THE ROLE OF BIOMARKERS IN THE TREATMENT OF ALCOHOL USE DISORDERS, 2012 REVISION

This *Advisory* is a revision of the 2006 *Substance Abuse Treatment Advisory,* The Role of Biomarkers in the Treatment of Alcohol Use Disorders. The revision was necessitated by increased scientific knowledge about alcohol biomarkers and requests from clinical and judicial professionals for greater clarification on the use of biomarkers. This *Advisory* reviews recent scientific biomarker data and discusses their relevance for clinical, medical, and forensic purposes. Potential strategies for the use and interpretation of biomarkers in varying circumstances such as clinical, criminal justice, and impaired healthcare provider settings are discussed. This *Advisory* does not discuss the measurement of the physical presence of alcohol in expired air, blood, or saliva; nonoxidative alcohol metabolites in hair or other tissues; or behavioral and cognitive performance measures that may be affected by alcohol use.

What are alcohol biomarkers?

Alcohol biomarkers are physiological indicators of alcohol exposure or ingestion and may reflect the presence of chronic and/or high level of use of alcohol. Most readily measurable biomarkers are indirectly correlated with *alcohol problems*, such as alcohol dependence. Some of the newer biomarker tests can directly measure *alcohol exposure or use*. Key characteristics of the biomarkers discussed in this *Advisory* are presented in Exhibit 1 (see page 2). Exhibit 1 also provides a rough index of *sensitivity* (the ability of the test to correctly identify those individuals *with* the condition of interest when used on an affected population) and *specificity* (the ability of the test to correctly identify those individuals among the individuals *without* the condition of interest). *Low* represents values approximately 40 percent or less and *high* represents 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, such as the National Institute on Alcohol Abuse and Alcoholism[1] single-question screen; Alcohol Use Disorders Identification Test;[2] Michigan Alcoholism Screening Test;[3] and CAGE[4] should be considered *complementary* because self-report measures and biomarkers may identify somewhat different individuals.[5] Thus, their use in combination is often desirable.

What are the categories of 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.[6] Included in this class are the blood-based measures of gamma glutamyl transferase (GGT), aspartate amino transferase (AST), alanine amino transferase (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, liver damage, or many drugs including prescription

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Exhibit 1. Characteristics of Several Alcohol Biomarkers[6,7,8,9,10,11]

Biomarker	Type of Drinking Characterized	Sensitivity/ Specificity	Examples of Possible Sources of False Positives	General Comments
Aspartate Amino Transferase (AST), Alanine Amino Transferase (ALT)	Unknown, but heavy and lasting for several weeks	Moderate/Moderate (somewhat lower sensitivity than GGT as screen for heavy drinking)	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 greater than 2 may suggest liver damage that is alcohol related. Performs best in adults ages 30 to 60 years.
Carbohydrate-Deficient Transferrin (CDT)	Probably at least 5 drinks/day for approximately 2 weeks	Moderate/High (as screen for alcohol dependence)	Rare genetic transferring variant, primary biliary cirrhosis, chronic end-stage liver disease, fulminant hepatitis C. Values are also altered due to smoking or obesity.	Equal to, or possibly slightly better than, GGT, but much more specific. Biomarker of relapse to heavy 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/High (as indicator of relapse)	Extraneous alcohol exposure, such as alcohol in medications, hygiene products, cosmetics, foods, etc., can elevate values of biomarkers.	As direct analytes of nonoxidative breakdown of alcohol, highly sensitive. Probably little gender, age, or ethnicity effect. New, but promising biomarkers; more research is warranted.
Gamma Glutamyl Transferase (GGT)	Probably at least 5 drinks/day for several weeks	Moderate/Moderate (as screen for heavy drinking)	Liver and biliary disease, smoking, obesity, diabetes, 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 years.
Mean Corpuscular Volume (MCV)	Unknown, but heavy and lasting up to several months	Moderate/Moderate (sensitivity somewhat below GGT as screen for heavy drinking)	Hemolysis, bleeding disorders, anemia, folate deficiency, hypothyroidism, hyperglycemia, and medications reducing folate.	Poor biomarker for relapse because of sluggish response to drinking. Higher sensitivity in women than men. Performs best in adults ages 30 to 60 years.
Phosphatidyl Ethanol (PEth)	Possibly 3 or 4 drinks/day for several days	High/High (additional research is needed)	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.

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medications. AST and ALT elevations often 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 four tests are not very sensitive, and many heavy drinkers may 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 episodic, 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 can be measured in the 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 1 to 2 days.[6,10] Because of the high sensitivity of these tests, exposure to alcohol that is present in many daily use products might also result in a positive laboratory test result for these biomarkers. Upper respiratory infections as well as beta glucuronidase hydrolysis may lower levels of EtG but do not seem to affect EtS. On the other hand, EtG levels may be raised by the presence of alcohol or glucose in the urine.

EtG is used in monitoring abstinence in clinical and justice system settings. However, whereas EtG can be measured at very low concentrations in vivo, the source of EtG cannot always be determined. Many products used or consumed daily (e.g., hand sanitizers and mouthwash) contain alcohol. Extraneous exposures, such as these, can elevate EtG levels, creating false positive responses. False positive responses can be detrimental in medical and forensic settings where an individual's freedom or career is in jeopardy. Recent investigations have aimed at identifying the degree to which extraneous exposures and conditions affect EtG levels to determine how EtG can be used successfully to indicate intentional alcohol use. In addition, more research is needed on how the test results may be influenced by various diseases, ethnicity, gender, genetic variation in enzyme systems, or the use of drugs.

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, which is only beginning to be studied by researchers in alcohol studies.[12]

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,[13] GGT and MCV,[14] sequential use of biomarkers,[15] and mathematical combinations of various blood constituents.[16] Biomarkers for monitoring abstinence that can be used in combination include urine alcohol, EtG, and/or EtS. EtG and EtS when used together seem to offer slightly greater sensitivity to alcohol use than either biomarker alone.[17]

Interpreting even a very good alcohol biomarker 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 information gathered about the patient. It is important to precisely describe 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 awareness 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. A test's negative predictive value refers to the percentage of negative tests in which relapse has not occurred.

Although sources of false positives have been identified for the traditional biomarkers and CDT, research continues to be needed on the new direct biomarkers, particularly

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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 can cause elevation in EtG or EtS that could suggest the person has resumed drinking. Exposure to these products, combined with possible influences of individual variables such as gender, age, and health status on alcohol biomarker responses, is still being studied.

Respective *windows of assessment* (i.e., the amount of time during which the biomarker remains measurable in the body after drinking ceases) are presented in Exhibit 2.

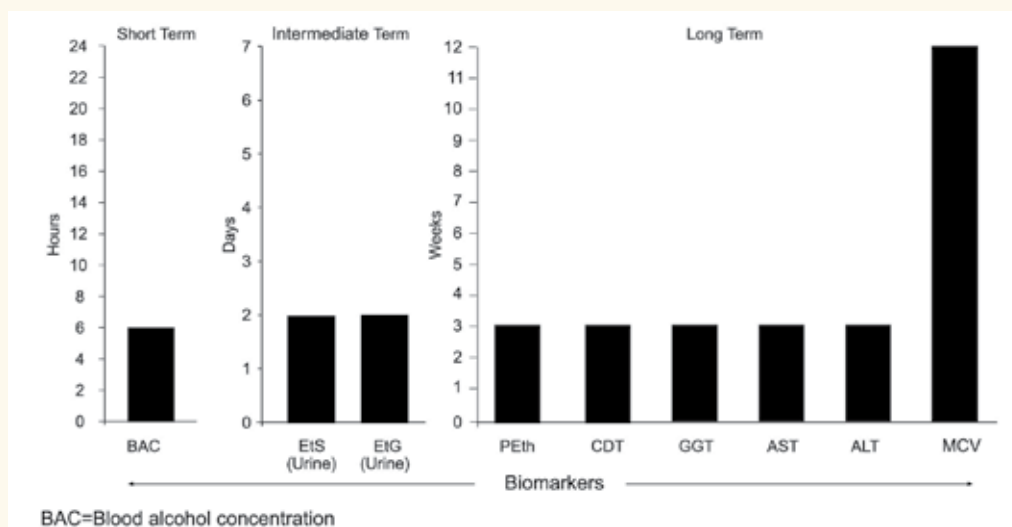## How can alcohol biomarkers be used?

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.[18,19] Biomarkers also may assist in differential diagnosis by determining the possible role of alcohol use in a disease process

(e.g., hypertension or diabetes).[20] Biomarkers, however, should not be used as the sole screening tool in light of their low-to-moderate sensitivity and specificity, and in the case of EtG, because of exposure to alcohol from sources other than drinking.

- **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 lowered scores 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.[21] In a classic study,[22] 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.

- **Identifying relapse to drinking.** Relapse is not unexpected in alcohol treatment and 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 well as a relapse biomarker, sometimes elevating before the patient acknowledges a return to drinking.[13] Interestingly, CDT seems to re-

Exhibit 2. Window of Assessment for Various Alcohol Biomarkers[6,11]

BAC=Blood alcohol concentration

elevate with lower amounts of alcohol use after a period of abstinence than the intensity of drinking initially required to raise it.[23]

Exhibit 3 summarizes some of the uses of biomarkers.

How can alcohol biomarkers be used to document abstinence?

This section addresses specific issues related to the use of alcohol biomarkers in settings where the individual participating in the test is required to abstain from consuming alcohol. The direct biomarkers, especially EtG and EtS, can be very helpful in monitoring individuals mandated to maintain abstinence. These groups of individuals include:

- Individuals younger than the legal drinking age and members of the Armed Forces in combat zones where, regardless of age, drinking is prohibited.
- Individuals on probation, including adolescents, who have committed alcohol-related crimes.
- Individuals who have previous alcohol-related problems but have been allowed visitation with or custody of children with the stipulation that these individuals remain abstinent.
- Motorists who have had alcohol-related traffic convictions and who are now required to abstain as a condition of maintaining driving privileges.
- Medical personnel, pilots, attorneys, and others who, because of previous alcohol- or drug-related problems, have agreed to maintain total abstinence and accept 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 result. One strategy for minimizing this problem is to use a contract that stipulates that individuals for whom abstinence is required avoid using products that may result in a positive test, such as alcohol-based mouthwash, hand sanitizers, and hygiene products.

What responses should be considered in response to positive biomarker results for individuals mandated to be abstinent?

Establishing rapport and trust between the treatment provider or monitor and the patient is essential to encourage candor on the part of the patient. 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

Exhibit 3. Summary Table of Alcohol Biomarkers by Particular Use[6]

Biomarker	Screening for Heavy Drinking	Identify Relapse, Especially to Heavy Drinking	Time To Return to Normal With Abstinence	Monitoring Abstinence
CDT	✓	✓	2–3 weeks	
EtG, EtS		✓	1–3 days	✓
GGT	✓		2–4 weeks	
MCV	✓		Up to several months	
PEth		✓	2–4 weeks	
Sensor Device		✓	Continual	
SGOT/AST*	✓		2–4 weeks	
SGPT/ALT**	✓		2–4 weeks	

* Serum glutamic-oxaloacetic transaminase/aspartate transaminase
** Serum glutamic pyruvic transaminase/alanine aminotransferas

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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 incentives to disregard the intent of abstinence monitoring and may even provide incentives to use because the individual has "nothing to lose."

The response to positive tests on EtG and EtS in questionable cases should be reasonable and include:

- Considering 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.
- Possibly 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 may 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.
- Possible monitoring by means of a transdermal alcohol sensing device. Transdermal sensing devices capture and record the vapors of alcohol extruded through the skin in sweat.
- Forewarning the individual, perhaps a day in advance, that his or her EtG or EtS, or both, will be measured. Warning the patient not to use ethanol-containing products due to their potential impact on EtS and EtG measurements would allow the patient to be sure to avoid exposure to environmental products that may contain ethanol. This, however, could lead to increased risk of tampering. Tampering refers to intentional alteration of a urine sample through dilution or addition of components in an effort to pass a test. If a person is given a 24-hour notice, he or she could use different methods to dilute his or her urine. However, dilution can be caught by other measures such as testing the sample for creatinine and specific gravity.

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, an individual's likely exposure to products containing nonbeverage alcohol, and the consequences for the individual and society of the individual being erroneously labeled. Establishing a reliable cutoff with high positive predictive value (proportion of subjects with positive tests results who are correctly diagnosed) requires research in the population and discussion of the various contexts in which the test may be applied.

Because of the common use of EtG to document abstinence in various settings and the grave consequences for false positive, much attention has been given to the cutoff values of EtG. Although further research is needed before firm cutoffs for EtG can be established, sufficient research has been completed to reach the following conclusions:[24]

- A "high" positive (e.g., >1,000 ng/mL) may indicate:
  - Heavy drinking on the same day or previously (e.g., previous day or two).
  - Light drinking the same day.
- A "low" positive (e.g., 500–1,000 ng/mL) may indicate:
  - Previous heavy drinking (previous 1–3 days).
  - Recent light drinking (e.g., past 24 hours).
  - Recent intense "extraneous" exposure (within 24 hours or less).
- A "very low" positive (100–500 ng/mL) may indicate:
  - Previous heavy drinking (1–3 days).
  - Previous light drinking (12–36 hours).
  - Recent "extraneous" exposure.

How are EtG and EtS best measured?

For most purposes, EtG and EtS are best measured in urine because their window of detection is wider in this matrix than in saliva or blood. These biomarkers can also be measured in hair and recently a test was developed to measure them in nails. However, in these instances the window of detection may be too long or undefined for most applied purposes. It is possible that hair-care products can influence measured levels of the alcohol metabolites. Instructions for processing the urine specimen must be followed rigorously, especially the instructions that the specimen must be refrigerated within a specified period.

The concern over refrigeration of specimens prior to analysis is more problematic for EtG than for EtS. However, it is also possible to use specimen containers that have been treated to retard bacterial degradation of the specimen. The method of analysis should be gas chromatography/mass spectrometry (GC/MS) or liquid chromatography-tandem mass spectrometry (LC/MS/MS). Enzyme immunoassay (EIA) analysis results in a fairly high number of false positives. If EIA is used and the urine sample tests positive, the result should be confirmed by the more accurate GC/MS or LC/MS/MS procedures. Because degree of hydration influences the concentration of EtG and EtS, reference laboratories should report scores corrected for level of creatinine or specific gravity.

Currently, tests for EtG and EtS do not have approval of the Food and Drug Administration; it is hoped this situation will improve in the future to facilitate insurance reimbursement for and acceptance by the additional practitioners.

How can biomarkers be used to evaluate interventions for alcohol problems?

Alcohol biomarkers provide objective outcome data in clinical trials of either new medications[25] or 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.

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 the consumption of beverage alcohol from exposure to alcohol in environmental products.

- Identification of possible factors, such as genetic differences, gender, age, ethnic group, medical or psychiatric comorbidity, disease, genetic polymorphism, and use of medications that may influence an individual's biomarker response to alcohol use.
- Identification of the window of assessment associated with varying levels of alcohol use.
- Determination of the reliability of laboratory testing procedures.
- Determination of products that may give a positive test result at specific cutoffs.

Notes

[1] National Institute on Alcohol Abuse and Alcoholism (2005). *Helping Patients Who Drink too Much: A Clinician's Guide, Updated 2005 Edition.* U.S. Department of Health & Human Services, National Institutes of Health, Bethesda, MD.

[2] Saunders, J., Aasland, O., Babor, T., De La Fuente, J., & Grant, M. (1993). Development of Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addiction, 88,* 791–804.

[3] Kristenson, H., & Trell, E. (1982). Indicators of alcohol consumption: Comparisons between a questionnaire (Mm-Mast), interviews and serum gamma-glutamyltransferase (GGT) in a health survey of middle aged males. *British Journal of Addiction, 77*(3), 297–304.

[4] Mayfield, D., McLeod, G., & Hall, P. (1974). The CAGE questionnaire: Validation of a new alcoholism screening instrument. *American Journal of Psychiatry, 131,* 1121–1123.

[5] Hermansson, U., Helander, A., Huss, A., Brandt, L., & Ronnberg, S. (2000). Alcohol Use Disorders Identification Test and carbohydrate deficient transferrin (CDT) in a routine workplace health examination. *Alcoholism: Clinical and Experimental Research, 24*(2), 180–187.

[6] Litten, R. Z., Bradley, A. M., & Moss, H. B. (2010). Alcohol biomarkers in applied settings: Recent advances and future research opportunities. *Alcoholism: Clinical and Experimental Research, 34*(6), 955–967.

[7] Conigrave, K. M., Saunders, J. B., & Whitfield, J. B. (1995). Diagnostic tests for alcohol consumption. *Alcohol & Alcoholism, 30,* 13–26.

[8] Fleming, M. F., Anton, R. F., & Spies, C. D. (2004). A review of genetic, biological, pharmacological, and clinical factors that affect carbohydrate-deficient transferrin levels. *Alcoholism: Clinical and Experimental Research, 28*(9), 1347–1355.

[9] Jeppsson, J.-O., Arndt, T., Schellenberg, F., Wielders, J. P. M., Anton, R. F., Whitfield, J. B., et al. (2007). Toward standardization of carbohydrate-deficient transferring (CDT) measurements: I. Analyte definition and proposal of a candidate reference method. *Clinical Chemistry and Laboratory Medicine, 45*(4), 558–562.

[10] Kissack, J. C., Bishop, J., & Leatherwood, A. (2008). Ethylglucuronide as a biomarker for ethanol detection. *Pharmacotherapy, 28*(6), 769–781.

[11] Niemelä, O. (2007). Biomarkers in alcoholism. *Clinica Chimica Acta, 377,* 39–49.

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[12] Isaksson, A., Walther, L., Hansson, T., Andersson, A., & Alling, C. (2011). Phosphatidylethanol in blood (B-PEth): A marker for alcohol use and abuse. *Drug Testing and Analysis, 3*(4), 195–200.

[13] Allen, J. P., Litten, R. Z., Fertig, J. B., & Sillanaukee, P. (2000). Carbohydrate deficient transferrin, gamma glutamyl transferase and macrocytic volume as biomarkers of alcohol problems in women. *Alcoholism: Clinical and Experimental Research, 24*(4), 492–496.

[14] Golka, K., & Wiese, A. (2004). Carbohydrate–deficient transferrin (CDT)—A biomarker for long-term alcohol consumption. *Journal of Toxicology and Environmental Health, Part B, 7,* 319–337.

[15] Schwan, R., Albuisson, E., Malet, L., Loiseaux, M.-N., Reynaud, M., Shellenberg, F., et al. (2004). The use of biological laboratory markers in the diagnosis of alcohol misuse: An evidence-based approach. *Drug and Alcohol Dependence, 74,* 273–279.

[16] Harasymiw, J., Seaberg, J., & Bean, P. (2006). Using routine laboratory tests to detect heavy drinking in the general population. *Journal of Addictive Diseases, 25*(2), 59–63.

[17] Wurst, F. M., Dresen, S., Allen, J. P., Wisebeck, G., Graf, M., & Weinmann, W. (2006). Ethyl sulfate: A direct ethanol metabolite reflecting recent alcohol consumption. *Addiction, 101*(2), 204–211.

[18] Dillie, K. S., Mundt, M., French, M. T., & Fleming, M. F. (2005). Cost-benefit analysis of a new biomarker, carbohydrate deficient transferrin, in a chronic illness primary care sample. *Alcoholism: Clinical and Experimental Research, 29*(11), 2008–2014.

[19] Spies, C. D., Kissner, M., Neumann, T., Blum, S., Voigt, D., & Funk, T. (1998). Elevated carbohydrate-deficient transferrin predicts prolonged intensive care unit stay in traumatized men. *Alcohol and Alcoholism, 33*(6), 661–669.

[20] Sillanaukee, P., Strid, N., Jousilahti, P., Vartiainen, E., Poikolainen, K., Nikkari, S., et al. (2001). Association of self-reported diseases and health care use with commonly used laboratory markers for alcohol consumption. *Alcohol and Alcoholism, 36*(4), 339–345.

[21] Conigrave, K. M., Davies, P., Haber, P., & Whitfield, J. B. (2003). Traditional markers of excessive alcohol use. *Addiction, 98*(Suppl 2), S31–S43.

[22] Kristenson, H., Trell, E., & Hood, B. (1981). Serum gamma-glutamyltransferase in screening and continuous control of heavy drinking in middle-aged men. *American Journal of Epidemiology, 114*(6), 862–872.

[23] Allen, J. P., Litten, R. Z., Fertig, J. B., & Sillanaukee, P. (2001). Carbohydrate-deficient transferrin: An aid to early recognition of alcohol relapse. *American Journal on Addictions, 10*(Suppl), S24–S28.

[24] Jatlow, P., & O'Malley, S. S. (2010). Clinical (nonforensic) application of ethyl glucuronide measurement: Are we ready? *Alcoholism: Clinical and Experimental Research, 34*(6), 968–975.

[25] Allen, J. P., & Litten, R. Z. (2003). Recommendations on use of biomarkers in alcoholism treatment trials. *Alcoholism: Clinical and Experimental Research, 27*(10), 1667–1670.

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