mutations in recognized genes, whereas the genetic basis of the same disease phenotype in the larger population is unclear. The search for the genetic factors that contribute to many common diseases remains a topic of intense research interest. It is now clear that essentially all tumors have genetic abnormalities. Although there is an inherited predisposition in some families, most of these genetic changes are acquired. Identification of the genetic abnormalities in cancer offers new tools for clinical laboratory diagnosis and classification of tumors in ways that surpass traditional histopathology and also provides insights into cellular processes that may be targets for treatment.

6. Clinical laboratory results should always be interpreted in the context of the patient's history and physical examination as well as any other relevant information (e.g., imaging studies). The clinician should avoid treating laboratory results rather than the patient.
7. Recommended clinical laboratory tests change with time. As new markers of disease emerge, they may replace older markers. For example, measurement of serum creatine kinase (CK) levels was introduced for diagnosis of acute myocardial infarction in the 1980s. Use of the cardiac-specific isoenzyme CK-MB later became widespread in clinical practice. Today, cardiac troponins are replacing CK (or CK-MB) measurements in recommended guidelines. Many other assays have fallen out of use as better assays have become available. Measurement of urine 17-ketosteroids (arising from androgens) and of urine 17-hydroxycorticosteroids (arising from glucocorticoids) has been supplanted by immunoassays or mass spectroscopy determinations of specific steroid hormones. Today, many steroid hormones are measured by mass spectrometry, often with better analytic specificity than is provided by immunoassays. As new tests are introduced, it is essential that they be evaluated critically before adoption for clinical use. At a minimum, consideration needs to be given to questions of clinical validation, specimen stability, diagnostic sensitivity and specificity, positive and negative predictive values, analytic accuracy and precision, and relative costs.

REFERENCE RANGES

In the interpretation of clinical laboratory results, comparison is usually made to a reference range (sometimes called a normal range) that defines the values seen in health or considered to be desirable for health. Several common methods are used to describe reference ranges in the clinical laboratory.

1. For many quantitative clinical laboratory tests, the range of observed values in a healthy population shows an approximately Gaussian distribution. The factors that contribute to this range include the inter- and intraindividual variation in the concentration of the analyte and the analytic imprecision. When there is an approximately Gaussian distribution of values in the population, the reference range is commonly defined as being the central 95% of the range of distribution of those values. According to this method, 2.5% of the population will have a measured value that is below the reference range for the analyte, and 2.5% will have a value that is above the reference range. The fact that 5% of healthy individuals will have a test value that is outside the reference range has important implications when multiple tests are ordered. If N independent tests are performed on a specimen, then the probability that at least one result will be outside the reference range is $(1–0.95^N)$. The greater the number of tests ordered (even for a healthy individual), the greater is the likelihood of an abnormal result (Fig. 480e-1). If 20 independent tests are performed on a healthy subject, the probability of at least one abnormal result is almost two-thirds.

In some settings, a narrower range of values is considered to be abnormal. For example, current American Heart Association guidelines recommend the use of a serum level of cardiac troponins that is greater than the 99th percentile of values found in a healthy population as evidence of acute myocardial infarction.

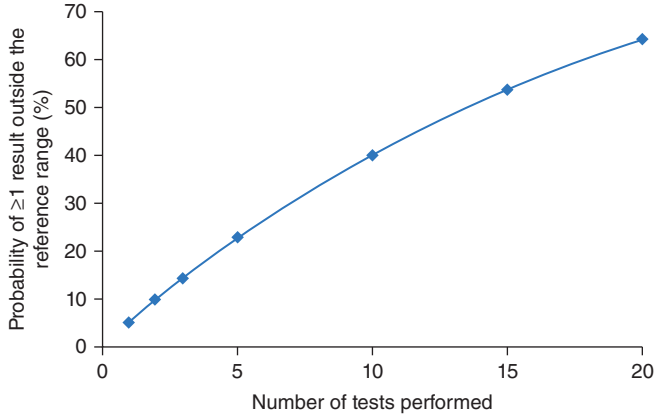

FIGURE 480e-1 Probability that at least one laboratory result will be abnormal in a healthy individual as an increasing number of independent tests are performed. The reference range is the central 95% of values measured in a healthy population.

2. An alternative approach to using population means and standard deviations is to define a range of analyte values that is judged to be consistent with health on the basis of expert consensus opinion. These ranges are often referred to as *decision limits*. Examples of reference ranges established in this way include those for total, high-density, and low-density cholesterol (Table 480e-2). Such ranges may deviate considerably from those that would be established if the analyte concentrations of the population (mean ± 2 standard deviations) were used as a basis for establishing the reference range. For example, the "desirable" total cholesterol value according to the National Cholesterol Education Program is <200 mg/dL. This value is actually very close to the mean concentration among U.S. adults; in fact, almost one-half of U.S. adults have a total cholesterol concentration that is above the "desirable" range. If the central 95% of cholesterol concentrations in the population were taken as the reference range, the upper end of that range would be ~240 mg/dL, well beyond what is considered desirable.

Reference ranges may vary with age, gender, ethnic background, and physiologic state (e.g., pregnancy, high-altitude adaptation). Some examples of these variations are shown in the Appendix. The existence of different reference ranges poses challenges for interpretation of results. In particular, creatinine stands out as an analyte for which conventional reference ranges are not always easy to apply in clinical practice. Plasma levels of creatinine vary with age, gender, and ethnic group. This fact makes it difficult in practice to use a simple reference

TABLE 480e-2 NATIONAL CHOLESTEROL EDUCATION PROGRAM ADULT TREATMENT PANEL III GUIDELINES FOR CHOLESTEROL

Cholesterol Type	Level (mg/dL)
LDL	
Optimal	<100
Near optimal/above optimal	100–129
Borderline high	130–159
High	160–189
Very high	≥190
Total	
Desirable	<200
Borderline high	200–239
High	≥240
HDL	
Low	<40
High	≥60

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.