Behind the Basic: Nontraditional Markers with Big Clinical Impact in Primary Care

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Disclosures

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- **Charles Vega, MD, FAAFP (Moderator):** Consultant for Boehringer Ingelheim

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Learning Objectives

1. Identify nontraditional biomarkers currently available for use in primary care, including inflammatory, metabolic, cardiac, and renal markers
2. Determine when incorporating these tests may enhance diagnosis, risk stratification, or management decisions
3. Recognize emerging biomarkers in development and their potential future clinical applications

Biomarkers

Cellular, biochemical or molecular alterations that are measurable in body tissues, cells, or fluids

- Risk assessment, diagnosis, prognosis & disease monitoring.
- Blood test are the biomarkers used in primary care
  - CSF by neurology
  - Tissue/cell markers often used in oncology

Mayeux R. Biomarkers: potential uses and limitations. NeuroRx. 2004 Apr;1(2):182-8. doi: 10.1602/neurorx.1.2.182. PMID: 15717018; PMCID: PMC534923.

Emerging Biomarkers…

- Cardiovascular Risk Assessment
- Chronic Renal Disease Diagnosis/Treatment
- Pulmonary Assessment/Treatment
- Dementia Risk Assessment/Treatment
- Cancer Diagnosis

Cardiovascular Biomarkers…

“When should I order a nontraditional CVD Biomarker?”

STEP 1: Start with standard assessment

- Lipid panel, A1c
- BP, BMI
- Smoking, Family history

Calculate 10-year ASCVD risk with PREVENT-ASCVD equations

The American Heart Association PREVENT™ Online Calculator - Professional Heart Daily | American Heart Association

STEP 2: What is the patient's 10-year CVD risk?

Low risk (≤ 3%) → **No** biomarkers needed → Preventive Lifestyle
High risk (> 10%) → **No** biomarkers needed at this time → Add Meds!

Borderline risk (3 - 10%) → Go to **Step 3**

Blumenthal, R, Morris, P, Gaudino, M. et al. 2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. JACC. null2026, 0 (0) . https://doi.org/10.1016/j.jacc.2025.11.016

STEP 3 → Borderline risk

Are there risk enhancers or uncertainty?

- Strong family history premature ASCVD
  - 1st degree relative (parent, sibling) with an MI, stroke, or revascularization—before 55 for men or 65 for women.
- Metabolic syndrome
- Chronic inflammation

👉 If YES → consider targeted biomarkers

So which cardiac biomarker??

ASCVD Biomarker Risk Refinement

- Lipoprotein(a)
- Apolipoprotein B (ApoB)
- High-sensitivity C-Reactive Protein (hs-CRP)
- Coronary Artery Calcium (CAC)

Lipoprotein(a) [Lp(a)]

LDL-like particle with a bound apoprotein (**a**).

- Proatherogenic and proinflammatory effects
- ↑ ASCVD & calcific aortic stenosis, independent of other risk factors.

- Lp(a) primarily determined by genetics (autosomal codominant)
  - Highest levels in African & Southeast Asian ancestry
  - If elevated, check 1st degree family members (parent, sibling, offspring)

  AHA/ACA recommend measuring Lp(a) at least once in all adults.
  - Lp(a) concentrations remain stable over time – thus 1 measurement
  - Fasting not required

Lipoprotein(a) [Lp(a)]

Levels ≥ 125 nmol/L (50 mg/dL) → 1.4-fold increased ASCVD risk

Levels ≥ 250 nmol/L (100 mg/dL) → 2-fold higher risk

- Secondary causes of high Lp(a) include kidney, liver, or thyroid disease; pregnancy; menopause; and some medications.
- Inflammation may increase or decrease Lp(a).

Minimally modified by lifestyle factors → Elevation requires intensified statin, consider non-statins and management of other risk factor

Apolipoprotein B (ApoB) ?

ApoB - a protein attached to all atherogenic lipoproteins – LDL/VLDL/IDL/Lp(a)

- Predicts ASCVD risk more accurately than LDL

Clinical discordance occurs when LDL is at goal but apoB remains elevated

- Persistent atherogenic particle burden
- Seen in cardiometabolic disease - ASCVD, CKM syndrome, diabetes, and/or TG >150 mg/dL.
- Signal to consider intensifying lipid lowering therapy.

In primary prevention, apoB is associated with incident MI

high-sensitivity C-Reactive Protein (hs-CRP)

CRP produced when immune system is responding to an infection or injury…

- hsCRP increases reflect low grade, chronic inflammation
  - Autoimmune diseases
  - ASCVD plaques can trigger a low-grade autoimmune attack..
- Elevated hsCRP in otherwise healthy individuals puts them into a higher-risk group, even w/normal lipids
  - Strongly predicts recurrent cardiovascular events
- Measure when no current infection/injury or treated/controlled autoimmune disease

Ramón Arroyo-Espliguero, María Carmen Viana-Llamas, Alberto Silva-Obregón, Pablo Avanzas, The Role of C-reactive Protein in Patient Risk Stratification and Treatment, *European Cardiology Review 2021;16:e28.* https://doi.org/10.15420/ecr.2020.49

Elevated hsCRP…

hs-CRP Level	Cardiovascular Risk
Below 1.0	Low Risk
1.0 to 3.0	Average/Intermediate Risk
Above 3.0	High Risk
Above 10	Acute event, such as a recent infection, injury, or major surgery

- Diet, exercise, weight loss, and tobacco cessation reduce hsCRP.
- Statins may also help to lower CRP levels.

https://www.jacc.org/toc/jacc/87/11 Inflammation and Cardiovascular Disease: 2025 ACC Scientific Statement: A Report of the American College of Cardiology 29 Sept 2025
Paul M Ridker, M.D., Christopher P. Cannon, M.D., David Morrow, M.D., Nader Rifai, Ph.D., Lynda M. Rose, M.S., Carolyn H. McCabe, B.S., Marc A. Pfeffer, M.D., Ph.D., and Eugene Braunwald, M.D., for the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) N Engl J Med 2005;352:20-28 DOI: 10.1056/NEJMoa042378

Coronary Artery Calcium (CAC)

A low-dose CT scan

- Detects calcified plaque in the coronary arteries
- Interpreted as an Agatston score, reflecting the amount/density of calcium

CAC Score	Plaque	Risk
1-100	Mild	Early → Preventive measures
100-300	Moderate	↑ Risk for CV event in next 3-5 years
> 300	Significant	↑↑ Risk, plaque burden similar to someone who has had an MI

Lower LDL & Treat All Other Risk Factors Aggressively

Coronary Artery Calcium Test | American Heart Association

Practical Tips

For ASCVD risk assessment – start with traditional risk markers to determine the 10 Risk using the PREVENT calculator.

If **low** risk – counsel in lifestyle modifications

If **high** risk – add a statin; manage HTN, DM

For **intermediate** – gather more information with novel biomarkers:

- Lipoprotein(a)
- Apolipoprotein B (ApoB)
- High-sensitivity C-Reactive Protein (hs-CRP)
- Coronary Artery Calcium (CAC)

Renal Biomarkers…
Diagnosis & Treatment

“When should I use Renal Biomarkers?”

STEP 1: The traditional assessment

- eGFR
- BP, BMI
- Smoking, Family history

The eGFR determines the degree of Chronic Kidney Disease (CKD)

Grade 1: eGFR with >90ml/min - considered normal

Grade 2: eGFR 60-90 - mildly decreased

Grades 3 -5: eGFR < 60 ml/min → now considered to have **CKD**

https://doi.org/10.7326/ANNALS-25-03499
Diabetes Care. 2024;48(Supplement_1):S239-S251. doi:10.2337/dc25-S011

Urine Albumin to Creatinine Ratio (uACR)

Guidelines suggest the eGFR along with uACR to screen for CKD:

- > 60 years age
- Dx'd with DM, HTN,CVD for CKD.

ADA defines CKD if eGFR <60 ml/min **or** UACR is > 30 mg/g

https://doi.org/10.7326/ANNALS-25-03499
Diabetes Care. 2024;48(Supplement_1):S239-S251. doi:10.2337/dc25-S011

Urine Albumin to Creatinine Ratio (UACR)

An early marker of kidney disease – albuminuria seen before GFR decreases.

- The urinary albumin concentration (mg) / creatinine (gm)
  - A spot urine suffices, with a first morning void recommended.
- The results classify albuminuria

  A1 (<30 mg/g) - normal - mild
  A2 (30-299 mg/g) - moderately increased
  A3 (≥ 300 mg/g) - severely increased

https://doi.org/10.7326/ANNALS-25-03499
Diabetes Care. 2024;48(Supplement_1):S239-S251. doi:10.2337/dc25-S011

CKD Management based on uACR

uACR >30 mg/g

- For hypertensives → ACE-I or ARB (slows progression)
- For T2DM→ also add a GLP1 (reduces coronary events & mortality

uACR >200 mg/g

- If either Type 2DM or heart failure - add a SGLT2 to their ACE-I or ARB

https://doi.org/10.7326/ANNALS-25-03499
Diabetes Care. 2024;48(Supplement_1):S239-S251. doi:10.2337/dc25-S011

What about Cystatin C?

A protein produced at a constant rate, not secreted, and catabolized in the tubules without returning to bloodstream, making it a reliable CKD marker.

- The National Kidney Foundation suggest using it as an alternative GFR marker (less muscle-dependent) rather than creatinine to estimate the GFR in individuals with low muscle mass:
  - Children
  - Elderly
  - Chronic steroid use…

However - not widely available in the US at this time

Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Lernmark Å, Metzger BE, Nathan DM, Kirkman MS. Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus. Diabetes Care. 2023 Oct 1;46(10):e151-e199. doi: 10.2337/dci23-0036. PMID: 37471273; PMCID: PMC10516260.

Pulmonary Biomarkers…

COPD management

Blood Eosinophil Count (BEC)

To identify Inflammatory endotypes

- Patients with high circulating eosinophil counts:
  - Higher risk of exacerbations
  - Inhaled corticosteroids (ICS) more effective
  - To consider the use of biologics (e.g. dupilumab)

https://pubmed.ncbi.nlm.nih.gov/30592902

2025 GOLD "Triple Therapy" Thresholds based on BEC…

< 100 cells/µL: Do not add ICS. Consider roflumilast or macrolide

100 - 300 cells/µL: Consider ICS only if exacerbations persist AND benefits outweigh pneumonia risk….

300 cells/µL: Strongest indication for Triple Therapy

- (LABA/LAMA/ICS)

Practical Tips

- Obtain a Urine Albumin to Creatinine Ratio (**uACR**) to help diagnose and determine treatment for CKD
- Consider obtaining a **Cystatin C** eGFR if concern over renal function in a patient with low muscle mass
- Obtain a Blood Eosinophil Count (**BEC**) for COPD patients to assist with management

Dementia Biomarkers…

Risk Assessment/Treatment ?

67-yo woman presents for her annual MWV. She is worried about 'word finding' as her mother was diagnosed with dementia in her early 70s. She heard about blood tests for Alzheimer's and asks if she can get one.

Blood-based AD biomarkers

- APOE
- *Beta*-Amyloid
- pTau

Not yet standard in primary care or widely covered by insurance

Let's take a look at these biomarkers…

Apolipoprotein E - APOE

The APOE gene codes for the protein (apoE) – associated with AD

3 major APOE alleles - differ by 2 amino acids at positions 112 &158

- **ε2** - may be protective (5-10% penetrance)
- **ε3** - most common (80-90% penetrance)
- **ε4** - ↑ AD risk, ~15% carry at least one ε4 allele

All three are normal, inherited variants — not errors, not rare, and not classified as pathogenic mutations.

The APOE-4 Allele (↑ AD risk)

2 copies of the APOE gene – inheriting 1 from each parent.

➢ The specific alleles determine the individual genetic risk profile.

APOe3/e3: Most common genotype → "neutral" risk.
APOe3/e4 (1 copy): ↑ AD risk 2–3 times.
APO e4/e4 (2 copies): ↑ ↑ ↑ AD risk 10–15 times → associated with an earlier onset of symptoms.

Rajič Bumber J, Rački V, Mežnarić S, Pelčić G, Mršić-Pelčić J. Clinical Significance of APOE4 Genotyping: Potential for Personalized Therapy and Early Diagnosis of Alzheimer's Disease. J Clin Med. 2025 Aug 26;14(17):6047. doi: 10.3390/jcm14176047. PMID: 40943807; PMCID: PMC12429504.

APOE-4 - Available OTC…

The test has "limited predictive value“ – a Risk Factor

- Many homozygous carriers (e4/e4) never get AD
- Many non-carriers (e3/e3) do…

FDA requires APOE testing before starting anti-amyloid therapies (eg, lecanemab, donanemab).

- APOE4 homozygotes (2 copies) have a **9.2%** risk of symptomatic brain swelling compared to **1.4%** in non-carriers

New FDA approved Alzheimer's Disease Markers –…

Lumipulse G: Ratio of pTau 217/β-Amyloid 1-42 in blood

Elecsys: Blood concentration of pTau 181

Both tests approved for individuals exhibiting cognitive decline.

- Blood tests providing information previously required lumbar puncture or positron emission tomography.

The biologically based diagnosis also determines eligibility for anti-amyloid therapies (eg, lecanemab, donanemab).

beta-Amyloid or Amyloid-beta…

Amyloid Plaques have long been associated with Alzheimer's disease…

The 2 primary forms amyloid protein in the brain are:

- $A\beta_{1-40}$ — the most abundant form
- $A\beta_{1-42}$ — aggregation-prone and plaque-forming form → linked to AD

phosphorylated Tau (pTau) Proteins

Recent attention to ‘tau tangles’ in addition to amyloid plaques..

- Tau proteins stabilize microtubules in neurons.
- When phosphorylated → tau deforms
  - Aggregate into tangled toxic filaments
- Higher levels of p-Tau are correlated with cognitive decline.
- p-Tau181 & 217 proteins associated with AD pathology…

Rawat P, Sehar U, Bisht J, Selman A, Culberson J, Reddy PH. Phosphorylated Tau in Alzheimer's Disease and Other Tauopathies. Int J Mol Sci. 2022 Oct 25;23(21):12841. doi: 10.3390/ijms232112841. PMID: 36361631; PMCID: PMC9654278.

Women's Health Initiative Memory Study of p-Tau217

2,766 women w/normal cognition (age 65-79) enrolled in 1990s, 25 year F/U..

- Some developed memory/thinking problems, including dementia.
- p-Tau217 levels measure in their blood obtained at enrollment.

Women with ↑ p-Tau217 levels significantly more likely to develop dementia.

- Risk rose steadily, with the highest p-Tau217 levels corresponding to the greatest likelihood of long-term cognitive decline.
- The association was also stronger in women carrying the APOE-4 variant.

"Plasma Phosphorylated Tau 217 and Incident Mild Cognitive Impairment and Dementia in Older Women" by Aladdin H. Shadyab, Bowei Zhang, Andrea Z. LaCroix, Michelle M. Mielke, Susan M. Resnick, Steve Nguyen, Luigi Ferrucci, Towia A. Libermann, Long Ngo, Ramon Casanova, Alexander P. Reiner, Danni Li, Caroline M. Nievergelt, Adam X. Maihofer, JoAnn E. Manson and Linda K. McEvoy, 10 March 2026, *JAMA Network Open*.
DOI: 10.1001/jamanetworkopen.2026.1295

Elecsys Test – a measure of pTau 181 protein levels in the blood

97.9% Negative Predictive Value (NPV).

Negative result means that cognitive symptoms are likely not caused by AD

- Investigate other causes (depression, thyroid, medication side effects, etc.)
- Other forms of dementia – vascular, Lewy body, etc

A positive test is not diagnostic

Need for confirmatory testing (CSF, PET scan)

Alzheimer's pathology has two core processes

- As tau is phosphorylated, more is released into the blood
- As amyloid develops plaques in the brain, less is released

As AD pathology evolves, plasma p-Tau ↑, while β-Amyloid levels ↓

→ ***p-Tau/βAmyloid ratio rises***

Blood levels influenced by factors unrelated to AD, such as CKD, Obesity

The ratio focuses on the relationship between the two proteins rather than their raw amounts, it effectively "cancels out" these external factors, making the result more stable across different patients.

Lehmann S, Gabelle A, Duchiron M et al. **Comparative performance of plasma pTau181/Aβ42, pTau217/Aβ42 ratios, and individual measurements in detecting brain amyloidosis** eBioMedicine, 2025; 117

Lumipulse test measures the ratio of pTau217 to ß-Amyloid1-42

1 marker goes up as the other goes down, the ratio amplifies the signal

High ratio (above the positive cutoff)
- Strongly suggests amyloid pathology consistent with Alzheimer's disease

Low ratio (below the negative cutoff)
- Strongly suggests absence of amyloid pathology

Intermediate ratio
- ~ 20% of those tested..
- Uncertain zone – need confirmatory testing (PET or CSF)

Lumitest Interpretation..

99% sensitivity, 85% specificity in a risk-enriched cohort

➢ 99% sensitivity, 23% specificity in a real-world clinic cohort

Pt w/unimpaired cognition - low pretest probability of brain amyloid

- A test with low specificity → ↑ false-positive results.

➢ Thus, recommended for those ≥ 50 who are experiencing memory or cognitive issues.

- Not for screening asymptomatic individuals.

- FDA approval to aid in determining eligibility for AD therapies.

Practical Tips

- APOE-4 is a marker for Alzheimer's disease but should not be ordered without genetic counseling.
- The new biomarkers (pTau/*B*-amyloid) are recommended for those with cognitive decline, not for general screening
  – Performing a comprehensive clinical evaluation with cognitive screening, medication review, mood, sleep, and vascular risk factors remain the foundation for assessment in primary care at this time.

Cancer Biomarkers

……beyond PSA, CEA, CA-125

Multi-Cancer Early Detection (MCED) tests

- Blood & urine-based ‘liquid biopsies’ detecting circulating tumor-derived DNA/RNA or protein fragments.
- Designed to find cancer early, often before symptoms.
  - Think PSA
  - Detect cancers with no standard screening (e.g., pancreatic, ovarian).
- Need confirmatory tissue diagnosis - but what do you biopsy?
- Generally, not yet routinely covered by insurance ($700–$950/test)

MCED tests are not FDA-approved for population screening

Name	Cancers Detected	Sensitivity	Specificity	FDA Status
Galleri (GRAIL)	**Many**	~51% **<20% for Stage I**	~99.5%	*Not approved* (LDT)
CancerGuard	Many	Varies	Varies	*Not approved*
Prenetics CIRCLE	5	Variable	Variable	FDA-approved
Delfi Diagnostics	Lung	~80% sensitivity	~58%	FDA-approved
Freenome	Many	Not disclosed	Not disclosed	In development

https://www.cancer.org/cancer/screening/multi-cancer-early-detection-tests.html

The Cancerguard™ test

- Intended for use in adults ages 50–84 with no known cancer diagnosis in the last three years.
- Detects circulating tumor DNA and tumor-associated proteins.
- Does not detect all cancers
- Not a replacement for existing recommended cancer screening or diagnostic modalities for cancer.

Sensitivity (~51% to 64%) and Specificity (~97.4%)

Exact Sciences Unveils Data Showing Promise of Multi-Cancer Early Detection at AACR

A 54-year-old man schedules a visit after ordering a CancerGuard test online. His results are positive as below. He reports no symptoms but is extremely anxious….

	Value	Normal Value
CANCERGUARD INTERPRETATION	**Positive (A)**	Negative

POSITIVE TEST RESULT (CANCER SIGNAL DETECTED): A positive Cancerguard test result means that the blood test identified a signal that may indicate the presence of cancer. This result alone does not confirm the presence of cancer. Further clinical evaluation by a healthcare provider and follow-up imaging are needed to determine if a cancer is present or absent and to locate and diagnose a cancer when it is present. EpicPDFSpooler_48DA917C5E134C3AAFAF2886FBCAE174

- Sensitivity (~51% to 64%) and specificity (~97.4%)
- PPV ≈ 21% - A positive test → only about 1 in 5 actually have cancer
- NPV ≈ 99.7% - A negative test → very reassuring (~99.7%)

What do you do???

Exact Sciences Unveils Data Showing Promise of Multi-Cancer Early Detection at AACR

This is a ‘liquid biopsy’

- You find a lump or a lesion on a scan – then biopsy it…
- But with a liquid biopsy you don’t know where the CA is – so on a hunt to find the lesion …
  - So what do you order?
  - How do you get PA??

Next Steps…

- Thorough history/physical exam, address any possible cancer symptoms
- Update age- and risk-based cancer screening (colon, prostate, lung, etc.).

No guidelines for imaging following a positive test. A proposed workflow:

- IV contrast CT of chest, abdomen/pelvis, and soft-tissue neck
- If necessary, positron emission tomography-computed tomography (18F FDG PET-CT) CT skull-base to mid-thigh
- Follow-up procedures (e.g., targeted imaging, endoscopic procedures, CT without IV-contrast) may be appropriate in the context of the medical history/clinical evaluation.

Lennon AM, Buchanan AH, Kinde I, et al. Feasibility of blood testing combined with PET-CT to screen for cancer and guide intervention. Science. 2020;369(6499):eabb9601
Kisiel JB, et al. Shifting the cancer screening paradigm: developing a multi-biomarker class approach to multi-cancer early detection testing. Life. 2024;14(925) doi.org/10.3390/life14080925

Key Takeaways

1. For ASCVD risk assessment – start with traditional risk markers to determine the 10 Risk using the PREVENT calculator. For **intermediate** risk – gather more information with novel biomarkers.
2. The AHA/ACA recommend measuring Lipoprotein-a **Lp(a)** at least once in all adults.
3. Obtain a Urine Albumin to Creatinine Ratio (**uACR**) to help diagnose and determine treatment for CKD
4. Obtain a Blood Eosinophil Count (**BEC**) for COPD patients to assist with management
5. **APOE-4** should not be ordered without genetic counseling.
6. Perform a comprehensive clinical evaluation with cognitive screening for those patients concerned about memory issues/cognitive decline.
7. Currently, most insurances do not cover most emerging blood-based biomarker tests—including the Alzheimer's and cancer screening panels.