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Laboratory News and Analysis for Clinicians December 2020

A New, Improved Calculation for Low-density Lipoprotein Cholesterol (LDL-C)

Jeff Pearson, MD, Medical Director of Laboratories

Heart disease remains the leading cause of the death in the United States, even during the pandemic, with an estimated 655,000 deaths in 2018. Although cardiovascular heart disease (CVD) is multifactorial, one of the most common targets to monitor and treat with is LDL-C. Epidemiologic data has shown a graded relationship between elevations in LDL-C and the occurrence of CVD. Lowering the LDL-C reduces the risk of CVD, both in patients with and without a history of a cardiovascular event.

Although direct measurement of LDL-C is available, the majority of lipid evaluations are done by the AMA defined lipid panel (CPT 80061) that includes a calculated LDL-C. Most labs use the Friedewald equation to calculate the LDL-C. The Friedewald equation rapidly loses accuracy when triglycerides (TG) are less than 70 mg/dl or greater than 400 mg/dl. The impact of elevated TG on this calculation has been the primary reason for a recommendation of fasting for the lipid panel.

The NIH, in collaboration with LabCorp, the Mayo Clinic and other institutions has come up with a new equation and validated it on over 250,000 patient samples. The NIH LDL-C equation is valid with TG up to 800 mg/dl and is not affected by fasting. In their publication they estimate 35% fewer misclassifications into treatment groups when the TG are between 400-800 mg/dl. At Bronson on the standard lipid panel (Epic LAB18) we will change from TG >400 mg/dl to >800 mg/dl to initiate a reflex order for the measured LDL. We will also continue to offer the lipid panel without the reflex option (Epic LAB2211).

The Bronson Laboratories plans to implement the new equation on January 5, 2021.

Summary

- The NIH LDL-C equation is more accurate and allows better classification into risk and treatment groups for cardiovascular heart disease
- Patient fasting is not required or even recommended
- The new equation will result in cost savings with fewer direct LDL-C measurements being needed

Reference:

A New Equation for Calculation of Low-Density Lipoprotein Cholesterol in Patients With Normolipidemia and/or Hypertriglyceridemia
Maureen Sampson, BS[1]; Clarence Ling, PhD[1]; Qian Sun, PhD[1]et al *JAMA Cardiol.* 2020;5(5):540-548. https://www.labcorp.com/provider-services/resources/publications/new-equation-calculation-low-density-lipoprotein

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New Targets for Blood Culture Identification Panel

Dr. Christopher Wienczewski

The Department of Microbiology recently upgraded to the Biofire FilmArray Blood Culture ID 2.0, which allows for the detection of several new organisms and resistance targets. The full detection panel (see Table 1.) and specific blood draw requirements can be found in the Bronson lab test catalog: https://bronsonlab.testcatalog.org/show/BCUL-Blood-Culture. This technology allows for rapid speciation of target organisms in approximately 75 minutes. This time does not include the initial step in blood culture processing, which takes approximately 6 to 26 hours depending on the organism.

Blood cultures are an important component of patient management and the interplay between clinical laboratory, clinicians, and pharmacy has many layers. A quick review of the overall process will broaden understanding and improve communication between providers while setting realistic expectations for laboratory testing and turn-around times.
The patient's blood culture bottles are received in the laboratory and placed into the BD Bactec FX. This large instrument holds hundreds of patient samples and constantly monitors changes in pH as a surrogate marker for organism growth. The earliest organism growth is detected is about 6 to 8 hours for Gram negative rods and around 12 hours for Gram positive cocci. Overall, most organisms are detected in 18 to 26 hours.

Once an organism is detected, multiple additional steps are performed off of the original bottle: a Gram stain is generated, appropriate culture plates are prepared, and a portion of the specimen is loaded onto the Biofire FilmArray Blood Culture instrument. Again, in approximately 75 minutes, most of the organisms will be identified along with some resistance targets (if applicable). The results are called to the floor and simultaneously transmitted to Pharmacy, allowing pharmacists to play an active role in patient management by ensuring appropriate antibiotic utilization. As a quality control metric, the Gram stain is compared with the Biofire result. This is especially important when multiple organisms are present.

In a small number of cases, the Biofire instrument cannot accurately classify organisms. In these instances, organisms are taken from the culture plates and processed on the Maldi-TOF platform. Susceptibility testing is also performed on the organisms from the culture plates, which takes approximately 12-24 hours to complete.

All results are reported under the blood culture order and may include: Gram stain result, blood culture ID panel result/ Maldi-TOF result, and susceptibility testing.

Table 1. Updated targets

Gram Negative Bacteria	Gram Positive Bacteria	Yeast	Antimicrobial Resistance Targets	
Acinetobacter calcoaceticus-baumannii complex	**Enterococcus faecalis**	Candida albicans	**CTX-M**	**Extended Spectrum Beta-Lacatam Resistance**
Bacteroides fragilis	**Enterococcus faecium**	**Candida auris**	**IMP**	**Carbapenem Resistance**
Enteric bacteria	Listeria monocytogenes	Candida glabrata	KPC	Carbapenem Resistance
Enterobacter cloacae complex	Staphylococcus spp.	Candida krusei	**mcr-1**	**Colistin Resistance**
Escherichia coli	Staphylococcus aureus	Candida parapsilosis	**mecA/C**	**Methacillin Resistance in Non-*Staphylococcus aureus***
Klebsiella aerogenes	**Staphylococcus epidermidis**	Candida tropicalis	**mecA/C and MREJ (MRSA)**	**Methacillin Resistance**
Klebsiella oxytoca	**Staphylococcus lugdunensis**	**Cryptococcus neoformans/gattii**	**NDM**	**Carbapenem Resistance**
Klebsiella pneumoniae group	Streptococcus spp.		**OXA-48-like**	**Carbapenem Resistance**
Proteus spp.	Streptococcus agalactiae (Group B)		vanA/B	Vancomycin Resistance
Salmonella spp.	Streptococcus pneumoniae		**VIM**	**Carbapenem Resistance**
Serratia marcescens	Streptococcus pyogenes (Group A)			
Haemophilus influenzae				
Neisseria meningitidis				
Pseudomonas aeruginosa				
Stenotrophomonas maltophilia				

Bolded organisms are new or revised

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CSF Flow Order and Process Update

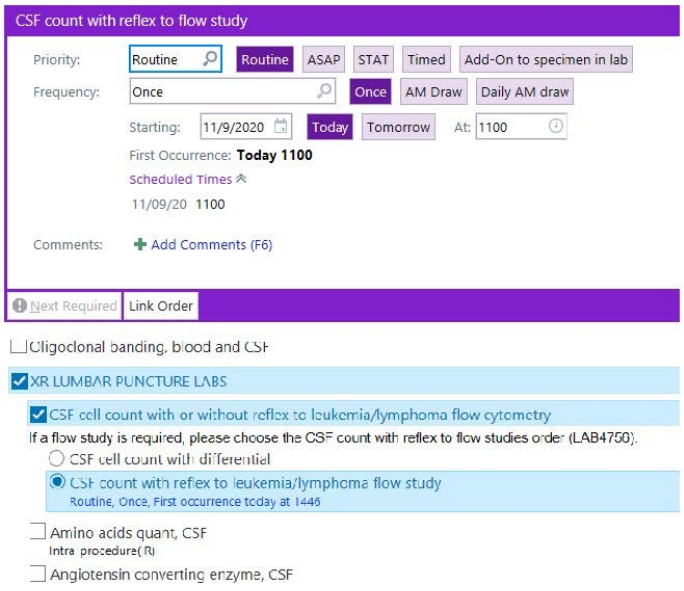
Dr. Ellen Flatley M.D., Hematopathologist

Flow cytometric analysis of cerebrospinal fluid (CSF) can be a valuable tool in the diagnosis, prognostication and treatment-planning of hematopoietic neoplasms. Challenges exist, however, including the often low cellularity of these specimens and the in vitro cellular environment of this fluid that leads to relatively quick loss of cell viability compared to blood and other body fluids.

An internal review of CSF flow cytometric analysis reports lead by Dr. K. Dunning M.D., found that those without elevated white blood cell counts resulted in insufficient material for interpretable results (note, this finding is common, and not specifically unique to this system). Therefore, in keeping with our ongoing goal of appropriate lab utilization, and after discussion with our hematopathology partners at The Mayo Clinic we will be rolling out a new process that takes into account the CSF cell count. To facilitate this, the EPIC orderable is now termed "FLCNT" and CSF has been removed as an option from the generic "LCMS". To make this functional, it requires that providers use FLCNT and do not write-in CSF as an "other" under LCMS.

How will the new process be reported? If the nucleated cell count is 5 or less cells/uL, the cell count will be resulted in addition to the comment: "CSF cell count does not meet criteria for Leukemia/Lymphoma flow cytometry. If you determine that flow cytometry is necessary due to patient history, please call Send outs at 341-8488 to have LCMS (LAB3217) added to the specimen." Note, overriding this should be few and far between; the only exceptions we realistically expect to see are when a cytopathologist identifies an atypical population and directs the Send-Out Department to override this system. In discussion with Dr. M. Usman M.D., Oncologist, this practice of having a lower limit is used in other systems and an acceptable practice in patient care. CSF specimen with cell counts that do meet criteria will be sent-on for testing, with a comment indicating this.

See provided images below of what this new ordering system will look like both under FLCNT and the XR lumbar puncture labs. Please save this code so that it makes ordering efficient in your future work.



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More Specific Tests Will Replace Genital Culture

Dr. Christopher Wienczewski

Historically, specimens from genital sources have had their own culture – "Genital Culture" (GCUL). However, due to technologic advances in laboratory medicine over the years, the traditional genital culture has become obsolete. This culture lacks sensitivity and specificity and often does not answer the clinical question being asked. Many times the requisition accompanying the specimen contains additional information in the comment field, such as "rule out BV". In these scenarios the laboratory is tasked with modifying orders to meet the needs of the clinician. Ordering appropriate test(s) up front will not only aid in answering the clinical question(s), but streamline the process within the laboratory and decrease unnecessary or undesired testing.

Moving forward the Genital Culture (GCUL) will no longer be available as an orderable. All genital source cultures will be performed as routine bacterial cultures. This culture will identify bacterial pathogens associated with genital ulcers, lesions, or abscesses, but is not recommended to diagnose bacterial vaginosis. Furthermore these cultures will no longer be screened for Group B streptococcus (GBS). However, if this organism is recovered it will be noted. Please keep in mind that no additional media will be used to enhance to growth of GBS organisms as it is in the GBS screen (**GBSDNA**).

Available testing options are listed below. Importantly, all of these tests can be performed from the same Eswab collection device so no new or additional collection materials are required.

Orderable tests

Group B Screen **GBSDNA**: Highly sensitive PCR screen for Group B Streptococcus. Vaginal/Rectal collection is recommended for pregnancy screening. This source is rarely collected in a genital culture collection.

Fungal Culture **FCUL:** Culture specific for recovery of fungus and yeast. Fungal media suppresses normal urogenital flora and the culture plates are held for two weeks and in a different incubation environment allowing for optimal growth of yeast and fungus.

KOH preparation/Wet mount **KOHB:** Direct examination for fungal elements gives quick interpretation, but is not as sensitive as fungal culture.

Gram Stain for Bacterial Vaginosis **GRMBV:** Gram stain interpretation with interpretation for bacterial vaginosis. Clue cells and yeast will be noted if seen.

Chlamydia/Gonorrhoeae and Trichomonas PCR **AMPCGT**: Highly sensitive PCR method for the diagnosing these sexually transmitted infections caused by organisms that may not grow under culture conditions or be reliably detected by Gram stain. (Collected in Hologic Aptima collection transport)

Herpes Simplex and Varicella Zoster Virus PCR **HS12VZ**: Highly sensitive test to detect Herpes Simplex 1, 2 and Varicella Zoster from cutaneous and mucocutaneous lesions from symptomatic patients. (Collected with swab and placed in Viral transport Medium VTM)

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Change in Equation Used for Estimated Glomerular Filtration Rate (eGFR)

Paul Guthrie, Lab Technical Clinical Consultant

Bronson Laboratory began reporting eGFR in 2005 using the Modification of Diet in Renal Disease (MDRD) equation. On 1/5/2021, we will change to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for eGFR calculation.

The eGFR provides a more clinically useful measure of kidney function than serum creatinine alone. The equations take into account several factors that impact creatinine production, including age, gender, and race. The MDRD and CKD-EPI are equally accurate in the eGFR range of <60 mL/min/1.73m^2. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) recommends reporting eGFR values from either equation which are greater than or equal to 60 mL/min/1.73m^2 as >60. However, there is interest amongst health care providers to screen for and detect chronic kidney disease (CKD) before the eGFR falls to 60 mL/min/1.73m^2. In response, NIDDK offers this statement:

> **"A laboratory that reports eGFR numeric values > 60 mL/min/1.73 m^2 should use the CKD-EPI equation, because the CKD-EPI equation is more accurate for values > 60 mL/min/1.73 m^2 than is the MDRD Study equation.** However, the influence of imprecision of creatinine assays on the uncertainty of an eGFR value is greater at higher eGFR values and should be considered when determining the highest eGFR value to report"

In consultation with other major laboratories who have switched to the CKD-EPI formula, we have determined the highest value to report with the new equation is 90 mL/min/1.73m^2. Values above this level will be reported as >90.

Abnormal flagging will remain unchanged; only values below 60 will be flagged as abnormal. Use of this reliable abnormal value is due to the wide variation in "normal" between individuals of any age, gender or race with regards to various factors influencing creatinine production and kidney function. NIDDK lists the following patient specific factors as sources of variation and possible misinterpretation of eGFR:

> "Persons with extremes in muscle mass and diet. This includes, but is not limited to, individuals who are amputees, paraplegics, bodybuilders, or obese; patients who have a muscle-wasting disease or a neuromuscular disorder; and those suffering from malnutrition, eating a vegetarian or low-meat diet, or taking creatine dietary supplements"

Please direct any questions you may have to Paul Guthrie MLS (ASCP), Clinical Technical Specialist
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Reference:
https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease/laboratory-evaluation/glomerular-filtration-rate/estimating

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