The reason for this is that a small change in Hb A1c is limiting the use of outcome-based or population-based reference limits for test interpretation and will therefore also limit the use of a fixed cutoff value of 48 mmol/mol (6.5% DCCT) for the diagnosis of diabetes for all individuals/patients. The CVwp of stable diabetic patients should especially be used for monitoring purposes. However, as shown by Carlsen et al. (3), the CVwp of stable diabetic patients does not differ significantly from that of healthy individuals, and therefore it is probable that the findings in this study will also refer to stable diabetes patients.

In conclusion, the within-person biological variation of Hb A1c in healthy individuals is very low compared with the between-person biological variation of Hb A1c, affirming the absolute individuality of Hb A1c. The data also suggest that population-based reference limits and fixed cutoff values should be more closely examined for the diagnosis of diabetes. CVs in DCCT units are lower than CVs in SI units and therefore cannot be directly compared.

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1 Nonstandard abbreviations: CEA, carcinoembryonic antigen; FACS, Follow-up After Colorectal Surgery; AUC, area under the curve.

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rence at an early stage, thus increasing the number of recurrences that can be treated with curative intent. However, the threshold we applied to define an abnormal CEA concentration (7 µg/L above the patient’s postoperative concentration at trial entry) was more conservative than current guidelines, so we decided to reevaluate our data to assess retrospectively whether we could have done better by applying a different strategy to interpret the CEA result and trigger further investigation.

We assessed 3 strategies for interpreting the CEA result based on (a) the result of each test individually; (b) the difference between the individual test result and the patient’s own postoperative baseline; and (c) the trend in results over time, calculated by linear regression of the log-transformed CEA values. For each strategy, we assessed the outcome of applying different cutoff thresholds by ROC analysis.

In the CEA arms of the FACS trial, blood CEA was measured every 3 months for 2 years after primary treatment was complete, followed by every 6 months for 3 years. All CEA measurements were made by use of a Siemens Centaur XP analyzer using a chemiluminescence immunoassay, at the John Radcliffe Hospital in Oxford, U.K. (which participates in the national external quality assurance scheme). The analysis we report here is based on 6259 individual CEA measurements in 559 patients (90 of whom experienced recurrence). Patients with <2 CEA measurements, repeat tests, and measurements taken after confirmation of cancer recurrence were excluded.

The ROC curves for each strategy are shown in Fig. 1. This figure illustrates why CEA should not be used as the only method of monitoring, since no strategy achieved 100% diagnostic sensitivity even when applying cutoff thresholds with unacceptably low levels of diagnostic specificity. The figure also shows that calculating the difference from the patient’s baseline concentration is no better than considering the result of each test individually [area under the curve (AUC) 0.73 and 0.74]. However, taking account of the trend in CEA concentrations over time was substantially better than either of the other 2 strategies (AUC 0.90, 95% CI 0.85–0.95). The CEA slope that provided maximal diagnostic sensitivity and specificity was a monthly increase of 1.02 µg/L.

A review of the literature shows that this observation is not new. One of the first papers drawing attention to the value of CEA in detecting covert recurrence of colorectal cancer, published in The Lancet 40 years ago, stressed the importance of the velocity of change (2). A number of subsequent papers have repeated the message that the rate of change in CEA concentrations over time (i.e., the slope of the curve) has diagnostic and prognostic value over and above the absolute concentration at any 1 time (3). However, this has never been taken up as routine practice, perhaps because CEA is still perceived as a diagnostic test and its potential as a monitoring test (i.e., a diagnostic test with a time dimension) (4) has not been widely recognized.

Estimating trend in a series of test results is made much easier by the increasing use of electronic records in clinical practice. For example, in the UK all medical records in primary care facilities (where CEA monitoring was done in the FACS trial) are computerized, and reporting results in terms of trend is no harder than reporting the individual test result. However, estimating the trend in CEA for an individual does require several measurements to be performed. An important clinical implication of these findings is the need to consider increasing the frequency of CEA testing, particularly at the beginning of follow-up (5). The results we report here are based on a retrospective analysis (i.e., we analyzed all the measurements that we had available for each individual) and therefore require prospective validation in an independent dataset before this strategy can be implemented in clinical practice.

Fig. 1. ROC curves for 3 alternative strategies for interpreting CEA test results in detecting colorectal cancer recurrence.
Letters to the Editor

We would welcome collaboration to achieve this end.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

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References


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Assessment of the 99th or 97.5th Percentile for Cardiac Troponin I in a Healthy Pediatric Cohort

To the Editor:

Recent publications on high-sensitivity cardiac troponin in Clinical Chemistry have detailed how to derive an appropriate 99th percentile cutoff (1), highlighted its impact on health outcomes (2), and even questioned the 99th percentile in the diagnosis of acute coronary syndrome (3). Much attention has focused on the selection of a “healthy population,” with differences in high-sensitivity cardiac troponin T (hs-cTnT)1 and hs-cTnI concentrations being evident between sexes in the adult population (1). Accordingly, it is plausible that biological differences in high-sensitivity cardiac troponin concentrations between ethnic groups may also be apparent. This issue has recently been addressed via the study by Gaggin and colleagues, who found no significant difference in hs-cTnT concentrations in a US population (i.e., 98.8% with concentrations <14.0 ng/L) vs a Vietnamese population (98.1% with concentrations <14.0 ng/L) (4). Unfortunately, it is not clear why the derived 99th percentile in the Vietnamese population (19.0 ng/L) was higher than in the US population (15.1 ng/L). The authors noted that there were 3 additional Vietnamese participants with concentrations above the 99th percentile, yet it is unclear whether common statistical techniques were used to remove potential outliers. Although there are publications emphasizing additional laboratory and imaging tests required to define a healthy population (1, 3), there have been no recommendations made regarding what statistical tests to use for the detection of potential outliers when deriving reference intervals with high-sensitivity cardiac troponin assays. To address this point and further explore potential sex and age effects on high-sensitivity cardiac troponin concentrations, we measured hs-cTnI in a group of healthy children in the Canadian Laboratory Initiative in Pediatric Reference Intervals (CALIPER) population (5).

For this study, to avoid potential inclusion of unhealthy individuals when deriving population percentiles, no samples from hospital outpatients were analyzed. Specifically, serum samples from healthy community children (n = 315) between 1 and 18 years of age comprised the healthy cohort (5). There was equal representation of children age 1–9 years (n = 157) and 10 to <19 years (n = 158) and both sexes within these age groups (<10 years, 79 females/78 males; ≥10 years, 76 females/82 males). The serum samples were analyzed with the Abbott hs-cTnI assay [see (2) for analytical performance]. Visual examination of the data revealed 2 outliers (251 and 313