was flawed in that despite stratifying persons into those with myocardial infarction and those without (unstable angina), the death rates were identical after 2 years (11). The prognostic importance of a very low concentration of cardiac troponin has recently been confirmed by Morrow et al. (8), who found that troponin concentrations that were detectable but below that corresponding to an analytical CV of 10% had adverse prognostic significance. Thus the clinical evidence is in disagreement with the proposal from Apple and Wu (1).

The sole purpose of laboratory medicine is to provide clinically useful information. In this context, it appears that the clinically useful information is that any detectable cardiac troponin has pathologic significance. With the procedures we have outlined here, clinically significant low concentrations of cardiac troponin can now be defined with some confidence.

References
erated from the 10% CV value of 0.03 µg/L to 0.01 µg/L (7). Despite the increased number of patients identified at high risk by use of this lower cutoff, the authors of this last study nevertheless went against their own evidence and recommended use of the higher 10% CV cutpoint.

Although the data from these clinical trials are compelling, the use of a biomarker for acute MI (AMI) diagnosis is different from its use for risk stratification. Although all patients with confirmed AMI will require immediate medical attention, those patients in whom an AMI was ruled out but who are identified as having high future risk can be managed on a more elective basis. It is also important to consider differences in the prevalence and pretest likelihood of patients who present acutely with a suspicion of AMI from those with confirmed ischemic disease where future risks are being assessed. The TACTICS-TIMI Trial enrolled 2220 patients, all with ACS (6). The composite adverse event rate (death, MI, or rehospitalization for ACS) for the enrolled patients was 9.2% at 30 days and 17.7% at 6 months. If the purpose of measuring troponin is only to risk-stratify patients with ACS for adverse events, consideration should be given to lowering the troponin cutoff below the 10% CV value, as suggested by Tate et al. However, these low troponin cutoffs are not likely appropriate for the primary diagnosis of AMI or acute ischemia in a cohort of patients with chest pain, where the prevalence of disease is 15–25% (8–10).

Tate et al. indicated that use of the mean + 3 SD method might produce one false positive among 100 positive test results. This might be an acceptable cutoff in a confirmed ACS population in which 10% of the individuals develop an adverse event at 4 weeks. However, in a chest pain population, the prevalence of an individual having ACS and developing an adverse event is much lower. Consider, for example, the case of testing a population of chest pain patients who have an ACS prevalence of 20% and total population rate of adverse events of 2% (i.e., 10% of the 20% with ACS). If 10,000 patients were screened by a troponin assay with a low cutoff that yields a 1% false-positive rate, 9800 would be negative for ACS, with 9702 having a true-negative troponin result and 98 a false-positive result (1%). The remaining 200 patients would have ACS, and presumably all of these would have a positive troponin. Given these assumptions, the false-positive rate is roughly one-third of all patients with a positive troponin (98 of 298). This high fraction of false positives for this population would be inappropriate given the potential for adverse reactions produced by the therapy, as stated by Tate et al. In actual clinical practice, however, one would also factor in the clinical history, type and severity of chest pain, electrocardiographic changes, and other measures, which would reduce the number of patients undergoing unnecessary therapy.

The principal question then becomes, “Should laboratories have one troponin cutoff for AMI diagnosis and a second, lower troponin cutoff for risk stratification of patients with confirmed ACS?” It is our feeling that administration of antithrombotic and antiplatelet therapies on the basis of a very liberal low biomarker cutoff concentration alone in a low-risk population is difficult to justify. On the other hand, a patient with independent evidence of ischemia, e.g., ST-segment depression on the electrocardiogram, might benefit from therapy even if the troponin is below the AMI cutoff but above the risk stratification cutoff. Although we do not endorse two cutoffs for cardiac troponin, clinicians should be aware of the clinical evidence that any increase in troponin predicts increased cardiovascular risk (11). In summary, we commend the efforts of Tate et al. We believe, however, that this will only lead to further confusion, as their formula is not evidence-based with clinical trial support. One must also not lose sight of the continued need to monitor biomarkers over time, to continue to assess serial patterns documenting an increasing (or decreasing) cardiac troponin pattern after presentation. The impact of lower cutoff values on society, epidemiologic studies, clinical trials, and routine clinical practice are and will continue to be critically important and must not be taken lightly. We sense that there will be more evidence in support of the 99th percentile and 10% CV cutoffs. The 10% CV cutoff can be determined in each laboratory by performing day-to-day precision studies using serum or plasma samples containing low concentrations of troponin. Many manufacturers are now listing the 10% CV cutoff value in their package inserts.

References
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Serologic Testing for Celiac Disease

To the Editor:

We read with interest the report by Martini et al. (1). The authors compared the accuracy of five commercially available IgA anti-tissue transglutaminase (anti-tTG) ELISAs with data from anti-endomysial antibodies (EmAs) in the diagnosis and follow-up of adult patients with celiac disease (CD) and supported the superiority of the EmA test over ELISAs. They reported high sensitivities and specificities for some ELISAs that overlapped those of the EmA test.

We studied 285 children (107 males, 178 females; mean age, 8 years; range, 2–18 years), of whom 134 had CD and had been on a gluten-free diet for 3 (n = 17), 6 (n = 9), 12 (n = 16), 24 (n = 19), or >24 (n = 73) months. Histology in 108 children after 1 year on the diet showed a consistent improvement or complete recovery in all cases. One hundred fifty-one of the patients were children who consecutively underwent upper gastrointestinal endoscopy: CD was histologically diagnosed in 81 and excluded in 70 control cases. Diagnoses included absence of any lesion (n = 20), mild antral gastritis (n = 27), Helicobacter pylori infection (n = 15), reflux gastritis (n = 2), antral erosions (n = 2), Crohn disease (n = 2), graft-vs-host disease (n = 1), and portal hypertension (n = 1).

IgA or IgG anti-tTG autoantibodies in the sera were measured with seven different quantitative ELISAs that use human (h) or murine (m) antigen: h-tTG 1 IgA (EU-tTG IgA; Eurospital S.p.A.); h-tTG 2 IgA (Inova Diagnostics Inc.); h-tTG 3 IgA (Celikey™; Pharmacia & Upjohn); h-tTG 4 IgG (Inova); h-tTG 5 IgG (Celikey); m-tTG 6 IgA (EU-tTG IgA); and m-tTG 7 IgA (Inova). The areas under the ROC curves (95% confidence intervals) and the sensitivities (at cutoffs corresponding to a 95% specificity for control cases) were as follows: 0.88 (0.77–0.97) and 86% (7 arbitrary units) for h-tTG 1 IgA; 0.97 (0.92–1.00) and 96% (20 units) for h-tTG 2 IgA; 0.98 (0.96–1.00) and 95% (1.0 unit/mL) for h-tTG 3 IgA; 0.82 (0.73–0.91) and 54% (6.0 units) for h-tTG 4 IgG; 0.93 (0.87–0.99) and 89% (1.75 units/mL) for h-tTG 5 IgG; 0.92 (0.85–1.00) and 86% (5.0 arbitrary units) for m-tTG 6 IgA; and 0.92 (0.87–0.97) and 86% (10.0 units) for m-tTG 7 IgA. The three CD patients with false-negative results in one of the two more sensitive ELISAs (h-tTG 2 IgA) had negative results with all the other ELISAs. These three patients were EmA-negative, and although they did not have complete deficiency, total IgA values were low enough (0.41–0.82 g/L) to cause false negativity with any assay based on IgA antibody. Fig. 1 shows the h-tTG 2 IgA, m-tTG 7 IgA, h-tTG 3 IgA, and h-tTG 5 IgG results for the CD patients subdivided on the basis of the period of gluten withdrawal. Similar results were obtained with other ELISAs.

The study by Martini et al. (1) was prospective and concerned adults, whereas ours was retrospective and concerned children. Both studies show that ELISAs that use the human antigen have a very high sensitivity and specificity in diagnosing CD in both children and adults (e.g., Celikey had 95% sensitivity and specificity in our hands and 91% sensitivity and 94% specificity in the

![Image](https://via.placeholder.com/150)

Fig. 1. Mean values and SE (error bars) obtained with four different ELISAs in CD children after gluten withdrawal. (A), comparison of anti-tTG antibodies of the IgA and IgG classes; (B), comparison of anti-tTG antibodies of the IgG class that recognize human or murine antigens.

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