Recommendations for investigating liver chemistry abnormalities are unworkable

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October 2017—A new guideline on the evaluation of abnormal liver chemistries was published in the January 2017 issue of the *American Journal of Gastroenterology* (AJG).[1] The guideline, developed by the American College of Gastroenterology's practice parameters committee, is based on three resources, the first of which is a review of published research. The other two resources are notably similar and largely based in expert opinion. The authors rate all of the 19 recommendations, which collectively endorse more aggressive workups, as strong recommendations based on very low levels of evidence. International experts in the field of clinical chemistry responded to these new guideline recommendations in the July 2017 issue of *Clinical Chemistry*, where they voiced several concerns, including the problem of analytical variation among assays and the burden of follow-up testing and treatment without added benefit.[2] We share these concerns and believe that adopting these guidelines under the current circumstances is ill-advised.

Among the most impactful of the ACG recommendations is to lower the upper limit of normal (ULN) for two of the most common liver chemistries, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST). This recommendation is based on studies that demonstrate a lower upper limit of normal in truly healthy populations that excluded individuals for various reasons. These reasons included but were not limited to viral hepatitis, abnormal viral serologies, significant alcohol use, diabetes, high-risk behaviors, enlarged waist circumference, abnormal liver biopsy, or nonalcoholic fatty liver disease risk factors such as elevated BMI, triglycerides, glucose, or cholesterol. The guideline authors cite studies that demonstrate a correlation between morbidity and mortality when ALT is elevated above the suggested ranges, and they share a belief that this justifies an effort to lower the ALT reference interval so as to identify individuals with ALT levels that might not be considered elevated using conventional reference intervals but who may nevertheless have an increased risk of adverse long-term outcomes.

By the guideline authors' estimate the proposed change would result in one-third of apparently healthy individuals being newly identified as having elevated ALT. Given that the comprehensive metabolic panel is among the most commonly ordered screening panels, this would result in tens of millions of new "abnormal" results per year in the United States alone. With the incidence of overweight and obesity now collectively accounting for about two-thirds of the U.S. population, mildly elevated liver enzymes will often be related to nonalcoholic fatty liver disease (NAFLD), a condition best treated with lifestyle modification that can be screened for by a simple risk calculation.[3-5]

It is not only the enormousness of the proposed change that is concerning. So too is the lack of studies demonstrating that a tightened reference range would alter treatment plans and improve outcomes. Our colleagues mention a similar concern, noting that they " . . . have not seen any outcome data on patients screened vs. not screened by ALT for NAFLD."[2] We emphasize their point because outcome-based data is needed to demonstrate that a correlation with elevated ALTs yields *actionable* information and is not a mere result of correlations between obesity and other leading contributors to U.S. morbidity and mortality, including diabetes, cardiovascular disease, chronic kidney disease, and cancer.[6,7]

Setting aside clinical concerns, the recommendation is problematic also from a logistical standpoint since the lack of harmonization between liver enzyme assays prevents the development of universal reference ranges. Details on the analytical variation between assays and the impossibility of calibrating some of these assays are available in the published *Clinical Chemistry* opinion.[2] The take-home point is, however, relatively simple: The state of our current assays cannot support a unified treatment approach.

For these reasons, we believe that the proposal for a new and narrowed reference range is not only logistically unrealistic but also premature from a clinical perspective. Given the enormous impact of such a proposed change, on the lives of millions of Americans as well as on the economics of U.S. health care, we feel that such a change should only be reconsidered once we have achieved better assay harmonization and demonstrated convincing evidence for an improvement in patient care.

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