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Using biomarkers to quantify problematic alcohol use

Direct biomarkers detect alcohol even in small amounts shortly after ingestion. But which one is nearly 100% specific for alcohol use?

PRACTICE RECOMMENDATIONS

❯ *Use a quick screening instrument such as the single-question tool or the AUDIT 1-3 to objectively determine whether patients' drinking is risky for themselves or for others.* Ⓒ

❯ *Suspect alcoholic liver disease if the ratio of aspartate aminotransferase to alanine aminotransferase is > 3.* Ⓒ

❯ *Consider using the PEth assay in high-risk patients to differentiate between heavy alcohol use and social drinking.* Ⓒ

Strength of recommendation (SOR)

Ⓐ Good-quality patient-oriented evidence

Ⓑ Inconsistent or limited-quality patient-oriented evidence

Ⓒ Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE ▶

A 34-year-old woman presents with fatigue. She appears defensive when asked about her alcohol use. She answers No to all questions on the CAGE (cut down, annoyed, guilty, eye-opener) screening tool, but acknowledges drinking excessively on rare occasions. Her physician has a high suspicion for alcohol use disorder (AUD) and recommends further testing. The patient agrees but denies having used alcohol over the past several days. Which of the following is most likely to help support the suspicion of a heavy drinking pattern?
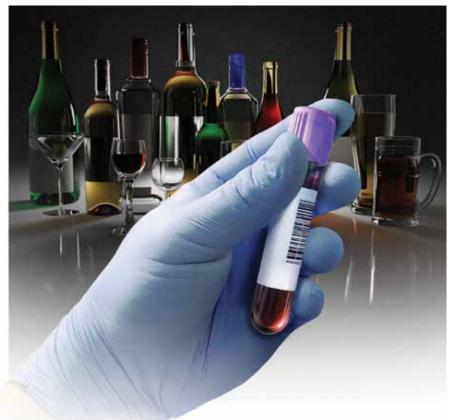
1. Routine lab tests (liver panel and complete blood count).
2. Blood or urine alcohol level.
3. Phosphatidylethanol (PEth) level in the blood.
4. Ethyl glucuronide (EtG) in the urine.
5. Carbohydrate-deficient transferrin (CDT) in the blood.

(See "Case answer" on page 480).

About 1 in 12 Americans have AUD,[1] and 1 in 10 children live in a home with a parent who has a drinking problem.[2] While the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) succinctly defines AUD with specific criteria,[1] the term generally refers to an inability to control or stop drinking despite adverse social or health consequences. AUD is regarded as > 4 drinks per day for men and > 3 drinks per day for women.[3] A "standard drink" would be a 12-oz bottle of beer, a 5-oz glass of wine, or 1.5 oz of distilled spirits. Effects of chronic alcohol use are vast and include malnutrition, alcohol withdrawal syndrome, alcoholic liver disease, pancreatitis/pancreatic cancer, cardiomyopathy, and stroke.[4-6] Alcohol use by a pregnant woman can lead to fetal alcohol syndrome in her child.[7]

❚ **AUD may be more prevalent in the wake of COVID-19.** Primary care practitioners tend to miss a large fraction of patients with AUD in their practice, especially younger patients and those without somatic comorbidities.[8] Systematic screen-

> Primary care practitioners tend to miss a large fraction of patients with alcohol use disorder in their practice. Systematic screening for AUD can identify many of these patients.

ing for AUD can identify many of these people.[8] Particularly as the COVID-19 pandemic continues to unfold and increases stress for everyone, risk of worsening drinking increases both in individuals with current AUD and for those in remission.[9] Contrary to common belief, patients visiting primary care favor screening for at-risk drinking.[10] Thus, awareness of the prevalence of AUD and patient acceptance of screening should encourage wider testing.

■ **Screening tools.** The 2014 guidelines published by the Centers for Disease Control and Prevention recommend using quick screening tools—ie, single question or AUDIT 1-3 (**TABLE 1**[11-18])—as an objective means of determining whether patients' drinking creates a risk for themselves or others.[11] Excessive drinking identified using alcohol questionnaires can help reduce medical complications and health care costs.[19] The questionnaires we review do not provide a diagnosis but help identify individuals who might benefit from more thorough assessment.[20] Following up, as needed, by testing for alcohol biomarkers can provide quantitative insight into problematic alcohol use.[2]

But before we discuss the utility of biomarkers, it's important to quickly review how alcohol is eliminated from the body.

Alcohol elimination

The stomach and small intestine are the primary sites for alcohol absorption. Alcohol elimination from the body occurs through 3 pathways. The first involves oxidative metabolism, which eliminates most ethanol (95%) through the actions of alcohol dehydrogenase, cytochrome P4502E1, or catalase. A lesser amount of alcohol (2%-5%) is eliminated, unchanged, via the second pathway, which includes urine, sweat, and breath. Nonoxidative metabolism makes up the third pathway. Nonoxidative metabolism removes a very small amount (0.1%) of alcohol and involves the direct ethanol biomarkers PEth, EtG, ethyl sulfate (EtS), and fatty acid ethyl esters (FAEEs).[21] Our emphasis in this article is on assays of direct metabolites of alcohol—particularly PEth.

To understand the utility of these direct biomarkers, it is helpful to look at the indirect biomarkers first.

Indirect biomarkers have limited sensitivity and specificity

When alcohol is consumed in large enough quantities over time, indirect biomarkers of alcohol can become abnormal.[22] The major indirect biomarkers are the liver enzymes aspartate and alanine aminotransferase (AST

TABLE 1

Screening tools for alcohol use disorder

Test name	Format of questions	Comments
Single-question alcohol screen[11,12]	How many times in the past year have you had X or more drinks in a day? X = 5 for men, 3 for women and suggests AUD.	**Advantage:** Simple, quick, and easy to administer and score. **Disadvantage:** Patients who do not exceed the single-day drinking limit but drink enough to exceed the weekly limit might be missed.
CAGE[13]	Have you ever felt you should **Cut down** on your drinking? Have people **Annoyed** you by criticizing your drinking? Have you ever felt bad or **Guilty** about your drinking? Have you ever had a drink first thing in the morning as an **Eye-opener** to get rid of a hangover? *2 Yes answers suggest AUD.*	**Advantage**: Easy to use; physicians are familiar with it. **Disadvantage**: It's not accurate for older people, White women, or African- or Hispanic-Americans.
T-ACE[14]	**Tolerance**: How many drinks does it take to make you feel high? Have you ever been **Annoyed** by people's criticism of your drinking? Are you trying to **Cut down** on drinking? Have you ever used alcohol as an **Eye-opener** in the morning? *Yes to A, C, or E questions = 1 point each; a T-question response of > 2 = 2 points.* *Maximum score is 5; a score of ≥ 2 is positive.*	Developed for use with pregnant women and is the first validated sensitive screen for ObGyn practice. **Advantages:** - Takes ~1 min to administer. - Valuable for identifying lifetime alcohol use and prenatal use. - More sensitive than the CAGE test (69% vs 38%), with specificity being roughly equal (89% vs 92%).[14]
RAPS4[15]	Similar to the CAGE test. *A response of Yes to 1 question suggests a possible alcohol abuse problem.*	**Advantage:** Results are accurate across gender and ethnic groups.
AUDIT[16]	10 multiple-choice questions developed by the World Health Organization. *A score ≥ 8 indicates a problem with alcohol.*	**Advantages:** - Globally accepted test - 94% accuracy across ethnic and gender groups - Shorter version AUDIT 1-3 has just 3 questions. **Disadvantage:** Full test takes longer to administer than other tests.
MAST[17,18]	22 Yes or No questions. *6 positive responses suggest AUD.*	**Advantage:** Effectively diagnoses AUD in adults and adolescents. **Disadvantage:** Takes longer to administer and score than other tests.

AUD, alcohol use disorder; AUDIT, Alcohol Use Disorders Identification Test; CAGE, cut down, annoyed, guilty, eye-opener; MAST, Michigan Alcohol Screening Test; RAPS4, rapid alcohol problems screen; T-ACE, tolerance, annoyed, cut down, eye-opener.

and ALT), gamma-glutamyl transferase (GGT), mean corpuscular volume (MCV) of red blood cells, and carbohydrate-deficient transferrin (CDT). Indirect biomarkers have limited sensitivity and specificity for AUD. (For specifics on sensitivity and specificity of indirect and direct biomarkers, see **TABLE 2**.[23-31])

▌**Liver enzymes.** AST and ALT are also present in the heart, muscle, and kidneys. Elevated levels usually imply injury to hepatocytes, with ALT being more reflective of liver involvement than AST. Both AST and ALT are

elevated in other common liver conditions including hepatitis C virus infection and fatty liver disease. In alcoholic liver disease (ALD), AST is elevated more than ALT; an AST-to-ALT ratio > 3 suggests ALD. An elevated GGT often indicates hepatic injury and is used to confirm that elevated alkaline phosphatase is of hepatic origin.[32]

❚ **MCV** is the average volume of erythrocytes,[33] and an elevated MCV is a potential indicator of excessive alcohol intake. Macrocytosis requires sustained alcohol use, and the test has low sensitivity. Other diseases such as vitamin B12 or folic acid deficiency, hypothyroidism, hematologic diseases (eg, cold agglutinin disease, multiple myeloma, amyloidosis), and certain medications can also increase MCV.[34] Moreover, MCV responds slowly to alcohol use, abstinence, and relapse because red cells have a life span of 120 days.[35]

❚ **CDT.** Transferrin is a glycoprotein produced in the liver. The level of transferrin with sialic acid chains increases with alcohol consumption as well as in the carbohydrate deficient glycoprotein syndrome, leading to so-called carbohydrate deficient transferrin.[36] It is a sensitive marker for detecting alcohol relapse and monitoring sobriety. Moderate-to-heavy alcohol use, averaging ≥ 40 g of alcohol per day for 2 weeks,[36] can decrease the amount of carbohydrate attached to transferrin. Two weeks after complete alcohol cessation, CDT levels will return to normal.[37]

CDT is approved by the FDA as an assay for alcohol consumption.[37] While CDT is felt to be one of the better indirect markers of AUD and can extend the window of detection, there are still issues with its sensitivity and specificity.[38] This biomarker can be elevated with other liver diseases and can be affected by the patient's age, body mass index, gender, and tobacco use.[39,40] Testing for CDT has never achieved widespread clinical use and has been largely supplanted by the more accurate PEth test (described in a bit).

Direct biomarkers offer insight into recent alcohol use

Other than ethanol itself, direct biomarkers of alcohol use are minor ethanol metabolites created through biochemical reactions when ethanol is coupled to endogenous compounds. Hence, the presence of these metabolites is usually directly related to ethanol consumption.[41] Direct alcohol biomarkers are EtG, EtS, FAEEs, and PEth (**TABLE 2**[23-31]). They reflect alcohol consumption over a period of several days, making them useful when paired with questionnaire data, especially for identifying young adults who engage in binge drinking.[42]

❚ **Ethanol** can be measured in blood, urine, and breath and is detectable a bit longer in urine than in blood. However, alcohol is detectable in the blood only for 6 to 12 hours after drinking. After alcohol consumption, concentrations peak in the blood within 2 hours. The window for detecting ethanol in the blood depends on the amount of alcohol consumed and the elimination rate of alcohol, which is about 12 mg/dL/h (or 0.012%)—approximately the same amount of alcohol contained in a standard drink (14 g).

Checking the blood alcohol level might be helpful in the office if a patient appears intoxicated but denies alcohol use. A blood alcohol level > 300 mg/dL, or > 150 mg/dL without gross evidence of intoxication, or > 100 mg/dL upon routine examination indicates AUD with a high degree of reliability.[33,43] But the short half-life of ethanol in blood limits its use as a biomarker,[33] and it is not a good indicator of chronic drinking.[44]

❚ **EtG and EtS.** Less than 0.1% of ethanol is secreted as the metabolites EtG and EtS, which are generated, respectively, by the enzymes uridine diphosphate glucuronosyltransferase and sulfotransferase.[45] They have value in the diagnosis of AUD because of the length of time in which they can be detected. Urinary EtG and EtS have been especially important biomarkers for monitoring relapse in outpatients treated for alcohol-related problems.[46] Generally, EtG and EtS can be detected in urine for 13 to 20 hours after a single drink (0.1 g/kg), and for up to 4 to 5 days following ingestion of large amounts of alcohol.[47]

EtG has been detectable in urine for ≥ 24 hours following only 1 or 2 drinks, and for up to 4 days following heavy consumption.[48] Shortly after alcohol intake, even in

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> **EtG can be detected in urine for ≥ 24 hours after just 1 or 2 drinks, and for up to 4 days after heavy consumption.**

TABLE 2

Indirect and direct alcohol biomarkers[a]:
Sensitivity, specificity, and window of utility

Biomarker	Sensitivity (%) Specificity (%)	Time to return to normal	Source	Comments
Indirect biomarkers				
GGT[23,24]	41-73 63-85	2-6 wk	Blood	Many sources of false-positive results
AST[25]	47-68 80-95	1 wk	Blood	Many sources of false-positive results
ALT[25]	32-50 87-92	1 wk	Blood	Many sources of false-positive results
MCV[24,26]	40-50 80-90	Unknown Half-life, 40 d	Blood	Elevated levels indicate excessive drinking Many sources of false-positive results
CDT[25]	63-84 92-98	2-4 wk	Blood	Most accurate in middle-aged White men Better sensitivity in men than women Combined use of GGT and CDT in women increases sensitivity
Alcohol	100 100	6-12 h after last drink	Blood, urine, breath	Restricted to conditions where ethanol is still present in the individual's circulation
Direct biomarkers				
EtG[27]	62-91 88-98	2-5 d (12 h in serum but up to 7 d in urine)	Urine, serum, vitreous humor, hair, nails	UTI can result in false-negative results[28]
EtS[27]	70-95 78-93	2-5 d (12 h in serum but up to 7 d in urine)	Urine, serum, vitreous humor, hair, nails	Little clinical advantage over EtG alone, but if used in combination, sensitivity/specificity increase Not affected by UTI[28]
FAEEs[29,30]	> 75 > 75	24 h after last drink, or 99 h in heavy drinkers; up to several months in hair	Blood, hair	Can help distinguish between binge drinking and chronic alcohol use
PEth[31]	94.5 ~100	21-28 d	Blood, dry blood spots	Most sensitive test and highly specific Reliable biomarker when liver-function test results cannot determine alcohol consumption in damaged liver

[a] Values vary considerably according to gender, age, drinking patterns.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CDT, carbohydrate-deficient transferrin; EtG, ethyl glucuronide; EtS, ethyl sulfate; FAEEs, fatty acid ethyl esters; GGT, gamma-glutamyl transferase; MCV, mean corpuscular volume; PEth, phosphatidylethanol; UTI, urinary tract infection.

small amounts, EtG is detectable. Analysis of EtG in urine is helpful in monitoring alcohol consumption during withdrawal treatment, for workplace testing, and to check for abstinence in legal matters. The EtG urine test is useful in detecting alcohol consumption in a person who claims to be abstinent but who drank 2 or 3 days before the evaluation. Although accurate, EtG's window for detection is narrower than that of the PEth assay.

EtS is a good marker of acute short-term alcohol use, up to 12 hours in the blood (or longer in heavier drinkers) and up to 5 days in urine.[49] Its sensitivity is highest in heavy drinkers. Post-sampling formation and degradation of EtS have not been known to oc-

cur in urine samples. Testing for this second metabolite of ethanol can slightly improve the sensitivity and specificity of the EtG test. A urine test for EtS has a wider detection window. But it has little practical advantage compared with EtG.[50]

For better clinical specificity, a combination of both EtG and EtS testing has been recommended. However, the EtS assay is more cumbersome and provides little advantage over EtG. EtG values do not correlate precisely with the amount or frequency of ethanol use, but the magnitude of the EtG finding roughly corresponds to the amount of alcohol recently consumed.

False-positive and false-negative results for EtG and EtS are uncommon in practice. However, false-positive results are possible with the EtG test in certain circumstances: presence of *Escherichia coli* in the specimen, use of ethanol-based hand sanitizers (> 20 times a day) or mouthwashes, and the consumption of substances like pralines, nonalcoholic beer, pharmaceutical products, and fruit juice. Similarly, false-negative results of EtG can occur from degradation if the samples are contaminated with other bacteria, transported without cooling, or stored improperly.[51] In practice, this is uncommon, and the test is believed to be specific with few false-positive results. Commercially available EtG colorimetric test strips permit on-site analysis of urine samples.

❚ **FAEEs** are a combination of different esters and products of alcohol metabolism through a nonoxidative pathway. They are formed by esterification of endogenous free fatty acids and ethanol in blood and several tissues.[29] These are sensitive and specific markers of alcohol ingestion and can differentiate chronic alcohol consumption from binge drinking.[29] It is elevated for up to 99 hours in heavy alcohol drinkers.[30] It can be detected in hair for a longer period than in blood.[52] Detection of FAEEs in meconium can help establish fetal alcohol exposure.[53]

❚ **PEth.** Use of the PEth assay has increased in recent years and its accuracy has had a transformative effect on the diagnosis of AUD.[54] PEth is a phospholipid found in erythrocyte membranes, formed by an interaction between ethanol and phosphatidyl-

choline, catalyzed by phospholipase D.[55,56] Major advantages of PEth include an unusually long half-life and specificity. Red cells lack enzymes to degrade PEth, therefore PEth accumulates in red cells and has a half-life of 4 to 10 days[57,58] allowing for detection of significant ethanol consumption extending back 3 to 4 weeks.[59] There is no evidence that PEth is formed in the absence of ethanol, making the test essentially 100% specific, particularly at higher cutoff values of ≥ 150 ng/mL.[31,60]

PEth levels are not affected by age, gender, or underlying liver or renal disease.[61] PEth can differentiate between heavy alcohol use and social drinking and can therefore identify chronic excessive use.[62] With chronic excessive alcohol consumption, PEth is detectable in blood up to 28 days after sobriety.[63] A correlation exists between PEth concentrations in blood and the amount of consumed ethanol. PEth has increased specificity and sensitivity for the detection of latent ethanol use compared with other direct biomarkers.[21] It can identify recent heavy drinking earlier than indirect biomarkers, as it does not rely on hepatic injury.

Using a cutoff level of 20 ng/mL, PEth assays have a sensitivity of 73% for any alcohol use in the past month; at 80 ng/mL, the sensitivity is 91% for > 4 drinks/d.[61] PEth is considered semi-quantitative. The World Health Organization defines acceptable social alcohol use at a PEth value < 40 ng/dL for men and < 20 ng/dL for women. Chronic excessive use is defined by a level > 60 ng/dL.[55] The cutoff levels tend to be arbitrary and vary with different guidelines.

Although false-positive PEth test results may be possible, most experts believe that dishonesty in self-reporting by test subjects is more likely. That said, the true specificity of PEth remains unknown; a lower value detected should not be regarded as absolute proof of relapse or chronic alcoholism.

Studies have shown a positive correlation between the AUDIT-C score and PEth values combined with self-reported alcohol consumption, indicating that PEth may be a useful marker in difficult-to-assess settings, or in confirming or invalidating self-reported alcohol consumption.[61,64,65] The PEth test is now widely available and, in the authors' ex-

> **PEth is known to be formed only in the presence of ethanol, making the test virtually 100% specific.**

TABLE 3
PEth values and their significance[22,68]

PEth level (ng/mL)	Alcohol consumption	Comments
< 20	None/light	Abstinence or light drinking (averaging < 2 drinks/d for several days/wk)
20-200	Significant	Moderate level of drinking (2-4 drinks/d for several days/wk), corresponding to NIAAA "low risk" and WHO "low risk"/"medium risk" categories[a]
> 200	Heavy	Heavy consumption (at least 4 drinks/d for several days/wk), corresponding to NIAAA and SAMHSA "heavy drinking" and WHO "high risk" and "very high risk"[a]

NIAAA, National Institute on Alcohol Abuse and Alcoholism; PEth, phosphatidylethanol; SAMHSA, Substance Abuse and Mental Health Services Administration; WHO, World Health Organization.

[a] WHO risk categories per daily consumption
Low: ≤ 40 g (men); ≤ 20 g (women)
Medium: 41-60 g (men); 21-40 g (women)
High: 61-100 g (men); 41-60 g (women)
Very high: > 101 g (7.2 drinks men); > 61 g (4.3 drinks, women).

perience, usually costs $100 to $200. Analysis typically costs $40 to $100,[66] and costs could decrease as the test becomes more widely used. Turnaround time for PEth is 5 to 10 days. It is now the recommended assay by transplant hepatologists for detecting alcohol use.[67] **TABLE 3**[22,68] explains the currently accepted ranges for various PEth results.

CASE ANSWER ▶

While every test mentioned can aid in detecting alcohol consumption, the PEth assay in this scenario would be the most clinically useful. **JFP**

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> **PEth may be a useful marker in difficult-to-assess settings, or in confirming or invalidating self-reported alcohol consumption.**

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