High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study

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Summary

Background Suspected acute coronary syndrome is the commonest reason for emergency admission to hospital and is a major burden on health-care resources. Strategies to identify low-risk patients suitable for immediate discharge would have major benefits.

Methods We did a prospective cohort study of 6304 consecutively enrolled patients with suspected acute coronary syndrome presenting to four secondary and tertiary care hospitals in Scotland. We measured plasma troponin concentrations at presentation using a high-sensitivity cardiac troponin I assay. In derivation and validation cohorts, we evaluated the negative predictive value of a range of troponin concentrations for the primary outcome of index myocardial infarction, or subsequent myocardial infarction or cardiac death at 30 days. This trial is registered with ClinicalTrials.gov (number NCT01852123).

Findings 782 (16%) of 4870 patients in the derivation cohort had index myocardial infarction, with a further 32 (1%) re-presenting with myocardial infarction and 75 (2%) cardiac deaths at 30 days. In patients without myocardial infarction at presentation, troponin concentrations were less than 5 ng/L in 2311 (61%) of 3799 patients, with a negative predictive value of 99·6% (95% CI 99·3–99·8) for the primary outcome. The negative predictive value was consistent across groups stratified by age, sex, risk factors, and previous cardiovascular disease. In two independent validation cohorts, troponin concentrations were less than 5 ng/L in 594 (56%) of 1061 patients, with an overall negative predictive value of 99·4% (98·8–99·9). At 1 year, these patients had a lower risk of myocardial infarction and cardiac death than did those with a troponin concentration of 5 ng/L or more (0·6% vs 3·3%; adjusted hazard ratio 0·41, 95% CI 0·21–0·80; p<0·0001).

Interpretation Low plasma troponin concentrations identify two-thirds of patients at very low risk of cardiac events who could be discharged from hospital. Implementation of this approach could substantially reduce hospital admissions and have major benefits for both patients and health-care providers.

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Introduction

Chest pain is a common cause of hospital admission worldwide and is a major burden on health-care resources.1 In the UK, chest pain is responsible for roughly 1 million visits to emergency departments each year.2 Although many of these patients might be suitable for direct discharge from the emergency department,3 current care pathways are unable to rule out myocardial infarction at presentation, and guidelines recommend serial troponin tests requiring hospital admission in most patients.4 Because most of these patients do not have myocardial infarction, this approach leads to a large number of potentially avoidable hospital admissions.4,5

High-sensitivity cardiac troponin assays with high precision at very low concentrations enable accurate quantification of troponin in most healthy people.6,7 These assays could transform the assessment of patients with chest pain through the development of safe and effective strategies to exclude myocardial infarction in the emergency department.8 Although international guidelines9 recommend that cardiac troponin concentrations above the 99th centile be used for the diagnosis of myocardial infarction, some studies suggest that patients with undetectable troponin concentrations are at low risk.10–12

In a prospective study of the use of a high-sensitivity cardiac troponin I assay, we aimed to define a threshold that identifies patients with suspected acute coronary syndrome at presentation who are at low risk of myocardial infarction and potentially suitable for immediate discharge.

Methods

Study design and participants

For the derivation cohort, we prospectively identified consecutive patients with suspected acute coronary syndrome presenting to emergency departments of secondary care hospitals (St John’s Hospital, Western General Hospital) and a tertiary care hospital (Royal
Evidence before this study
Patients with suspected acute coronary syndrome are admitted to hospital for serial cardiac troponin testing to rule out myocardial infarction at the 99th centile upper limit. Cohort studies and a recent systematic review and meta-analysis suggest that patients with undetectable plasma troponin concentrations at presentation are at low risk of myocardial infarction. However, the optimal approach and threshold of cardiac troponin to identify low-risk patients who would be suitable for immediate discharge is unknown.

Added value of this study
We prospectively and systematically assessed a range of troponin concentrations using a high-sensitivity cardiac troponin I assay in consecutive unselected patients with suspected acute coronary syndrome across different health-care settings. We established a threshold (<5 ng/L) that identified a large proportion of patients at very low risk of cardiac events who were admitted to hospital but could have been safely discharged.

Implications of all the available evidence
Low plasma cardiac troponin I concentrations at presentation can enable the immediate and safe discharge of up to two-thirds of patients with suspected acute coronary syndrome. This approach could have major benefits for both patients and health-care providers.

Research in context

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independently reviewed all clinical information, including non-invasive and invasive investigations, and outcomes from presentation to 30 days. Patients were classified as having type 1 or type 2 myocardial infarction, or having myocardial injury according to the universal definition of myocardial infarction. Type 1 myocardial infarction was defined as myocardial necrosis at an isolated presentation with suspected acute coronary syndrome with chest pain or evidence of myocardial ischaemia on an electrocardiogram. Patients with symptoms or signs of myocardial ischaemia due to increased oxygen demand or decreased supply (eg, tachyarrhythmia, hypotension, or anaemia) and myocardial necrosis were classified as type 2 myocardial infarction. Myocardial injury was defined as evidence of myocardial necrosis in the absence of any clinical features of myocardial ischaemia. Any discrepancies were resolved by the adjudication of a third independent reviewer (NLM). Index myocardial infarction was defined as any type 1 myocardial infarction arising during the first clinical episode. Agreement for an adjudicated diagnosis of type 1 myocardial infarction was excellent (κ 0.83, 95% CI 0.80–0.86).

We used regional and national registries to ensure that follow-up was complete for the entire study population. TrakCare (InterSystems; Cambridge, MA, USA) is a regional electronic patient record system, which provides data on all hospital admissions to both tertiary or secondary care hospitals in southeast Scotland. When assessing readmissions with myocardial infarction, all patients were re-adjudicated and classified after review of all clinical notes and investigations, and according to the same criteria used for their index admission. All in-hospital and community deaths are recorded in a comprehensive national database, the General Register of Scotland. Cardiac death was defined as any death due to myocardial infarction, arrhythmia, or heart failure. Cardiac death was defined with ICD-10 codes I20–25, I26, I27, I28, I29, I30, I31, I32, I33, I34–37, I42, I43, I46, and I48–51.

Outcomes
The primary outcome was a composite of index type 1 myocardial infarction, or type 1 myocardial infarction or cardiac death at 30 days. The secondary outcome was 1-year survival from myocardial infarction or cardiac death following the index presentation.

Statistical analysis
We established the negative predictive values for the primary outcome across a range of troponin concentrations starting at 1 ng/L. Patients with ST-segment elevation myocardial infarction and troponin concentrations above the 99th centile on presentation were not included in this analysis. Previous analyses of high-sensitivity cardiac troponin T assay have used a threshold based on the lowest detectable concentration. However, the precision of the high-sensitivity cardiac troponin I assay at low concentrations is sufficient to enable the assessment of a

<table>
<thead>
<tr>
<th>All patients (n=4870)</th>
<th>&lt;99th centile at presentation* (n=3799)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>64 (16)</td>
</tr>
<tr>
<td>Women</td>
<td>2061 (43%)</td>
</tr>
<tr>
<td>Presenting complaint</td>
<td>n=4870</td>
</tr>
<tr>
<td>Chest pain</td>
<td>4043 (83%)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>269 (6%)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>127 (3%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>181 (4%)</td>
</tr>
<tr>
<td>Other</td>
<td>250 (5%)</td>
</tr>
<tr>
<td>≤2 h since onset of chest pain</td>
<td>657/4043 (16%)</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td>n=4277</td>
</tr>
<tr>
<td>Diabetes</td>
<td>669 (16%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1393 (33%)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>1122 (27%)</td>
</tr>
<tr>
<td>Coronovascular accident</td>
<td>337 (8%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>796 (19%)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>1393 (33%)</td>
</tr>
<tr>
<td>Previous revascularisation</td>
<td>n=4269</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>447 (11%)</td>
</tr>
<tr>
<td>Coronary artery bypass graft</td>
<td>245 (6%)</td>
</tr>
<tr>
<td><strong>Current drugs†</strong></td>
<td>n=3004</td>
</tr>
<tr>
<td>Statin</td>
<td>1124 (38%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>926 (32%)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>335 (11%)</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>962 (33%)</td>
</tr>
<tr>
<td>ß blockers</td>
<td>772 (26%)</td>
</tr>
<tr>
<td>Oral anticoagulant</td>
<td>211 (7%)</td>
</tr>
<tr>
<td><strong>Cardiac troponin concentrations</strong></td>
<td></td>
</tr>
<tr>
<td>At presentation (ng/L)</td>
<td>5 (2–19)</td>
</tr>
<tr>
<td>Peak (ng/L)</td>
<td>6 (2–26)</td>
</tr>
<tr>
<td><strong>Electrocardiograph results</strong></td>
<td></td>
</tr>
<tr>
<td>Bundle branch block</td>
<td>278 (7%)</td>
</tr>
<tr>
<td>ST-segment elevation</td>
<td>143 (3%)</td>
</tr>
<tr>
<td>ST-segment depression</td>
<td>307 (7%)</td>
</tr>
<tr>
<td>T-wave inversion</td>
<td>515 (13%)</td>
</tr>
<tr>
<td>Heart rate (beats per min)</td>
<td>82 (23)</td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>128 (26)</td>
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<tr>
<td><strong>Adjudicated diagnosis</strong></td>
<td>n=4870</td>
</tr>
<tr>
<td>Non-ST-elevation type 1 myocardial infarction</td>
<td>651 (13%)</td>
</tr>
<tr>
<td>ST-elevation type 1 myocardial infarction</td>
<td>131 (3%)</td>
</tr>
<tr>
<td>Type 2 myocardial infarction</td>
<td>173 (4%)</td>
</tr>
<tr>
<td>Myocardial injury</td>
<td>301 (6%)</td>
</tr>
<tr>
<td><strong>Admitted to hospital</strong></td>
<td>2978 (61%)</td>
</tr>
<tr>
<td><strong>Outcome at 30 days</strong></td>
<td>n=4870</td>
</tr>
<tr>
<td>Readmission with myocardial infarction</td>
<td>32 (1%)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>75 (2%)</td>
</tr>
<tr>
<td><strong>Readmission with type 1 myocardial infarction or cardiac death</strong></td>
<td>814 (17%)</td>
</tr>
</tbody>
</table>

Data are mean (SD), n (%), or median (IQR). ACE=angiotensin converting enzyme. ARB=angiotensin receptor blocker.
*Excludes patients presenting with ST-segment elevation myocardial infarction. †Drugs patients were already taking at presentation.

Table 1: Baseline characteristics of the derivation cohort
range of thresholds. As such, we selected a threshold on the basis of clinical need rather than assay performance. The trial steering committee prespecified that the cardiac troponin threshold on presentation should achieve a negative predictive value of at least 99.5% for the primary outcome. In sample size calculations, we estimated that 3500 patients would enable us to estimate a negative predictive value of 99.5% with a 95% CI of 99.2–99.7, and that we had 92% power for an α of 0.05 to test the null hypothesis that the negative predictive value was less than 99%.

We assessed the proportion of patients with troponin concentrations below each threshold who reached the primary outcome. We did subgroup analyses to estimate the negative predictive value, stratifying by age, sex, duration of symptoms, cardiovascular risk factors, history of cardiovascular disease, and presence of myocardial ischaemia on the presenting electrocardiogram. We expected the negative predictive value to be close to 100%; therefore, we estimated the proportion by sampling from a binomial likelihood with a Jeffreys’s prior (β distribution shape parameters both equal to 0.5) because intervals produced with this approach have good coverage for proportions close to 0 or 1. We compared survival free from myocardial infarction or cardiac death between patients with troponin

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**Figure 1: Cardiac troponin I concentration at presentation and risk of myocardial infarction**

(A) Negative predictive value of a range of troponin I concentrations at presentation for the composite outcome of index myocardial infarction, and myocardial infarction or cardiac death at 30 days. (B) Cumulative proportion of patients with suspected acute coronary syndrome with troponin concentrations below each threshold.
concentrations above and below the threshold using Cox proportional hazard models adjusted for age and sex. For the validation cohort, we estimated the proportion of patients with troponin concentrations below the threshold determined in the derivation cohort who reached the primary outcome, using the same method. We did the analyses with R (version 3.2.2).

Role of the funding source
The funder had no role in study design, data collection, analysis, or interpretation, or the writing of the report. The trial steering committee and NLM were responsible for the decision to submit the report for publication.

Results
We enrolled 6304 patients with suspected acute coronary syndrome: 4870 in the derivation cohort (table 1, appendix), 1126 in the internal validation cohort (appendix), and 308 in the external validation cohort (appendix).

In the derivation cohort, most patients presented with chest pain that began more than 2 h before troponin testing (table 1, appendix p 10). The median time from arrival in the emergency department to blood sampling for measurement of cardiac troponin was 54 min (IQR 33–85; appendix p 11). Repeat testing was done for 1608 (42%) of 3799 patients with troponin concentrations at presentation of below the 99th centile. Troponin concentrations were above the limit of detection in 4304 (88%) of 4870 patients and were above the 99th centile in 1253 (26%) of 4870 patients, with 782 (16%) judged to have type 1 myocardial infarction and 173 (4%) to have type 2 myocardial infarction. A further 301 (6%) of 4870 patients, with 75 (2%) died from cardiac causes.

In the derivation cohort, low plasma troponin concentrations at presentation gave excellent negative predictive value for the composite endpoint of index type 1 myocardial infarction, or type 1 myocardial infarction or cardiac death at 30 days. A troponin concentration <5 ng/L was present in 2311 (61%) of 3799 patients below the 99th centile at presentation, giving a negative predictive value of 99·9% (95% CI 99·7–100%; appendix p 4). The negative predictive value decreased at higher troponin concentrations and was less than 99·5% at concentrations of 5 ng/L or more.

The negative predictive value of a troponin concentration less than 5 ng/L was similar in men and women and when stratified by age, cardiovascular risk factors, previous cardiovascular disease, or the presence of myocardial ischaemia on the presenting electrocardiograph (figure 2). In 2017 patients with a troponin concentration of less than 5 ng/L and an available electrocardiograph, 1833 (91%) had no evidence of ischaemia. The negative predictive value was similar across groups stratified by GRACE risk score (low risk 99·7%, 95% CI 99·4–100% vs intermediate–high risk 98·4%, 97·0–99·7%). The negative predictive value was lower in the 482 (15%) of 3251 patients who were tested for troponin within 2 h of the onset of chest pain (97·6%, 95% CI 95·8–99·2) than in the 2769 (85%) who had had chest pain for more than 2 h (99·8%, 95% CI 99·6–100·0). In a post-hoc sensitivity analysis in which type 2 myocardial infarction and myocardial injury were incorporated into the primary outcome (a troponin concentration >99th centile irrespective of clinical presentation), a troponin concentration of less than 5 ng/L gave a negative predictive value of 99·4% (95% CI 99·0–99·7).

In the two validation cohorts, a troponin concentration less than 5 ng/L was present in 470 (57%) of 829 and 124 (54%) of 232 patients without myocardial infarction at presentation, and had a negative predictive value of 99·3% (95% CI 98·5–99·9) and 99·8% (98·0–100·0), respectively. Overall troponin concentrations were less...
Compared with patients with peak troponin concentrations between 5 ng/L and the 99th centile (appendix p 7), patients with troponin concentrations of less than 5 ng/L at presentation were less likely to have myocardial infarction or cardiac death at 1 year (p=0·0001; table 2). This association persisted after adjustment for differences in age and sex (p=0·0001; table 2).

### Discussion

In more than 6000 patients with suspected acute coronary syndrome, we have defined a cardiac troponin threshold at presentation that identifies almost two-thirds of patients as being at very low risk of myocardial infarction or cardiac death, and who could potentially be safely discharged from the emergency department. Implementation of this approach would reduce avoidable hospital admission and have major benefits for both patients and health-care providers.

Our study has several strengths that distinguish it from previous studies. First, we prospectively identified all consecutive unselected patients presenting to both secondary and tertiary care hospitals, including patients admitted out of hours. As such, we believe our findings to be both representative and generalisable, and that this approach will be widely applicable across different health-care settings. Second, our study population exceeded the combined number of patients in a meta-analysis,\(^3\) which enabled us to analyse clinically important subgroups, such as patients who present early or have previous cardiovascular disease. Third, we have systematically assessed a range of troponin concentrations to identify a threshold that maximised the proportion of patients to be safely discharged. Finally, we used an assay with the necessary precision under routine laboratory conditions to report troponin concentrations at this threshold and to use this approach to guide patient care.

One of the main limitations was that we did not test the implementation of this threshold in routine clinical practice. Although we determined the number of patients who could be safely discharged, whether clinicians can effectively implement this threshold in clinical practice and whether this will substantially improve rates of discharge, is unknown. Conversely, this threshold should not be implemented in isolation and without regard to appropriate clinical assessment. One in 200 patients still had an index or 30-day event and many had other evidence of myocardial ischaemia. Finally, we have no data about later investigations and treatments. Implementation of this threshold is expected to reduce health-care costs but these benefits might be lost if recurrent presentations or additional outpatient consultations increase.

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**Table 2:** Subsequent myocardial infarction or cardiac death in patients with troponin concentrations below the 99th centile in the derivation cohort

<table>
<thead>
<tr>
<th></th>
<th>&lt;5 ng/L (n=2160)</th>
<th>5 ng/L to 99th centile (n=1453)</th>
<th>Unadjusted hazard ratio (95% CI)</th>
<th>Adjusted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>30 days</td>
<td>0 (0.0%)</td>
<td>6 (0.4%)</td>
<td>0.21 (0.08–0.51)</td>
<td>0.36 (0.13–0.99)</td>
</tr>
<tr>
<td>1 year</td>
<td>6 (0.3%)</td>
<td>19 (1.3%)</td>
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<td></td>
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<tr>
<td><strong>Cardiac death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 days</td>
<td>0 (0.0%)</td>
<td>6 (0.4%)</td>
<td>0.14 (0.06–0.31)</td>
<td>0.41 (0.17–0.98)</td>
</tr>
<tr>
<td>1 year</td>
<td>6 (0.3%)</td>
<td>32 (2.2%)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Myocardial infarction or cardiac death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 days</td>
<td>0 (0.0%)</td>
<td>12 (0.8%)</td>
<td>0.17 (0.09–0.31)</td>
<td>0.41 (0.21–0.80)</td>
</tr>
<tr>
<td>1 year</td>
<td>12 (0.6%)</td>
<td>48 (3.3%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are n (%) unless stated otherwise. The hazard ratios are derived from a Cox regression model using all follow-up data. The median follow up was 427 days (IQR 371–489 days).
A troponin concentration of less than 5 ng/L met our prespecified criteria for a negative predictive value of at least 99.5%. At this threshold, almost two-thirds of patients with suspected acute coronary syndrome could have been discharged with very few cardiac events. Indeed, implementation of this threshold could double the number of patients discharged directly from the emergency department. Lower thresholds did not improve the negative predictive value, and would identify fewer patients suitable for discharge. Increasing the threshold to less than 6 ng/L would identify an additional 6% of patients suitable for discharge, but would double the number of adverse events. Moreover, we have internally and externally validated this threshold, and a troponin concentration less than 5 ng/L seems to be the best threshold for our study populations.

The negative predictive value of our approach was 99.6% across the entire study population, and was similar for men and women, between age groups, and in patients with previous cardiovascular disease. The use of risk scores to stratify patients with suspected acute coronary syndrome is common, but few scores have been developed or validated in this population, in which most patients did not have myocardial infarction. Stratification by GRACE score did not significantly improve the negative predictive value. The negative predictive value remained high in patients with a high pre-test probability of myocardial infarction, suggesting that this approach is probably valid even in higher risk populations. The only factor that seemed to affect the negative predictive value was the time from onset of chest pain to troponin testing. The negative predictive value of patients presenting within 2 h of chest pain was 97.6% but such patients were a small proportion of the overall population and could be addressed by repeat testing.

Of the 2905 patients with troponin concentrations of less than 5 ng/L at presentation, only 12 had an adverse event, of whom ten had an index myocardial infarction with five having clear diagnostic evidence of myocardial ischaemia on the presenting electrocardiograph. Two further patients were in cardiac arrest at presentation and did not survive. We included all consecutive patients without selection to make our safety estimates conservative. However, most of these adverse events would have been identified at presentation and therefore these patients would probably not have been discharged from hospital. This finding also shows the importance of not applying this threshold in isolation and that all available information should be used for clinical decision making.

Our observations complement previous studies of the use of cardiac troponins to triage patients with suspected acute coronary syndrome in emergency departments. The limit of detection and the limit of blank of a high-sensitivity cardiac troponin T assay both show promise for the assessment of patients at presentation.5-11 These studies were included in a systematic review and meta-analysis5 showing that cardiac troponin T concentrations below the limit of detection had a false negative rate of 1-5% and identified 25% of patients as low risk. However, half of the studies used a contemporary troponin assay as a reference and would have missed smaller myocardial infarctions that could only be detected with a high-sensitivity assay, which will inflate the negative predictive value. In our analysis, we judged the final diagnosis using a high-sensitivity assay to ensure robust case ascertainment. Unlike previous studies of the cardiac troponin T assay, our analysis was the first to use a high-sensitivity cardiac troponin I assay, which has greater precision and reproducibility at low concentrations and at the proposed threshold. This will ensure the application of this approach is consistent across sites, analysers, and reagent batches: a prerequisite for use in clinical practice. Furthermore, use of cardiac troponin I at our threshold identifies two-to-three-times more low-risk patients than do previous approaches,20-12,13 which would avoid the need for repeat testing in most patients, or the incorporation of clinical risk scores used in accelerated diagnostic pathways.24-26 Studies are needed assess the clinical and cost-effectiveness of our approach in routine clinical practice.

Contributors
The High-STEACS investigators contributed to the conception or design of the work, or the acquisition, analysis, or interpretation of data. They were all involved in drafting and revising the report.

High-STEACS investigators

Declaration of interests
ASVS has acted as a consultant for Abbott Laboratories. FSA has acted as a consultant for Philips Incubator and has received research funding (non-salaried) from Abbott Laboratories, Alere, Siemens, Ortho-Clinical Diagnostics, Beckman Coulter, and Roche Diagnostics. NLM has acted as a consultant for Abbott Laboratories, Beckman-Coulter, Roche, and Singules. The other authors declare no competing interests.

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