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The Role of Biomarkers in the Treatment of Alcohol Use Disorders

What are alcohol biomarkers?

Alcohol biomarkers are physiological indicators of alcohol exposure or ingestion and may reflect the presence of an alcohol use disorder. Most readily measurable biomarkers are indirectly correlated with *alcohol problems*, such as alcohol dependence or chronic heavy alcohol consumption. Some of the newer biomarker tests can directly measure *alcohol exposure or use*. This *Advisory* addresses both types of alcohol biomarkers. The *Advisory* does not discuss the measurement of the physical presence of alcohol in expired air, blood, saliva, or sweat; nonoxidative alcohol metabolites in hair or other tissues; or behavioral and cognitive performance measures that may be affected by alcohol use.

Key characteristics of the biomarkers discussed in this *Advisory* are presented in Exhibit 1 on page 2. Exhibit 1 also provides a rough index of *sensitivity* (among the individuals *with* the condition of interest, the ability of the test to correctly identify those individuals) and *specificity* (among the individuals *without* the condition of interest, the ability of the test to correctly identify those individuals) with *low* representing values approximately 40 percent or less and *high* representing values usually above 70 percent. Sensitivity and specificity also depend on what defines the condition of interest and the cutoff value being used for the test.

Why are alcohol biomarkers needed?

Alcohol biomarkers are not a substitute for self-report measures or information that would otherwise be gathered from a comprehensive patient history and physical by an appropriately trained health professional. They can, however, make a unique and important contribution in serving as *objective* measures and are helpful as (1) *outcome measures* in studies to evaluate new medications or behavioral interventions for alcohol problems, (2) *screens* for possible alcohol problems in individuals unwilling or unable to provide accurate self-reports of their drinking or its effects, and (3) *evidence of abstinence* in individuals prohibited from drinking.

Alcohol biomarkers and self-report measures of drinking (e.g., the National Institute on Alcohol Abuse and Alcoholism single-question screen, the Alcohol Use Disorders Identification Test, Michigan Alcoholism Screening Test, and CAGE) should be considered *complementary* because self-report measures and biomarkers may identify somewhat different individuals.[1] Thus, their use in combination is often desirable.

> Currently, the use of an EtG test in determining abstinence lacks sufficient proven specificity for use as primary or sole evidence that an individual prohibited from drinking, in a criminal justice or a regulatory compliance context, has truly been drinking. Legal or disciplinary action based solely on a positive EtG, or other test discussed in this *Advisory,* is inappropriate and scientifically unsupportable at this time. These tests should currently be considered as potential valuable clinical tools, but their use in forensic settings is premature.

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Exhibit 1: Characteristics of Several Alcohol Biomarkers

Biomarker	Type of Drinking Characterized	Sensitivity/ Specificity	Examples of Possible Sources of False Positives	General Comments
Gamma Glutamyl Transferase (GGT)	Probably at least 5 drinks/day for several weeks	Moderate/ Moderate (as screen for alcohol dependence)	Liver and biliary disease, smoking, obesity, and medications inducing microsomal enzymes.	Most commonly used traditional biomarker. Primarily reflects liver damage that is often related to alcohol consumption. Performs best in adults ages 30 to 60.
Aspartate Amino Transferase (AST) Alanine Amino Transferase (ALT)	Unknown, but heavy and lasting for several weeks	Moderate/ Moderate (somewhat lower than GGT as screen for alcohol dependence)	See GGT. Excessive coffee consumption can lower values.	Primarily reflects liver damage that is often related to alcohol. ALT seems less sensitive than AST. Ratios of AST to ALT>2 may suggest liver damage that is alcohol related. Performs best in adults ages 30 to 70.
Mean Corpuscular Volume (MCV)	Unknown, but heavy and lasting at least a few months	Low/Moderate-High (sensitivity somewhat below GGT as screen for dependence)	Liver disease, hemolysis, bleeding disorders, anemia, folate deficiency, and medications reducing folate.	Poor biomarker for relapse because of sluggish response to drinking. Accuracy does not seem to show a gender effect, whereas other traditional biomarkers often perform better for men than women.
Carbohydrate-Deficient Transferrin (CDT)	Probably at least 5 drinks/day for 2 weeks or so	Moderate/High (as screen for alcohol dependence)	Iron deficiency, hormonal status in women, carbohydrate-deficient glycoprotein syndrome, fulminant hepatitis C, and severe alcohol disease.	Equal to, or possibly slightly better than, GGT but much more specific. Very good biomarker of relapse to drinking following a period of abstinence. Likely less sensitive for women and younger people.
Ethyl Glucuronide (EtG) Ethyl Sulfate (EtS)	Perhaps as little as a single drink	High/Unknown (as indicator of relapse)	Unknown, but alcohol is often in medications, hygiene products, cosmetics, foods, etc. Research is needed to determine whether incidental alcohol exposure can substantially influence the biomarkers.	As direct analytes of nonoxidative breakdown of alcohol, highly sensitive. Probably little gender, age, or ethnicity effect. A new, but promising biomarker; more research is warranted.
Phosphatidyl Ethanol (PEth)	Possibly 3 or 4 drinks/day for a few days	High/Unknown (as indicator of relapse)	None likely but still unknown due to paucity of research.	Probably little gender, age, or ethnicity effect. Linear dose–response relationship with recent drinking levels. A new, but promising biomarker; more research is warranted.

What are the primary alcohol biomarkers?

Traditional alcohol biomarkers have generally been of an *indirect* nature because they suggest heavy alcohol consumption by detecting the toxic effects that alcohol may have had on organ systems or body chemistry. Included in this class are the blood-based measures of gamma glutamyltransferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and mean corpuscular volume (MCV). The first three are serum enzymes produced by the liver. GGT elevation is caused by liver enzyme induction by alcohol or by many other drugs including prescription drugs. AST and ALT elevations, on the other hand, indicate injury and death of liver cells. Such elevations may be a result of heavy drinking, but none of these tests are specific for alcohol. MCV refers to the average size of red blood cells and is measured in whole blood. Elevated MCV can be caused by many things, including heavy drinking. These tests are not very sensitive, and many heavy drinkers do not have elevations.

A newer indirect alcohol biomarker, carbohydrate-deficient transferrin (CDT), is now widely available in the United States. Although the mechanisms responsible for elevation of CDT are not clearly understood, moderately heavy to heavy alcohol consumption for about 2 weeks can cause the transferrin molecule to be lacking in carbohydrate residue in some of its terminal chains. To "normalize" differences in total transferrin levels across individuals, CDT is usually measured in serum as the *percentage* of total transferrin that is carbohydrate deficient rather than as the absolute amount of CDT. CDT and GGT are approximately equal in their ability to identify alcohol problems. The particular advantage of CDT over GGT is that fewer factors other than alcohol use can cause elevation. However, CDT is also quite insensitive to heavy alcohol use, resulting in false negatives.

Direct biomarkers of drinking have recently been developed. They are termed "direct" because they are analytes of alcohol metabolism. Although most alcohol that is consumed is metabolized by oxidative processes in the liver, a very small amount is broken down nonoxidatively, thereby creating analytes that can be measured for a longer period than when alcohol itself remains in the body and could be measured in the breath, blood, or urine.

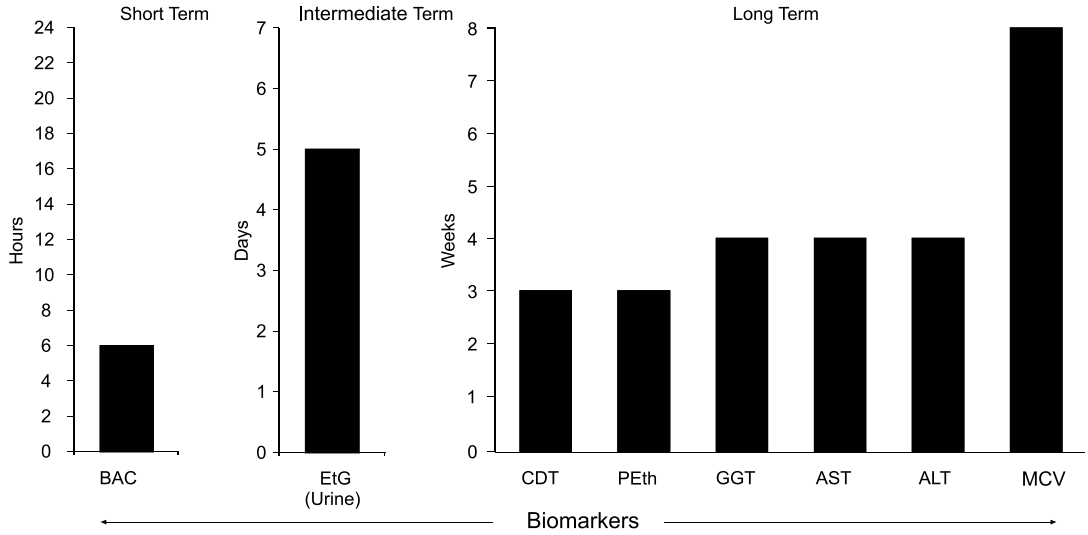
Among the more recently available direct biomarker laboratory tests are tests for ethyl glucuronide (EtG) and ethyl sulfate (EtS). Although present in all body fluids and tissues, EtG and EtS are usually measured in urine. EtG and EtS tests may become positive shortly after even low-level exposure to alcohol and may remain detectable in urine for several days. Because of the purported high sensitivity of these tests, exposure to alcohol that is present in many daily use products might also result in a positive laboratory test for these biomarkers. EtG is becoming widely available in the United States, and some laboratories have also begun to test for EtS. At the current time, EtG and EtS testing may have a supportive role in therapeutic interventions in an environment where breath or blood alcohol tests are used to monitor abstinence. However, until further research has been conducted, the high sensitivity of the EtG and EtS tests does not permit the distinction between alcohol exposure and alcohol consumption at lower levels of possible biomarker detection.

Phosphatidyl ethanol (PEth) is a direct serum-based biomarker. A test for PEth is promising because of PEth's persistence in blood for as long as 3 weeks after even only a few days of moderately heavy drinking (about four drinks per day). There is still little research on PEth, and it is only beginning to be offered commercially to practitioners.

These direct markers of alcohol consumption do not have a strong research base, however. The most extensively studied marker, EtG, has been tested primarily in one laboratory in Europe. Although the results published by this laboratory show promise, it is prudent to await replication of results from another independent investigator. Furthermore, it is not known at this time how the test results might be affected by the presence of physical diseases, ethnicity, gender, time, or the use of other drugs. Until considerable more research has occurred, use of these markers should be considered experimental.

Because biomarkers have differing strengths and weaknesses, they are often used together, especially for screening for alcohol use problems. Common combinations include simultaneous use of CDT and GGT,[2] sequential use of biomarkers,[3] and mathematical combinations of various blood constituents.[4] Biomarkers for monitoring abstinence that can be used in combination include urine alcohol, EtG,

Exhibit 2: Windows of Assessment for Various Alcohol Biomarkers



BAC=Blood alcohol concentration

and/or EtS. EtG and EtS when used together seem to offer greater sensitivity to alcohol use than either biomarker alone.[5]

Respective *windows of assessment* (i.e., the period during which the level of the biomarker may remain high after it originally rose and assuming that no further drinking has occurred) are presented in Exhibit 2.

How can alcohol biomarkers be used in treatment?

Alcohol biomarkers can be used in several ways. Their major uses are—

- **Screening for alcohol problems.** The role of alcohol in either causing or exacerbating medical problems is often missed even in medical care contexts where the prevalence of alcohol misuse is quite high, such as hospital emergency departments, psychiatric practices, and internal medicine clinics. Physician awareness of a possible co-occurring alcohol problem can improve differential diagnosis and treatment.[6,7] Biomarkers also may assist in differential diagnosis by determining the possible role of alcohol use in a disease process (e.g., hypertension or diabetes).[8]
- **Motivating change in drinking behavior.** An important goal of alcohol treatment is motivating a patient to reduce or cease drinking. Giving feedback on elevations in biomarkers and reviewing with the patient declines in biomarker levels as treatment proceeds provide objective evidence of the patient's personal need for and benefit of stopping or reducing alcohol use. Feedback focusing on levels of the traditional biomarkers may be especially compelling for drinking reduction because biomarker elevation can tangibly demonstrate serious physiological consequences.[9] In a classic study, Kristenson, Trell, and Hood found that providing individuals recurrent feedback on their levels of GGT led to reduction not only in subsequent GGT levels but also in alcohol use, rates of hospitalization, days absent from work, and mortality.[10]
- **Identifying relapse to drinking.** Relapse is unfortunately rather common in alcohol treatment, especially in the early stages of recovery. Frequent monitoring of the patient's abstinence and addressing relapses as early as possible are important aspects of alcohol treatment. CDT has been shown to perform particularly well as a relapse biomarker, often elevating before the patient acknowledges a return to drinking.[11] Curiously, CDT seems to reelevate with lower amounts of alcohol use after a period of abstinence than the levels of drinking initially required to raise it.[11]

- **Evaluating interventions for alcohol problems.** Alcohol biomarkers provide objective outcome data in clinical trials of new medications[12] or of behavioral treatments to treat alcohol use disorders. Although in other instances alcohol biomarkers must accurately identify specific individuals with alcohol problems, in clinical trials or evaluations of community alcohol treatment programs, identification of the drinking status of particular subjects is usually not a primary issue; rather, the goal is determination of average differences between the experimental group and the control group. Thus, with a sufficiently large sample size, even biomarkers with fairly low accuracy can provide useful information about treatment efficacy.
- **Documenting abstinence.** Several population groups may be mandated to sign abstinence contracts or agreements or are required to be abstinent by social convention or laws. These groups include—
  - Individuals younger than age 21, especially in the armed services;
  - Individuals on probation, including adolescents, who have committed alcohol-related crimes (e.g., minor in possession);
  - Individuals who have previous alcohol-related problems but have been allowed visitation with or custody of children with the stipulation that they remain abstinent;
  - Some motorists who have had alcohol-related traffic convictions and who are now required to abstain as a condition of maintaining driving privileges; and
  - Medical personnel, pilots, attorneys, and others who, because of previous alcohol- or drug-related problems, have agreed to abstinence and ongoing monitoring as conditions for continued licensure or employment.

What cautions should be observed in reviewing positive biomarker results of individuals mandated to be abstinent?

Biomarkers provide an important indication of drinking status when used appropriately, but they must always be used with a clear understanding of their strengths and potential weaknesses. This is especially true when the consequences of misidentification of alcohol consumption are grave, such as for a healthcare provider whose license, livelihood, and reputation depend on demonstration of abstinence or for an individual who will be ordered to return to jail because of a positive test. Medical review officers and others who investigate positive test results should be especially cognizant of two issues:

- **Understanding the difference between a test's sensitivity and positive predictive value.** Interpreting even a very good test requires considerable knowledge of both the patient and the population of individuals similar to the patient. Tests should help a provider make a decision based on a variety of sources of information gathered about the patient. The first step is to precisely define the condition that is to be detected by the test, such as early relapse, as defined by specific criteria related to alcohol consumption or drinking status. As noted earlier, a test's sensitivity refers to the percentage of individuals with the condition that the test correctly identifies, for example, early relapse. On the other hand, determination of the *positive predictive value* of the test requires knowledge of its specificity (the percentage of people who have not relapsed and are negative on the test) as well as knowledge of the prevalence of relapse in the group under consideration. The *positive predictive value* refers to the percentage of positive tests in which relapse has actually occurred. For completeness, a test's *negative predictive value* refers to the percentage of negative tests in which relapse has not occurred.

  The critical role played by prevalence in determining positive predictive value may be illustrated. Although the base rate of drinking among healthcare professionals required to refrain from drinking to maintain their license to practice is unknown, it is likely quite low.[13] Assume a new test has perfect 100-percent sensitivity and an excellent specificity of 90 percent for identifying early relapse among this population. If the prevalence of early relapse is in fact 50 percent, the test will have a positive predictive value of 91 percent. However, in keeping with the "quite low" assumption, if the prevalence of drinking is in fact 10 percent, the positive predictive value falls to 53 percent. If, indeed, the true prevalence is as low as 1 percent, the positive predictive value drops to 9.2 percent. In this last scenario almost 91 percent of those who had positive test results would be erroneously labeled as relapsing when, in fact, they had not. Note that in this

scenario, with 100-percent sensitivity, the test's negative predictive value is also 100 percent so a negative test will correctly predict an individual has not relapsed. For determining the drinking status of an individual who no longer has alcohol physically present in the body, there is no known lab test that has the research required to achieve a 100-percent positive predictive value.

- **Potential sources of false positives.** Although sources of false positives have been identified for the traditional biomarkers and CDT, as yet there has been little research on the new direct biomarkers, particularly on the very sensitive biomarkers, EtG and EtS. At issue is whether exposure to alcohol or to the vapors of alcohol in many commercial products, such as personal care items, over-the-counter medications, cleaning products, desserts, wine vinegar, and the like or combinations of these products may cause elevation in EtG or EtS that could appear to be a return to drinking. Exposure to these products combined with possible influences of individual variables such as gender, age, and health status on alcohol biomarker responses has not been adequately studied to date.

How should a test cutoff value be chosen?

The cutoff value selected to distinguish specimens as positive or negative should consider the base rate of problem drinking in the population being evaluated, the individual's likely exposure to products containing nonbeverage alcohol, and the consequences for the individual and society of the individual's being erroneously labeled. Establishing a reliable cutoff with high positive predictive value requires research in the population and discussion of the various contexts in which the test might be applied.

What recommendations can be made for using biomarkers most effectively in monitoring drinking?

Although positive biomarker results should be taken seriously, use of certain biomarkers, such as EtG, is not warranted as stand-alone confirmation of relapse because research has not yet established an acceptable standard to distinguish possible exposure to alcohol in various commercial products from consumption of alcoholic beverages. (A helpful list of many of these products is available at **www.householdproducts.nlm.nih.gov/cgi-bin/household/brands?tbl=chem&id=26**.)

The response to positive tests in questionable cases should be reasonable and include—

- Consideration of clinical and other information about the individual that may or may not be suggestive of drinking;
- Possibly increasing the frequency of testing to monitor drinking status;
- Following up by using additional biomarkers, especially CDT (PEth, when it becomes more available in the United States, would also be a good followup test. GGT might be used as a followup test because it is readily available. However, there are many sources for false positives on GGT, and GGT elevates only with considerable drinking.);
- Perhaps inviting the individual to undergo a controlled trial of exposure to the product or products he or she believes may explain the positive result; and
- Possible monitoring by means of a transdermal alcohol-sensing device (when it becomes more available). Transdermal-sensing devices capture and record the vapors of alcohol extruded through the skin in sweat. Their availability is somewhat limited. Testing for the presence of alcohol in expired air, blood, or urine would provide direct information on drinking, but the windows of assessment are limited to the small number of hours when alcohol is physically present in the system; hence, monitoring would likely need to be done frequently and randomly.

Establishing rapport and trust between the treatment provider or monitor and the client is essential to encourage candor on the part of the client. It is important for individuals in safety-sensitive positions to have supervisors who understand that fair evaluation, treatment, and eventual reinstatement are possible options. Although violations of abstinence must be taken very seriously, consideration may be given to a standard less rigid than "one strike, you're out." Reasonable consequences will encourage openness and earlier reporting of problems. The determination of drinking and the safeguarding of one's livelihood ultimately involve informed human judgment based on all available relevant information. A cornerstone of recovery is honesty.

A biomarker that is positive because of exposure or unintentional consumption, which results in an allegation of use or misuse, casts a cloud on the recovery process. False allegations provide incentive to disregard the intent of abstinence monitoring and may even provide incentives to use because the individual has "nothing to lose."

What research is needed on direct alcohol biomarkers?

Direct measurement of the nonoxidative metabolites of the breakdown of alcohol is an emerging and exciting technology but several lines of research are still needed. These include—

- Establishment of a cutoff that can clearly distinguish consumption of beverage alcohol from exposure to alcohol in other products;
- Identification of possible factors, such as genetic differences, gender, age, physical diseases, and use of other medications, that may influence an individual's biomarker response to alcohol;
- Identification of the window of assessment associated with varying levels of alcohol use;
- Determination of the reliability of laboratory testing procedures; and
- Determination of products that may give a positive test result at specific cutoffs.

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