1C shows 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
- Hyperinsulinemia drives atherosclerosis, fatty liver, and cognitive decline — before A1C rises

Insulin identifies cardiovascular risk before glucose ever becomes abnormal. A1C is not an early warning system — it is a confirmation of late failure.

Lawlor DA, et al. PLoS Med 2007;4:e173 | Lin Z, et al. 2024 | Rooney MR, et al. 2023 | Liao J, et al. NHANES 2025 | Saravia G, et al. 2015

LEVEL 05 — SYSTEM PERFORMANCE

Muscle Strength

7

Grip strength. Lower body. Both predict your future.

7

LEVEL 05 — SYSTEM PERFORMANCE

Muscle Strength — Grip & Lower Body

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

- Grip strength: best simple office biomarker for all-cause mortality. Cheap, fast, scalable
- García-Hermoso 2018 (Arch PMR, n=1.9M): High grip → 31% lower all-cause mortality (HR 0.69)
- Leong 2015 (PURE/Lancet): Grip predicts all-cause death, CV death, CV events — globally
- Wu 2017 (JAMDA, n=3M+): Each 5-kg decrease in grip → 16% higher all-cause mortality
- Lower-extremity: best biomarker for functional independence and frailty trajectory
- LaMonte 2026 (JAMA Netw Open, n=5,472 women): Chair-stand HR 0.63 for mortality
- Núñez-Cortés 2025 (n=43,605): Grip wins overall; chair-stand more relevant in older women
- Guralnik 1995 (NEJM): Lower-extremity function predicts disability, nursing home admission, death

Grip strength tells you who is aging badly. Lower-extremity strength tells you who is about to lose their life in motion. Test both. Act on both.

García-Hermoso A, et al. Arch PMR 2018;99:2196 | Leong DP, et al. Lancet 2015;386:266 | Wu Y, et al. JAMDA 2017 | LaMonte MJ, et al. JAMA Netw Open 2026 | Guralnik JM, et al. NEJM 1995;332:556

LEVEL 03 — STRUCTURAL RISK

Glycocalyx

6

The endothelial protective layer. Where vascular disease begins.

6

LEVEL 03 — STRUCTURAL RISK

The Glycocalyx — Where Vascular Disease Begins

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

- Endothelial glycocalyx = the vascular protective layer lining every blood vessel. Loss → ↑ permeability → plaque → impaired O_2 delivery
- Dane 2015 (Circulation): Reduced glycocalyx (↑ PBR) → impaired microvascular perfusion + ↑ cardiovascular risk
- Lee 2019 (Diabetes Care): Diabetics show significantly increased PBR, correlating with microvascular complications
- Broekhuizen 2009 (JACC): Reduced glycocalyx integrity → higher CV risk + endothelial dysfunction
- LDL particles damage it. Hyperglycemia strips it. Inflammation degrades it. Measurable in clinic today via sublingual GlycoCheck (PBR)
- Sits upstream of: atherosclerosis · insulin resistance · hypertension · microvascular dysfunction · organ hypoxia

Glycocalyx damage is where vascular disease begins — upstream of every condition we're already treating downstream.

Dane MJC, et al. Circulation 2015;131:1548 | Lee DH, et al. Diabetes Care 2019 | Broekhuizen LN, et al. JACC 2009;53:1175 | Becker BF, et al. Cardiovasc Res 2010;87:300

hs-CRP

5

Systemic inflammatory burden. Risk even with normal LDL.

5

LEVEL 02 — ROOT PHYSIOLOGY

hs-CRP — Systemic Inflammatory Burden

"Risk exists even with normal LDL and normal A1C. CANTOS proved inflammation CAUSES disease."

- Liver-produced, IL-6 driven — reflects chronic low-grade inflammation. A global signal, not a diagnosis
- Ridker 2000 (NEJM): hs-CRP independently predicts CV events in apparently healthy individuals
- ERFC 2010 (Lancet, ~160,000 participants): CRP associated with CAD, stroke, vascular + 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
- Li 2017 (NHANES): Higher hs-CRP → ↑ all-cause mortality independent of traditional risk factors
- Mechanism: endothelial dysfunction + IL-6 cytokine activation + plaque instability + insulin resistance
- Position as: 'A global signal, not a diagnosis' — non-specific, but powerful as a screening tool

CANTOS: Lowering inflammation without touching LDL still saves lives. Inflammation is causal, not just associative.

Ridker PM, et al. NEJM 2000;342:836 | ERFC, Lancet 2010;375:132 | Ridker PM, et al. NEJM 2008 (JUPITER) | Ridker PM, et al. NEJM 2017 (CANTOS)

LEVEL 02 + 04 — ROOT PHYSIOLOGY + ORGAN DAMAGE

GGT & Cystatin C

4

Hidden in plain sight — already in your lab panel.

4

LEVEL 02 + 04 — ROOT PHYSIOLOGY + 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

- Traditionally a 'liver enzyme' — actually tracks oxidative stress + glutathione metabolism
- Ho FK 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
- Rises early in the metabolic cascade; predicts diabetes, hypertension, metabolic syndrome

Cystatin C — The Better Kidney Marker

- Less affected by muscle mass; 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 → ↑ all-cause + cardiovascular mortality. Cleaner signal, less noise

GGT: 'Not a liver enzyme — a metabolic stress sensor.' Cystatin C: 'Creatinine tells you when the kidneys are failing. Cystatin C tells you when the system is starting to fail.'

Ho FK, et al. EClinicalMedicine 2022 (UK Biobank n=293,012) | ARDS Cohort PMC 2020 | NHANES cohort PMC 2025

LEVEL 04 — ORGAN DAMAGE

FibroScan

3

Cumulative metabolic injury. Measurable. Reversible if caught.

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:

< 10 kPa	~2.6% event rate
10–20 kPa	Moderate risk — rising steeply
≥ 40 kPa	**34% event rate at 2 years**

- Bril 2026 (JAMA Netw Open, NHANES): 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 + liver-related mortality
- Loomba 2023 (Gut BMJ): Liver stiffness ≥16.6 kPa → progression to cirrhosis
- JAMA 2024: FibroScan-based scoring accurate for liver events; viable biopsy alternative

FibroScan = cumulative metabolic injury made visible. Risk increases linearly with every kPa. Fibrosis is one of the strongest predictors of mortality in chronic disease.

Pang et al. PLoS ONE 2014 | Bril et al. JAMA Netw Open 2026 | Braude et al. PMC 2022 | Loomba et al. Gut 2023;72:581 | JAMA 2024

LEVEL 05 — SYSTEM PERFORMANCE

VO_2 Max

2

The integrated survival metric. Every system, simultaneously.

2

LEVEL 05 — SYSTEM PERFORMANCE

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."

~12–13%

mortality reduction
per +1 MET increase

Myers NEJM 2002;
Kodama JAMA 2009

~80%

lower mortality:
elite vs low fitness

Mandsager
JAMA Netw Open 2018

NO CEILING

no upper limit
where fitness stops helping

Mandsager 2018:
elite athletes still benefit

- Blair 1989 (JAMA/Cooper Clinic): Higher CRF → lower all-cause mortality independent of traditional risk factors. Launched the entire field.
- Harber 2017 (Circulation): CRF often outperforms hypertension, smoking, and diabetes as a mortality predictor
- VO_2 max integrates: mitochondrial density · stroke volume · capillary density · O_2 extraction — all systems, simultaneously

Every 1 MET increase reduces your risk of death by ~12%. No upper limit. No drug has this profile.

Blair SN, et al. JAMA 1989;262:2395 | Myers J, et al. NEJM 2002;346:793 | Kodama S, et al. JAMA 2009;301:2024 | Mandsager K, et al. JAMA Netw Open 2018;1:e183605

And the #1 biomarker...

...is one we don't even measure.

You can optimize every biomarker we've discussed tonight and still be carrying a 20-year life expectancy penalty if you ignore this one.

20 years.

LEVEL 01 — ORIGIN

ACE Score

1

Adverse Childhood Experiences. The origin of the entire cascade.

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."

~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% risk

- ACEs → HPA axis dysregulation → chronic cortisol → systemic inflammation → insulin resistance → earlier death
- Brown 2009 (Am J Prev Med): ≥6 ACEs → 20-year lifespan delta. One of the largest differences in the entire literature
- Graded dose-response: each additional ACE adds ~10% incremental premature mortality risk
- This is upstream of everything else presented tonight. ACE score is the origin of the entire cascade

'A biologic risk factor — established early in life — that shapes every downstream system we've measured tonight.'

Brown DW, et al. Am J Prev Med 2009;37:389 | CDC-Kaiser ACE Study | Longitudinal cohort (n=46,000+) | Meta-analysis: OR ~1.64 all-cause mortality

THE COMPLETE PICTURE

#1

ACE Score

programs stress response + inflammation + behavior

#8 · #5 · #4

Fasting Insulin · hs-CRP · GGT

metabolic dysfunction · inflammation · oxidative stress

#10 · #9 · #6

ApoB · WHR · Glycocalyx

atherogenic burden · visceral fat · endothelial injury

#3 · #4

FibroScan · Cystatin C

cumulative fibrosis · early renal + vascular failure

#7 · #2

Muscle Strength · VO_2 Max

functional reserve · integrated survival capacity

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

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

Thank you.

Mollie James, DO, MPH, IFCMP | IMA Senior Fellow – Surgery