PART I

BASIC CONCEPTS AND TEST INTERPRETATIONS

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 and qualitative 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 to consider 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 (the substance measured by the assay) 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 (ie, the agreement of results when the specimen is assayed many times). An assay with high precision means that the methodology is consistently able to produce results in close agreement.

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 physiologic 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. 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

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(δ bilirubin). *Direct bilirubin* refers to the sum of the conjugated plus the δ 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: CK1 (CK-BB), CK2 (CK-MB), and CK3 (CK-MM).

Biomarker

A *biomarker* (biological marker) is a marker (not necessarily a quantifiable laboratory parameter) defined by the Food and Drug Administration (FDA) as "A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutics interventions."[3] Biomarkers are used to diagnose and stage disease (ie, determine the extent of disease), assess disease progression, and predict or assess response to therapeutic interventions. For example, 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, glycosylated hemoglobin A1c (HbA1c) is used to assess average blood sugar levels over the past three months in patients with diabetes.

Noninvasive Versus Invasive Tests

A *noninvasive test* is a procedure that examines fluids or other substances (eg, 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 (eg, 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 (eg, 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 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 true positives. For a test with equal sensitivity and specificity, the predictive value of a positive result increases as the prevalence 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 as a result of the higher prevalence of diabetes in pregnancy compared with the general population due to gestational diabetes. A borderline abnormal serum creatinine 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 true negatives (refer to **Minicase 1**).

TABLE 1-1. Relationship of Sensitivity, Specificity, Disease Prevalence, and Predictive Value of a Positive Test (the predictive value of a positive test increases as the disease prevalence and sensitivity and specificity of the test increase)

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

Predictive value of positive test = [TP ÷ (TP + FP)] × 100%.
Predictive value of negative test = [TN ÷ (TN + FN)] × 100%.
Disease prevalence = (TP + FN) ÷ number of patients tested.
TP = diseased persons detected by test (true positives).
FP = nondiseased persons positive to test (false positives).
FN = diseased persons not detected by test (false negatives).
TN = nondiseased persons negative to test (true negatives).

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 virus (HCV) 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.

MINICASE 1

Bladder Urothelial Carcinoma Recurrence Surveillance

Frequent active surveillance is recommended for patients following treatment for nonmuscle-invasive bladder cancer (NMIBC). The gold standard active surveillance monitoring strategies for NMIBC include cystoscopy and urine cytology. For patients with a low risk of recurrence, the American Urological Association/Society of Urologic Oncology recommends patients undergo the first surveillance cystoscopy within three to four months after initial treatment, then six to nine months later, and then annually for five years; more frequent active surveillance is recommended for patients at a greater risk of recurrence.[1] Cystoscopy is an invasive test with well-described risks; a noninvasive active surveillance laboratory test would reduce healthcare costs and patient risk.

The sensitivity and specificity of a new noninvasive Bladder EpiCheck test in 353 subjects with incident or recurrent bladder urothelial carcinoma undergoing active surveillance with cystoscopy and cytology were assessed.[2]

QUESTION: After reviewing the following results, what conclusions can be made about the clinical performance of the Bladder EpiCheck test?

Bladder EpiCheck Results ($n = 353$)

True positives (TP): 30 True negatives (TN): 272

False positives (FP): 37 False negatives (FN): 14

DISCUSSION: Calculate sensitivity, specificity, predictive value of a positive test, and predictive value of a negative test.

Sensitivity = (TP ÷ [TP + FN]) × 100% = (30 ÷ [30 + 14]) × 100% = 68.2%

Specificity = (TN ÷ [TN + FP]) × 100% = (272 ÷ [272 + 37]) × 100% = 88%

Predictive value of positive test = (TP ÷ [TP + FP]) × 100% = (30 ÷ [30 + 37]) × 100% = 44.8%

Predictive value of negative test = (TN ÷ [TN + FN]) × 100% = (272 ÷ [272 + 14]) × 100% = 95.1%

In this study, the noninvasive Bladder EpiCheck urine test had a high overall negative predictive value (NPV), high specificity, and clinically acceptable sensitivity. The clinical application of this test is to surveil for cancer recurrence to determine if a more invasive, but more sensitive, monitoring strategy is necessary. If patients test negative and are truly negative, additional testing is not necessary. A high overall negative predictive value of 95.1% makes this test useful for this application despite a lower predictive value of positive test.

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 commonly reported in milliequivalents per liter, creatinine clearance is commonly reported in milliliters per minute, fractional exhaled nitric oxide (FeNO) is commonly reported in parts per billion, and LDH is commonly reported in units per liter. Some test results are reported as titers (dilutions). For example, a serum antinuclear antibody titer of 1:160 is usually associated with active systemic lupus erythematosus (SLE) or other autoimmune diseases, though some patients may have "low titer" disease with titers of 1:40 or 1:80.

Reference Range

The *reference range* (also known as *the reference interval* or the *reference value*) is a statistically-derived numerical range obtained by testing a sample of individuals assumed to be healthy. The upper and lower limits of the range are not absolute (ie, normal versus abnormal), but rather points beyond which the probability of clinical significance begins to increase. The term *reference range* is preferred over the term *normal range*.[4] The reference population is assumed to have a Gaussian distribution with 68% of the values within one standard deviation (SD) above and below the mean (±1 SD), 95% within ±2 SD, and 99.7% within ±3 SD (**Figure 1-1**).

The reference range for a given analyte is usually established in the clinical laboratory as the mean or average value plus or minus two SDs. Acceptance of the mean ±2 SD indicates that one in 20 normal individuals will have test results outside the reference range (2.5% have values below the lower limit of the reference range and 2.5% have values above the upper limit of the reference range). Accepting a wider range (eg, ±3 SD) includes a larger percentage (99.7%) of normal individuals but increases the chance of including individuals with values only slightly outside of a narrower range, thus decreasing the sensitivity of the test.

Qualitative laboratory tests are either negative or positive and lack a reference range; any positivity is considered abnormal. For example, any amount of serum acetone, porphobilinogen, or alcohol in serum or plasma is considered abnormal. The presence of glucose, ketones, blood, bile, or nitrate in urine is abnormal. The results of the Venereal Disease Research Laboratory (VDRL) test, tests for red blood cell (RBC) sickling, and the malaria smear are either positive or negative.

Factors That Influence the Reference Range

Many factors influence the reference range. Reference ranges may differ between laboratories depending on analytical technique, reagent, and equipment. The initial assumption that the sample population is normal may be false. For example, the reference range is inaccurate if too many individuals with covert

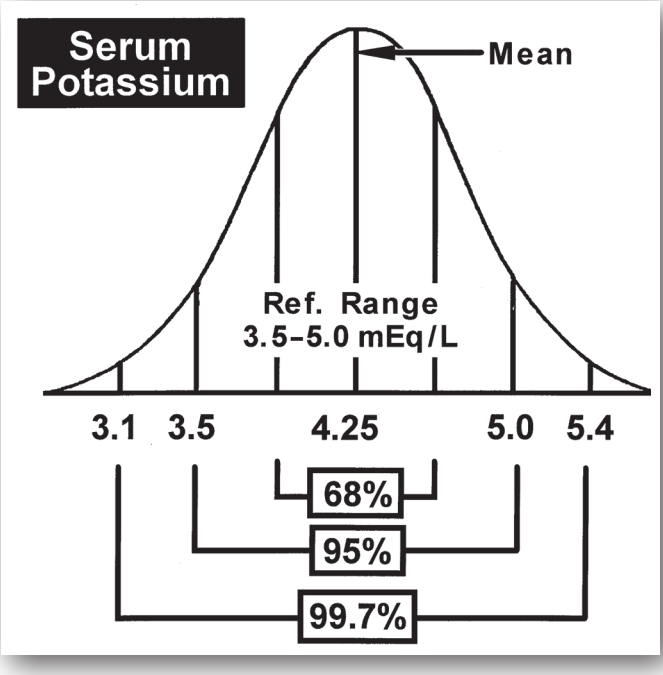

FIGURE 1-1. Gaussian (random) value distribution with a visual display of the area included within increments of standard deviation (SD) above and below the mean: ±1 SD = 68% of total values; ±2 SD = 95% of total values; and ±3 SD = 99.7% of total values. (*Source*: Reprinted with permission from Basic Skills in Interpreting Laboratory Data, 6th edition.)

disease (ie, no signs or symptoms of disease) are included in the sample population. Failure to control for physiologic variables (eg, age, gender, ethnicity, body mass, diet, posture, and time of day) introduces factors that may result in an inaccurate reference range. Reference ranges calculated from nonrandomly distributed (non-Gaussian) test results or from a small number of samples may not be accurate.

Reference ranges may change as new information relating to disease and treatments becomes available. For example, the generally accepted upper limit of normal for thyroid-stimulating hormone (TSH) (4.12 milli-international units per liter) is based on data from the National Health and Nutrition Examination Survey (NHANES III).[5] But the availability of more sensitive assays and the recognition that the original reference population data were skewed has led some clinicians to conclude that the upper limit of normal for TSH should be lowered.[6] In contrast, recent data supports extending the upper limit of normal for TSH for patients 80 years and older.[7]

Critical Value

The term *critical value* refers to a result that is far enough outside the reference range that it indicates impending morbidity (eg, potassium < 2.8 mEq/L). Because laboratory personnel are not in a position to consider mitigating circumstances, a designated member of the healthcare team is notified immediately on discovery of a critical value test result. Critical values may not always be clinically relevant, however, because the reference range varies for the reasons discussed previously.

Semiquantitative Tests

A *semiquantitative test* is a test whose results are reported as either negative or with varying degrees of positivity but without exact quantification. For example, urine glucose and urine ketones may be reported as negative or trace, 1+, 2+, 3+, or 4+; the higher numbers represent a greater amount of the measured substance in the urine, but not a specific concentration.

Sensitivity

The *sensitivity* of a test refers to the ability of the test to identify positive results in patients who actually have the disease (the true positive rate).[8,9] Sensitivity assesses the proportion of true positives disclosed by the test (**Table 1-2**). A test is completely sensitive (100% sensitivity) if it is positive in every patient who actually has the disease. The higher the test sensitivity, the lower the chance of a false negative result; the lower the test sensitivity, the higher the chance of a false negative result. However, a highly sensitive test is not necessarily a highly specific test (see below).

Highly sensitive tests are preferred when the consequences of not identifying the disease are serious; less sensitive tests may be acceptable if the consequence of a false negative is less significant or if low sensitivity tests are combined with other tests. For example, inherited phenylalanine hydroxylase deficiency (phenylketonuria or PKU) results in increased phenylalanine concentrations. High phenylalanine concentrations damage the central nervous system and are associated with intellectual developmental disorder. Intellectual disability is preventable if PKU is diagnosed and dietary interventions are initiated before 30 days of age. The phenylalanine blood screening test, used to screen newborns for PKU, is a highly sensitive test when testing infants at least 24 hours of age.[10] In contrast, the prostate specific antigen (PSA) test, a test commonly used to screen men for prostate cancer, is highly specific but has low sensitivity, especially at low PSA cut-off values of 4–10 ng/mL.[11] Thus, PSA cannot be relied on as the sole prostate cancer screening method.

Sensitivity also refers to the range over which a quantitative assay can accurately measure the analyte. In this context, a sensitive test is one that can measure low levels of the substance; an insensitive test cannot measure low levels of the substance accurately. For example, a digoxin assay with low sensitivity might measure digoxin concentrations as low as 0.7 ng/mL. Concentrations below 0.7 ng/mL would not be measurable and would be reported as "less than 0.7 ng/mL" whether the digoxin concentration was 0.6 ng/mL or 0.1 ng/mL. Thus, this relatively insensitive digoxin assay would not differentiate between medication nonadherence with an expected digoxin concentration of zero and low concentrations associated with inadequate dosage regimens.

TABLE 1-2. Calculation of Sensitivity and Specificity[a,b]

SCREENING TEST RESULT	DISEASED	NONDISEASED	TOTAL
Positive	TP	FP	TP + FP
Negative	FN	TN	FN + TN
Total	TP + FN	FP + TN	TP + FP + FN + TN

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); TP = diseased persons detected by test (true positives).
[a]Sensitivity = [TP ÷ (TP + FN)] × 100%.
[b]Specificity = [TN ÷ (FP + TN)] × 100%.

Specificity

Specificity refers to the percent of correctly identified negative results in people without the disease (the true negative rate).[8,9] Specificity assesses the proportion of true negatives disclosed by the test (Table 1-2); the lower the specificity, the higher the chance of a false positive result. A test with a specificity of 95% for the disease in question indicates that the disease will be detected in 5% of people without the disease. Tests with high specificity are best for confirming a diagnosis because the tests are rarely positive in the absence of the disease. Several newborn screening tests (eg, PKU, galactosemia, biotinidase deficiency, congenital hypothyroidism, and congenital adrenal hyperplasia) have specificity levels above 99%.[12] In contrast, the erythrocyte sedimentation rate (ESR) is a nonspecific test; infection, inflammation, and plasma cell dyscrasias increase the ESR.

Specificity as applied to quantitative laboratory tests refers to the degree of cross-reactivity of the analyte with other substances in the sample. Quinine may cross-react with or be measured as quinidine in some assays, falsely elevating reported quinidine concentrations. Phenazopyridine interferes with urine ketone tests using sodium nitroprusside (eg, Ketostix).

Specimen

A *specimen* is a sample (eg, whole blood, plasma, serum, urine, stool, sputum, sweat, gastric secretions, exhaled air, cerebrospinal fluid, or tissues) used for laboratory analysis. Whole blood contains all blood constituents (red blood cells, white blood cells, platelets, and plasma). Plasma is the watery acellular portion of blood. Plasma contains dissolved proteins (eg, albumin, globulins, fibrinogen, enzymes, and hormones), electrolytes (eg, sodium, potassium, chloride, calcium, and magnesium), lipids, carbohydrates, amino acids, and other organic substances (eg, urea, uric acid, creatinine, bilirubin, ammonium ions). Serum is the liquid that remains after the fibrin clot is removed from plasma. While some laboratory tests are performed only on plasma (eg, prothrombin time, activated partial thromboplastin time, D-dimer, and fibrinogen concentrations) or serum (eg, albumin, creatinine, bilirubin, and acetaminophen concentrations), other laboratory tests can be performed on either plasma or serum (eg, glucose, cortisol, electrolytes, and phenytoin concentrations). Some tests are performed on whole blood (eg, blood gases, hemoglobin, hematocrit, complete blood count, and erythrocyte sedimentation rate).

LABORATORY TEST RESULTS

Units Used in Reporting Laboratory Results

Laboratory test results are reported with a variety of units. For example, four different units are used to report serum magnesium concentration (1.0 mEq/L = 1.22 mg/dL = 0.5 mmol/L = 12.2 mg/L). Additionally, the same units may be reported in different ways. For example, mg/dL, mg/100 mL, and mg% are equivalent units. Enzyme activity is usually reported in terms of units, but the magnitude varies widely and depends on the methodology. Rates are usually reported in volume per unit of time (eg, creatinine clearance is measured in mL/min or L/hr), but the ESR is reported in mm/hr and coagulation test results are reported in seconds or minutes. This lack of standardization is confusing and may lead to misinterpretation of the test results.

The International System of Units (Système Internationale d'Unités, or SI) was created over 60 years ago to standardize quantitative units worldwide.[13] Seven base units and symbols are designated: length (meter, m), mass (kilogram, kg), time (second, s), electric current (ampere, A), thermodynamic temperature (kelvin, K), luminous intensity (candela, cd) and amount of substance (mole, mol). Twenty-two derived units are designated. However, it is difficult for clinicians to relate to molar concentrations (eg, serum cholesterol 4.14 mmol/L versus 160 mg/dL or HbA1c 10 mmol/L versus 8%). In the United States, most laboratory results are reported in conventional units.

Rationale for Ordering Laboratory Tests

Laboratory tests are performed with the expectation that the results will:

- Discover occult disease
- Confirm a suspected diagnosis
- Differentiate among possible diagnoses
- Determine the stage, activity, or severity of disease
- Detect disease recurrence
- Assess the effectiveness of therapy
- Guide the course of therapy

TABLE 1-3. Comparative Features of Screening and Diagnostic Laboratory Tests[14]

FEATURE	SCREENING TEST	DIAGNOSTIC TEST
Simplicity of test	Fairly simple	More complex
Target population	Individuals without signs or symptoms of the disease	Individuals with signs or symptoms of the disease
Characteristic	High sensitivity	High specificity
Disease prevalence	Relatively common	Common or rare
Risks	Acceptable to population	Acceptable to individual

Laboratory tests are categorized as *screening* or *diagnostic* tests. Screening tests, performed in individuals without signs or symptoms of disease, detect disease early when interventions (eg, lifestyle modifications, drug therapy, and surgery) are likely to be effective. Screening tests are performed on healthy individuals and are generally inexpensive, quick and easy to perform, and reliable, but they do not provide a definitive answer. Screening tests require confirmation with other clinical tests. Diagnostic tests, performed on at-risk individuals, are typically more expensive, and are associated with some degree of risk, but they provide a definitive answer.

Comparative features of screening tests are listed in **Table 1-3**. Examples of screening tests include the Papanicolaou smear, human papillomavirus (HPV) deoxyribonucleic acid (DNA) test, lipid profile, PSA, fecal occult blood (FOB), tuberculin skin test, human immunodeficiency virus (HIV) antibody/HIV antigen test, sickle cell tests, fasting blood glucose (FBG), blood coagulation tests, and serum chemistries. Screening tests may be performed on healthy outpatients (eg, ordered by the patient's primary care provider or performed during public health fairs) or on admission to an acute care facility (eg, prior to scheduled surgery). Abnormalities identified during screening are followed by more specific tests to confirm the results.

Screening tests must be cost-effective and population appropriate. The number needed to screen (NNS) is defined as "the number of people that need to be screened for a given duration to prevent one death or one adverse event."[15] For example, 2,726 women between the ages of 20 and 64 years need to be screened for cervical cancer to identify one woman with cancer.[16]

Diagnostic tests are performed in individuals with signs or symptoms of disease, a history suggestive of a specific disease or disorder, or an abnormal screening test. Diagnostic tests are used to confirm a suspected diagnosis, differentiate among possible diagnoses, determine the stage of activity of disease, detect disease recurrence, and assess and guide the therapeutic course. Diagnostic test features are listed in Table 1-3. Examples of diagnostic tests include serum human chorionic gonadotropin (HCG), B-type natriuretic peptide (BNP), FeNO, blood cultures, serum cardiac-specific troponin I and T, kidney biopsy, and the cosyntropin test.

Many laboratories group a series of related tests (screening and/or diagnostic) into a set called a *profile*. For example, the basic metabolic panel (BMP) includes common serum electrolytes (sodium, potassium, and chloride), carbon dioxide content, blood urea nitrogen (BUN), calcium, creatinine, and glucose. The comprehensive metabolic panel (CMP) includes the BMP plus albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, and total protein. Grouped together for convenience, some profiles may be less costly to perform than the sum of the cost of each individual test. However, profiles may generate unnecessary patient data. Attention to cost is especially important in the current cost-conscious era. A test should not be done if it is unnecessary, redundant, or provides suboptimal clinical data (eg, non-steady-state serum drug concentrations). Before ordering a test, the clinician should consider the following questions:

- Was the test recently performed and in all probability the results have not changed at this time?
- Were other tests performed that provide the same information?
- Can the needed information be estimated with adequate reliability from existing data? For example, creatinine clearance can be estimated using age, height, weight, and serum creatinine rather than measured from a 24-hour urine collection. Serum osmolality can be calculated from electrolytes and glucose rather than measured directly.
- What will I do if results are positive or negative? For example, if the test result will not aid in clinical decisions or change the diagnosis, prognosis, or treatment course, the benefits from the test are not worth the cost of the test.

Factors That Influence Laboratory Test Results

Laboratory results may be inconsistent with patient signs, symptoms, or clinical status. Before accepting reported laboratory values, clinicians should consider the numerous laboratory- and patient-specific factors that may influence the results (**Table 1-4**). For most of the major tests discussed in this book, a Quickview chart summarizes information helpful in interpreting results. **Figure 1-2** depicts the format and content of a typical Quickview chart.

Laboratory-Specific Factors

Laboratory errors are uncommon but may occur. Defined as a test result that is not the true result, laboratory error most appropriately refers to inaccurate results that occur because of an error made by laboratory personnel or equipment. However, laboratory error is sometimes used to refer to otherwise accurate results rendered inaccurate by specimen-related issues. Laboratory errors should be suspected for one or more of the following situations:

- The result is inconsistent with trends in serial test results.
- The magnitude of error is great.
- The result is not in agreement with a confirmatory test result.
- The result is inconsistent with clinical signs or symptoms or other patient-specific information.

True laboratory errors (inaccurate results) are caused by one or more laboratory processing or equipment errors, such as deteriorated reagents, calibration errors, calculation errors, misreading the results, computer entry or other documentation errors, or improper sample preparation. For example, incorrect entry of thromboplastin activity (International Sensitivity Index [ISI]) when calculating the International Normalized Ratio (INR) results in accurately assayed but incorrectly reported INR results.

Accurate results may be rendered inaccurate by one or more specimen-related problems. Improper specimen handling prior to or during transport to the laboratory may alter analyte concentrations between the time the sample was obtained from the patient and the time the sample was analyzed in the laboratory.[17] For example, arterial blood withdrawn for blood gas analysis must be transported on ice to prevent continued in vitro changes in pH, carbon dioxide, and oxygen. Failure to remove the plasma or serum from the clot within 4 hours of obtaining blood for serum potassium analysis may elevate the reported serum potassium concentration. Red blood cell hemolysis elevates the serum potassium and phosphate concentrations. Failure to refrigerate samples may cause falsely low concentrations of serum enzymes (eg, CK). Prolonged tourniquet time may hemoconcentrate analytes, especially those that are highly protein bound (eg, calcium).

Patient-Specific Factors

Laboratory test values cannot be interpreted in isolation of the patient. Numerous age-related (eg, decreased renal function) and other patient-specific factors (eg, time of day, posture) as well as disease-specific factors (eg, time course) affect lab results. The astute clinician assesses laboratory data in context of all that is known about the patient.

Time course. Incorrectly timed laboratory tests produce misleading laboratory results. Disease states, normal physiologic patterns, pharmacodynamics, and pharmacokinetics time courses must be considered when interpreting laboratory values. For example, digoxin has a prolonged distribution phase. Digoxin serum concentrations obtained before tissue distribution is complete do not accurately reflect true tissue drug concentrations. Postmyocardial infarction enzyme patterns are complex and evolve over a prolonged period of time. For example, CK increases about 6 hours following myocardial

TABLE 1-4. Factors That Influence Assessment of Laboratory Results

Assay used and form of analyte
Free form
Bound form
Clinical situation
Acuity of disease
Severity of disease
Demographics
Age
Gender
Ethnicity
Height
Weight
Body surface area
Drugs
Drug–drug interactions
Drug–assay interactions
Food
Time of last meal
Type of food ingested
Nutritional status
Well nourished
Poorly nourished
Posture
Upright
Supine
Pregnancy
Specimen analyzed
Serum
Plasma
Whole blood (venous or arterial)
Cerebrospinal fluid
Urine
Stool
Sputum
Other (eg, tissue, sweat, gastric contents, effusions, breath)
Temporal relationships
Time of day
Time of last dose

QUICKVIEW | Contents of a typical Quickview chart

PARAMETER	DESCRIPTION	COMMENTS
Common reference ranges		
Adults	Reference range in adults	Variability and factors affecting range
Pediatrics	Reference range in children	Variability, factors affecting range, age grouping
Critical value	Value beyond which immediate action usually needs to be taken	Disease-dependent factors; relative to reference range; value is a multiple of upper normal limit
Inherent activity	Does substance have any physiologic activity?	Description of activity and factors affecting activity
Location		
Production	Is substance produced? If so, where?	Factors affecting production
Storage	Is substance stored? If so, where?	Factors affecting storage
Secretion/excretion	Is substance secreted/excreted? If so, where/how?	Factors affecting secretion or excretion
Causes of abnormal values		
High	Major causes	Modification of circumstances, other related causes or drugs that are commonly monitored with this test
Low	Major causes	
Signs and symptoms		
High level	Major signs and symptoms with a high or positive result	Modification of circumstances/other related signs and symptoms
Low level	Major signs and symptoms with a low result	Modification of circumstances/other related causes
After event, time to…		
Initial elevation	Minutes, hours, days, weeks	Assumes acute insult
Peak values	Minutes, hours, days, weeks	Assumes insult not yet removed
Normalization	Minutes, hours, days, weeks	Assumes insult removed and nonpermanent damage
Causes of spurious results	List of common causes	Modification of circumstances/assay specific
Additional information	Any other pertinent information regarding the laboratory value of assay	

FIGURE 1-2. Contents of a typical Quickview chart. (*Source*: Reprinted with permission from Basic Skills in Interpreting Laboratory Data, 6th edition.)

infarction (MI) and returns to baseline about 48–72 hours after the MI. Lactate dehydrogenase increases about 12–24 hours following MI and returns to baseline about 10 days after the MI. Troponin increases a few hours following MI and returns to baseline in about 5–7 days. Serial samples are used to assess myocardial damage.

Lab samples obtained too early or too late may miss critical changes and lead to incorrect assessments. For example, cosyntropin (synthetic adrenocorticotropic hormone [ACTH]) tests adrenal gland responsiveness. The baseline 8 a.m. plasma cortisol is compared with the stimulated plasma cortisol obtained 30 and 60 minutes following injection of the drug. Incorrect timing leads to incorrect results. The sputum acid-fast bacilli (AFB) smear may become AFB-negative with just a few doses of antituberculosis drugs, but the sputum culture may remain positive for several weeks. Expectations of a negative sputum culture too early in the time course may lead to the inappropriate addition of unnecessary antituberculosis drugs.

Non-steady-state drug concentrations are difficult to interpret; inappropriate dosage adjustments (usually inappropriate dosage increases) may occur if the clinician fails to recognize that a drug has not reached steady-state concentrations. Although non-steady-state drug concentrations may be useful when assessing possible drug toxicity (eg, overdose situations and new onset adverse drug events), all results need to be interpreted in the context of the drug's pharmacokinetics. Absorption, distribution, metabolism, and elimination may change with changing physiology. For example, increased/decreased hepatic or renal perfusion may affect the clearance of a drug. Some drugs (eg, phenytoin) have very long half-lives; constantly changing hemodynamics during an acute care hospitalization may prevent the drug from achieving steady-state while the patient is acutely ill.

Age. Age influences many physiologic systems. Age-related changes are well-described for neonates and young children, but less data is available for the elderly and the very elderly (usually described as ≥ 90 years of age). Age influences some but not all laboratory values; not all changes are clinically significant.

Pediatric reference ranges often reflect physiologic immaturity, with laboratory values approaching those of healthy adults with increasing age. For example, the complete blood count (CBC) (hemoglobin, hematocrit, RBC count, and RBC indices) ranges are greatly dependent on age with different values reported for premature neonates, term neonates, and young children. The fasting blood glucose reference range in premature neonates is approximately 20–65 mg/dL compared with 60–105 mg/dL for children 2 years of age and older and 70–110 mg/dL for adults. The serum creatinine reference range for children 1–5 years of age differs from the reference range for children 5–10 years of age (0.3–0.5 mg/dL versus 0.5–0.8 mg/dL). Reference ranges for children are well-described because it is relatively easy to identify age-differentiated populations of healthy children. Most laboratory reference texts provide age-specific reference values.

Geriatric reference ranges are more difficult to establish because of physiologic variability with increasing age and the presence of symptomatic and asymptomatic disease states that influence reference values. Dental problems and digestive issues may lead to inadequate nutrition influencing some laboratory tests. Some physiologic functions (eg, cardiac, pulmonary, renal, and metabolic functions) progressively decline with age, but each organ declines at a different rate.[18] Other physiologic changes associated with aging include decreased body weight, decreased height, decreased total body water, increased extracellular water, increased fat percentage, and decreased lean tissue percentage; and loss of cell membranes integrity.[18] Published studies sometimes lead to contradictory conclusions due to differences in study methodology (eg, single point versus longitudinal evaluations) and populations assessed (eg, nursing home residents versus general population). Little data is available for the very elderly (≥ 90 years of age).[19,20] Most laboratory reference texts provide age-specific reference values.

Despite the paucity of data and difficulties imposed by different study designs and study populations, there is general consensus that some laboratory reference ranges are unchanged, some are different but of uncertain clinical significance, and some are significantly different in the elderly (**Table 1-5**). For example, decreased lean muscle mass with increased age results in decreased creatinine production. Decreased renal function is associated with decreased creatinine elimination. Taken together, the serum creatinine reference range in the elderly is not different from younger populations though creatinine clearance declines with age. Significant age-related changes are reported for the 2-hour postprandial glucose test, serum lipids, and arterial oxygen pressure (Table 1-5). The 2-hour postprandial glucose increases by about 5–10 mg/dL per decade. Progressive ventilation-perfusion mismatching from loss of elastic recoil with increasing age causes progressively decreased arterial oxygen pressure with increasing age. Total cholesterol and LDL-cholesterol (LDL-C) increase with age then decline in the very old.

Genetics, ethnicity, and gender. Inherited ethnic and/or gender differences are identified for some laboratory tests. For example, the hereditary anemias (eg, thalassemias and sickling disorders such as sickle cell anemia) are more common in individuals with sub-Saharan African, Asian, and Mediterranean ancestry.[28] Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an example of an inherited sex-linked (X-chromosome) enzyme deficiency found primarily in men of African, Asian, Middle Eastern, and Mediterranean ancestry.[29] The A-G6PD variant occurs mostly in Africans and affects about 13% of African-American males and 3% of African-American females in the United States. The Mediterranean G6PD variant, associated with a less common but more severe enzyme deficiency state, occurs mostly in individuals of Greek, Sardinian, Kurdish, Asian, and Sephardic Jewish ancestry.

Other enzyme polymorphisms influence drug metabolism. The genetically linked absence of an enzyme may lead to drug

TABLE 1-5. Laboratory Testing: Tests Affected by Aging[18;20-27]

No Change
Amylase
Lipase
Hemoglobin
Hematocrit
Red blood cell count
Red blood cell indices
Platelet count
White blood cell count and differential
Serum electrolytes (sodium, potassium, chloride, bicarbonate, magnesium)
Coagulation
Total iron binding capacity
Thyroid function tests (thyroxine, T_3RU)
Liver function tests (AST, ALT, LDH)
Some change (unclear clinical significance)
Alkaline phosphatase
Erythrocyte sedimentation rate
Serum albumin
Serum calcium
Serum uric acid
Thyroid function tests (TSH, T_3)
Clinically significant change
Arterial oxygen pressure
2-hr postprandial glucose
Serum lipids (total cholesterol, low-density lipoprotein, triglycerides)
Serum testosterone (in men)
Serum estradiol (in women)
No change but clinically significant decrease in renal function
Serum creatinine

ALT = alanine aminotransferase; AST = aspartate aminotransferase; LDH = lactate dehydrogenase; TSH = thyroid-stimulating hormone; T_3RU = triiodothyronine resin uptake; T_3 = triiodothyronine.

toxicity secondary to drug accumulation or lack of drug effect if the parent compound is an inactive prodrug (eg, codeine). The cytochrome P450 (CYP450) superfamily consists of greater than 100 isoenzymes with selective but overlapping substrate specificity. Some individuals are poor metabolizers while some are ultra-rapid metabolizers. Several of the cytochrome P450 phenotypes vary by race. For example, the CYP2D6 poor metabolism phenotype occurs in 5%–10% of Caucasians and the CYP2C19 poor metabolism phenotype occurs in 10%–30% of Asians.[30,31]

Additional enzyme polymorphisms include pseudocholinesterase deficiency, phenytoin hydroxylation deficiency, inefficient *N*-acetyltransferase activity, inefficient or rapid debrisoquine hydroxylase activity, diminished thiopurine methyltransferase activity, partial dihydropyrimidine dehydrogenase inactivity, and defective uridine diphosphate glucuronosyl transferase activity.[32] Other examples of genetic polymorphisms include variations in the β-2 adrenoceptor gene that influence response to sympathomimetic amines and variations in drug transporters such as P-glycoprotein (P-gp), multidrug resistance gene associated proteins (MRP1, MRP2, MRP3), and organic anion transporting peptide (OATP).[32]

Biologic rhythms. Biologic rhythms are oscillatory (cyclical) temporal patterns of varying lengths. The master clock, located in the suprachiasmatic nucleus of the hypothalamus, coordinates timing signals and multiple peripheral clocks.[33] A circadian rhythm is an approximately 24-hour endogenously generated cycle.[34] Ultradian rhythms are shorter than 24-hour; infradian rhythms are longer than 24-hour.[35,36]

Well-described, human circadian rhythms include body temperature, cortisol production, melatonin production, and hormonal production. Platelet function, cardiac function, and cognition also follow a circadian rhythm.[37] Other biologic rhythms include the 8-hour rhythm for circulating endothelin, the approximately weekly (circaseptan) rhythm for urinary 17-ketosteroid excretion, and the seasonal rhythms for cholesterol and 25-hydroxycholecalciferol.[38,39]

Statistically significant circadian rhythms have been reported for CK, ALT, γ glutamyl transferase (GGT), LDH, and some serum lipids.[40,41] Glomerular filtration has a circadian rhythm.[42] Circadian variations in aminoglycoside pharmacokinetics, including netilmicin, amikacin, and gentamicin, have been reported.[43] Though the clinical significance of diurnally variable laboratory results is not well understood, diurnal variability should be considered when assessing laboratory values. Obtaining laboratory results at the same time of day (eg, routine 7 a.m. blood draws) minimizes variability due to circadian rhythms. Different results obtained at different times of the day may be due to circadian variability rather than acute physiologic changes.

Drugs. The four generally accepted categories of drug–laboratory interactions include methodological interference; drug-induced end-organ damage; direct pharmacologic effect; and a miscellaneous category. Many drugs interfere with analytical methodology. Drugs that discolor the urine interfere with fluorometric, colorimetric, and photometric tests and

mask abnormal urine colors. For example, amitriptyline and propofol turn the urine a blue–green color, phenazopyridine and rifampin turn the urine an orange–red color, and doxorubicin turns the urine red. Other drugs directly interfere with the laboratory assay. For example, high doses of ascorbic acid (greater than 500 mg/day) cause false negative stool occult blood tests. Some drugs interfere with urinary fluorescence tests for urine catecholamines by producing urinary fluorescence themselves (eg, ampicillin, chloral hydrate, and erythromycin). Monoclonal antibodies interfere with a variety of laboratory tests.[44] For example, daratumumab (Darzalex) FDA-approved in 2015 for treatment of multiple myeloma, interferes with indirect antiglobulin tests (indirect Coombs test), serum protein electrophoresis (SPE), and immunofixation electrophoresis (IFE) assays.[45] Omalizumab (Xolair) complexes with immunoglobulin E (IgE) elevating serum total IgE for up to a year following administration.[46]

Direct drug-induced, end-organ damage (eg, kidney, liver, and bone marrow) change the expected laboratory results. For example, amphotericin B causes renal damage evidenced by increased serum creatinine. Bone marrow suppressants, such as doxorubicin and bleomycin, cause thrombocytopenia. Some drugs alter laboratory results as a consequence of a direct pharmacologic effect. For example, thiazide and loop diuretics increase serum uric acid by decreasing uric acid renal clearance or tubular secretion. Narcotics, such as codeine and morphine sulfate, increase serum lipase by inducing spasms of the sphincter of Oddi. Urinary specific gravity is increased in the presence of dextran. Other examples of drug–laboratory interactions include drugs that cause a positive direct Coombs test (eg, isoniazid, sulfonamides, and quinidine), drugs that cause a positive antinuclear antibody test (eg, penicillins, sulfonamides, and tetracyclines), drugs that interfere with the C-urea breath test (eg, proton pump inhibitors), and drugs that inhibit bacterial growth in blood or urine cultures (eg, antibiotics).

Thyroid function tests are a good example of the complexity of potential drug-induced laboratory test changes. Thyroxine (T_4) and triiodothyronine (T_3) are displaced from binding proteins by salicylates, heparin, and high-doses of furosemide. Free T_4 levels initially increase, but chronic drug administration results in decreased T_4 levels with normal TSH levels. Phenytoin, phenobarbital, rifampin, and carbamazepine stimulate hepatic metabolism of thyroid hormone, resulting in decreased serum hormone concentration. Amiodarone, high-dose β-adrenergic blocking drugs, glucocorticosteroids, and some iodine contrast dyes interfere with the conversion of T_4 to T_3. Ferrous sulfate, aluminum hydroxide, sucralfate, colestipol, and cholestyramine decrease T_4 absorption. Somatostatin, octreotide, and glucocorticosteroids suppress TSH production.

Pregnancy. Pregnancy is a normal physiologic condition that alters the reference range for many laboratory tests. Normal pregnancy increases serum hormone concentrations (eg, estrogen, testosterone, progesterone, human chorionic gonadotropin, prolactin, corticotropin-releasing hormone (CRH), ACTH, cortisol, and atrial natriuretic hormone). The plasma volume increases by 30%–50%, resulting in a relative hyponatremia (eg, serum sodium decreased by about 5 mEq/L) and modest decreases in hematocrit. The metabolic adaptations to pregnancy include increased RBC mass and altered carbohydrate (eg, 10%–20% decrease in fasting blood glucose) and lipid (eg, 300% increase in triglycerides (TG) and a 50% increase in total cholesterol) metabolism. Pregnancy changes the production and elimination of thyroid hormones, resulting in different reference values over the course of pregnancy.[47] For example, thyroxine-binding globulin increases during the first trimester, but pregnancy-associated accelerated thyroid hormone metabolism occurs later in the pregnancy. Other physiologic changes during pregnancy include an increased cardiac output (increases by 30%–50%), decreased systemic vascular resistance, increased glomerular filtration rate (increases by 40%–50%), shortened prothrombin and partial thromboplastin times, and hyperventilation resulting in compensated respiratory alkalosis and increased arterial oxygenation.[48]

Other Factors

Organ function, diet, fluid status, patient posture, and altitude affect some laboratory tests.

Organ Function

Renal dysfunction may lead to hyperkalemia, decreased creatinine clearance, and hyperphosphatemia. Hepatic dysfunction may lead to reduced clotting factor production with prolonged partial thromboplastin times and prothrombin times. Bone marrow dysfunction may lead to pancytopenia.

Diet

Serum glucose and lipid profiles are best assessed in the fasting state. Unprocessed grapefruit juice down-regulates intestinal CYP3A4 and increases the bioavailability of some orally administered drugs.

Fluid Status

Hypovolemia is associated with a decreased amount of fluid in the bloodstream; all blood constituents (eg, sodium, potassium, creatinine, glucose, and BUN) become more concentrated. This effect is called *hemoconcentration.* Although the absolute amount of the substance in the body has not changed, the loss of fluid results in an abnormally high concentration of the measured analyte. The converse is true with hemodilution. Relativity must be applied or false impressions may arise (refer to **Minicase 2**).

Posture

Plasma renin release is stimulated by upright posture, diuretics, and low-sodium diets; plasma renin testing usually occurs after 2–4 weeks of normal sodium diets under fasting supine conditions.

Altitude

At high altitude, hemoglobin initially increases secondary to dehydration. However, hypoxia stimulates erythropoietin production, which in turn stimulates hemoglobin production,

MINICASE 2

Interpretation of Laboratory Parameters in Dehydration

Christopher, a 67-year-old male with a long history of asthma, presented to the emergency department (ED) with a one-day history of sudden onset fever, chills, dry cough, nasal congestion, muscle aches, fatigue, nausea, and diarrhea. On admission to the ED, his temperature was 100.4°F (oral) and he was hypotensive and tachycardic with decreased skin turgor and dry mucus membranes. A BMP and CBC were ordered. The BMP was notable for elevated serum electrolytes, BUN, and serum creatinine. The BUN to creatinine ratio was greater than 20 to 1. The CBC was notable for an elevated white blood cell (WBC) count with an increased percentage of lymphocytes and elevated platelets, hematocrit, and hemoglobin. A rapid influenza diagnostic test was positive. Fluid resuscitation and peramivir (Rapivab) were ordered.

QUESTION: Peramivir (Rapivab) is dosed according to renal function. Dose reduction is required if the estimated creatinine clearance is less than 50 mL/min. The manufacturer provides dosing recommendations based on estimated creatinine clearance using the Cockcroft Gault equation. Is it appropriate to use Christopher's admission creatinine to estimate his creatinine clearance?

DISCUSSION: No. Christopher is severely dehydrated; all laboratory parameters are hemoconcentrated. His admission serum creatinine is high and underestimates his renal function. The regimen for patients with estimated creatinine clearance at least 50 mL/min is a one-time 600 mg dose. Given that Christopher has two risk factors for influenza complications (age ≥ 65 y and chronic pulmonary disease), the peramivir (Rapivab) dose needs to be optimal. The best approach is to recheck the serum creatinine after the couple of hours of rehydration, and then estimate the creatinine clearance.

resulting in increased hemoglobin concentration and increased blood viscosity. Physiologic changes depend on altitude and duration of exposure. Serum hemoglobin reference ranges are adjusted progressively upward for individuals living 1000 m or more above sea level.[49]

NONCENTRALIZED LABORATORY TESTS

Point-of-Care Testing

Point-of-care (POC) testing (POCT), also known as *near patient testing*, *bedside testing*, or *extra-laboratory testing*, is clinician-directed diagnostic testing performed at or near the site of patient care rather than in a centralized laboratory.[50] Typically, nonlaboratory healthcare personnel (eg, pharmacists, physicians, physician assistants, nurses, nursing assistants, respiratory therapists, and paramedics) perform POC testing. POC test equipment ranges from small, hand-held devices to table-top analyzers. In vitro, in vivo, and ex vivo POC testing refer to tests performed near the patient (eg, fingerstick blood glucose), in the patient (eg, specialized intra-arterial catheter that measures lactate), and just outside the patient (eg, intra-arterial catheter attached to an external analyzer), respectively. Although POC testing is not a new concept, recent technological advances (eg, microcomputerization, miniaturization, biosensor development, and electrochemical advances) and apps enabled by smart phones, smart watches (wearable testing), and tablets have rapidly expanded the variety of available POC tests beyond the traditional urinalysis dipsticks or fingerstick blood glucose monitors.[51] The availability of multiplexed point-of-care testing (xPOCT), defined as the simultaneous detection of more than one analyte from a single specimen, will expand as technology advances.[52]

The major advantages of POC testing include reduced turnaround time (TAT) and test portability.[53] Reduced TAT is especially advantageous in settings where rapidly available laboratory test results may improve patient care (eg, emergency departments, operating rooms, critical care units, accident scenes, and patient transport). Reduced TAT also enhances patient care in more traditional ambulatory settings by reducing patient and provider time and minimizing delays in initiating therapeutic interventions. Patient care sites without local access to centralized laboratories (eg, nursing homes, rural physician practices, and military field operations) also benefit from POC testing. Other POC advantages include blood conservation (POC tests usually require drops of blood as opposed to the several milliliters required for traditional testing); less chance of preanalytical error from inappropriate transport, storage, or labeling of samples; and overall cost savings. Although the per test cost is usually higher with POC testing, cost analyses must consider the per unit cost of the test as well as other costs such as personnel time, length of stay, and quality of life.

The major disadvantages of POC testing include misuse or misinterpretation of results, loss of centrally-generated epidemiologic data, documentation errors, inappropriate test material disposal, and quality assurance issues.[53] All laboratory testing must meet the minimum standards established by the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88).[54] Under CLIA-88, tests are categorized into one of three groups based on potential public health risk: waived tests, tests of moderate complexity, and tests of high complexity. Waived tests (eg, fecal occult blood test) pose no risk of harm to the patient if used incorrectly or use such simple and accurate methodologies that inaccurate results are unlikely. Many POC tests meet the criteria for waived status but increasingly sophisticated POC tests may be subject to more stringent control. State-specific regulations may be more stringent than federal regulations.

Home Testing

Home testing refers to patient-directed diagnostic and monitoring testing usually performed by the patient or family member at home. Numerous FDA-approved, home-use, nonprescription laboratory test kits are marketed; home glucose and pregnancy testing are among the most popular. The FDA's Office of In Vitro Diagnostics and Radiological Health (OIR) maintains a searchable list of approved home-testing kits. Many non-FDA-approved home testing kits are marketed via the Internet.

Nonprescription home testing kits are available for the screening, detection, and monitoring of a wide range of medical conditions. Home testing laboratory test kits are marketed for pregnancy (HCG), menopause (follicle stimulating hormone [FSH]), ovulation (luteinizing hormone [LH]), drugs of abuse, FOB, breath alcohol, blood glucose, HbA1c, ketones, prothrombin time (PT), carcinoembryonic antigen (CEA), PSA, allergies, thyroid hormones, estrogen, testosterone, urinary tract infections, sexually transmitted infections, group A Streptococcus infection, HIV, hepatitis C, Lyme disease, and paternity and genetic testing. Specimens tested include urine, blood, hair, breath, feces, semen, saliva, and oropharyngeal secretions.

Advantages of home testing include convenience, cost-savings (as compared with physician office visit), quickly available results, and privacy. Home monitoring of chronic drug therapy, such as blood glucose control with insulin therapy, may give the patient a better sense of control over the disease and improve patient outcomes. Disadvantages of home testing include misinterpretation of test results, delays in seeking medical advice, and lack of pre- and posttest counseling and psychological support. In addition, home test kits typically do not provide the consumer with information regarding sensitivity, specificity, precision, or accuracy. Home-use test kits are marketed either as complete test kits (the individual obtains his or her own sample, tests the sample and reads the results) or as collection kits (the individual obtains the sample, mails the sample to the laboratory, and receives the results by mail, Internet, or telephone). Consumers should read and follow the test instructions to minimize testing error.

GUIDELINES FOR INTERPRETING LABORATORY RESULTS

Laboratory results must be interpreted in context of the patient and the limitations of the laboratory test. However, a laboratory result is only one piece of information; diagnostic and therapeutic decisions cannot be made on the basis of one piece of information. Clinicians typically give more weight to the presence or absence of signs and symptoms associated with the medical problem rather than to an isolated laboratory report. For example, an asymptomatic patient with a serum potassium concentration of 3.1 mEq/L (reference range: 3.5–5.0 mEq/L) does not cause as much concern as a patient who has a potassium concentration of 3.3 mEq/L and is symptomatic. Tests for occult disease, such as colon cancer, cervical cancer, and hyperlipidemia, are exceptions to this logic because, by definition, the patients being tested are asymptomatic. Baseline results, rate of change, and patterns should be considered when interpreting laboratory results.

Baseline Results

Baseline studies establish relativity and are especially useful when reference ranges are wide or when reference values vary significantly among patients. For example, lovastatin and other hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitors cause myopathy and liver dysfunction in a small percentage of patients. The myopathy is symptomatic (muscle pain or weakness) and elevates CK concentrations. The drug-induced liver dysfunction is asymptomatic and causes elevated AST and ALT. FDA labeling for statins recommends obtaining liver function tests before starting therapy then as clinically indicated.[55] Baseline laboratory values are also used to establish relative therapeutic goals. For example, the activated partial thromboplastin time (aPTT) is used to assess patient response to heparin anticoagulation. Therapeutic targets are expressed in terms of how much higher the patient's aPTT is compared with the baseline control.

Laboratory Value Compared with Reference Range

Not all laboratory values above the upper limit of normal (ULN) require intervention. Some elevations may be transient and resolve with continued drug administration. Risk-to-benefit considerations may require that some evidence of drug-induced organ damage is acceptable given the ultimate benefit of the drug. For example, a 6-month course of combination drug therapy, including isoniazid, a known hepatotoxin, is recommended for treatment of latent tuberculosis.[56] The potential benefit of at least 6 months of therapy (ie, lifetime protection from tuberculosis in the absence of reinfection) means that clinicians are willing to accept some evidence of liver toxicity with continued drug therapy (eg, isoniazid is continued until AST is greater than five times the ULN in asymptomatic individuals or greater than three times the ULN in symptomatic patients).[57]

Rate of Change

The *rate of change* of a laboratory value provides the clinician with a sense of risks associated with the particular signs and symptoms. For example, a patient whose RBC count falls from 5 million/mm^3 to 3.5 million/mm^3 over several hours is more likely to need immediate therapeutic intervention than if the decline took place over several months.

Isolated Results Versus Trends

An isolated abnormal test result is difficult to interpret. However, one of several values in a series of results or similar results from the same test performed at two different times suggests a pattern or trend. For example, a random serum glucose concentration of 300 mg/dL (reference range ≤ 200 mg/dL in adults) might cause concern unless it was known that the patient was admitted to the hospital the previous night for treatment of diabetic ketoacidosis with an admission random serum glucose of 960 mg/dL. A series of laboratory values adds perspective to an interpretation but may increase overall costs.

Spurious Results

A *spurious laboratory value* is a false laboratory value. The only way to differentiate between an actual and a spurious laboratory value is to interpret the value in context of what else is known about the patient. For example, a serum potassium concentration of 5.5 mEq/L (reference range: 3.5–5.0 mEq/L) in the absence of significant electrocardiographic changes (ie, wide, flat P waves, wide QRS complexes, and peaked T waves) and risk factors for hyperkalemia (ie, renal insufficiency) is most likely a spurious value. Possible causes of falsely elevated potassium, such as hemolysis, acidosis, and laboratory error, have to be ruled out before accepting that the elevated potassium accurately reflects the patient's actual serum potassium. Repeat testing of suspected spurious laboratory values increases the cost of patient care but may be necessary to rule out an actual abnormality.

FUTURE TRENDS

Point-of-care testing will progress and become more widely available as technological advances produce smaller and more portable analytical devices. Real-time, in vivo mobile and wearable POC testing may become standard in many patient care areas. Laboratory test specificity and sensitivity will improve with more sophisticated testing. Genetic testing (laboratory analysis of human DNA, RNA, chromosomes, and proteins) will undergo rapid growth and development in the next few decades; genetic testing will be increasingly used to predict an individual's risk for disease, identify carriers of disease, establish diagnoses, and provide prognostic data. Genetic links for a diverse group of diseases including cystic fibrosis, Down syndrome, Huntington disease, breast cancer, Alzheimer disease, schizophrenia, PKU, and familial hypercholesterolemia are established; genetic links for many additional diseases will be established. Variations in DNA sequences will be well-described and linked to individualized disease management strategies.[58] Nanobiosensor-based POC technology is being developed for the detection, diagnosis, and monitoring of medical conditions such as cancer, diabetes, and HIV.[59] Advances in array-based technologies (ie, simultaneous evaluation of multiple analytes from one sample) will reduce sample volume and cost.

PATIENT ASSESSMENT

The evaluation of patient laboratory data is an important component of designing, implementing, monitoring, evaluating, and modifying patient-specific medication therapy management plans. Depending on the setting, state laws, and collaborative practice agreements, some pharmacists have the authority to order and assess specific laboratory tests (eg, drug serum concentrations, serum creatinine, liver function tests, serum electrolytes) or to perform POCT (eg, lipid screening profiles, prothrombin time, HbA1c, rapid strep test). Pharmacists in ambulatory clinics and acute care inpatient settings have routine access to the same patient laboratory data as all other members of the healthcare team, but many community-based pharmacists do not have access to patient laboratory data. Though lack of access to laboratory data is currently a barrier, the increasing use of electronic health records will improve pharmacist access to patient laboratory data.

SUMMARY

Clinical laboratory tests are convenient methods to investigate disease- and drug-related patient issues, especially since knowledge of pathophysiology and therapeutics alone is insufficient to provide high-quality clinical considerations. This chapter should help clinicians appreciate general causes and mechanisms of abnormal test results. However, results within the reference range are not always associated with a lack of signs and symptoms. Many factors influence the reference range. Knowing the sensitivity, specificity, and predictive value is important in selecting an assay and interpreting its results. Additionally, an understanding of the definitions, concepts, and strategies discussed should also facilitate mastering information in the following chapters.

LEARNING POINTS

1. ***What factors should be considered when assessing a laboratory parameter that is outside the reference range?***

   ANSWER: The upper and lower limits of the reference range are not absolute; by definition, some normal results fall outside the reference range. Other factors to consider include the sensitivity and specificity of the test, the critical value for the test, the acuity of the change, drug-drug and drug-test interactions, patient signs and symptoms, laboratory error, specimen handling, patient age, and the timing of the test.

2. ***What factors should be considered when assessing laboratory parameters in a pregnant patient?***

   ANSWER: Physiologic changes during pregnancy, including increased plasma volume, increased RBC mass, altered carbohydrate and lipid metabolism, serum hormone changes, increased cardiac output, increased glomerular filtration rates, and acid-base alterations, result in different laboratory reference ranges. Be aware of and check for pregnancy-specific reference values when assessing laboratory parameters in a pregnant patient.

3. ***What factors should be considered when recommending at-home laboratory testing kits?***

   ANSWER: Advantages of patient-directed diagnostic and monitoring testing include convenience, cost-savings as compared with a physician office-visit, quickly available results, and privacy. Disadvantages include lack of information regarding sensitivity, specificity, precision, or accuracy; misinterpretation of the test results; the absence of pre- and post-test counseling; and delays in seeking medical advice. Patients who wish to purchase FDA-approved home-testing kits should be cautioned to seek advice before making treatment decisions based solely on home-testing laboratory results.

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