CardioChek®

# Cholesterol Reference Method Laboratory Network (CRMLN) Overview

**BACKGROUND:**

**Cholesterol Reference Method Laboratory Network (CRMLN) — General Information**

With guidance from the US Centers for Disease Control and Prevention (CDC), headquartered in Atlanta, Georgia, USA, the CRMLN is a network of labs in the US and around the world that was established to certify manufacturers of clinical diagnostic products that measure Total Cholesterol (TC), HDL Cholesterol (HDL-C), or LDL Cholesterol (LDL-C). Certification provides evidence of traceability to the National Reference System for Cholesterol (NRS/Chol).

The CRMLN also issues guidelines regarding the performance of products used to analyze blood samples for specific lipid levels. The CRMLN uses reference methods that are rigorously standardized to the CDC reference methods to ensure uniformity of lipid measurements worldwide.


**Certification Protocol for Manufacturers**

The National Cholesterol Education Program (NCEP) Adult Treatment Panel has recommended specific medical decision points for serum cholesterol to aid in the detection, evaluation, and treatment of people with elevated cholesterol levels. These medical decision points were derived from national population studies in which the cholesterol assays were standardized to the Abell-Kendall reference method at the Centers for Disease Control and Prevention (CDC), a major component of the National Reference System for Cholesterol (NRS/CHOL). The NCEP Laboratory Standardization Panel has urged that clinical laboratories standardize their assays to the NRS/CHOL accuracy base to properly classify patients according to the NCEP medical decision points. The panel agreed that standardization could be achieved most effectively through the manufacturers of analytical instruments and reagents. To facilitate standardization, CDC requested the Cholesterol Reference Method Laboratory Network (CRMLN) provide access to the NRS/CHOL for both manufacturers and clinical laboratories. The CRMLN then developed a method comparison protocol leading to certification for analytical systems, reagent applications, calibrators, and reference materials.

# Criteria for CRMLN Cholesterol Certification

The CRMLN established test protocols use accepted "gold standard" reference methods. In order to be CRMLN certified, results must meet the following criteria:

### Table 1: CRMLN Cholesterol Certification Criteria

| Parameter | Total Cholesterol | HDL Cholesterol | LDL Cholesterol |
|---|---|---|---|
| $R^2$ | >0.975 | >0.975 | >0.975 |
| Bias at medical decision points | ≤3% at 200 mg/dL (5.18 mmol/L)<br>≤3% at 240 mg/dL (6.22 mmol/L) | ≤5% at 40 mg/dL (1.04 mmol/L)<br>≤5% at 60 mg/dL (1.55 mmol/L) | ≤4% at 100 mg/dL (2.59 mmol/L)<br>≤4% at 130 mg/dL (3.37 mmol/L)<br>≤4% a t 160 mg/dL (4.14 mmol/L) |
| Average % bias | ≤3% | ≤5% | ≤4% |
| Among-run CV | ≤3% | ≤4% | ≤4% |

### NCEP Guidelines for Total Error (TE)

The National Cholesterol Education Program (NCEP) of the National Institutes of Health (NIH) has established test protocols and guidelines for acceptable deviation from "truth" (defined as the National Reference System for Cholesterol [NRS/Chol] reference value).

These guidelines state that TE should be within the following limits from the reference value when these test protocols are followed:

### Total Error Criteria

| | Total Cholesterol | HDL Cholesterol | LDL Cholesterol |
|---|---|---|---|
| Total Error | ≤8.9% | ≤13% | ≤12% |

# NCEP - Adult Treatment Panel (ATP) III Guidelines for Cholesterol Management

In addition to device certification guidelines, NCEP also publishes patient care guidelines and recommends a complete lipid profile for coronary heart disease risk assessment. Periodically NCEP updates its clinical guidelines for cholesterol testing and management. However, these current guidelines are not meant to replace the physician's clinical judgment; based on all the clinical and diagnostic information available, the physician must ultimately determine the appropriate treatment for each patient.

## ATP III Classification of LDL, TC, and HDL Cholesterol[1]

| LDL Cholesterol—Primary target of therapy | | |
|---|---|---|
| **US Units** | **SI Units** | |
| <100 mg/dL | <2.59 mmol/L | Optimal |
| 100-129 mg/dL | 2.59-3.35 mmol/L | Near optimal/above optimal |
| 130-159 mg/dL | 3.36-4.12 mmol/L | Borderline high |
| 160-189 mg/dL | 4.13-4.91 mmol/L | High |
| ≥190 mg/dL | ≥4.92 mmol/L | Very high |
| **Total Cholesterol** | | |
| <200 mg/dL | <5.18 mmol/L | Desirable |
| 200-239 mg/dL | 5.18-6.20 mmol/L | Borderline high |
| ≥240 mg/dL | ≥6.21 mmol/L | High |
| **HDL Cholesterol** | | |
| <40 mg/dL | <1.04 mmol/L | Low |
| ≥60 mg/dL | ≥1.55 mmol/L | High |

1. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486-2497.

## Why Certify Products for Accuracy — What Makes Accuracy and Precision so Necessary?

Accuracy and precision are extremely important in the field of science; without them there would be no way to determine if what is being measured is true. Accuracy refers to the degree of conformity of a measured or calculated quantity to an actual (true) value.

Precision, on the other hand, is the degree to which repeat measurements or calculations yield the same or similar results. Accuracy is closely related to precision, but it's not the same thing. A result is said to be valid when it is both accurate and precise.

Let's look at a common analogy to illustrate the difference between accuracy and precision.

**Figure 1. High accuracy with high precision**
When results have both a high degree of accuracy and precision, they will be clustered together around the target area (true value).

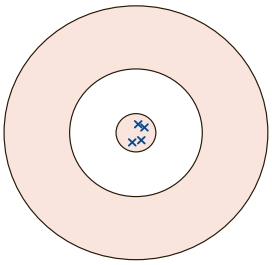


**Figure 2. Low accuracy with high precision**
Results that are precise will be clustered together, but because they are inaccurate they will not be near the target area (true value).

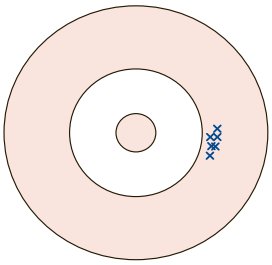
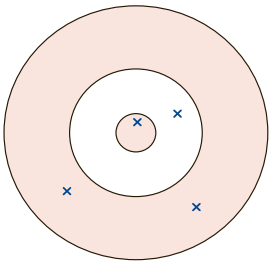


**Figure 3. Low accuracy with low precision**
Results with both low precision and low accuracy will be scattered about, and may not be near each other or the target area.



## How is Accuracy Determined?

A primary method for determining accuracy is to compare test results from one method to the values achieved from a method that is accepted as accurate, oftentimes referred to as the gold standard.

# Variables that Influence Accuracy

**Bias**, a function of accuracy, is used to describe how far results are from the true value, but bias does not tell the whole story. The precision of the results must also be considered.

Precision is often discussed in terms of the **standard deviation (SD)** and the **percent coefficient of variation (% CV)**. SD is a measure of how spread out the data points of a sample are.

$$1SD = \sqrt{\frac{\sum (x - \bar{x})^2}{n - 1}}$$

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Statistics demonstrate that in normally distributed data sets, 68% of the results will fall in a range that is within 1 SD of the mean and 95% of the results will fall within 2 SD of the mean.


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The % CV is another measure of the variability of data that allows comparison of data across different data sets. The % CV is defined as SD as a percent of the average value.

$$\%CV = \frac{1SD}{\bar{x}} \times 100$$

Once the **accuracy (bias)** and **precision (% CV)** of an instrument have been calculated, one can determine a critical measurement known as the total error (TE).

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The calculation for TE is:

$$TE = \%\ Bias + 1.96\ \%\ CV$$

The TE is important in determining the acceptable range of systematic and random errors.

The **coefficient of determination (R2)** is a statistical measure of how well a model approximates real data points. In other words, R2 shows what is generally referred to as the "goodness of fit" of a model. In cases with a single variable, it is the square of the correlation coefficient (r), which shows the tendency of two variables to move together. R2 can range from 0 to 1; the closer to 1 the better the model fits the data.

## Please Contact your Distributor for More Information.

References:

1. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285(19):2486-2497.
2. National Reference System for Cholesterol, Cholesterol Reference Method Laboratory Network. (2004), *Total Cholesterol Certification Protocol for Manufacturers - Revised - [Brochure].*

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