A Review of SAMHSA’s Revised Alcohol Biomarkers (EtG/EtS) Advisory - Spring 2012

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A bit of history:

September 25, 2006, the U.S. Department of Health and Human Services released an advisory from the Center for Substance Abuse Treatment (CSAT) entitled: The Role of Biomarkers in the Treatment of Alcohol Use Disorders.
“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.”
EtG/EtS Timeline

- EtG testing commercially available 2004
- Problem-solving courts began testing 2005
  - steady growth in EtG testing
- First SAMHSA Advisory - September, 2006
  - “chilling” effect - usage drops
- Between 2007 - 2012 - usage patterns showed renewed growth as courts appreciate EtG utility in abstinence monitoring
- February 2011 - meeting with SAMHSA
- Building concern about impact of revised Advisory
Placing Alcohol Metabolite Testing into Perspective:

- Urine substance abuse testing became popularized in the mid 1970’s.
- 40+ years of analytical & legal experience.
- EtG testing became readily available around 2005.
- EtS testing became readily available in 2008.
- Far less analytical & legal experience with alcohol metabolite testing compared to urine drug abuse testing.
- Alcohol metabolite testing continues to be in a state of evolution.
- Most significant abstinence monitoring tool in decades.
Alcohol is the most commonly abused substance by drug court clients yet the most difficult substance to detect via abstinence monitoring when attempting to detect alcohol.
Advantages of Ethyl Glucuronide

- unique biological marker of alcohol use (no false positives)
- direct marker indicating recent use
- longer detection window than alcohol
- stable in stored specimens (non-volatile)
- is not detected in the urine of abstinent subjects
Extending the detection window

![Bar chart showing duration of detection for different specimen types. Blood Alcohol, Saliva Alcohol, Breath Alcohol, Urine Alcohol, and Urine EtG/EtS are compared against hours after drinking cessation.]
Disadvantages of Ethyl Glucuronide

- testing available at relatively few laboratories
- EtG/EtS testing more costly than abused drugs
  - expensive LC/MS/MS technology
- not a quantitative determination

- most significant concern – casual, inadvertent, environmental alcohol exposure causing positive results
What prompted SAMHSA Advisory?

- The science of EtG testing - our capability to employ highly sensitive testing procedures to detect recent ethyl alcohol exposure - has outpaced our ability to appropriately interpret the test results in a forensically defensible manner.
- Consumption vs. unintended exposure.
- CSAT (National Advisory Council) concluded that there is inadequate research data about the populations being tested.
Sources of “Incidental” Alcohol Exposure

- OTC medications (Nyquil, Vicks 44)
- mouthwashes (Listermint, Scope, Cepacol)
- herbal/homeopathic medications (i.e., tincture of gingko biloba - memory)
- foods containing alcohol (such as vanilla extract, baked Alaska, cherries jubilee, etc.)
- “non-alcoholic” beers (O’Doul’s, Sharps)
- colognes & body sprays
- insecticides (DEET)
- alcohol-based hand sanitizers (Purell, GermX)
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's single-question screen; 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. 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. 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...
What This Advisory Is and Isn’t

- not revolutionary
- is incremental progress report state of the science
- is tempered versus strident
- is *clinically*-oriented: word “patient” used 14 times
- “forensic” “legal” “criminal” “justice” do not appear
What This Advisory Is and Isn’t

- not a legal/forensic document
- is treatment document
- legal justification for EtG/EtS testing - case law, evidential hearings & judicial rulings
- new advisory adds support for the use of EtG/EtS as a recovery tool
- *not* a roadblock to current drug court policies & practices
### Exhibit 1. Characteristics of Several Alcohol Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Type of Drinking Characterized</th>
<th>Sensitivity/Specificity</th>
<th>Examples of Possible Sources of False Positives</th>
<th>General Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspartate Amino Transferase (AST), Alanine Amino Transferase (ALT)</td>
<td>Unknown, but heavy and lasting for several weeks</td>
<td>Moderate/Moderate (somewhat lower sensitivity than GGT as screen for heavy drinking)</td>
<td>See GGT. Excessive coffee consumption can lower values.</td>
<td>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 80 years.</td>
</tr>
<tr>
<td>Carbohydrate-Deficient Transferrin (CDT)</td>
<td>Probably at least 5 drinks/day for approximately 2 weeks</td>
<td>Moderate/High (as screen for alcohol dependence)</td>
<td>Rare genetic transferring variant, primary biliary cirrhosis, chronic end-stage liver disease, fulminant hepatitis C. Values are also altered due to smoking or obesity.</td>
<td>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.</td>
</tr>
<tr>
<td>Ethyl Glucuronide (EtG), Ethyl Sulfate (EtS)</td>
<td>Perhaps as little as a single crunk</td>
<td>High/High (as indicator of release)</td>
<td>Extraneous alcohol exposure, such as alcohol in medications, hygiene products, cosmetics, foods, etc., can elevate values of biomarkers.</td>
<td>As direct analytes of nonoxidative breakdown of alcohol, highly sensitive. Probably little gender, age, or ethnicity effect. Now, but promising biomarkers; more research is warranted.</td>
</tr>
<tr>
<td>Gamma Glutamyl Transferase (GGT)</td>
<td>Probably at least 5 drinks/day for several weeks</td>
<td>Moderate/Moderate (as screen for heavy drinking)</td>
<td>Liver and biliary disease, smoking, obesity, diabetes, and medications inducing microsomal enzymes.</td>
<td>Most commonly used traditional biomarker. Primarily reflects liver damage that is often related to alcohol consumption. Performs best in adults ages 30 to 80 years.</td>
</tr>
<tr>
<td>Mean Corpuscular Volume (MCV)</td>
<td>Unknown, but heavy and lasting up to several months</td>
<td>Moderate/Moderate (sensitivity somewhat below GGT as screen for heavy drinking)</td>
<td>Hemolysis, bleeding disorders, anemia, folate deficiency, hypothyroidism, hyperglycemia, and medications reducing folate.</td>
<td>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.</td>
</tr>
<tr>
<td>Phosphatidylyl Ethanol (PEth)</td>
<td>Possibly 3 or 4 drinks/day for several days</td>
<td>High/High (additional research is needed)</td>
<td>None likely but still unknown due to paucity of research.</td>
<td>Probably little gender, age, or ethnicity effect. Linear dose–response relationship with recent drinking levels. A new but promising biomarker; more research is warranted.</td>
</tr>
</tbody>
</table>
EtG Cutoff Carnival:

- EtG cutoffs range from 100 - 2000 ng/mL
- EtG cutoff should be considered inversely proportional to a program's willingness and flexibility to consider alternative sources of alcohol exposure other than covert ingestion in violation of a program's rules
  - high willingness – set cutoff LOW
  - low flexibility (strict, unyielding requirements) – set cutoff HIGH (avoid possible sources of "incidental" exposure)
EtG Cutoff Carnival:

- EtG cutoffs of 100 - 250 ng/mL likely to low for criminal justice
- EtG cutoff of 2000 ng/mL likely to high for effective abstinence monitoring
- Goldilocks cutoff for EtG is 500 ng/mL - just right!
  - up to 48 hour detection window
  - avoids sources of "incidental" exposure
  - consistent with “preponderance of the evidence” admissibility standard
2012 Advisory EtG Cutoff levels

- > 1000 ng/mL “heavy drinking” prior 48 hours
- 500 - 1000 ng/mL
  - previous heavy drinking (1 - 3 days)
  - recent light drinking (prior 24 hours)
  - recent intense “extraneous” exposure (within 24 hours)
2012 Advisory EtG Cutoff levels

- 100 - 500 ng/mL
  - previous heavy drinking (1 - 3 days)
  - previous light drinking (12 - 36 hours)
  - recent “extraneous” exposure

- consensus EtG cutoff level currently used by most drug courts 500 ng/mL

- no inconsistency with revised Advisory based upon “preponderance” standard

- admissibility enhanced with addition of EtS and client contract
Forensic Cutoff:

- EtG minimum of 500 ng/mL
- EtS minimum of 100 ng/mL
Positive EtG/EtS Result (500/100 ng/mL):

- is consistent with the recent ingestion of alcohol-containing products (1-2 days prior to specimen collection) by a monitored client
- studies examining “extraneous” exposure widely conclude that results in excess of the 500/100 ng/mL cutoffs are not associated with “environment” alcohol sources
- meets “preponderance of the evidence” standard
Negative EtG/EtS Result (500/100 ng/mL):

- A result reported as EtG negative is indicative of a client who has not ingested beverage alcohol within 1-2 days prior to specimen collection.
- A negative result is not proof of abstinence.
Exhibit 2: Windows of Assessment for Various Alcohol Biomarkers

2006

2012
2012 Advisory EtG/EtS Testing Methodologies

- no on-site testing devices – “rapid” or “instant” tests
- LC/MS/MS - reference method
- GC/MS also recommended
- automated method for use on auto-analyzers and other drug testing instrumentation
  - no EtS testing
Advisory’s Stance on Testing Methods

- EtG/EtS best measured in urine
- hair & nail testing problematic (undefined detection window)
- recommends GC/MS or LC/MS/MS
- immunoassay tests may produce “false positives” results
- confirm results of positive screening tests
If your court is using an EtG “screening” test (enzyme-immunoassay) - confirm positive results using the LC/MS/MS.

DRI® Ethyl Glucuronide Assay

| Catalog No. | 10011725 (1 ml/Kit) | 10012970 (5 ml/Kit) | 10011226 (500 ml/Kit) |

**Intended Use**

The DRI® Ethyl Glucuronide Enzyme immunoassay is intended for qualitative and semi-quantitative determination of Ethyl Glucuronide in human urine at cutoffs of 100 and 1000 ng/mL.

This assay provides only a preliminary analytical test result. A more specific alternative method must be used in order to obtain a confirmed analytical result. Gas Chromatography/Mass spectrometry (GC/MS) and Liquid chromatography/tandem mass spectrometry (LC/MS/MS) are the preferred confirmatory methods. Clinical consideration and professional judgment should be applied to any drug of abuse test result, particularly when preliminary positive results are used.

**Summary and Explanation of the Test**

Ethyl Glucuronide (EtG) is a direct metabolite of ethanol, which is formed by enzymatic conjugation of ethanol with glucuronic acid. Alcohol in urine is normally detected only a few hours after complete elimination of alcohol from the body. Therefore, EtG can be a useful diagnostic biomarker for determining recent alcohol use and monitoring abstinence in alcoholics or alcohol withdrawal treatment programs. Ethanol can be produced in vivo due to fermentation of urine samples containing sugars (diabetics), bacteria or yeast when samples are exposed to warm temperatures. In such cases, EtG can be used, as a confirmatory test to determine if the alcohol in the sample is due to consumption of alcohol or if it is formed in vivo as a result of fermentation. Currently, EtG is monitored by GC/MS and LC/MS/MS.

The DRI® Ethyl Glucuronide Assay is supplied as a liquid ready-to-use homogeneous enzyme immunoassay. The assay uses specific antibodies that can detect Ethyl Glucuronide without any significant cross-reactivity to other glucuronide compounds. The assay is based on competition between a drug labeled with glucose-6-phosphate dehydrogenase (G6PDH), and free drug from the urine sample for a fixed amount of specific antibody binding sites. The absence of free drug from the sample, the specific antibody blocks the drug-labeled with G6PDH and causes a decrease in enzyme activity. This phenomenon creates a direct relationship between the drug concentration in urine and enzyme activity. Active enzyme converts NAD to NADH resulting in an absorbance change that can be measured spectrophotometrically at 340 nm.

**Reagents**

**Assay Procedure**

Clinical chemistry analyzers capable of maintaining a constant temperature, pipetting samples, mixing reagents, measuring enzymatic rates at 340 nm and timing the reaction accurately can be used to perform this immunoassay.

Refer to specific application instructions for each analyzer for chemistry parameters before performing the assay.

**Quality Control and Calibration**

Good laboratory practices suggests the use of control samples to ensure proper assay performance.

Ensure that control results are within the established range, as determined by laboratory procedures and guidelines. If results fall outside of the established ranges, assay results are invalid. For qualitative analysis, use 500 ng/mL, or 1000 ng/mL calibrator as cutoff level. For semi-quantitative analysis, use all calibrators. All QC requirements should be performed in conformance with local, state and/or federal regulations or accreditation requirements.

**Results and Expected Values**

**Qualitative**

Either the 500 ng/mL, or 1000 ng/mL, calibrators can be used as a cutoff reference for distinguishing “positive” from “negative” samples. A sample that exhibits a change in absorbance value (ΔA) equal to or greater than that obtained with the cutoff calibrator is considered positive. A sample that exhibits a change in absorbance value (ΔA) lower than that obtained with cutoff calibrator is considered negative.

**Semi-quantitative**

A rough estimate of Ethyl Glucuronide concentration in the samples can be obtained by running a standard curve with all calibrators and quantitating samples off the standard curve. When the concentration of EtG in the sample is greater than the highest calibrator, it may be diluted with the negative calibrator and retested.

**Reportable Range**

The DRI® Ethyl Glucuronide Assay is designed for semi-quantitative use in the range between 100 ng/mL, the lowest calibrator and 2000 ng/mL, the value of the high calibrator.
Why Drug Courts Should Use EtG/EtS

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

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

- define & establish cutoffs
- identify influencing factors (genetics, age, gender, ethnic groups, disease, etc.)
- how detection window effected by varying levels of alcohol use
- establish reliability of laboratory testing
- determine commercial product influence
What does this Revised Advisory Change for Drug Courts?

NOTHING, if . . . .
Best Practices for EtG/EtS Testing:

- provide those being monitored with an alcohol use advisory document - EtG/EtS specific contract - mandatory
- use appropriate cutoffs:
  - EtG - 500 ng/mL
  - EtS - 100 ng/mL
- test for EtS (ethyl sulfate) - biomarker of choice
EtG/EtS- Specific Contract:

- outlines the behavioral requirements and compliance standards necessary for continued participation in drug court
- educate, alert and advise drug court clients of the potential (incidental) sources of alcohol that could produce a positive urine EtG/EtS test result
- listing the numerous commercial products that contain ethyl alcohol and provides a list of substances to avoid while in a drug court program
Prohibited Items:

- OTC medications
- non-alcoholic beer & wine
- foods that contain alcohol
- alcohol-based mouthwashes
- alcohol-based hand sanitizers
- alcohol-based hygiene products
When in doubt, don't use, consume or apply!
Is a positive urine EtG/EtS test result a definitive indicator of relapse or prohibited drinking?

Is a positive urine EtG/EtS test result sufficient justification for client sanctioning?
EtG/EtS Admissibility?

- are EtG/EtS results legally admissible
- Kelly-Frye, Daubert, Rule 703
- use of proper cutoffs 500/100 ng/mL
- use of appropriate methodologies (LC/MS/MS for confirmation of positives)
- use client contract
- interpret results correctly
- YES!
Current State of EtG/EtS Testing in Drug Courts

- reliable & accurate approach to alcohol abstinence monitoring supported by the science
- EtG/EtS valuable tool for therapeutic intervention - EtS more stable
- provide clients with alcohol avoidance information
- use positive EtG/EtS results to leverage self-admissions
- if using EtG screening - use LC/MS/MS method for confirmation
- employ appropriate cutoff levels
- use results to support recovery
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