

January 2019**Calculated LDL Reliability**

Insoluble lipids, including cholesterol and triglycerides are transported in plasma by means of lipoproteins. The five major lipoproteins include chylomicrons, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL).

The standard lipid profile includes results for total cholesterol, HDL cholesterol (HDL-C), calculated non-HDL cholesterol, calculated LDL cholesterol (LDL-C), and triglycerides. Additionally, the total-to-HDL ratio is provided as an additional tool for risk stratification. The biological variability of total cholesterol measurement is up to 10%, depending on a number of factors including acute illness, stress, smoking, and posture during specimen collection. Triglyceride levels fluctuate more widely than cholesterol values due to diurnal variation. Total cholesterol and LDL-C are not subject to diurnal variation, but are affected by seasonal variation. Levels increase as much as 5% in winter.

Of the five lipoproteins, LDL carries the majority of cholesterol and LDL-C lowering therapy is recommended to reduce the risk of cardiovascular events. Standard protocol for most laboratories performing lipid profile analysis includes calculation of the LDL-C value when triglycerides are below 400 mg/dL. This calculation is based on the Friedewald equation:

$$\text{LDLC} = \text{Total cholesterol} - \text{HDL-C} - \frac{\text{Triglycerides}}{5}$$

For several decades, the Friedewald equation has been accepted as an accurate alternative to less cost-effective and labor intense direct measurement of LDL cholesterol. As noted, triglycerides must be <400 mg/dL in order for the laboratory to provide a calculated LDL-C result, because the Friedewald equation increasingly underestimates the LDL-C value as triglyceride levels increase. A falsely low LDL-C level may result in suboptimal therapy or undertreatment based on cholesterol-lowering guidelines. Within the last few years, analyses have also shown the Friedewald equation to be less reliable at lower LDL-C levels of < 70 mg/dL. As LDL-C decreases below 70 mg/dL, calculation of LDL-C leads to moderate underestimation of true LDL-C and this increases substantially as LDL-C decreases further. For example, a calculated LDL-C of 70 mg/dL may vary from 60 to 86 mg/dL on direct measurement, while a calculated LDL-C of 30 mg/dL may vary from 24 to 60 mg/dL.

Clinicians who evaluate lipid disorders should be aware of the limitations of calculated LDL-C values. Considering these limitations in situations of elevated triglycerides and low LDL-C, non-HDL-C has been suggested as a more reliable alternative for assessment of risk and treatment goals. Non-HDL-C includes all atherogenic lipoprotein-associated cholesterol.

Lipid panel testing is performed daily by Saint Luke's Regional Laboratory. Specimen requirement is one serum gel tube or green top (heparin) tube. Measured or direct LDL-C is available through a reference laboratory with specimen requirement of one plain red top or serum

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gel tube (preferred), lavender top (EDTA) or green top (heparin) tube. A recent analysis performed, revealed a total of 9000 lipid panel tests ordered in the month of November, 2018 with approximately, 33 concurrent direct LDL tests requested. Of these 9000 lipid panel tests performed, approximately 7 showed serum triglyceride levels > 400 mg/dL.

New International Guidelines for Polycystic Ovarian Syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is common condition affecting 10% of woman during their reproductive years. The presenting symptoms of PCOS are varied and may include anxiety, depression, irregular menstrual cycle, infertility, and metabolic problems. Approximately two-thirds of women with PCOS go undiagnosed partly due to existence of individual guidelines issued by various specialty groups in different countries, resulting in confusion and failure to provide necessary information, for accurate diagnosis.

With an intent to be comprehensive, and reduce confusion, the international evidence-based guidelines for assessment and management of PCOS were issued earlier in 2018. The guidelines recommend satisfying two of the three Rotterdam Criteria, namely presence of oligo- and/or anovulation, clinical and/or biochemical signs of hypergonadism, and polycystic ovaries (by ultrasound), for the diagnosis of PCOS. The guidelines recommend against the use of ultrasound for confirmation PCOS

in adolescent patients due to high incidence of multi-follicular ovarian morphology. Adolescents with features of PCOS but not meeting the diagnostic criteria, instead may be considered at “increased risk” with reassessment advised at or before full reproductive maturity, 8 years post menarche.

The biochemical signs in Rotterdam Criteria refers to the use of appropriate laboratory testing for best identification of hyperandrogenism. These include calculated free testosterone level, free androgen index (FAI), or calculated bioavailable testosterone. For accurate measurement of serum levels, high quality assays such as liquid chromatography-mass spectrometry (LCMS), mass spectrometry, and extraction/chromatography immunoassays are recommended. Pre-analytical factors such as use of hormonal contraceptives should be considered for accurate interpretation of the results, due to their effect on sex-binding globulin and altered production of gonadotrophin-dependent androgen. Withdrawal from hormonal contraceptives for at least 3 months or longer is recommended before laboratory measurement.

The inclusion of FAI in the guidelines as an option is controversial due to the observation that FAI performs differently in men compared to women. If free or total testosterone is not elevated, androstenedione or dehydroepiandrosterone sulphate (DHEAS) assays may be considered as an alternate. Overall, the interpretation of androgen levels need to be guided by the references ranges provided by the testing laboratory, acknowledging that the ranges for different methods and laboratories vary widely.

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Heartland Virus Seroprevalence

The anti-Mullerian hormone (AMH), a regulator of folliculogenesis, and produced by granulosa cells, normally increases during infancy with levels plateauing at adolescence until age 25 years. Due to an inverse proportional relationship with age, serum AMH levels have recently gained attention especially in women 25 years and older, as a marker of ovarian reserve. It has been applied in various clinical settings including assisted reproduction, menopause, reproductive disorders, and assessment of ovarian damage/toxicity.

However, in a recent study AMH levels provided only a modest ability to diagnose PCOS (Arch Gynecol Obstet 2018;298:207), when used as an alternate to ultrasonography. Additionally, many different AMH assays exist requiring standardization and correlation of fluctuating levels with age/ menopausal state. Consequently, the guidelines have recommended against use of AMH levels as a replacement for ultrasonography. Future studies including large multi-center trials may be instrumental in providing good standardization of AMH assays and define its role in PCOS.

Since the recommended methods for PCOS laboratory testing are complex, these are not performed at Saint Luke's Hospital and are sent-out to a reference laboratory. For more information, please call Saint Luke's reference laboratory.

Heartland virus, first identified in northwest Missouri in 2012, has a similar presentation to ehrlichiosis and is also transmitted by a tick vector. A recently published study (Lindsey, et al, Emerg Infect Dis. 2018; 25: 358-60) estimates the seroprevalence of Heartland virus in 10 northwest Missouri counties at 0.9%. The conclusion is based on samples collected from 487 blood donors by Community Blood Center of Kansas City with testing and data analysis done jointly with CDC. Since the clinical spectrum of this disease remains to be determined including existence of asymptomatic infection, Heartland virus should be considered in patients with tick exposure and acute febrile illness with leukopenia or thrombocytopenia not responding to doxycycline therapy or attributable to another infection.

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