

## Myths and Facts of Direct LDL Cholesterol Testing

LDL cholesterol (LDL-C) results have been determined for many years by calculation using the Friedewald formula. These results have been used in the epidemiologic studies and therapeutic trials that form the backbone of hyperlipidemia management today. Recently, homogeneous methods to directly measure LDL-C have been developed.

**Friedewald formula:**  $LDL-C = TC - HDL - (TG/5)$ , where TG/5 is a good approximation of very low density lipoprotein cholesterol (VLDL-C) when TG is less than 400 mg/dL.

**Myth:** A direct LDL-C measurement is more accurate than a calculated LDL-C value.

**Fact:** Direct methods are no better than the Friedewald-calculated value when TG is <400 mg/dL.

There is similar agreement between calculated or direct methods with the CDC reference method.<sup>1</sup> Imprecision of calculated and direct methods are also similar.<sup>1</sup>

The direct methods offered no improvement compared with Friedewald-calculated LDL-C for classifying individuals into treatment groups on the basis of cutoffs recommended by the National Cholesterol Education Program (NCEP). The following table shows that the Friedewald-calculated LDL-C results were just as good if not better than the four direct LDL-C methods used.<sup>2</sup>

Classification according to NCEP cutoffs					
Correct classification for individual measurement vs Reference Method, %					
Classification group	Genzyme N-Geneous LDL	Reference Diagnostics LDL	Roche LDL-C plus	Sigma EZ-LDL	Friedewald LDL-C <sup>a</sup>
<130 mg/dL	98	100	92	76	96
130-160 mg/dL	69	67	75	75	75
>160 mg/dL	91	91	94	100	100

<sup>a</sup>Calculated for specimens with TG concentrations <400 mg/dL.

A recent expert review made the following conclusions about direct LDL-C methods:

“Limited evaluations to date raise questions about their reliability and specificity, especially in samples with atypical lipoproteins. Before the homogeneous assays can be confidently recommended to replace the calculation in routine practice, more evaluation is needed.”<sup>1</sup>

**Myth:** Direct LDL-C can be measured when individuals have not fasted.

**Fact:** Direct LDL-C variability measured with currently available tests is too great among individuals to recommend its measurement in nonfasting individuals.

The direct methods offer no advantage over a Friedewald-calculated value at <400 mg/dL TG. The practical utility of these direct methods is their potential ability to measure LDL-C in specimens with moderately increased TG for which the Friedewald calculation does not apply. However, all the methods exhibit progressively poorer performance as the TG concentration of the specimens increased. Measured LDL-C in nonfasting specimens is not recommended because of variable interferences among individuals.<sup>2</sup>

**Myth:** The NCEP ATP III Guidelines recommend using a direct LDL-C method.

**Fact:** No such recommendation appears in the ATP III report.

While the NCEP ATP III report recognizes the theoretical benefit of a truly accurate direct LDL-C that could be used in the nonfasting state, it concluded that, “such methods will grow in use but still require careful quality control and monitoring.”<sup>3</sup> The report further commented that for initial testing, fasting TG provide additional important information.<sup>3</sup>

NCEP emphasizes the value of calculated LDL-C determined by the Friedewald equation: “ATP III recommends measurement of LDL cholesterol for initial classification. This measurement requires a fasting lipoprotein profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides).”<sup>3</sup>

**Myth:** Direct LDL-C methods solve the problem of not being able to report LDL-C values when TG values are >400mg/dL.

**Fact:** Currently available direct LDL-C methods suffer from various inaccuracies when TG exceeds 400mg/dL.<sup>1,2</sup>

NCEP concluded in the ATP III report that, “for persons with triglycerides over 400 mg/dL, estimation of LDL cholesterol by this method is not accurate. A more complex ultracentrifugation method in a specialized laboratory is required for accuracy. In addition, individuals with significantly elevated triglycerides need further evaluation.”<sup>4</sup>

In the NHANES III study, a nationally representative survey of lipid levels in Americans, significantly fewer than 5% of adults had TG levels exceeding 400 mg/dL.<sup>5</sup> Thus, the calculated method serves the needs of measuring LDL-C in the vast majority of individuals.

## References

1. Nauck M, Warnick GR, Rifai N. Methods for measurement of LDL-cholesterol: a critical assessment of direct measurement by homogeneous assays versus calculation. *Clin Chem* 2002; 48:236-54.
2. Miller WG, Waymack PP, Anderson FP, Ethridge SF, Jayne EC. Performance of four homogeneous direct methods for LDL-cholesterol. *Clin Chem* 2002; 48:489-98.
3. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 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; 285:2486-97.
4. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 1-284. 2001. National Institutes of Health.
5. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Appendix III-A: distributions of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides in the U.S. adult population, NHANES III data (1988-1994) (serum). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. National Institutes of Health, 2001: III-A-1-4.