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The question raised in the title cannot be reasonably answered until we define what we mean by the terms 'screening' and 'harmful drinking'. Different answers could be given if these terms are alternatively considered in the perspectives of: preventive medicine policy; control of patients under therapy for alcohol addiction; workplace testing; license to carry firearms; or driving license regranting. Quite obviously, the size of the investigated populations and the associated costs strongly depend on the scope of the screening, as does the chance of finding positive versus negative results, and the risks associated with false conclusions. In the present Editorial, 'harmful drinking' is considered in its chronic feature, which involves some degree of durable habit or even physical or psychological craving.

In general, harmful drinking is screened by a combination of different means, including medical examination of symptoms and history of the inspected subject, administration of focused questionnaires, and laboratory determination of biomarkers. While this multifaceted approach to harmful drinking has remained roughly the same over the years, dramatic changes have occurred in the ability to analyze alcohol biomarkers and in interpreting their diagnostic value.

Alcohol biomarkers can be distinguished as direct and indirect. Direct biomarkers are alcohol metabolites, whose concentration in the biological specimens collected from the inspected subject correlates with the amount of alcohol he/she has ingested. Typical direct biomarkers are ethanol itself, ethyl glucuronide (EtG), ethyl sulfate, phosphatidylethanol (PEth) and fatty acid ethyl esters (FAEE). Indirect biomarkers are biochemical parameters influenced by excessive alcohol consumption, in the sense that alcohol abuse may determine an organ's damage in the individual or have an effect on a certain metabolic process, resulting in altered value of the associated parameters. These include, for example, AST, ALT, g-GT, ALP, mean corpuscular volume and carbohydrate-deficient transferrin (CDT).

Indirect biomarkers generally show modest performances, in terms of sensitivity and specificity, as they represent an effect of excessive alcohol consumption, which can possibly be induced by pathological or genetic causes other than alcohol abuse. However, only some of these indirect biomarkers exhibit highly correlated values (e.g., liver failure arising from either alcohol abuse or other diseases may result in anomalous values of both AST and ALT), while some other

biomarkers provide substantially independent information. More specifically, CDT is not influenced by liver diseases, unlike AST, ALT, g-GT and ALP. In so much as unrelated parameters strengthen the information provided by each one, a strategy of combining independent biomarkers is progressively acknowledged to decrease the chance of obtaining false-positive and false-negative outcomes. In particular, the comprehensive evaluation of multiple indirect biomarkers gradually evolved from numerical algorithms [1,2] to multivariate statistical models [3–5]. Using a model based on unequal dispersed classes (UNEQ), 90% sensitivity combined with 90% specificity could be obtained from indirect biomarkers [4].

Direct biomarkers have significantly evolved over the years, in terms of general availability, diagnostic reliability, performance (e.g., sensitivity and specificity), quality assurance, and comprehension (e.g., potential, limitations and sources of bias). Some of them can be determined in several matrices, with different significance with respect to the covered interval, during which alcohol has been consumed. To assess chronic harmful drinking, EtG and FAEE are typically determined in hair samples [6,7], whereas PEth is measured in blood, where it is still detectable 2 weeks after the last alcohol intake [8]. Among these, EtG determination in hair gained increasing credit and diffusion over the years [5,9–11] to such an extent that it became the first choice in the prescribed procedures for driving-license regranting in certain countries. Even if the quantitative analysis of FAEE in hair still represents a valuable tool to ascertain alcohol consumption over extended periods of time, its main practical use has recently been confined to the circumstances when a concern exists that hair EtG results have been biased [7], for example, as a consequence of strong hair cosmetic treatments and/or inherent EtG washing out [12,13]. Whenever there are no reasons to suspect biased results, the determination of EtG in hair is currently used as the gold standard to effectively ascertain chronic excessive consumption of alcohol [101]. The main reason that EtG is imposed upon other direct alcohol biomarkers (e.g., ethyl sulfate, FAEE and PEth) is that it provides the highest specificity (~99%) and sensitivity (90–97%) at a comparable cost [5,11]. The latter depends on the labour-intensive hair sample treatment and the instrumentation required to complete the analysis (either GC–MS or LC–MS/MS) [14].

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The EtG concentration, measured in 3 cm-long scalp hair, is nowadays considered a reliable parameter to measure the average daily intake of alcohol over a 3-month period. Careful washing of hair samples is necessary before the analysis to remove any possible external contamination, so that only the EtG trapped inside the keratin matrix is positively determined. Quite obviously, caution is recommended in interpreting the analytical results, with respect to individual and collecting site variability, as well as other potential sources of bias, including hair porosity [15], hair care products used [12,13,16] and unusual hygiene habits, taking into account the hydrophilic character of EtG.

Bearing in mind these concepts, an EtG concentration above 30 pg/mg hair is almost universally considered as a clear indication of harmful drinking [101]. This cut-off value easily lies within the calibration range of any analytical method, no matter whether GC–MS/MS or LC–MS/MS instrumentation is used to quantify EtG. LODs close to or even below 1 pg/mg hair are nowadays reached to measure EtG in the scalp hair of alcohol abstainers and teetotalers [17–19].

From the above considerations, it is evident that several laboratory tests are currently available to elaborate an appropriate strategy for the screening of harmful drinking. A unique scheme, universally applicable, does not exist, but rather technical aspects (e.g., sensitivity, specificity, general applicability and speed) and socio-economic issues (e.g., costs and benefits, and risks and legal implications of harmful drinking misrecognition) should be taken into consideration before planning a strategy. When large populations of alleged nonheavy drinkers have to be considered, a thoughtful balance between costs and benefits should be appraised, with reference to the risks associated to false-negative results and the costs of false-positive results, the latter needing further follow-up inspection. This is certainly the case of preventive medicine campaigns and, to an extent, workplace testing, when the choice of less-performing indirect biomarkers is justified by their lower cost and higher processing speed. However, it is evident that no single indirect biomarker can be used to draw a reliable conclusion: for example, the relatively high specificity of CDT (90–95%) corresponds to low sensitivity (50–60%), resulting in an excessive risk of misrecognition [4,5]. If the CDT cut-off is lowered to increase its sensitivity, then its high specificity gets lost, which dramatically increases costs of follow-up inspection. A combination of various indirect biomarkers may be used instead, possibly interpreted by multivariate statistical models as mentioned before [4]. Nonetheless, the resulting pair of specificity– sensitivity indexes (either 90% specificity–90% sensitivity, or 95–80% in the cited study) may be acceptable in preventive medicine, but not in some workplace testing when employees in jobs that involve high risks for third parties have to be screened, such as truck, bus and taxi drivers, airplane pilots, policemen, and so on. In all these cases, the risks of chronic alcohol-abuse misrecognition is so high that the recourse to direct biomarkers (typically hair EtG), together with clinical evaluation, appears to be mandatory.

The same strategy – based on the combination of direct and indirect biomarkers – is recommended to screen subjects in which the suspicion of them being alcohol abusers is founded on their previous drinking history, and individuals formerly found to drive under the effect of alcohol whose driving licence has been withdrawn. Indeed, the information provided uniquely from indirect biomarkers proves not to be adequate in these cases, even when it is supported by meticulous clinical examination. This conclusion refers to subjects apparently not showing evident symptoms of alcohol abuse, whose daily alcohol intake, although excessive, is still compatible with observed biomarker values falling inside the normality range. These borderline subjects are particularly risky, since they have already been shown to undertake dangerous behavior, and their misrecognition as potential alcohol abusers consistently results in serious legal consequences whenever an alcohol-

related accident may occur. In our opinion, the combination of direct and indirect biomarkers (e.g., hair EtG and CDT) represents the most reliable approach to single out these ambiguous cases of harmful drinking and provide conclusive evidence to support the medical diagnosis.

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