1 DEFINITIONS AND CONCEPTS

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OBJECTIVES

After completing this chapter, the reader should be able to

- Differentiate between accuracy and precision
- Distinguish between quantitative, qualitative, and semiqualitative laboratory tests
- Define reference range and identify factors that affect a reference range
- Differentiate between sensitivity and specificity, and calculate and assess these parameters
- Identify potential sources of laboratory errors and state the impact of these errors in the interpretation of laboratory tests
- Identify patient-specific factors that must be considered when assessing laboratory data
- Discuss the pros and cons of point-of-care and at-home laboratory testing
- Describe a rational approach to interpreting laboratory results

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 [FNs]) or identify abnormalities that are not present (false positives [FPs]). This chapter defines terms used to describe and differentiate laboratory tests and describes factors that must be considered when assessing and applying laboratory test results.

DEFINITIONS

Many terms are used to describe and differentiate laboratory test characteristics and results. The clinician should recognize and understand these terms before assessing and applying test results to individual patients.

Accuracy and Precision

Accuracy and *precision* are important laboratory quality control measures. Laboratories are expected to test analytes with accuracy and precision and to document the quality control procedures. Accuracy of a quantitative assay is usually measured in terms of analytical performance, which includes accuracy and precision. *Accuracy* is defined as the extent to which the mean measurement is close to the true value. A sample spiked with a known quantity of an analyte is measured repeatedly; the mean measurement is calculated. A highly accurate assay means that the repeated analyses produce a mean value that is the same as or very close to the known spiked quantity. Accuracy of a qualitative assay is calculated as the sum of the true positives (TPs) and true negatives (TNs) divided by the number of samples tested (accuracy = [(TP + TN) ÷ number of samples tested] × 100%). *Precision* refers to assay reproducibility (i.e., the agreement of results when the specimen is assayed many times). An assay with high precision means the methodology is consistently able to produce results in close agreement. The accuracy of those results is a separate issue.

Analyte

The *analyte* is the substance measured by the assay. Some substances, such as phenytoin and calcium, are bound extensively to proteins such as albumin. Although the unbound fraction elicits the physiological or pharmacological effect (bound substances are inactive), most routine assays measure the total substance (bound plus unbound). The free fraction may be assayable, but the assays are not routine. Therefore, the reference range for total and free substances may be quite different. For example, the reference range is 10–20 mcg/mL for total phenytoin, 1–2 mcg/mL for free phenytoin, 9.2–11 mg/dL for total serum calcium, and 4–4.8 mg/dL for free (also called *ionized*) calcium.

Some analytes exist in several forms and each has a different reference range. These forms are referred to as *fractions, subtypes, subforms, isoenzymes*, or *isoforms*.

Note: This chapter is based, in part, on the second edition chapter titled "Definitions and Concepts" by Scott L. Traub.

Results for the total and each form are reported. For example, bilirubin circulates in conjugated and unconjugated subforms as well as bound irreversibly to albumin (delta bilirubin). *Direct bilirubin* refers to the sum of the conjugated plus the delta forms (water soluble forms); *indirect bilirubin* refers to the unconjugated form (water insoluble form). Lactate dehydrogenase (LDH) is separated electrophoretically into five different isoenzymes: LDH1, LDH2, LDH3, LDH4, and LDH5. Creatine kinase (CK) exists in three isoforms: CK-BB (CK1), CK-MB (CK2), and CK-MM (CK3).

Biomarker

A *biomarker* (biological marker) is a marker (not necessarily a quantifiable laboratory parameter) defined by the National Institutes of Health as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[1] Biomarkers are used to diagnose and stage disease (i.e., determine the extent of disease), assess disease progression, and predict or assess response to therapeutic interventions. Tumor markers are biomarkers used to identify the presence of some cancers, to stage disease, or to assess patient response to drug and nondrug cancer treatments. Many biomarkers are common laboratory parameters. For example, glycated hemoglobin A1c (HbA1c) is used to assess long-term glucose control in patients with diabetes.

Noninvasive Versus Invasive Tests

A *noninvasive test* is a procedure that examines fluids or other substances (e.g., urine and exhaled air) obtained without using a needle, tube, device, or scope to penetrate the skin or enter the body. An *invasive test* is a procedure that examines fluids or tissues (e.g., venous blood and skin biopsy) obtained by using a needle, tube, device, or scope to penetrate the skin or enter the body. Invasive tests pose variable risk depending on the method of specimen collection (e.g., pain and bruising associated with venipuncture) and are less convenient than noninvasive tests.

Predictive Value

The *predictive value*, derived from a test's sensitivity, specificity, and prevalence (incidence) of the disease in the population being tested, is used to assess a test's reliability (**Table 1-1**). As applied to a positive test result, the predictive value indicates the percent of positives that are TPs. For a test with equal sensitivity and specificity, the predictive value of a positive result increases as the incidence of the disease in the population increases. For example, the glucose tolerance test has a higher predictive value for diabetes in women who are pregnant than in the general population. A borderline abnormal serum creatinine (SCr) concentration has a higher predictive value for kidney disease in patients in a nephrology unit than in patients in a general medical unit. The lower the prevalence of disease in the population tested, the greater the chance that a positive test result is in error. The predictive value may also be applied to negative results. As applied to a negative test result, the predictive value indicates the percent of negatives that are TNs (**Minicase 1**).

TABLE 1-1. Relationship of Sensitivity, Specificity, Disease Prevalence, and Predictive Value of Positive Test[a,b]

SENSITIVITY AND SPECIFICITY (%)	PREVALENCE (%)	PREDICTIVE VALUE OF POSITIVE TEST (%)
95	0.1	1.9
	1	16.1
	2	27.9
	5	50
	50	95
99	0.1	9
	1	50
	2	66.9
	5	83.9
	50	99

[a]The predictive value of a positive test increases as the disease prevalence and sensitivity and specificity of the test increase.
[b]Predictive value of positive test = [TP ÷ (TP + FP)] x 100%. Predictive value of negative test = [TN ÷ (TN + FN)] x 100%. Disease prevalence = (TP + FN) ÷ number of patients tested. FN = diseased persons not detected by test (false negatives); FP = nondiseased persons positive to test (false positives); TN = nondiseased persons negative to test (true negatives); and TP = diseased persons detected by test (true positives).

Qualitative Tests

A *qualitative test* is a test whose results are reported as either positive or negative without further characterization of the degree of positivity or negativity. Exact quantities may be measured in the laboratory but are still reported qualitatively using predetermined ranges. For example, a serum or urine pregnancy test is reported as either positive or negative; a bacterial wound culture is reported as either positive for one or more specific microorganisms or reported as no growth; a urine toxicology drug screen is reported as either positive or negative for specific drugs; a hepatitis C viral ribonucleic acid (RNA) test is reported as positive or negative for hepatitis C viral RNA; and an acid-fast stain for *Mycobacterium* is reported as either positive or negative.

Quantitative Tests

A *quantitative test* is a test whose results are reported as an exact numeric measurement (usually a specific mass per unit measurement) and assessed in the context of a reference range of values. For example, serum potassium is reported in milliequivalents per liter, creatinine clearance (CrCl) is reported in milliliters per minute, and LDH is reported in units per liter. Some test results are reported as titers (dilutions). A serum antinuclear antibody titer of 1:160 is usually associated with active systemic lupus erythematosus or other autoimmune diseases, although some patients may have "low titer" disease with titers of 1:40 or 1:80.