these precollection alterations, specimens should be processed or transported to the clinical laboratory as soon as possible after collection. The list of known preanalytic variables and their effects is extensive, and the reader is referred to the compendium on this subject (see Young DS: *Effects of Preanalytical Variables on Clinical Laboratory Tests,* 3rd ed. Washington, DC, AACC Press, 2007).

POINT-OF-CARE TESTING

The great majority of tests continue to be performed in dedicated clinical laboratory facilities, but for several decades there has been a trend toward point-of-care testing. This change has been made possible by the development of portable analytic devices, including single-purpose instruments such as glucometers and oxygen saturation monitors, and multifunction instruments that can perform a wider variety of analyses, particularly in chemistry and hematology but also in some areas of microbiology. The use of these devices is driven largely by the convenience of faster result availability. In some settings (e.g., in rural areas and developing countries), there may be no easily accessible clinical laboratory and a point-of-care device may be the best or only option for testing. However, the per-specimen cost of point-of-care testing, in terms both of reagents and supplies and of personnel, is often greater than that of centralized testing. Other concerns relate to the adequacy of personnel training for point-of-care testing, the quality of the results, and the incorporation of results into the medical record.

HOME TESTING BY PATIENTS

One of the largest markets for point-of-care testing is home testing by patients, which has long been an important element in the management of persons with diabetes who monitor their own blood glucose levels. Over-the-counter kits for home pregnancy testing have been available for decades. More recently, kits have become available for home testing of the international normalized ratio or prothrombin time by patients taking oral anticoagulants. Kits are also available for cholesterol monitoring, fecal occult-blood detection, and hemoglobin measurement. In these areas, there is often little information on the quality of test performance, the accuracy of the results, or the correctness of result interpretation.

ISSUES SPECIFIC TO GENETIC TESTING

The principles of genetic medicine in clinical practice are discussed in Chaps. 82–84. Here we will concentrate on issues related to clinical laboratory testing for genetic disease.

The distinction between genetic testing for inherited disorders and that for acquired disorders affects the type of tissue that should be obtained for analysis. In inherited disorders, all nucleated cells are expected to carry the inherited mutation; thus white blood cells or buccal cells (obtained by scraping the inside of the cheek) are convenient sources of DNA for clinical laboratory testing. For prenatal testing of the fetus, chorionic villi or amniocytes are commonly used. In tests for acquired genetic disorders (e.g., in tumors), the tissue of interest that contains a suspected mutation must be sampled. It is often useful to compare tumor DNA with the patient's normal DNA in order to identify acquired mutations (e.g., testing for microsatellite instability in colorectal cancer; Chap. 101e).

INFORMED CONSENT FOR GENETIC TESTING

Although it is assumed that all clinical laboratory testing is performed with the consent of the patient (or, in the case of minors, the parents), regulations may require formal written consent for genetic testing. Such regulations vary among jurisdictions, and the practicing clinician should be aware of local regulations. In some jurisdictions, there are regulations on the storage and use of genetic information and on the maximal period for which genetic specimens may be stored.

For some late-onset genetic diseases, such as Huntington's disease (Chap. 449), genetic testing allows a prediction about the future development of the disease. The degree of certainty that is possible on the basis of this testing surpasses that associated with identification of more traditional disease risk factors (e.g., hyperlipidemia as a risk factor for future myocardial infarction). When deciding to undertake predictive genetic testing, it is important for the patient to consider the broad implications of a positive or negative test result, to be made aware of any support and counseling that is available, and to understand the implications of a result for other family members. In dealing with these issues, genetic counselors play an important role (Chap. 84). Their expertise includes the ability to explain genetic disorders at an understandable level to patients and their families, to arrange for support services, and to provide genetic risk assessments to members of families with genetic disorders.

When testing for genetic disorders, the clinical laboratory will use different analytic approaches according to the disease of interest. Some disorders, such as sickle cell anemia, are caused by single-point mutations. Testing for these disorders involves mere assessment for one or a few mutations in a single gene. Other disorders (e.g., hyperphenylalaninemias) may be caused by numerous mutations in a single gene. Still others (e.g., hereditary breast cancer) may be caused by mutations in many genes. The number of possible mutations and genes that underlie a clinical phenotype affects the cost of and time required for clinical laboratory testing as well as the likelihood of finding a disease-causing mutation.

If a disease phenotype can be caused by many mutations, a clinical laboratory result that is negative should be interpreted with care. For example, it is common to screen healthy pregnant women (and their partners) for mutations in the *CFTR* gene, which is mutated in patients with cystic fibrosis (CF). The goal of this screening is to identify women who are carriers of a *CFTR* mutation and therefore are at increased risk of having a baby with CF. Because CF is an autosomal recessive disorder, a fetus has a 1:4 chance of being affected if both parents are carriers of disease-causing *CFTR* mutations. The screening test approach that is commonly used to identify mutations in carriers detects 80–85% of all known disease-causing *CFTR* mutations in Caucasians and up to 97% of mutations among Ashkenazi Jews. A negative screening result therefore does not completely eliminate the possibility that a woman (or her partner) actually has a mutation. What can be inferred from a negative test result is that the risk of having a CF-affected baby has decreased significantly to an extent that depends on the woman's ethnic group and the mutations that were examined. The clinical laboratory should calculate and report the woman's new risk of being a carrier if the screening result is negative.

The increasing availability of large-scale (next-generation) sequencing of a patient's whole genome or exome will greatly affect genetic testing over the next decade, with implications for the number of mutations that can be detected and the increased complexity of result interpretation.

LIMITATIONS TO MOLECULAR GENETIC TESTING

Genetic testing has limitations that are often unique to this field. Results may be inconclusive. For example, a search for mutations in a gene that is suspected of causing a disease may fail to reveal any known disease-causing mutations. A mutation may be discovered that is of unknown clinical significance. In this situation, consideration of the predicted change in the amino acid sequence of the encoded protein may suggest a biologic effect—e.g., replacement of a charged amino acid by one of the opposite charge or by a neutral amino acid; replacement of an amino acid by one of a different size; or replacement of an amino acid that is conserved across multiple species. Further information may be obtained by determining whether the mutation is found in healthy individuals. Even with all of these considerations, it is not uncommon that the biologic significance of an identified mutation remains uncertain, and further research may be needed to assess its significance.

It is also important to understand the limitations of the clinical laboratory approach used to detect mutations. At this time, next-generation sequencing remains an impractical undertaking for financial reasons, although extensive sequence analysis has become the