Biochemical Markers as Measures of Return to Drinking

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Abstract
This article discusses the role of serum-based laboratory tests in identifying relapse to drinking by alcoholic patients. Particular emphasis is given to carbohydrate deficient transferrin (CDT), a marker of heavy drinking recently approved by the US Food and Drug Administration. After summarizing research on its sensitivity and specificity, several generalizations are offered about its performance and the benefits of its use in conjunction with gamma glutamyl transpeptidase, a commonly employed liver function test. The article concludes by suggesting fruitful directions for future research on biomarkers as aids in identifying return to drinking.

Introduction
Alcoholism has been termed a “chronic relapsing condition” (1). Although treatment for it tends to be at least moderately successful, periodic return to drinking, especially early in the recovery process, is quite common, with perhaps 2/3 of the patients engaging in at least some drinking in the first year (2). From the standpoint of minimizing harm to the patient as well as promoting public health and traffic safety it is important that these events be recognized as soon as possible so that treatment can be intensified or refocused to restore abstinence and help the patient bolster skills to cope with high-risk drinking stimuli. If drinking episodes can be detected quickly, there is also probably less risk of them becoming intractable relapses.

Although self-report measures are often employed to determine drinking status, several studies demonstrate that at least some alcoholics in treatment who have been drinking deny it (3). Hence, objective measures are needed to identify return to drinking. In most instances the measures that have been investigated are biochemical tests. Often these
tests are employed as well to initially screen for alcohol problems. Nevertheless, biomarkers of recurrence of drinking must be especially responsive to recent changes in drinking in order to not miscategorize patients early in treatment who are now abstinent. Biomarkers, such as macrocytic volume, must be used with care since they return to reference range values only slowly after drinking has ceased.

**Recent Studies on Biomarkers of Relapse to Drinking**

Apparently without exception, studies undertaken on biomarkers of relapse over the last several years have included CDT, often with GGT also being considered. Sensitivities and specificities reported by these projects are given in Table 1 (3).

**Table 1:** Sensitivity (Sens.) and Specificity (Spec.) for CDT, GGT, and Their Combination as Markers of Relapse to Drinking

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<td>(4)-Males Only</td>
<td>905</td>
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<td>.53</td>
<td>.81</td>
<td>.74</td>
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<tr>
<td>(4)-Females Only</td>
<td>310</td>
<td>.20</td>
<td>.31</td>
<td>.81</td>
<td>.91</td>
<td>.48</td>
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<td>(5)</td>
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<td>(6)</td>
<td>144</td>
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<td>(7)</td>
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Although the formal criterion for relapse in these studies has usually been return to any level of drinking, the actual pattern of consumption by subjects tended to be fairly heavy and sustained. It should be further noted that, with the exception of the study by Allen et al (4) on the Project MATCH data set, all of the investigations were conducted on male-only or almost entirely male samples. Thus, generalizations are, at best, tentative as they would pertain to women.

Across studies for males only or males and females combined the median sensitivity for CDT was .65 and for GGT was .57, with respective specificities of .92 and .78. As indicated by Table 1, four of these studies (4,6,7,10) additionally computed the sensitivity and specificity for the combination of CDT and GGT using the “simple binary rule” (i.e. if elevated on either of the markers, the patient would be labeled as positive). The median sensitivity and specificity for the combination were each .74. Thus, in these projects the gain in sensitivity by adding GGT over CDT alone was .23 with a corresponding loss in specificity of .16. On the other hand, the gain in sensitivity by
adding CDT to GGT was .20 with a decrease in specificity of only .04. (Due to the high specificity of CDT, including it with GGT resulted in minimal negative impact.) In the Project MATCH study (4) neither test appeared to do as well with women as with men. Curiously, GGT may actually perform at least marginally better with women than does CDT. The lower performance of both markers among women may be a function of the fact that women who relapsed in MATCH trial consumed only around half the amount of alcohol as did the men who relapsed (4).

Relapse duration appeared slightly related to the likelihood of the markers being above cutoff (4), although for women, only GGT demonstrated this phenomenon in the MATCH sample. Granted their sample was quite small, Rosman et al. (11) failed to detect this effect in male alcoholics at the CDT kit manufacturer’s recommended screening cutoff value of 20mg/l. However, they did find that use of a cutoff of 25 mg/l would have resulted in about half of the minor relapses being missed, while still allowing recognition of the more serious ones. Both markers have also been found to be related to the seriousness of consequences of relapse (9). The association was only slightly less than when drinking itself served as the criterion of relapse.

Importantly, a “heralding” effect has been observed for CDT with relapses often being identifiable by elevation of CDT elevation well in advance of patient self-admission (11). Forty-two percent of the relapses in this study were detected by elevated CDT at least 28 days before the patient’s acknowledgement of drinking. Finally, two of the studies noted that CDT responded to return to drinking more rapidly than did GGT (9,10).

Future Research Directions
Although biomarkers have demonstrated considerable value in identifying relapse in alcohol dependent patients receiving abstinence-oriented treatment, further research is needed on a variety of topics:

1. The capability of the markers to recognize reductions in drinking short of total abstinence remains largely unexplored. One important project in this regard (12), however, found that males accustomed to drinking between 20 to 60 g/day of alcohol who reduced their daily consumption for a month by at least two drinks demonstrated reductions in CDT and GGT of at least 10%. Respective sensitivities for CDT and GGT in indicating this decrease in drinking were .70 and .68, respectively, but the specificities of the two markers differed dramatically, with that of CDT being .80 and of GGT being 0. The markers in combination produced a sensitivity of .96. Studies dealing with this issue should consider lifetime history of alcohol dependence and smoking since a large scale trial by Whitfield et al (13) showed that these two factors mediate the relationship between level of consumption and CDT response.

2. As noted, almost all research to date on biomarkers as indicators of return to drinking has involved samples consisting entirely of males or including such a small number of females that it was impossible to disaggregate possible gender effects. Granted results from Project MATCH cited above (4), the response of CDT, GGT and their combination may well differ between the two sexes. Analyses of a subsample from that study, for example, suggested that for men CDT responded primarily to
frequency of drinking and GGT to intensity of drinking; whereas for women both markers responded primarily to intensity of drinking rather than to its frequency (14).

3. Research directly contrasting utility of scoring markers in an ipsative versus normative manner (i.e. within-subject change scores versus evaluating patient drinking status based on a common absolute value) is badly needed. This issue remains hotly contested in the field but could be resolved by projects reporting sensitivities and specificities derived from the two different scoring approaches.

4. Development of algorithms to optimally combine scores from various biomarkers as well as from other indicators of drinking status, such as observational and self-report measures would also be most valuable. Although a few examples have been found in the screening literature of formulas to combine biomarkers in ways other than use of the simple binary inclusion rule, no similar research seems to exist for biomarkers of return to drinking. One would wonder, for example if the drinking status is the same for patients low on all markers as for those with values just slightly below the cutoff on several markers.

5. Investigations are also needed on highly applied topics such as optimal scheduling of follow-up biomarker testing, possible reactive effects of biomarker testing on drinking behavior, and sequencing of biomarker tests.

6. A “gold standard” for recent drinking is needed as a criterion for determining the predictive validity of biomarker as well as other measures that may reflect drinking. Research on this topic has generally been limited to self-report criterion measures. Albeit these measures have often been collected in a more controlled context with special emphasis on getting accurate consumption information (e.g. assurance of confidentiality, intensive questioning, conferral with collaterals, financial incentives for participation in a research protocol, efforts to assure rapport with the interviewer, and use of short-half life, but direct physiological measures, such as 5 hydroxytryptophol and breath analysis) than would typically be possible in a general clinical practice, nevertheless, a reasonably long term objective measure of drinking is needed. With further engineering, the transdermal alcohol sensor (15) may satisfy this critical need or, in a driving context, the interlock device (16) may do so.

7. Although GGT has been most often combined with CDT as a measure of relapse, preliminary studies suggest that aspartate aminotransferase or beta-hexosaminidase might perform at least as well with CDT (17). Research is needed to further examine these alternative combinations as well as to develop new, accurate markers that may prove even more useful independently as well as in combination.

8. Finally, and most importantly, research is needed to develop response curves to drinking patterns for various biomarkers.

References


