LabWire
Laboratory News and Analysis for Clinicians January 2019

Advanced Hematology Parameters: Reticulocyte Hemoglobin Equivalent (RET-He)

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Curious about the quality of red cells produced in a patient? Reticulocyte hemoglobin equivalent might just be your new test of choice to answer this question. Reticulocyte hemoglobin equivalent, also referred to as RET-He and analogous to reticulocyte hemoglobin content (CHr), evaluates if a patient's marrow currently has adequate iron available for hemoglobin synthesis. Specifically, it measures the amount of hemoglobin in reticulocytes, or to the lay person, tells you the quality of the red blood cell. This test is a standard reported value when a reticulocyte count is ordered (Test code: RETIC / Epic: LAB296).

Why use this test? Advantages include the fact that it provides a much more real time assessment of the marrow than other tests can, as it only looks at reticulocytes, rather than the MCHC which evaluates red blood cells indiscriminately. This "real time" data can also show a response to therapy more quickly than waiting for a hemoglobin bump, as an example, in a study looking at preoperative orthopedic patients, changes related to therapy were seen after 2 days with RET-He but not reflected in the hemoglobin for 2-3 weeks (Muusze, see resources below). Furthermore, unlike ferritin, it is not an acute phase reactant and will not be influenced by inflammation or cytokine activity *itself*. It is of course important to note, however, that RET-He only tells you if there is adequate iron incorporated into the cells, if they are deficient it doesn't tell you why. Therefore, other testing and clinical work-up would still be necessary to determine if this is due to inadequate iron or unavailable iron (such as anemia of chronic disease/ chronic inflammation in which there can be adequate marrow iron stores but the iron is prevented from transferring to maturing erythroid precursors due to inflammatory milieu). A final advantage, it is performed on the same tube type as the CBC (an EDTA tube/ purple top) so it can be added on without recalling the patient for another draw.

To those who question the leap between the measurement of hemoglobin and iron status in developing red cells; your caution is appropriate. This is why in the comment when this test is reported there is a caveat underneath the results which states, "in the absence of hemoglobinopathy a less than normal hemoglobin content in the reticulocytes is an indication of inadequate iron supply relative to demand." Therefore this test would have uncertain value in patients with decreased globin production (thalassemias) or structural hemoglobin variants (such as sickle cell anemia).

Key Points:

- This test is another tool in the evaluation of anemia, in that it provides a snapshot of the amount of iron available to young "just released" red cells (reticulocytes) at the time they developed.
- Potential uses include detecting inadequate iron before anemia develops, evaluating a known anemia or assessing if a patient is responding to therapy.
- This test can be performed on the same tube as the CBC. This allows care providers to add-on the test following an unexpected anemia result. This is convenient both for the provider and the patient who does not have to go back for another blood draw (for this particular test).
- The interpretation of the test is uncertain in patients with a hemoglobinopathy. This is stated as a comment with the test results in EPIC.

Resources:

1. Monitoring response to erythropoiesis stimulating agents:

A. Muusze RG, Corbey AMH, Ulenkate HJLM. Protocol for transfusion-free major orthopaedic operations using Ret-He. Sysmex Journal International 2009; 19:1-8. (Adapted from the original in Dutch Kwaliteitsingtituut voor de gezondheidszorg CBO. Richtlijn Bloedtransfusie, Utrecht/Alphen a/d Rinin, 2004 with kind permission from the publisher.)

2. Ret-He in the infant and toddler population:

A. Keuhn D, Roberts SS, Olsen CH, Harvey DN, Charnock KM, Brewer BD, Maliakel PG, Lopreiato J. Reticulocyte Hemoglobin Content Testing for iron deficiency in healthy toddlers. Military Medicine 2012;177:91-95.

B. Shaker M, Jenkins P, Ullrich C, Brugnara C, Nghiem BT. An economic analysis of anemia prevention during infancy. Journal of Pediatrics 2009;154:44-49.

3. RET-He use in patients with chronic kidney disease:

A. KDOQI Guidelines for anemia management in ESRD patients. American Journal of Kidney Disease; 2006;47:S1-S145.

B. CMS CPM (Phase III ESRD clinical performance measures in effect April 1, 2008. Baltimore (MD): Centers for Medicare and Medicaid Services (CMS);2008 Apr 1 4p.) see also http://www.cms.gov/Medicare/End-Stage-Renal-Disease/CPMProject/downloads/ESRDPhaseIIICPM-04012008Final.pdf

References:

1. Reticulocyte Hemoglobin Content (RET-He): A Parameter with Well-Established Clinical Value. Sysmex America White Paper. 9/2013. Document Number MKT-10-1198.

2. Perkins SL, Hussong JW (2001). Red blood Cells. In Steven L. Jones (Ed.) Clinical Laboratory Pearls. (61-96) Philadelphia, PA: Lippincott Williams & Wilkins.

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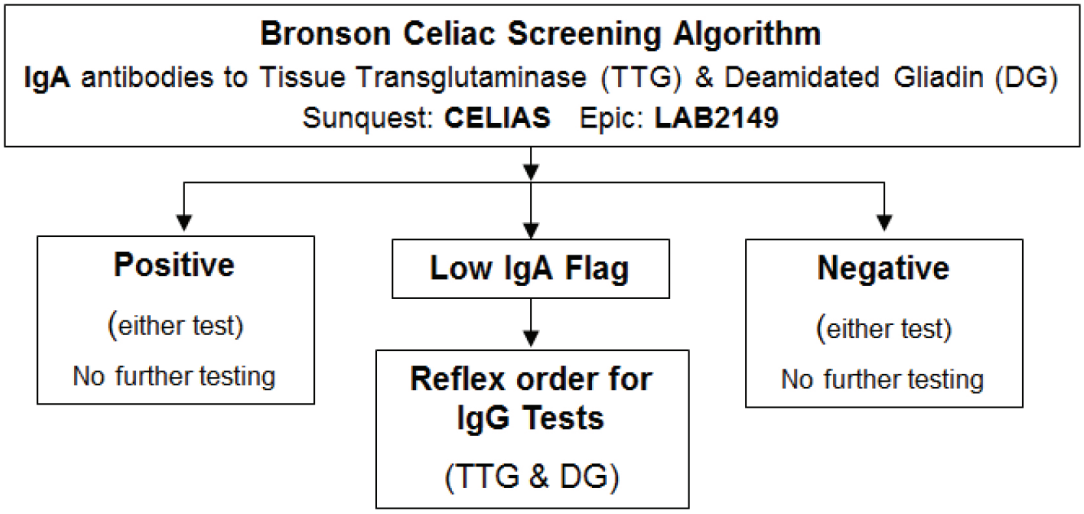
Methodology Change for Multiple Serological Tests

Effective 1/22/2019, Bronson laboratory will change methods for Double Stranded DNA (dsDNA), antibodies to Extractable Nuclear Antigens (ENA), Cyclic Citrullinated Peptide (CCPT), IgA & IgG Celiac Disease antibodies and Syphilis testing to a new analyzer, the BioRad BioPlex 2200. There are no changes in specimen requirements. The changes associated with the new methodology are described below.

- **Celiac Screen with Reflex (Order Codes: Epic LAB2149, Sunquest CELIAS)**

For a review of celiac disease testing, view this link from the **Nov 2010 LabWire**

The screen continues as before with initial testing for IgA antibodies to Tissue Transglutaminase (TTG) and Deamidated Gliadin (DG). The change with the BioPlex is the Celiac IgA tests have a built in marker to flag for IgA deficiency. A separate total IgA test no longer needs to be performed. Any patients tested for TTG and DG with low IgA values will automatically be tested for IgG antibodies to TTG and DG. There is also a change in reference/normal range value as noted on the table below.



Test Name	New Normal Range	Old Normal Range	Epic Order code	Sunquest Order Code
Celiac Screen	See individual tests	See individual tests	LAB2149*	CELIAS*
Tissue Transglutaminase IgA	<15 U/mL	<7 U/mL	LAB721 *	TTGA *
Tissue Transglutaminase IgG	<15 U/mL	<7 U/mL	LAB723 *	TTGG *
Deamidated Gliadin IgA	<15 U/mL	<7 U/mL	LAB2176 *	GLDA *
Deamidated Gliadin IgG	<15 U/mL	<7 U/mL	LAB2177 *	GLDG *
			* no change from current order codes	

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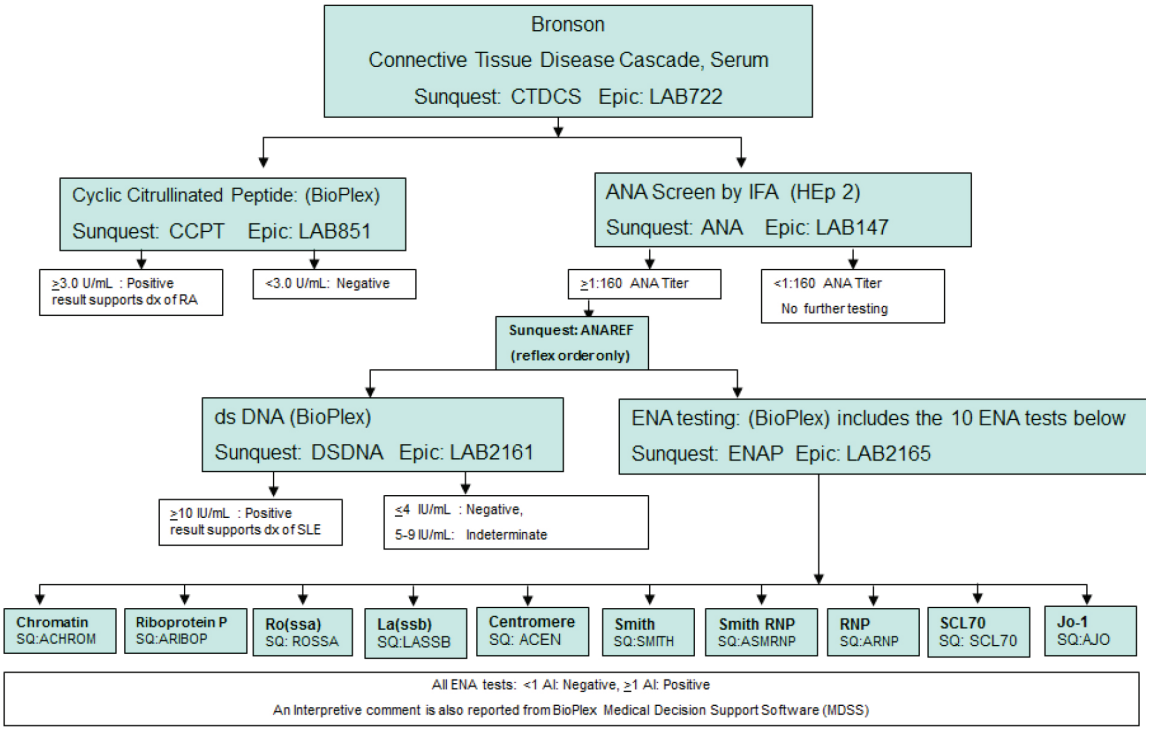
• Connective Tissue Disease Cascade (Order Codes: Epic LAB722, Sunquest CTDCS)

The individual tests and the ENA Panel remain orderable as would be appropriate for monitoring of patients. For screening, the cascade is recommended. The screen continues as before with CCPT and Anti-Nuclear Antibody (ANA) by Immuno-Fluorescence Assay (IFA) as the initial tests. If the IFA titer is >1:160, the ENA Panel and dsDNA are reflex ordered. An updated graphic of the screening algorithm posted below.



The new ENA Panel on the BioPlex includes several different antigens. There are also new reference/normal ranges for all tests. These are listed on the table below.

Test Name	New Normal Range	Old Normal Range	Epic Order code	Sunquest Order Code
Cyclic Citrullinated Peptide	<3 U/ml	<10 U/mL	LAB851*	CCPT *
Double Stranded DNA	≤ 4 IU/mL	<15 IU/mL	LAB2161 *	DSDNA *
Extractable Nuclear Antigen Panel	See list below	See list below	LAB2165	ENAP
Individual ENA tests:				
Anti-Chromatin	<1.0 AI	new test	LAB3534	ACHROM
Anti-Ribosomal P	<1.0 AI	new test	LAB3535	ARIBOP
Anti-Ro (SSA)	<1.0 AI	<7 U/mL	LAB2133*	ROSSA
Anti-La (SSB)	<1.0 AI	<7 U/mL	LAB2128*	LASSB
Anti-Centromere B	<1.0 AI	<7 U/mL	LAB2124*	ACEN
Anti-Smith	<1.0 AI	<7 U/mL	LAB2001*	SMITH
Anti-Smith RNP	<1.0 AI	new version (was U1RNP)	LAB3533	ASMRNP
Anti-RNP	<1.0 AI	new version (was RNP70)	LAB3128	ARNP
Anti-SCL 70	<1.0 AI	<7 U/mL	LAB771*	SCL70
Anti-Jo 1	<1.0 AI	<7 U/mL	LAB770*	AJO
			* no change from current order codes	

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In addition, the BioPlex software utilizes the built in Medical Decision Support Software (MDSS) program to generate an interpretive comment based on association of patient antibody results with predefined MDSS profiles. Profiles have been correlated with the following systemic autoimmune diseases: Systemic Lupus Erythematosus (SLE), Mixed Connective Tissue Disease (MCTD), Sjögren's Syndrome (SS), Scleroderma (Systemic Sclerosis) and Polymyositis.

Syphilis Testing (Order Codes: Epic LAB2594, Sunquest SYPHG)

For a review of syphilis testing, view this link from the **June 2011 LabWire**.

Testing for syphilis continues to follow the "reverse algorithm" which begins with the Treponemal specific antibody. Any positive treponemal antibody test has an automatic reflex order for a non-treponemal test (Reagin/RPR), with a titer reported for all positives. The change with the BioPlex is the RPR moving from the manual, visually read agglutination method to an automated multiplex flow immunoassay.

Please direct any questions you may have on these testing changes to:

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Test Updates:

Effective 3/1/19, CKMB testing will no longer be available.

Since the introduction of cardiac troponin testing 20 years ago, it has become progressively recognized that CK MB is an obsolescent test. Published studies have proven that CKMB has inferior sensitivity and specificity and offers no added benefit to troponin for the diagnosis of myocardial infarct.

The 2014 American College of Cardiology/American Heart Association Task Force states that with contemporary troponin assays, creatine kinase myocardial isoenzyme (CK-MB) and myoglobin are not useful for the diagnosis of acute coronary syndrome. (Level of Evidence: A). Bronson is joining the many medical centers that are no longer performing CK MB laboratory testing.

Reference:

Eliminating Creatine Kinase–Myocardial Band Testing in Suspected Acute Coronary Syndrome. A Value-Based Quality Improvement. Matthew D. Alvin, MD, MBA,MS, MA; Allan S. Jaffe, MD; Roy C. Ziegelstein, MD,MACP; Jeffrey C. Trost, MD JAMA Intern Med. doi:10.1001/jamainternmed.2017.3597. **Published online August 14, 2017**.

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