Letters

Comments and Responses

Drawing Conclusions about Short-Term Variability in Liver Function Test Results

TO THE EDITOR: We read with great interest the recent study by Lazo and colleagues (1) on the short-term variability of various biochemical liver tests and want to share some concerns. First, this study is based on a nonrandom, convenience sample that represents only 9.5% (1864 out of 19618) of the original NHANES (National Health and Nutrition Examination Survey) study population, raising questions about the generalizability of the findings, given the strong likelihood for selection bias. Second, the very small percentage of persons from racial or ethnic groups other than white, black, and Hispanic restricts the applicability of the results, particularly for Asians.

The cutoff values of “normal” levels of serum alanine aminotransferase (ALT) that were used in this study—40 IU/L for men and 31 IU/L for women—are probably overestimates, as has been shown in 2 large studies from Italy and Korea (2, 3). These studies recommend using cutoff values of 30 IU/L for men and 19 IU/L for women. On the basis of these recommended cutoff values, a substantial percentage of patients in Lazo and colleagues’ study classified as having elevated ALT levels at examination 1 (median, 43 IU/L) who returned to normal in examination 2 (median, 27 IU/L) would probably still have abnormal levels of ALT. These distinctions are not trivial, as evidenced by the increased risk for death in individuals with ALT levels greater than 20 IU/L compared with those with ALT levels less than 20 IU/L (relative risk for patients with ALT levels of 20 to 29 IU/L, 2.9; relative risk for patients with ALT levels of 30 to 39 IU/L, 9.5) (3). The American Association for the Study of Liver Diseases has also called for recalibration of the normal range for ALT level (4).

Finally, the Gilbert syndrome, a genetic disease with a prevalent homozygosity of 9% in the Western population, can result in values outside the normal range of total bilirubin level, varying with fasting homozygosity of 9% in the Western population, can result in values for ALT level (4).

TO THE EDITOR: I read with interest the article by Lazo and colleagues (1). The authors do not mention the possible effect of statin use in their study. They enrolled middle-aged participants with diabetes and hypertension; such status brought awareness of the metabolic syndrome. The volunteers may be prescribed statins, a widely used group of cholesterol-lowering drugs known to cause increased levels of aminotransferases (2–4). The increases in aminotransferase levels with statin use are asymptomatic, and these levels may return to normal with continuation of statin therapy (4). Approximately one third of adult participants in the study had transient increases in aminotransferase levels (1), which might be caused by unrecognized statin use rather than intranvidual variability. So it is important to specify whether the participants used statins during the study.

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Potential Financial Conflicts of Interest: None disclosed.

References

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Potential Financial Conflicts of Interest: None disclosed.

References
TO THE EDITOR: The recent article by Lazo and colleagues (1) shows that in the context of an epidemiologic survey, such as NHANES, abnormal liver test results in more than one third of participants (levels of aspartate aminotransferase, ALT, alkaline phosphatase, γ-glutamyltransferase, and bilirubin) would be reclassified as normal if retested 17 days apart. On the basis of their findings, Lazo and colleagues recommend that, to avoid unnecessary testing, individuals with abnormal liver test results on a first determination be routinely retested before undergoing further evaluation.

In our opinion, caution should be used in drawing practice recommendations from epidemiologic studies. We are particularly concerned that the proposed strategy could be highly misleading in a clinical setting. Liver tests results, particularly aminotransferases and γ-glutamyltransferase, typically fluctuate in patients with chronic liver disease (2). When evaluating a patient, even an asymptomatic one, with abnormal liver biochemistries, clinicians should interpret results according to the clinical context and consider an adequate work-up (2, 3). A repeated value in the normal range does not ensure that the initial value was truly erroneous.

In addition, substantial evidence indicates that high aminotransferase values are statistically significantly correlated with increased future mortality, suggesting that these blood tests are valuable indicators of long-term prognosis (4, 5). How should one differentiate between a clinically insignificant fluctuation of normality and a predictor of mortality in a single patient? To support their recommendations, Lazo and colleagues should have noted that patients with 2 discordant test results have the same long-term outcome as those with 2 concordant normal test results. Otherwise, normalization cannot be defined as proof of normality.

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: We appreciate the readers’ interest in our study. As indicated by Drs. Arora and Triadafilopoulos, because our study was based on a nonrandom sample of the NHANES III population, selection bias remains a possibility. However, even if selection bias were present, it doesn’t change the fact that, although sociodemographic and other patient-level characteristics may be associated with the absolute level of liver enzymes, such factors are unlikely to affect variability, which is a biological phenomenon. Indeed, we did not observe differences in estimates of variability by demographic or other patient-level characteristics. We agree that because Asians make up only a very small percentage of the NHANES III study population (<5%), it is not possible to draw firm conclusions regarding this population. Results of analyses using the cutoffs for an ALT level of 19 IU/L or greater for women and 30 IU/L or greater for men were essentially identical (31% returned to normal); however, the prevalence of elevated ALT levels using these cutoffs is higher: 17% versus 6%. We agree that defining the reference range for liver tests is an important area of debate (1–3). Finally, although the Gilbert syndrome is a common cause of elevated bilirubin levels, to our knowledge no evidence suggests that it affects the within-person variability of liver enzyme levels. In addition, our results were unchanged when we excluded adults with recent illness or those who fasted more than 8 hours at both examinations.

As pointed out by Dr. Kittisupamongkol, the use of statins can cause abnormal aminotransferase levels. Because NHANES III was conducted from 1988 to 1994, only 4.8% of participants reported taking lipid-lowering medications. Use was not associated with elevated liver enzyme levels or their within-person variability in our study.

Drs. Hong, Wu, and Fan raise an important question regarding factors that affect intraindividual variability. However, our paper focused on describing the intraindividual variability in liver test results in the U.S. population. Further studies are needed to examine factors that may contribute to variability in liver enzyme levels across individuals.

As Drs. Colli and Prati mention, one should certainly be cautious when drawing practice recommendations from epidemiologic studies. The development of guidelines for the reporting of observational studies, such as STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) (4), was the result of similar concerns and the appreciation that much of our clinical and population-based knowledge has been derived from observational studies. We took advantage of a large, multiracial sample of the U.S. population, with a vast amount of rigorously collected data. This study would have been very difficult to conduct otherwise.
Potential Financial Conflicts of Interest: None disclosed.

References

Not Sold on Performance Measures

TO THE EDITOR: I’ve practiced internal medicine with 3 colleagues for 28 years and have no desire to impede the improvement of patient safety and care quality. However, in their recent article, Landon and Normand (1) evoke more questions than answers, leaving me unconvinced of the value of performance measurements and unenthused about embracing them.

Where is the evidence that public reporting of performance measures and pay-for-performance programs improve (rather than worsen) outcomes and reduce (rather than increase) health care costs?

Are these programs the best place to invest limited resources in repairing today’s pressing health care problems, such as caring for the uninsured and addressing the decreased affordability and access of care?

Do these programs encourage career choices in primary care and address shortages of new primary care physicians or accelerate the exodus of currently practicing primary care physicians to other specialties or retirement? Do they boost dwindling physician morale or—more likely—further sap it?

Health plan reports to physicians are currently reported in aggregate, deidentified format. Without referencing an identifiable episode of care, are generic process recommendations (prescribe more generic drugs, order more mammograms) useful in changing physician behavior?

In regard to profit measures, are these programs ultimately designed to enhance insurer profits and investor returns? Are these zero-sum programs? Are payments shifted from poorly measured practices to good ones and does this hold the line on spending? Or do insurers profit by reducing payments to underperforming practices?

Do these programs assuage the nagging suspicion that the major benefit of physician-purchased electronic medical records to insurers is easy access to, acquisition of, and tracking of physician care, process, and prescribing measures? Why should small practices pay to prescribe electronically, when pharmaceutical benefit managers, pharmacy monitoring programs, and the American Medical Association sell the data for profit?

I’m swamped with dreaded requests to complete forms and copy charts for insurers. If patients benefit from these chores, shouldn’t they foot part of the cost, perhaps a premium surcharge returned to physicians to recoup costs?

Should physicians be penalized for patients who choose to be nonadherent, patients whose care and prescribing are shared by multiple physicians, and patients enrolled in self-directed or high-deductible plans who deliberately choose not to spend money on proven preventive measures included in performance assessment?

The United Kingdom experience of rewarding physicians for complying with performance measures resulted in substantial financial gain for physicians at great government cost. Given the current difficult economic conditions in the United States and negative attitudes toward physician compensation, can a similar program be developed here?

Please convince me!

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Potential Financial Conflicts of Interest: None disclosed.

Reference

IN RESPONSE: We sympathize with the sentiments expressed by Dr. Miller. One of us is a practicing physician and is aware of the extra burden imposed by many performance measurement programs with unclear patient benefits. Evidence suggests, however, that the proliferation, measurement, and dissemination of quality information have a substantial impact on measured areas of quality. Indeed, one measure (β-blocker use after a myocardial infarction) has been retired because performance has approached perfection (1). It is highly unlikely that performance on this measure and others would be so high if a spotlight had not been aimed at them. Although pay-for-performance and other programs have been shown to have a generally small impact over short periods, their cumulative effects over time remain unknown. The hope is that better use of population health management techniques and electronic resources, such as electronic health records and decision support, will improve the capacity of physician organizations to achieve higher-quality care.

Although space constraints prohibit us from addressing each of Dr. Miller’s questions, we comment on a few key points. First, given recent evidence that the quality of care produced by the U.S. health care system is suboptimal, we believe not only that limited resources should be directed toward improving care but that this investment should be much more substantial (2–4). Second, we disagree that these programs are at the root of the current primary care crisis. In fact, the United Kingdom has instituted a broad pay-for-performance program that includes substantial additional resources directed toward general practitioners, in part to stabilize the primary care workforce. Like Dr. Miller, we hope that onerous utilization...
management tools and requests used by health plans will diminish with time as the interconnectedness of the health care system is improved. Nonetheless, it is unlikely that these programs will disappear while there is still substantial evidence of overuse and variations in use that cannot be explained by clinical need. Some of these other issues have been discussed in other papers (5). Despite these problems, we believe that increased measurement and transparency are required for improving health systems.

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Potential Financial Conflicts of Interest: None disclosed.

References

CORRECTIONS

Correction: Screening for Type 2 Diabetes Mellitus in Adults

In the recent U.S. Preventive Services Task Force recommendation statement on screening for type 2 diabetes mellitus in adults (1), the Figure contained an error. In the suggestions for practice regarding insufficient evidence, the first sentence should have read: “When BP [blood pressure] is = 135/80 mm Hg [not = 135/80 mm Hg], screening may be considered on an individual basis when knowledge of diabetes status would help inform decisions about coronary heart disease (CHD) preventive strategies, including consideration of lipid-lowering agents or aspirin.” This correction has been applied to the online version of the article.

Reference

Correction: A Leading Medical School Seriously Damaged

In the article by Ernst (1), there is a typographical error in the historical background section: “Duke Gibenau, a Frenchman, postulated in the 1850s that the purity of races would be a determining factor in history.” The name should be Arthur de Gobineau, and his preferred title was “le comte de Gobineau,” translated as either Count Gobineau or Count de Gobineau.

Reference