CLINICAL LABORATORY TESTING:

BLOOD CHEMISTRY & CBC ANALYSIS

FROM A FUNCTIONAL MEDICINE PERSPECTIVE

Dr. Wayne Sodano, DC, DABCI, DACBN, CIHP, BCTN
Director of Clinical Support & Education, Evexia Diagnostics, Inc.

EVEXIA DIAGNOSTICS™

8 PART SERIES

Overview

Blood Chemistry & CBC Analysis from a Functional Medicine Perspective by Dr. Wayne Sodano, Director of Clinical Support and Education for Evexia Diagnostics.

Videos will be released every week, beginning with Video 1 on May 9th 2019, with one new video released each week and accessible via the **Evexia Clinical Laboratory** landing page.

Video 1: **Introduction to Clinical Laboratory Medicine** ***- Available May 9th***

Video 2: **Hematology** ***- Available May 16th***

Video 3**: Clinical Laboratory Medicine: Liver, Gallbladder, and Pancreas** ***- Available May 23th***

Video 4: **Clinical Laboratory Medicine: Electrolytes, Minerals, and Acid-Base** ***- Available May 30th***

Video 5: **Clinical Approach to Anemia** ***- Available June 6th***

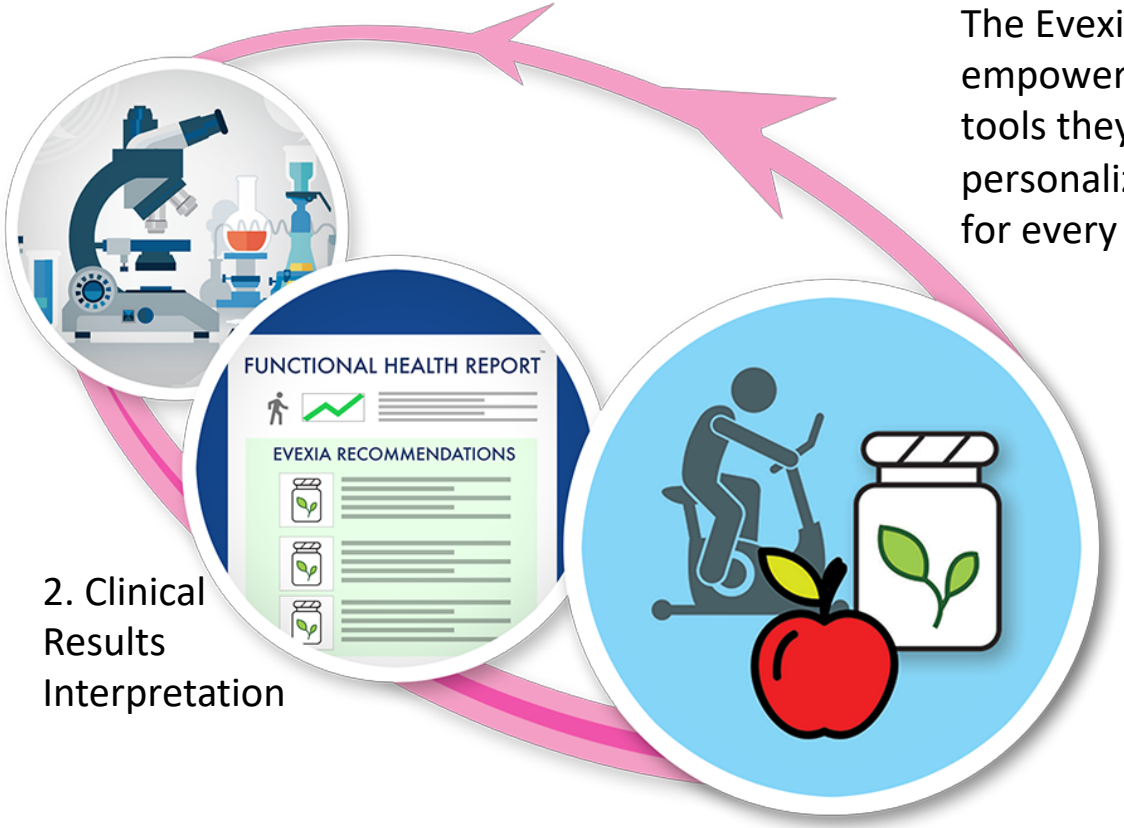
Video 6: **Clinical Laboratory Medicine: Integrative and Functional Medicine Perspective on Laboratory Interpretation – Patterns of Dysfunction** ***- Available June 13th***

Video 7: **The 'Must Know' Advanced Laboratory Tests for a Successful Treatment Outcome** ***- Available June 20th***

Video 8: **Test Review** ***- Available June 27th***

Course Objective
Become Versed in the 3 Steps of the Pathway to Wellness

1. Basic & Advanced Diagnostic Laboratory Testing



2. Clinical Results Interpretation

3 . Corresponding Nutraceutical Guidance

The Evexia Philosophy™ empowers clinicians with the tools they need to truly achieve personalized, optimal wellness for every patient.

Part 1 of 8 | Introduction to Clinical Laboratory Medicine

EVEXIA DIAGNOSTICS™

Introduction to Clinical Laboratory Medicine

Laboratory testing is used to detect disease, guide treatment, monitor response to treatment, and monitor disease progression.

However, it is an imperfect science. Laboratory testing may fail to identify abnormalities that are present (false negatives) or identify abnormalities that are not present (false positives)

R. Douglas Collins, MD:

No laboratory result could be taken at face value due to the fact that there are many possibilities in error both in performance of the test and in its interpretation.

However, the clinician **must never underestimate the value of the laboratory in clinical diagnosis**, but a healthy degree of skepticism is essential in interpreting laboratory results.

Collins RD. Illustrated Manual of Laboratory Diagnosis. 2nd Ed. Philadelphia: JB Lippincott Company; 1975. p. 9.

An **erroneous result** may set the physician off on a **wild goose chase** or commit to **radical or expensive therapy**

Negative laboratory values do not necessarily rule out a clinical diagnosis.

Incorrect test values or isolated individual variation in results may cause what's been called the **Ulysses Syndrome**, and result in loss of time, money, and peace of mind.

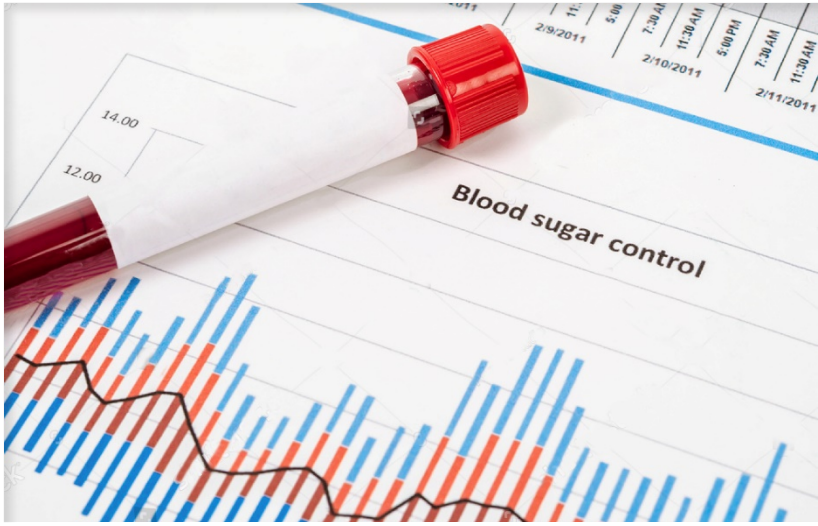
For the busy clinician, laboratory tests may become a substitute for a comprehensive patient history and physical examination leading to the clinician **treating the lab test results and NOT the patient**.

Treating lab test results exclusively will lead to decreased positive treatment outcomes and commence the “wild goose” chase.

Laboratory tests can be categorized into three sections:

- **Diagnostic**
- **Screening**
- **Routine**

Clinicians who object to routine tests are reminded of the many patients with anemia and leukemia who have been **saved from surgery by the routine CBC**, and the diabetes that would have been overlooked without routine blood sugars.



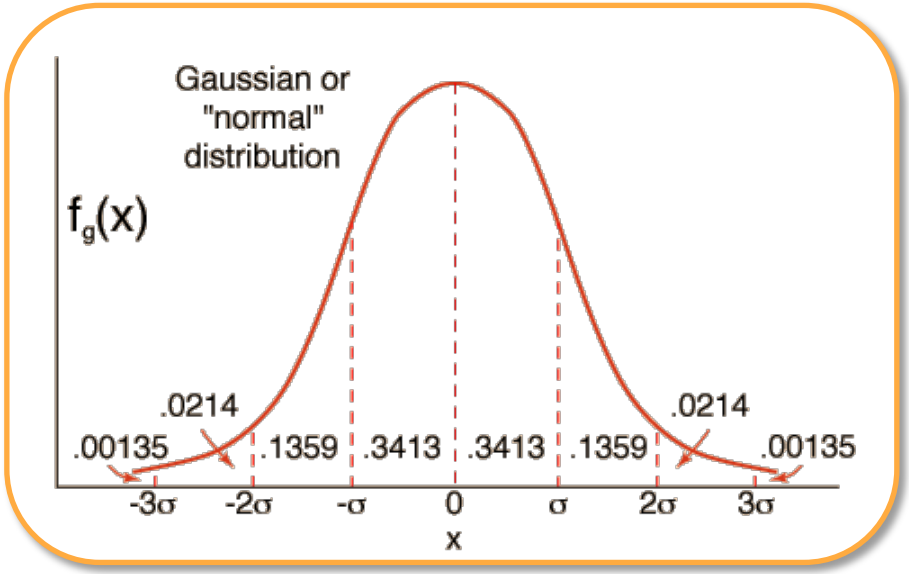
Rationale for Obtaining Laboratory Blood Studies

- **Establish a diagnosis**
- **Guide the course of treatment**
- **Differentiate/rule out possible diagnoses**
- **Detect disease recurrence**
- **Assess the effectiveness of treatment**
- **Determine the stage, activity, or severity of a disease**
- **Screen for disease**
- **Assessing nutriture**
- **Screen for toxins and drugs**

The “Reference Range”: Problem and Biologic Variation

- The reference range is a statistically-derived numerical range obtained by testing a sample of individuals <u>assumed</u> to be healthy. Reference ranges are usually established by obtaining a mean or average value plus and minus two standard deviations (SD), which follows a Gaussian distribution.

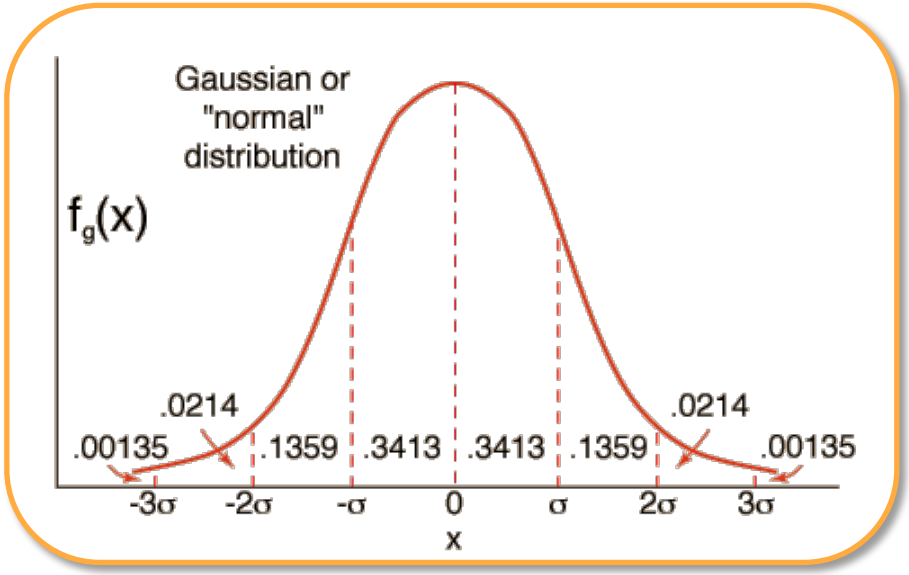
- The Gaussian distribution also **does not** account for subclinical and certain physiological conditions



The “Reference Range”: Problem and Biologic Variation

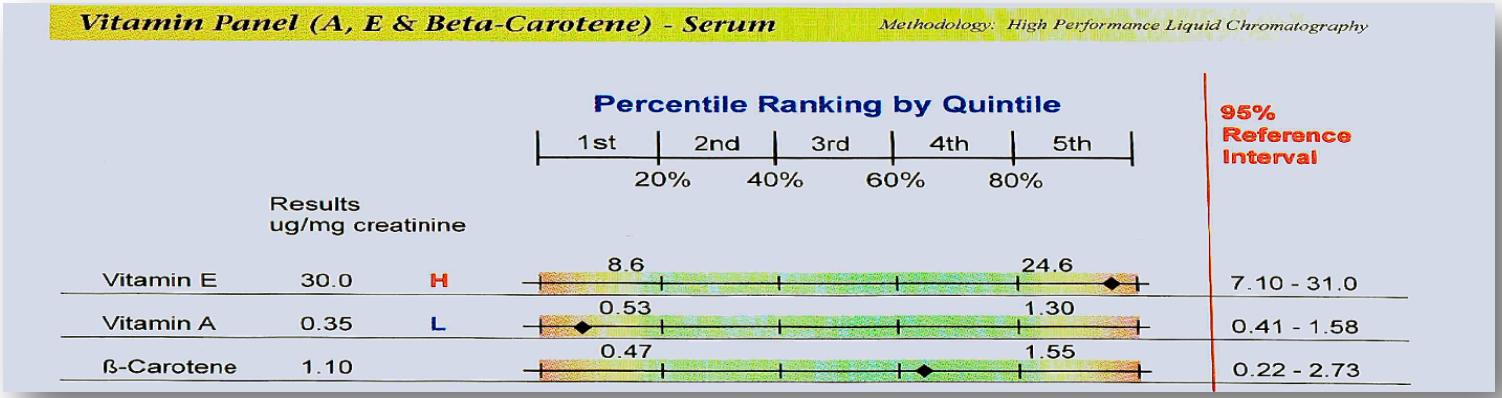
Gaussian Distribution: Reference range is the mean (0) ±2 standard deviations.

With this convention 5% (usually 2.5% on the low side and 2.5% on the high side) of the results can be expected to fall outside the ±2 SD limit, even in a normal population.



Quintile Ranking

A more reasonable and clinically useful approach for interpreting lab test result is percentile ranking.
This has been particularly useful in assessing the measure of risk factors for certain disease states.



High-sensitivity CRP measures have been developed in this way to relate levels to risk of cardiovascular disease. By dividing the populations tested into quintile ranks, researchers were able to correlate risk of cardiovascular events with these rankings.

By arranging the test data by quintile, the clinician can easily determine where a patient falls relative to a population from which the reference data were obtained. This allows the clinician to more easily assess the significance of the findings.

‘Optimal’ Reference Ranges

The history of optimal ranges dates back to the 1980’s. All roads in regard to establishing an optimal range to specific analytes appears to lead back to Dr. Harry Eidenier.

‘Biochemical Biopsy’

‘Optimal’ Reference Ranges

The information obtained from the blood chemistry analysis was compared to the history intake forms, physical examinations findings, symptom analysis, urinalysis, hair mineral analysis, stool analysis, and other diagnostic criteria. **Over 10,000 patients were analyzed during the research time.**

‘Optimal’ Reference Ranges

Dr. Eidenier proposed the term **‘optimal range’** due to the patterns of blood test results he observed healthy individuals.

Essentially, the optimal range of an analyte can be viewed as the range of **optimally functioning biochemistry**.

FALTS:

Factors Affecting Laboratory Tests

- **Pre-analytic factors**
- **Analytic factors**
- **Post-analytic factors**

Pre-Analytical Factors

Pregnancy	Concentrations of certain analytes change with time of gestation
Exercise	Individuals who exercise regularly: slight elevation in urea nitrogen and lactate dehydrogenase. Immediately after strenuous exercise: elevation of liver enzymes, lactate, phosphorous, creatinine, uric acid, catecholamines, leukocytes, transferrin and haptoglobin – decrease in albumin, iron and sodium.
Neonatal Period and Childhood	Use pediatric reference ranges
Older Individuals	Geriatric values
Body Weight	Possible effect due to increased systemic inflammation
Posture	Upright position: increased total protein, albumin, calcium, hemoglobin,, hematocrit, renin, catecholamines, alkaline phosphatase, cholesterol, ALT and iron.
Diet	Fasting vs. non-fasting. For many analytes, variation is controlled by obtaining specimens in the fasting state after two weeks on a diet of stable composition. Some common tests, which an overnight fast is recommended, are plasma glucose, lipids, iron, iron-binding capacity, vitamin B_{12}, folate, insulin and gastrin.

Pre-Analytical Factors

Ethanol	Ingestion of ethanol increased serum levels of uric acid, lactate, GGT, triglycerides, and AST. Long term alcohol abuse is associated with increases in bilirubin, alkaline phosphatase, and AST:ALT ratio.
Oral Contraceptives and Estrogens	These agents increase thyroxine-binding globulin, alpha$_1$-antitrypsin, iron, triglycerides, AST, and GGT. Albumin may be deceased.
Other Drugs	The potential effect of other drugs on laboratory tests is enormous. (The list of drugs can be found in the book titled "Effects of Drugs on Clinical Laboratory Tests" authored by Donald S. Young.
Sampling Problems	Tourniquets cause increases in potassium and lactate, and decrease in pH. In appropriate collection and containers, clotting sunlight exposure. Exposure to sunlight causes increases in leukocyte count, platelet count, and ESR, which bilirubin is decreased. Any delay beyond ≈ 5 minutes in analyzing blood gases causes significant errors.
Hemolysis	Hemolysis causes increases in lactate dehydrogenase, bilirubin, potassium, AST, CK, ALT and magnesium Hemolyzed blood can be caused by errors in specimen collection, specimen processing, and specimen transport.

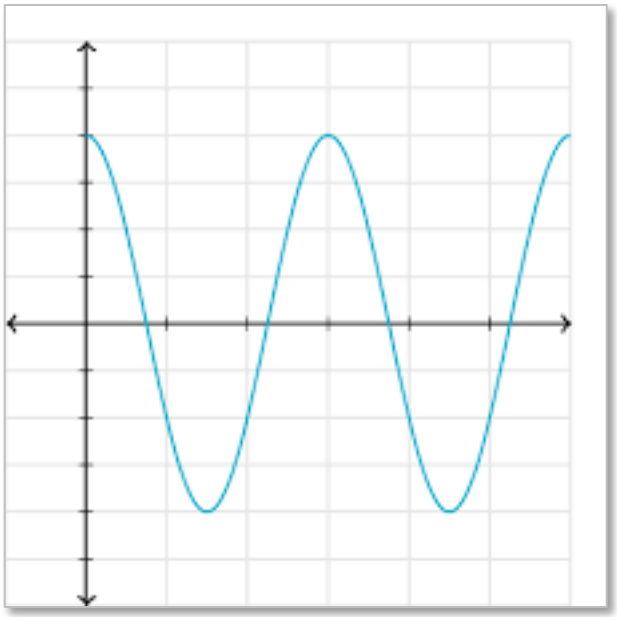
Pre-Analytical Factors

Biological Rhythms (see below for more details)	Circadian (approximately 24-hour) rhythms have implications for physiology, measurement of many laboratory tests, drug excretion, and responses to therapy. Levels fluctuating very significantly during the 24-hour cycle include cortisol, growth hormone, serum acid phosphatase, aldosterone, transferrin (maximum 4 pm to 8 pm), ACTH, serum iron, serum creatinine (7pm values 130% of 7am concentration), eosinophils low in afternoon), lymphocytes (maximum in early am), WBC (maximum in early am), and urine urobilinogen (maximum excretion in afternoon). Some hormone secretion cycles are longer (infradian) – e.g. menstrual cycle. An individuals' serum iron is highest in the morning. The results obtained from a specimen obtained at 2 pm may be as much as 50% less than the value obtained at 8 am. (**This reason I recommend having the patient have the majority of follow-up testing performed at the same time of day.**)
Altitude	"Serum hemoglobin reference ranges are adjusted progressively upward for individuals living above 1000 feet."[1]
Fluid Status	Dehydration causes hemoconcentration. Overhydration causes hemodilution.
Organ Function	e.g. bone marrow dysfunction leads to pancytopenia

[1] Tietze KJ. Definitions and Concepts. In: Lee M. Basic Skills in Interpreting Laboratory Data. 5th Ed. Bethesda: America Society of Health-System Pharmacist, Inc.; 2013. p. 11

Pre-Analytical Factors: Biological Rhythms

Biological rhythms are frequently observed for many physiologic and laboratory parameters. The types of rhythms that have the most influence on the interpretation of laboratory results are **circadian, ultradian,** and **infradian** rhythms. In addition, there are also **seasonal rhythms**.



Pre-analytical Factors: Biological Rhythms

Circadian rhythm: different concentrations of the same analyte over a 24-hour period. (e.g. lymphocyte count in whole blood shows a peak (i.e. high concentration) at midnight, and a trough (low concentration) at 8 am.

Ultradian rhythm: analytes released in an intermittent or pulse fashion within a 24-hour period. (Mostly glandular secretions e.g. testosterone)

Infradian: analytes that exhibits cycles greater than 24 hours. The most common example: menstrual cycle (pituitary gonadotropins and ovarian hormones).

Pre-Analytical Factors: Circadian Rhythms

Analyte	Time of Peak Concentration	Daily Percent Change of Analyte
Serum Sodium	1 pm	2%
Serum Potassium	11 am	19%
Serum Glucose	6 pm	59%
Serum Phosphorus	10 pm	38%
Serum Urea Nitrogen	11 pm	25%
Serum Cholesterol	10 pm	11%
Serum Total Bilirubin	7 am	62%
Serum Total Protein	6 pm	8%
Serum GGT	10 am	960%
Serum TSH	2 am	206%
Serum Cortisol	7:30 am	1111%
Serum Melatonin	3 am	211%
Serum Iron	8 am	32%
Serum Aldosterone	8 am	95%

Pre-Analytical Factors: Circadian Rhythms

Analyte	Time of Peak Concentration	Daily Percent Change of Analyte
Total WBCs	7 pm	38%
RBCs	4:30 am	10%
Lymphocytes	1:30 am	67%
Neutrophils	5 pm	61%
CD4+ Cells	12:30 am	51%
Urine - Volume	3 am	278%
Urine SG	4 pm	103%
Urine - Calcium	4 pm	333%
Urine Creatinine	9 pm	30%
Urine - Sodium	8 pm	54%

Biotin (vitamin B7) and its effects on certain laboratory tests:

WHAT YOU NEED TO KNOW

Always look for a discrepancy between the lab test result and the clinical presentation.

The risk for **biotin interference extends to assays critical to internal medicine**, such as tests for anemia, malignancies, autoimmune and infectious diseases and cardiac disease.

Erroneous Graves' disease has been reported due to biotin ingested lab interference

FACTS:

Biotin can also **mask a true diagnosis** such as causing a falsely low troponin level (troponin is a globular protein complex – positive in heart muscle injury)

Biotin does not interfere with laboratory tests at levels naturally found in foods and multivitamins, which is typically 30 micrograms per day.

Not all immunoassay systems are susceptible to biotin interference, in particular, the immunoassay systems that do not use what's known as the **biotin-streptavidin capture method.**

Biotin interference can be unpredictable. Daily amounts of 10 mg result in a misdiagnosis of thyrotoxicity and a failure to identify congestive heart failure.

There were also some immunoassay systems that were predicated to be associated with biotin interference, and did not!

Sandwich assay – *falsely* lowered laboratory test results; used for **large molecules**, such as hormones and proteins

- TSH
- Pituitary glycoprotein hormones
- Human chorionic gonadotropin
- Parathyroid hormone
- Insulin-like growth factor-1
- Insulin
- Thyroglobulin
- C-peptide
- Ferritin
- N-terminal pro B-type natriuretic peptide
- Prolactin
- PSA
- FSH
- LH

Competitive assay – *falsely* elevated laboratory test results; measures **small molecules**, such as steroids

- 25 hydroxyvitamin D
- **Free T3**
- **Free T4**
- **Total T3**
- **Total T4**
- Cortisol
- Estradiol
- Testosterone

How long does it take for biotin to clear the body?

- 8-hour washout period for healthy individuals taking 10 mg of biotin per day (assuming that the assay has a biotin interference threshold of 30 ng/mL or higher.

- **To be safe, it is recommended to have a 3-day washout**

"Unfortunately, susceptibility to biotin interference is variable in magnitude and can skew results to either falsely high or falsely low depending on the assay design and conditions."

Pharmacokinetic studies of a patient ingesting **megadose (30 mg)** of biotin revealed that its interfering effects on laboratory tests persisted for up to 24 hours.

For a patient on a megadose of biotin, this finding means that it is prudent to stop taking biotin for at least 2 days before blood draws.

Pertinent Laboratory Definitions

- Accuracy
- Precision
- Analyte
- Qualitative Test
- Quantitative Test
- Semi-quantitative Test
- Critical Value

Pertinent Laboratory Definitions

Sensitivity: ability of the test to identify positive results in patients who actually have the disease. A test with a high sensitivity indicates a lower number of false-negatives test results. [Sensitivity = true positive/true positive + false negative x 100%]

Specificity: percent of negative results in individuals without the disease. The lower the specificity of a test produces a greater amount of false-positive test results. A test with a 95% specificity means that 5% of the individuals who do not have the disease will test positive. [Specificity = true negative/true negative + false positive x 100%]

Pertinent Laboratory Definitions

Biomarker: a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic response to a therapeutic intervention. Biomarkers are used to diagnose and stage disease, assess disease progression, or assess response to therapeutic intervention. Examples of biomarkers are hemoglobin A1c, and tumor markers.

Pertinent Laboratory Definitions: Glossary of 'Omics'

Genomics	Large-scale, high-throughput molecular analyses of multiple genes, gene products, or regions of genetic material
Integromics	Use of high-throughput, multiplexed technologies – including microarrays- in combination to obtain an integrated picture at the DNA, PNA, tissue, and pharmacological levels.
Metabolomics	The study of the metabolite profile in biological samples
Metabonomics	The quantitative measurements of dynamic, multiparametric metabolic response of living systems to pathophysiological stimuli or genetic modification.
Pharmacogenetics	The study of the impact of genetic factors on the interindividual variation in response to drugs and drug toxicity.

Pertinent Laboratory Definitions: Glossary of 'Omics'

Pharmacogenomics	The study of genetic variations and their relations to drug effects and responses.
Phenomics	The study of the expressed clinical state (phenotypes) and its relations to the genomic and proteomic data, and the genotypes.
Physiomics	The study of the complete physiology of an organism, including all interacting metabolic pathways, structural and biochemical scaffolding, the proteins and accessories that make them up, and the gene regulatory networks.
Proteomics	The large-scale, high-throughput analysis of proteins that begin with systematic separation and identification of all proteins within a cell, tissue, or other biological sample.
Transcriptomics	The study of all cellular mRNA transcripts of an organism, often produced under a variety of conditions.

Laboratory Assay, Instrumentation and Technology

Assay	Tests
Ion-Selective electrodes	Electrolytes (sodium, potassium, chloride, lithium, total carbon dioxide)
Gas Chromatography	Toxicologic screens, organic acids, drugs
High-Performance Liquid Chromatography	Toxocological screens vanilmandeic acid, hydroxyl-vanilmandeic acid, amino acids, drugs
Enzyme-Linked Immunosorbent Assay	Serological tests (e.g. ANA, rheumatoid factor, hepatitis B, cytomegalovirus, HIV antigens and antibodies)
Enzyme-Multiplied Immunoassay Technique	General chemistries, enzymes, coagulation factors, drugs
Fluorescent Polarization Immunoassay	Therapeutic drug monitoring, general chemistries
Polymerase Chain Reaction (molecular diagnostics)	Microbiological and virologic markers of organisms and genetic markers. Microorganisms identified include: CMV, EBV, HIV, mycobacteria, and HSV. Essential, this test is able to assess DNA and RNA sequences to identify certain organisms.

In-Office Lab Testing (POLs)

In 1988, the United States Congress passed the **Clinical Laboratory Improvement Amendments**, which requires all clinical laboratories, except for those that perform only waived tests, to submit for compliance inspection. All clinicians performing in-office lab testing should contact state and federal agencies in order to comply with CLIA. Tests that are waived need to be report to the agency in order to obtain a waiver.

www.acponline.org/running_practice/mle/clia-and-your-lab.pdf

www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfclia/testswaived.cfm?start_search=1

www.cap.org

www.cms.hhs.gov

Evexia Test Eligibility & Reminders

Testing Services Availability: USA (except NJ, NY & RI), Puerto Rico, Canada

Licensed Practitioners: Order any Evexia Diagnostics Incorporated (EDI) test

Non-Licensed Practitioners: Must use the Evexia Internal Physician Network to order tests*

Laboratory Order Fee: $15.00 for each order placed by non-licensed practitioners or licensed practitioners ordering for out-of-state patients

Restrictions:

1. Patients must be 6 years old or older for test(s) that require any blood draws
2. Patients under the age of 18 require the parental/guardian consent form to be completed electronically through the EvexiaLink™ platform via your clinician portal on the EDI website

*Note: Certain tests can only be ordered by licensed clinicians – contact Customer Success Team for details on specific test eligibility at (888) 852-2723, Monday-Friday, 8AM – 8PM EST

To learn more about Evexia Diagnostics

www.evexiadiagnostics.com

(888) 852-2723

Live chat is available at www.evexiadiagnostics.com

info@evexiadiagnostics.com

18 Titus Road / PO Box 1272
Washington, CT 06793

Office Hours
Monday - Friday, 8am - 8pm ET

Next lesson: Part 2 of 8 Hematology

EVEXIA DIAGNOSTICS™