Accuracy in Cholesterol Assays

As a subject that once held limited appeal for labora-
torians, the assay of cholesterol has taken on new importance. 
From the medical community has begun to act upon the findings 
of recent studies showing that blood cholesterol strongly 
influences the development of atherosclerosis. The NIH 
Consensus Development Conference on Lowering Blood 
Cholesterol, after reviewing the findings of the Lipid Res-
search Clinics Coronary Primary Prevention Trial (LRC-
CPPT) and related studies, reached two conclusions: supra-
normal blood cholesterol is a major cause of coronary artery 
disease, and lowering it will reduce the risk of heart attacks 
attributable to coronary heart disease (CHD). In 1985 the 
Consensus Conference panel recommended classifying and 
appropriately treating adults with a blood cholesterol above 
the 75th percentile as borderline high risk and above the 
90th percentile as high risk (1). A sweeping national cam-
paign was launched in late 1985 with the formation of the 
National Institutes of Health (NIH) National Cholesterol 
Education Program (NCEP) to alert the medical profession 
and the public to the hazards of having a high blood 
cholesterol level (2). The purpose of the campaign is to 
identify and treat all adults who are at increased risk for 
CHD because of their increased blood cholesterol.

Both the Consensus Conference and the NCEP have 
redefined the reference limits to be used with cholesterol 
measurements. The upper limits currently recommended by 
the NCEP (3), 2.00 and 2.40 g/L (defining borderline-high 
and high blood cholesterol, respectively), are much farther 
removed from the tails of the cholesterol distribution than 
the 97.5% reference limits adopted for most other laboratory 
tests. In fact, when applied to the population at large, these 
values fall at approximately the 40th and 75th percentiles, 
respectively. The reports of Kroll, Ruddle, and Elin in this 
and the preceding issue (4, 5) clearly illustrate the difficulty 
that is created by use of reference limits near the middle of 
a test's distribution. The difficulty relates to the much larger 
fraction of the population that is affected by an error in a 
test result in the middle of a distribution than in the tails of 
the distribution. From their data, the absolute methodolog-
ical bias of the cholesterol assay must be kept below 1.6% to 
keep the percentage of the patient population misclassified 
below 3%.

Cholesterol assay methods in routine use have rarely 
achieved this level of accuracy. However, with careful 
attention to assay standardization and quality control, such 
accuracy appears to be possible. The Lipid Research Clinics 
(LRC) laboratories, over the 11-year life of the LRC, 
achieved an overall bias of <1.7% in cholesterol values as 
compared with the CDC reference values (6). The LRC have 
used standards and quality-control sera that have estab-
lished target values traceable to the CDC reference method 
in conjunction with a highly standardized continuous flow 
Liebermann–Burchard method. Similarly, using automated 
laboratory instrumentation and a state-of-the-art enzymatic 
method, the Air Force HEARTR Study was able to achieve an 
overall mean bias of <1.3% when compared with the CDC 
reference values (7).

The necessity of trying to achieve such stringent assay 
standards as those proposed by Kroll et al. (4) may be 
questioned. Clinicians have to contend with variables other 
than laboratory inaccuracy in the interpretation of choles-
terol results. There is the problem of intra-individual vari-
ability of cholesterol, which averages approximately 8% (8). 
With such variability, many replicate measurements are 
required to yield a value guaranteed to lie within 1.6% of 
the true value. Furthermore, biases can be introduced by 
postural change. Increases of 8 to 12% when the subject goes 
from the recumbent to the standing position have been 
reported (9, 10). In addition, anticoagulants may cause 
changes of as much as 5% in the reported value for choles-
terol (11). Finally, the influences of various drug therapies 
on cholesterol must be considered. The effects of these other 
factors on cholesterol concentrations make the provision of 
an extremely accurate analytical result appear less critical.

The NCEP Laboratory Standardization Panel (LSP) has 
set more moderate goals for the accuracy required of chole-
terol assays, recommending that the bias of cholesterol 
measurement methods currently in use should not exceed ±5% 
from the true value and should be no greater than ±3% from 
the true value within five years (12). The LSP noted that 
approximately half of the values from clinical laboratories 
that participated in a 1985 survey exceeded 5% from the true 
value.

This does not detract from the overall value of the study 
of Kroll and coworkers. They have pointed out a problem that 
will plague efforts to diagnose and treat patients with above-
normal cholesterol according to present national guidelines 
and have suggested an excellent approach for assessing the 
effects of laboratory bias. Clearly, clinical laboratories 
across the country will have to mount a significant effort to 
meet even the moderate goals suggested by the LSP for 
accuracy in cholesterol assays. The LSP has enumerated the 
resources that are available to help in the standardization of 
cholesterol measurements in all U.S. clinical laboratories 
(12). Clinical chemists must become familiar with these 
resources and utilize them efficiently if these goals are to be 
met.

References
1. NIH Consensus Development Conference. Lowering blood cho-
2. Lanfant O. A new challenge for America: the National Choles-
3. National Cholesterol Education Program: report of the National 
Cholesterol Education Program expert panel on detection, evalua-
tion and treatment of high blood cholesterol in adults. Arch Intern 
4. Kroll MH, Ruddle M, Elin RJ. Analytical bias for cholesterol and 
the percent of the population deemed at risk for coronary heart 
6. Haniline Jr A, Karon JM, Winn CL, Gill JB. Accuracy and comparabil-
ity of long-term measurements of cholesterol. Clin Chem 


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