CHAPTER 1

DEFINITIONS AND CONCEPTS

KAREN J. TIETZE

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

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 an 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 that the methodology is consistently able to produce results in close agreement. The accuracy of those results is another question.

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, 9.2–11.0 mg/dL for total serum calcium, and 4.0–4.8 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. 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; *indirect bilirubin* refers to the unconjugated form. Lactate dehydrogenase (LDH) is separated electrophoretically into five different isoenzymes: LDH1, LDH2,

MINICASE 1

Assays for Detecting Noroviruses

IN 411 PATIENTS WITH ACUTE GASTROENTERITIS SYMPTOMS, fecal specimens were tested for norovirus with a standard real-time reverse transcription-polymerase chain reaction (RT-PCR) molecular assay and a new immunochromatographic assay.[2] The new immunochromatographic assay provides very rapid results but may not be as sensitive as standard molecular assays.

Question: After reviewing the following results, what conclusions can be made about the clinical performance of the new immunochromatographic assay?

Immunochromatographic Assay Results (n=411):

True Positives	52	**True Negatives**	342
False Positives	1	**False Negatives**	16

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

Sensitivity = (TP ÷ [TP + FN]) × 100% = (52 ÷ [52 + 16]) × 100% = 76.5%

Specificity = (TN ÷ [FP +TN]) × 100% = (342 ÷ [342 + 1]) × 100% = 99.7%

Predictive value of positive test = (TP ÷ [TP + FP]) × 100% = (52 ÷ [52 + 1]) × 100% = 98.1%

Predictive value of negative test = (TN ÷ [TN + FN]) × 100% = (342 ÷ [342 + 16]) × 100% = 95.5%

In this study, the new immunochromatographic assay had high specificity but low sensitivity as compared to a standard real-time RT-PCR assay. The new immunochromatographic assay may be useful for the rapid detection of norovirus infections, but it is not sensitive enough to rule out norovirus infection in those with negative test results.

LDH3, LDH4, and LDH5. Creatine kinase (CK) exists in three isoforms: CK1, CK2, and 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, 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, glycosylated hemoglobin A1c (HbA1c) is used to assess long-term glucose control in people 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 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 (refer to Minicase 1).

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 lab 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; 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 is reported in milliliters per minute, and LDH is 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

TABLE 1-1. Relationship of Sensitivity, Specificity, Disease Prevalence, and Predictive Value of 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)] x 100%.
Predictive value of negative test = [TN ÷ (TN + FN)] x 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).

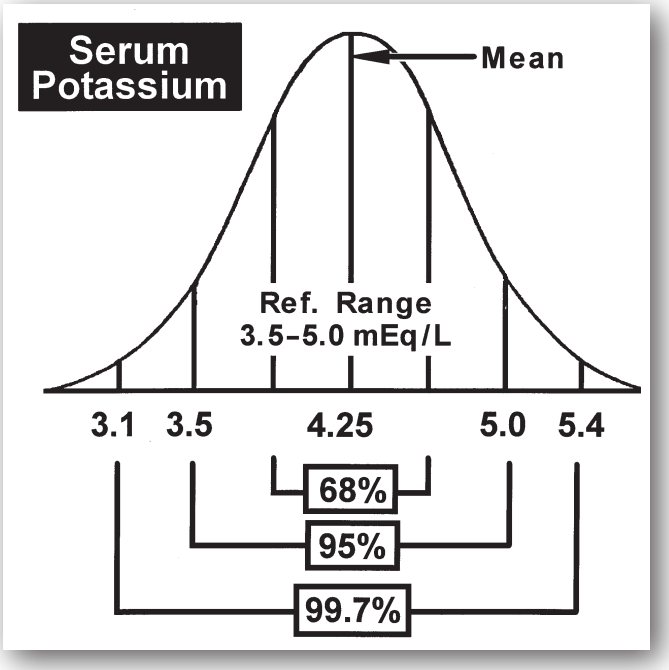

FIGURE 1-1. Gaussian (random) value distribution with a visual display of the area included within increments of standard deviation (SD) above and below the mean: ±1 SD = 68% of total values; ±2 SD = 95% of total values; and ±3 SD = 99.7% of total values.

with active systemic lupus erythematosus (LE) 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* 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 (i.e., 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*.[3] 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, 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 (e.g., ±3 SD) includes a larger percentage (97.5%) of normal individuals but increases the chance of including individuals with values only slightly outside of a more narrow range, thus decreasing the sensitivity of the test.

Qualitative laboratory tests are either negative or positive and without a reference range; any positivity is considered abnormal. For example, any amount of serum acetone, porphobilinogen, or alcohol 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, the LE prep 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 labs 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 disease (i.e., no signs or symptoms of disease) are included in the sample population. Failure to control for physiologic variables (e.g., age, gender, ethnicity, body mass, diet, posture, and time of day) introduces many unrelated factors and 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 National Cholesterol Education Program's (NCEP) Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III or ATP III), released in 2001, includes recommendations to lower and more closely space reference range cutoff points for low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides

(TGs).[4] The availability of more sensitive thyrotropin (thyroid-stimulating hormone [TSH]) assays and the recognition that the original reference population data was skewed has led some clinicians to conclude that there is a need to establish a revised reference range for this analyte.[5]

Critical Value

The term *critical value* refers to a result that is far enough outside the reference range that it indicates impending morbidity (e.g., potassium <2.8 mEq/L). Because laboratory personnel are not in a position to consider mitigating circumstances, a responsible 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 above.

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 are reported as negative or 1+, 2+, 3+; 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 (TP rate).[6,7] Sensitivity assesses the proportion of TPs 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 mental retardation. Mental retardation is preventable if PKU is diagnosed and dietary interventions 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.[8] In contrast, the prostate specific antigen (PSA) test, a test commonly used to screen men for prostate cancer, is highly sensitive at a low PSA cutoff value but highly specific only at a high PSA cutoff value.[9] 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 0.69 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 0 ng/mL and low concentrations associated with inadequate dosage regimens.

TABLE 1-2. Calculation of Sensitivity and Specificity

Screening Test Result	Diseased	Not Diseased	Total
Positive	TP	FP	TP + FP
Negative	FN	TN	FN + TN
Total	TP + FN	FP + TN	TP + FP + FN + TN

Sensitivity = [TP ÷ (TP + FN)] x 100%.
Specificity = [TN ÷ (FP + TN)] x 100%.
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).

Specificity

Specificity refers to the percent of negative results in people without the disease (TN rate).[6,7] Specificity assesses the proportion of TNs 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 (e.g., PKU, galactosemia, biotinidase deficiency, congenital hypothyroidism, and congenital adrenal hyperplasia) have specificity levels above 99%.[10] In contrast, the PSA test is an example of a test with low specificity. The PSA is specific for the prostate but not specific for prostate carcinoma. Urethral instrumentation, prostatitis, urinary retention, prostatic needle biopsy, and benign prostatic hyperplasia elevate the PSA. The erythrocyte sedimentation rate (ESR) is another 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. For example, vitamin C cross-reacts with glucose in some urine tests (e.g., Clinitest®), falsely elevating the urine glucose test results. Quinine may cross-react with or be measured as quinidine in some assays, falsely elevating reported quinidine concentrations.

Specimen

A *specimen* is a sample (e.g., whole blood, venous blood, arterial blood, urine, stool, sputum, sweat, gastric secretions, exhaled air, cerebrospinal fluid, or tissues) that is used for laboratory analysis. Plasma is the watery acellular portion of blood. Serum is the liquid that remains after the fibrin clot is removed from plasma. While some laboratory tests are performed only on plasma (e.g., renin activity and adrenocorticotropic hormone

[ACTH] concentration) or serum (e.g., serum electrophoresis and acetaminophen concentration), other laboratory tests can be performed on either plasma or serum (e.g., aldosterone, potassium, and sodium concentrations).

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 (e.g., 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 about 40 years ago to standardize quantitative units worldwide.[11] Four base units and symbols are designated: length (meter, m), mass (kilogram, kg), time (second, s), and substance (mole, mol). Five derived units are designated: volume (liter, L, 10^{-3} m^3), force (newton, N, kg ms^{-2}), pressure (pascal, Pa, kg m^{-1} s^{-2}), energy (joule, J, kg m^2 s^{-2}), and power (watt, W, kg m^2 s^{-3}). However, it is difficult for clinicians to relate to molar concentrations (e.g., serum cholesterol 4.14 mmol•L^{-1} versus 160 mg/dL, or HbA1c mmol/mL 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

1. Discover occult disease
2. Confirm a suspected diagnosis
3. Differentiate among possible diagnoses
4. Determine the stage, activity, or severity of disease
5. Detect disease recurrence
6. Assess the effectiveness of therapy
7. Guide the course of therapy

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 (e.g., 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 do not provide a definitive answer. Screening tests require confirmation with other clinical tests. Diagnostic tests are performed on at-risk individuals, are typically more expensive, and are associated with some degree of risk but provide a definitive answer.[12]

Comparative features of screening tests are listed in Table 1-3. Examples of screening tests include the Papanicolaou smear, lipid profile, PSA, fecal occult blood, tuberculin skin test, sickle cell tests, blood coagulation tests, and serum chemistries. Screening tests may be performed on healthy outpatients (e.g., ordered by the patient's primary care provider or performed during public health fairs) or on admission to an acute care facility (e.g., prior to scheduled surgery). Abnormal screening tests are followed by more specific tests to confirm the abnormality.

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."[14] For example, 465 women need to undergo mammographic screening every 24–33 months for 7 years to save one life from breast cancer.[15]

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 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), 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,

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

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
Performed by	Nonphysician providers and physicians	Physicians
Characteristic	High sensitivity	High specificity
Disease prevalence	Relatively common	Common or rare
Risks	Acceptable to population	Acceptable to individual

[a]Compiled from reference 13.

FIGURE 1-2. Contents of a typical Quickview chart.

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 physiological 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 lab value of assay	

redundant, or provides suboptimal clinical data (e.g., non-steady-state serum drug concentrations). Before ordering a test, the clinician should consider the following questions:

1. Was the test recently performed and in all probability the results have not changed at this time?
2. Were other tests performed that provide the same information?
3. 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. Additionally, a clinician should ask, "What will I do if results are positive or negative (or absent or normal)?" 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.

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

Assay used and form of analyte
Free
Bound
Clinical situation
Acuity
Severity
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
Posture
Pregnancy
Specimen analyzed
Serum
Blood (venous or arterial)
Cerebrospinal fluid
Urine
Temporal relationships
Time of day
Time of last dose

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:

1. The result is inconsistent with trend in serial test results.
2. The magnitude of error is great.
3. The result is not in agreement with a confirmatory test result.
4. 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.[16] For example, arterial blood withdrawn for blood gas analysis must be transported on ice to prevent continued in vitro changes in pH, $PaCO_2$, and PaO_2. 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 (e.g., CK). Prolonged tourniquet time may hemoconcentrate analytes, especially those that are highly protein bound (e.g., calcium).

Patient-Specific Factors

Laboratory test values cannot be interpreted in isolation of the patient. Numerous age-related (e.g., age and renal function) and other patient-specific factors (e.g., time of day, posture) as well as disease-specific factors (e.g., 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 lab results. Disease states, normal physiologic patterns, pharmacodynamics, and pharmacokinetics time courses must be considered when interpreting lab 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 an example of a more complex and prolonged postevent time course. Creatine kinase elevates about 6 hours following myocardial infarction (MI) and returns to baseline about 48–72 hours after the MI. Lactate dehydrogenase elevates about 12–24 hours following MI and returns to baseline about 10 days after the MI. Troponin elevates 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 ACTH) tests adrenal gland responsiveness. The baseline 8 a.m. plasma cortisol is compared to 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 antituberculous 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 antituberculous 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 (e.g., overdose situations and new onset adverse drug events), all results need to be interpreted in the context of the drug's pharmacokinetics. Absorption, distribution, and elimination may change with changing physiology. For example, increased/decreased hepatic or renal perfusion may affect the clearance of a drug. Some drugs (e.g., 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 are available for the elderly and the very elderly (usually described as ≥75 years of age). Age influences some but not all lab values; not all changes are clinically significant.

Pediatric reference ranges often reflect physiologic immaturity, with lab 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 to 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. Diet (e.g., malnutrition) also influences some lab results. Some physiologic functions (e.g., cardiac, pulmonary, renal and metabolic functions) progressively decline with age, but each organ declines at a different rate.[17] 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; cell membranes may leak.[17] Published studies sometimes lead to contradictory conclusions due to differences in study methodology (e.g., single point versus longitudinal evaluations) and populations assessed (e.g., nursing home residents versus general population). Little data are available for the very elderly (≥90 years of age).[18] 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 clearly 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. Cholesterol progressively increases from age 20 years reaching a plateau in the 5th to 6th decade in men and in the 6th to 7th decade in women followed by progressive decline. LDL and TG follow a similar pattern, though TG appears to progressively increase in women.

Genetics, ethnicity, and gender. Inherited ethnic and/or gender differences are identified for some laboratory tests. For example, the hereditary anemias (e.g., thalassemias and sickling disorders such as sickle cell anemia) are more common in individuals with African, Mediterranean, Middle Eastern, Indian, and southeast Asian ancestry.[24] Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an example of an inherited sex-linked (X-chromosome) enzyme deficiency found primarily in men of African and Mediterranean ancestry.[25] 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 toxicity secondary to drug accumulation or lack of drug effect if the parent compound is an inactive prodrug (e.g., 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 hyperextensive metabolizers. Several of the cytochrome P450 phenotypes vary by race. For example, the CYP2D6 poor metabolism phenotype occurs in 5% to 10% of Caucasians and the CYP2C19 poor metabolism phenotype occurs in 10% to 30% of Asians.[26,27]

Additional enzyme polymorphisms include pseudocholinesterase deficiency, phenytoin hydroxylation deficiency, inefficient N-acetyltransferase activity, inefficient or rapid debrisoquine hydroxylase activity, diminished thiopurine

TABLE 1-5. Laboratory Testing: Tests Affected by Aging[17-23]

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_3 resin uptake)
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, triiodothyronine)
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
Serum creatinine

ALT = alanine aminotransferase; AST = aspartate aminotransferase; LDH = lactate dehydrogenase; TSH = thyroid-stimulating hormone.

methyltransferase activity, partial dihydropyrimidine dehydrogenase inactivity, and defective uridine diphosphate glucuronosyl transferase activity.[28] Other examples of genetic polymorphisms include variations in the beta-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 (OATP1, OATP2).[28]

Biologic rhythms. Biologic rhythms are characterized as short (less than 30 minutes), intermediate (greater than 30 minutes but less than 6 days), and long (greater than 6 days).[29] The master clock, located in the suprachiasmatic nucleus of the hypothalamus, coordinates timing signals and multiple peripheral clocks.[30] A circadian rhythm is a 24-hour, endogenously generated cycle.[31] Well-described, human circadian rhythms include body temperature, cortisol production, melatonin production, and hormonal production (gonadotropin, testosterone, growth hormone, and thyrotropin). Platelet function, cardiac function, and cognition also follow a circadian rhythm.[32]

Other laboratory parameters follow circadian patterns. For example, statistically significant circadian rhythms have been reported for CK, ALT, gamma glutamyl transferase, LDH, and some serum lipids.[33,34] Glomerular filtration has a circadian rhythm.[35] Amikacin is almost completely excreted via glomerular filtration, and serum amikacin levels have been reported to have a diurnal variation.[36] 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 (e.g., 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.

Other well-described biologic rhythms include the 8-hour rhythm for circulating endothelin, the approximately weekly (circaseptan) rhythm for urinary 17-ketosteroid excretion, the monthly rhythms of follicle-stimulating hormone, luteinizing hormone, progesterone production, and the seasonal rhythms for cholesterol and 25-hydroxycholecalciferol.[37]

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 turns the urine a blue–green color and phenazopyridine and rifampin turn the urine an orange–red color. 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 as well as false-negative urine glucose oxidative tests. Some drugs interfere with urinary fluorescence tests for urine catecholamines by producing urinary fluorescence themselves (e.g., ampicillin, chloral hydrate, and erythromycin).

Direct drug-induced, end-organ damage (e.g., kidney, liver, and bone marrow) change the expected lab results. For example, amphotericin B causes renal damage evidenced by increased serum creatinine; and 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–lab interactions include drugs that cause a positive direct Coombs test (e.g., isoniazid,

MINICASE 2

Interpretation of Hemoglobin and Hematocrit

ANNA W., A 72-YEAR-OLD FEMALE nursing home resident, suffered a minor stroke about 5 weeks ago. Her neurological deficits improved leaving her with residual weakness on her left side. She returned from an acute care hospital 12 days ago. Since that time, Anna W. has not been eating much and has been drinking even less. She has a history of chronic iron and folate deficiency anemia with her usual Hgb around 10 g/dL (reference range: 12–16 g/dL), Hct around 30% (reference range: 37% to 47%), iron concentration around 35 mcg/dL (reference range: 60–150 mcg/dL), and folate less than 1–3 ng/mL (reference range 4–15 ng/mL).

Anna W. takes daily iron and folate supplements as well as many other drugs. Her blood pressure has remained stable, but her heart rate has increased from 70s to 90s over the past 5–7 days. Her mucous membranes became dry, her skin turgor diminished, and her urine output decreased over that same time period. A complete blood count is ordered. Tests results indicate an Hgb of 13 g/dL and an Hct of 40%. Her BUN is 40 mg/dL (reference range: 8–20 mg/dL), creatinine is 0.8 mg/dL (reference range: 0.5–1.1 mg/dL), and sodium is 145 mEq/L (reference range: 136–145 mEq/L).

Question: Has the patient's anemia resolved? What is happening here?

Discussion: All the patient's laboratory values, including Hgb and Hct, have become temporarily hemoconcentrated because the patient is dehydrated. Thirst mechanisms are sometimes disrupted after a stroke. Her dry mucous membranes, decreased skin turgor, diminished urine output, and increased heart rate are all consistent with dehydration. As the patient is rehydrated, Hgb and Hct values should return to baseline.

If the patient is overhydrated, the opposite scenario can occur. Of course, assay interference by drugs, metabolites, and other foreign substances (as well as laboratory error) should always be kept in mind. If hemoconcentration had not been so apparent, laboratory error and interferences might be considered. In that case the test should be repeated.

sulfonamides, and quinidine), drugs that cause a positive antinuclear antibody test (e.g., penicillins, sulfonamides, and tetracyclines), and drugs that inhibit bacterial growth in blood or urine cultures (e.g., 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 beta-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 (e.g., estrogen, testosterone, progesterone, human chorionic gonadotropin, prolactin, corticotropin-releasing hormone, ACTH, cortisol, and atrial natriuretic hormone). The plasma volume increases by 30% to 50%, resulting in a relative hyponatremia (e.g., 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 (e.g., 10% to 20% decrease in fasting blood glucose) and lipid (e.g., 300% increase in TGs 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.[38] 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% to 50%), decreased systemic vascular resistance, increased glomerular filtration rate (increases by 40% to 50%), shortened prothrombin and partial thromboplastin times, and hyperventilation resulting in compensated respiratory alkalosis and increased arterial oxygenation.[39]

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. Dehydration is associated with a decreased amount of fluid in the bloodstream; all blood constituents (e.g., 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 resulting in increased hemoglobin concentration and increased blood viscosity. Serum hemoglobin reference ranges are adjusted progressively upward for individuals living above 1000 feet.[40]

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.[41,42] Point-of-care 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 (e.g., fingerstick blood glucose), in the patient (e.g., specialized intra-arterial catheter that measures lactate), and just outside the patient (e.g., intra-arterial catheter attached to an external analyzer), respectively. Although POC testing is not a new concept, recent technological advances (e.g., microcomputerization, miniaturization, biosensor development, and electrochemical advances) have rapidly expanded the variety of available POC tests beyond the traditional urinalysis dipsticks or fingerstick blood glucose monitors (Table 1-6).

The major advantages of POC testing include reduced turnaround time (TAT) and test portability. Reduced TAT is especially advantageous in settings where rapidly available laboratory test results may improve patient care (e.g., 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 (e.g., 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.

TABLE 1-6. Point-of-Care Tests

Arterial blood gases
Blood chemistries
Blood glucose
Cholesterol
Coagulation
Lactate, whole blood
Microbiological tests (influenza, RSV, group A streptococcus, *Clostridium difficile, Helicobacter pylori*)
Myocardial injury markers (creatine kinase MB, cardiac troponin T and troponin I)
Pregnancy tests
Urinalysis (glucose, red cells, leukocyte esterase, and nitrite)

RSV = respiratory syncytial virus.

The major disadvantages of POC testing include misuse or misinterpretation of results, loss of centrally-generated epidemiological data, documentation errors, inappropriate test material disposal, and quality assurance issues. All laboratory testing must meet the minimum standards established by the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88).[43] 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 (e.g., 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. More than 500 FDA-approved, home-use, nonprescription lab test kits are marketed; home glucose and pregnancy testing are among the most popular (Table 1-7). Many non-FDA-approved home-testing kits are marketed via the Internet. The FDA's Office of In Vitro Diagnostic Device and Evaluation and Safety maintains a searchable list of approved home-testing kits (www.fda.gov). Advantages of home testing include convenience, cost-savings (as compared to 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 post-test 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 as either complete test kits (the individual obtains their 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 or telephone). Consumers should read and follow the test instructions to minimize testing error.

TABLE 1-7. Types of Nonprescription In Vitro Diagnostic Tests

TEST	BODY FLUID OR SPECIMEN TESTED
Alcohol	Breath
Blood, fecal occult	Feces
Drugs of abuse (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, methadone, methylenedioxymethamphetamine, morphine, phencyclidine)	Urine, hair
Fertility, male	Semen
Follicle-stimulating hormone (menopausal)	Urine
Glucose	Blood, urine
HDL cholesterol	Blood
Hemoglobin	Blood
HbA1c (glycosylated)	Blood
HIV-1	Blood
Human chorionic gonadotropin (pregnancy)	Urine, serum
Ketones	Blood, urine
Luteinizing hormone (ovulation)	Urine
Thyroid-stimulating hormone	Blood
Triglycerides	Blood

HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein; HIV = human immunodeficiency virus.

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 mEq/L (reference range: 3.5–5.0 mEq/L) should not cause as much concern as a patient who has a concentration of 3.3 mEq/L but 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 HMG CoA (hydroxymethyl glutamyl coenzyme A) 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. Some clinicians establish a pretreatment baseline profile including CK, AST, and ALT and then conduct periodic testing thereafter to identify potential drug-induced toxicity. Creatine kinase has a wide reference range (55–170 units/L); establishment of a baseline allows the clinician to identify early changes, even within the reference range. The baseline value is 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 to the baseline control.

Lab Value Compared to Reference Range

Not all lab values above the upper limit of normal (ULN) require intervention. 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.[44] The potential benefit of at least 6 months of therapy (i.e., 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 (e.g., isoniazid is continued until AST is greater than 5 times the ULN in asymptomatic individuals or greater than 3 times the ULN in symptomatic patients).[45]

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 5–3.5 million/mm^3 over several hours is more likely to be symptomatic and 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 a random serum glucose of 960 mg/dL. A series of lab values adds perspective to an interpretation but may increase overall costs.

Spurious Results

A *spurious lab value* is a false lab value. The only way to differentiate between an actual and a spurious lab 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 (i.e., wide, flat P waves, wide QRS complexes, and peaked T waves) and risk factors for hyperkalemia (i.e., renal insufficiency) is most likely a spurious value. Possible causes of falsely elevated potassium, such as hemolysis, acidosis, and lab 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 lab 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 advances in miniaturization produce smaller and more portable analytical devices. Real-time, in vivo 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 able 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.[46] Developments in nanotechnology will provide simple and inexpensive in vitro and in vivo assessments. Advances in array-based technologies (i.e., simultaneous evaluation of multiple analytes from one sample) will reduce sample volume and cost.[47]

PATIENT ASSESSMENT

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 (e.g., drug serum concentrations, serum creatinine, liver function tests, serum electrolytes) or to perform POTC (e.g., 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 patient charts and databases 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 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 subtherapeutic INR?

Answer: Patient- and laboratory-related factors should be considered when assessing a subtherapeutic INR. Patient factors include adherence, anticoagulant dose, historical dose-related INRs, concomitant nonprescription and prescription medications, complementary and alternative medications, concurrent disease states, smoking status, and diet. Laboratory factors include analytical accuracy and precision, sample handling and processing procedures, and accuracy when calculating and reporting the INR.

2. What factors should be considered when recommending PSA screening?

Answer: Sensitivity and specificity should be considered. Prostate specific antigen is specific for the prostate but has a low sensitivity for detecting prostate cancer. The PSA is elevated by urethral instrumentation, prostatitis, urinary retention, prostatic needle biopsy, and benign prostatic hyperplasia. Specificity for prostate cancer is lower in older men with benign prostatic hyperplasia than in younger men without prostatic hyperplasia. Thus, an elevated PSA level found during screening may result in unnecessary biopsies, treatment, and complications. Currently, there is not concurrence on the net benefit of PSA screening.[48]

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 to 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.

REFERENCES

1. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther.* 2001;69:89-96.
2. Park KS, Baek KA, Kim DU, et al. Evaluation of a new immunochromatographic assay kit for the rapid detection of norovirus in fecal specimens. *Ann Lab Med.* 2012;32:79-81.
3. Solberg HE. Approved recommendation (1986) on the theory of reference values. Part 1. The concept of reference values. *J Clin Chem Clin Biochem*. 1987;25:337-342.
4. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-2497.
5. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. *J Clin Endocrinol Metab.* 2005;90:5483-5488.
6. Lalkhen AG, McCluskey A. Clinical tests: sensitivity and specificity. *Continuing Education in Anaesthesia, Critical Care & Pain*. 2008;8:221-223.
7. Weinstein S, Obuchowski NA, Lieber ML. Clinical Evaluation of diagnostic tests. *AJR.* 2005;184:14-19.
8. Hanley WB, Demshar H, Preston MA, et al. Newborn phenylketonuria (PKU) Guthrie (BIA) screening and early hospital discharge. *Early Human Development.* 1997;47:87-96.
9. Holmstrom B, Johansson M, Bergh A, et al. Prostate specific antigen for early detection of prostate cancer: longitudinal study. *BMJ.* 2009;339:b3537 doi:10.1136/bmj.b3537.
10. Kwon C, Farrell PM. The magnitude and challenge of false-positive newborn screening test results. *Arch Pediatr Adolesc Med*. 2000;154:714-718.
11. Council on Scientific Affairs. SI units for clinical laboratory data. *JAMA*. 1985;253:2553-2554.
12. Evans MI, Galen RS, Britt DW. Principles of screening. *Sem Perinatol.* 2005;29:364-366.
13. Boardman LA, Peipert JF. Screening and diagnostic testing. *Clin Obstet Gynecol.* 1998;41:267-274.
14. Rembold CM. Number needed to screen: development of a statistic for disease screening. *Br Med J.* 1998;317:307-312.
15. Tabar I, Vitak B, Yen MFA, et al. Number needed to screen: lives saved over 20 years of follow-up in mammographic screening. *J Med Screen.* 2004;11:126-129.
16. Lippi G, Giuseppe G, Cesare G. Preanalytic indicators of laboratory performances and quality improvement of laboratory testing. *Clinical Laboratory.* 2006;5:457-462.
17. Coodley EL, Coodley GO. Laboratory changes associated with aging. *Hospital Physician.* 1993;Jan:12-18, 25-31.
18. Tietz NW, Shuney DF, Wekstein DR. Laboratory values in fit aging individuals-sexagenarians through centenarians. *Clin Chem*. 1992;38:1167-1185.
19. Tietz NW, Wekstein DR, Shuey DF, et al. A two-year longitudinal reference range study for selected serum enzymes in a population more than 60 years of age. *J Am Geriatr Soc.* 1984;32:563-570.
20. Kelso T. Laboratory values in the elderly. Are they different? *Emerg Med Clinics North America.* 1990;8:241-254.
21. Duthie EH, Abbasi AA. Laboratory testing: current recommendations for older adults. *Geriatrics.* 1991;46:41-50.
22. Fraser CG. Age-related changes in laboratory test results. *Clin Pharmacol.* 1993;3:246-257.
23. Siest G. Study of reference values and biological variation: a necessity and a model for Preventive Medicine Centers. *Clin Chem Lab Med.* 2004;42:810-816.
24. Weatherall DJ, Clegg JB. Inherited haemoglobin disorders: an increasing global health problem. *Bull World Health Org.* 2001;79:704-712.
25. Frank JE. Diagnosis and management of G6PD deficiency. *Am Fam Physician.* 2005;72:1277-1282.
26. Caraco Y. Genes and the response to drugs. *N Engl J Med.* 2004;351:2867-2869.
27. Nguyen A, Desta Z, Flockhart DA. Enhancing race-based prescribing precision with pharmacogenomics. *Clin Pharmcol Ther.* 2007;81:323-325.
28. Prandota J. Advances of molecular clinical pharmacology in gastroenterology and hepatology. *Am J Ther.* 2010:17:e137-e162.
29. Smolensky MH, Peppas NA. Chronobiology, drug delivery, and chronotherapeutics. *Adv Drug Del Rev.* 2007;59:828-851.

30. Mendoza J, Challet E. Brain clocks: from the suprachiasmatic nuclei to a cerebral network. *The Neuroscientist.* 2009;15:477-488.
31. Edery I. Circadian rhythms in a nutshell. *Physiol Genomics.* 2000;3:59-74.
32. Rivkees SA. Mechanisms and clinical significance of circadian rhythms in children. *Curr Opinion Pediatr.* 2001;13:352-357.
33. Rivera-Coll A, Fuentes-Arderiu X, Diez-Noguera A. Circadian rhythms of serum concentrations of 12 enzymes of clinical interest. *Chronobiology International.* 1993;10:190-200.
34. Rivera-Coll A, Fuentes-Arderiu X, Diez-Noguera A. Circadian rhythmic variations in serum concentrations of clinically important lipids. *Clin Chemistry.* 1994;40:1549-1553.
35. Koopman MG, Koonen GCM, Krediet RT, et al. Circadian rhythm of glomerular filtration rate in normal individuals. *Clin Sci.* 1989;77:105-111.
36. Bleyzac N, Allard-Latour B, Laffont A, et al. Diurnal changes in the pharmacokinetic behavior of amikacin. *Ther Drug Monit.* 2000;22:307-312.
37. Otsuka K, Cornelissen G, Halberg F. Circadian rhythms and clinical chronobiology. *Biomed Pharmacother*. 2001;55:7-18.
38. Soldin OP. Thyroid function testing in pregnancy and thyroid disease. *Ther Drug Monit.* 2006;28:8-11.
39. Foley MR. Maternal cardiovascular and hemodynamic adaptation to pregnancy. In: UpToDate. Waltham, MA: UpToDate Version 19.3; 2011.
40. Sullivan KM, Mei Z, Grummer-Strawn L, et al. Haemoglobin adjustments to define anemia. *Trop Med International Health.* 2008;13:1267-1271.
41. Gutierres SL, Welty TE. Point-of-care testing: an introduction. *Ann Pharmacother.* 2004;38:119-125.
42. Gilbert HC, Szokol JW. Point-of-care technologies. *Int Anesthesiol Clin*. 2004;42:73-94.
43. Medicare, Medicaid, and CLIA Programs. Extension of Certain Effective Dates for Clinical Laboratory Requirements Under CLIA: final rule. *Federal Register.* 1998;63:55031-55034.
44. Mitchison DA. The diagnosis and therapy of tuberculosis during the past 100 years. *Am J Respir Crit Care Med.* 2005;171:699-706.
45. Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med.* 2006;174:935-952.
46. Pene F, Courtine E, Cariou A, et al. Toward theragnostics. *Crit Care Med.* 2009;37:S50-S58.
47. Hadd AG, Brown JT, Andruss BF, et al. Adoption of array technologies into the clinical laboratory. *Expert Rev Mol Diagn.* 2005;5:409-420.
48. Chou R, Croswell JM, Dana T, et al. Screening for prostate cancer: a review of the evidence for the US Preventive Services Task Force. *Ann Intern Med.* 2011;155:762-771.

BIBLIOGRAPHY

Bakerman S, Bakerman P, Strausbauch P. *Bakerman's ABC's of Interpretive Laboratory Data.* 4th ed. Scottsdale, AZ: Interpretive Laboratory Data Inc; 2002.

Fischbach FT, Dunning III, MB. *A Manual of Laboratory and Diagnostic Tests.* 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.

Jacobs DS, DeMott WR, Oxley DK. *Laboratory Test Handbook Concise with Disease Index.* 3rd ed. Hudson, OH: Lexi-Comp Inc; 2004.

Jacobs DS, Oxley DK, DeMott WR. *Laboratory Test Handbook with Key Word Index.* 5th ed. Hudson, OH: Lexi-Comp Inc; 2001.

Kraemer HC. *Evaluating Medical Tests.* Newbury Park, CA: Sage Publications; 1992.

Laposata M. *Laboratory Medicine: The Diagnosis of Disease in the Clinical Laboratory*. New York, NY: McGraw-Hill Companies Inc; 2010.

Sacher RA, McPherson RA, Campos JM. *Widmann's Clinical Interpretation of Laboratory Tests.* 11th ed. Philadelphia, PA: FA Davis Company; 2000.

Speicher CE. *The Right Test: A Physician's Guide to Laboratory Medicine.* Philadelphia, PA: WB Saunders; 1998.

Williamson MA, Snyder LM (eds.). *Wallach's Interpretation of Diagnostic Tests.* 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.