INTRODUCTION

This chapter will focus on three aspects of laboratory testing in the intensive care unit (ICU) setting: choosing which point-of-care (POC) tests to offer, quality assurance (QA) in POC testing (POCT), and regulatory issues germane to POCT.

DEFINITION OF POINT-OF-CARE TESTING

POCT is the performance of laboratory tests in the immediate physical vicinity of the patient (1). A synonym for POCT is “near-patient testing.” By definition, samples for POCT are not sent by courier or tube system to another geographically distant site.

POCT can be performed in the patient’s home, business, or school; in a physician’s office (e.g., a physician office laboratory [POL]); in a clinic; or near the patient’s bedside in the hospital, emergency room, or operating room. POC tests can essentially be performed anywhere where trained personnel are present to provide patient care such as ICUs, operating rooms, ambulances, helicopters, ships, and airplanes. The most common POCT performed by patients is outpatient self-monitoring of blood glucose (SMBG) (2). In the outpatient setting, another commonly performed test—but far less common than SMBG—is self-testing for the prothrombin time-international normalized ratio (PT-INR) that is used to monitor and adjust warfarin doses in chronically anticoagulated patients (3).

Concerning inpatients, testing that is performed by medical technologists using central laboratory-type instruments near the patient’s bedside can—geographically—qualify as POCT. However, such testing is outside the scope of this chapter, as such testing is really central laboratory testing in a noncentral laboratory location.

There are several strengths to POCT:

- Better sample stability between the time of sample drawing and analysis, often seconds in duration
- Shorter turnaround time (TAT); some results are available within a minute or less of sample acquisition
- Reduced sample volume requirements
- Immediate result availability to the respiratory therapist, nurse, or physician caring for the patient
- Opportunity for instantaneous notification of staff in cases of critical (e.g., “panic”) values

CHOOSING WHICH TESTS TO RUN AT THE POINT OF CARE

POCT is most valuable when such test results immediately influence acute patient management (Tables 31.1 and 31.2) (1). An alternative way to provide rapid TATs is the placement of a satellite laboratory adjacent to the ICU or a tube system with direct sample delivery to a rapid response laboratory. Nevertheless, in resuscitations, it is difficult to argue against POCT being immediately adjacent to the patient.

If the test result will not immediately affect patient care, the higher cost of POCT compared with central laboratory testing is usually not justified. Also, POCT is usually not as accurate or precise as central laboratory testing, making central laboratory testing more advantageous in those regards. In addition, if a nurse or respiratory therapist is performing POCT, this takes time away from his or her direct patient care activities. Other experts argue that the time to perform POCT is no longer than the time it takes to draw and label a sample for transit to a central or satellite laboratory.

A list of tests appropriate for POCT in the ICU include arterial blood gas (ABG) analysis, sodium, potassium, ionized calcium, glucose, and lactate. In addition to pH, PaO₂, PaCO₂, and calculated bicarbonate and hemoglobin saturation—either estimated from the PaO₂ or measured directly via co-oximetry—ABG analysis provides a measurement of hemoglobin (g/dL) that can be of critical importance in postoperative patients or other patients who develop acute hypotension or manifest external evidence of bleeding, such as melena. If carbon monoxide poisoning or methemoglobinemia is present, dual-wavelength pulse oximetry will not reflect the true hemoglobin saturation. In such instances, hemoglobin saturation must be directly determined by co-oximetry or a multiwave pulse oximeter must be used. POCT for coagulation parameters is becoming increasingly important. Such tests include measurements of the PT-INR, the platelet count, thromboelastography (TEG), activated clotting time (ACT), plus a variety of more specialized tests such as the VerifyNow platelet function tests.

If cardiovascular intervention procedures are carried out in the ICU where heparin is administered in moderate to large doses, ACTs must be available within the unit to monitor heparin’s effects. The ACT is monitored in such settings because such high doses of heparin will prolong the aPTT to infinity, as no clot forms. ACT is then monitored in place of the aPTT to determine when the arterial sheath can be removed. If an intravascular sheath is in place, the ACT is monitored to confirm that excessive anticoagulation is not present prior to sheath removal. The intensivist must be aware that while the term “ACT” is generic, ACT measurements performed on devices produced by different manufacturers are most often not equivalent. Thus, clotting time guidelines from one device are not necessarily transferable to another device, and such clotting guidelines must be determined for each manufacturer’s ACT instrument.

While POC measurements of cardiac markers (troponin-I or troponin-T), markers of cardiac failure (B-type natriuretic peptide [BNP] or NT-proBNP [N-terminal-pro-B-type natriuretic peptide]), and emergency toxicology testing (ethanol, opiates, cocaine, methamphetamine, etc.)
advantages of superior accuracy and reproducibility available performance of these tests at the POC in the ICU is not justified. The room where patients require immediate triage (4), the perfor-
cocaine, PCP, and so forth) may be justified in the emergency 
Arterial blood gases (includes hemoglobin concentration) Lactate Potassium (with or without sodium) Glucose Ionized calcium 
Testing at a POC/satellite laboratory that is useful in special circumstances Activated clotting time Ionized magnesium 
Examples of tests not justified at the POC or satellite laboratory B-type natriuretic peptide/N-terminal-pro-B-type natriuretic peptide (BNP/N-proBNP) Cardiac markers Endocrine testing Iron studies (serum iron, total iron binding capacity, ferritin) Lipid testing Liver function testing Prothrombin time, activated partial thromboplastin time Renal function testing Total magnesium Toxicology testing 

TABLE 31.2 Examples of Laboratory Tests and the Decisions Based on their Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Possible Clinical Impacts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial blood gases</td>
<td>Administration of oxygen or ventilator support</td>
</tr>
<tr>
<td>Lactate</td>
<td>If elevated: Need for more aggressive acute intervention with intravenous fluids, pressors, and/or improved ventilation</td>
</tr>
<tr>
<td>Na+, K+, Cl−, total serum CO2, Cr, blood urea nitrogen, serum and urine osmolality</td>
<td>Rates and type of fluid resuscitation or fluid restriction, need for fluid boluses, des-amin-o-d-arginine vasopresin (DDAVP) administration, fluid restriction for renal failure</td>
</tr>
<tr>
<td>Glucose</td>
<td>Attainment and maintenance of tight glycemic control</td>
</tr>
<tr>
<td>Ionized calcium</td>
<td>Need for intravenous calcium administration</td>
</tr>
<tr>
<td>Hemoglobin/ hematocrit</td>
<td>Assessment of need for transfusion of red blood cells</td>
</tr>
<tr>
<td>Platelet count</td>
<td>Assessment of need for platelet transfusions</td>
</tr>
<tr>
<td>Activated clotting time</td>
<td>Management of heparin anticoagulation and reversal of anticoagulation (e.g., protamine sulfate administration)</td>
</tr>
<tr>
<td>Prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen</td>
<td>Assessment of possible coagulopathy</td>
</tr>
</tbody>
</table>

TABLE 31.1 Point-of-Care Testing Recommendations for ICUs

Testing available at the point of care (POC), in a satellite laboratory adjacent to the ICU, or via rapid tube transport to a central laboratory
Arterial blood gases (includes hemoglobin concentration) Lactate Potassium (with or without sodium) Glucose Ionized calcium

Because many ICU decisions are based upon the results of laboratory analyses (Table 31.1), the intensivist must understand the strengths and the limitations of laboratory testing, whether performed in a central laboratory, in a satellite laboratory, or at the POC (1).

In order to provide quality results, an overview of QA concepts in laboratory testing follows. The Clinical and Laboratory Standards Institute (CLSI, previously named the National Committee for Clinical Laboratory Standards) defined QA as “the practice which encompasses all endeavors, procedures, formats and activities directed towards ensuring that a specified quality or product is achieved and maintained.” QA programs encompass assessments of analytical quality control; monitoring of TATs, regulatory compliance, and success of proficiency testing; and supervision of personnel training and competency.

To provide quality results:
- Standard operating procedures (SOPs) must be developed and followed.
- Systems must be in place to recognize and solve random and systematic problems.
- Result reliability must be defined in terms of suitable precision and accuracy.

A QA program assesses all aspects of testing: preanalytical, analytical, and postanalytical events. Preanalytical issues concern proper patient identification and tube labeling, proper sample acquisition, appropriate transport to the central laboratory or to the POCT device (e.g., cooling of ABG samples), and timing of the test (e.g., proper timing for therapeutic drug monitoring). Analytical matters concern the instrument performance, and postanalytical issues concern proper result reporting (e.g., the correct result is reported on the correct patient).

Theoretically, the goal of laboratory testing is to produce timely and reliable (e.g., quality) measurements of analytes that assist in the diagnosis, management, and prevention of human diseases. “Analyte” is a generic term for any substance that is measured in any fluid; POCT testing is most commonly carried out on blood or urine samples, and the source of blood can be arterial, capillary, or venous.

In the ICU setting, the sample of choice is usually whole blood drawn from an artery when measuring blood gases, or arterial or venous whole blood when, for example, measuring sodium, potassium, glucose, lactate, or ionized calcium. If patients are not in shock and display normal peripheral perfusion, a warmed finger or toe can be lanced to obtain a capillary whole-blood sample for glucose measurement. In the ICU setting, besides hematocrit and glucose measurements, there are no other common reasons to obtain capillary blood.
such as pH, PaCO₂, PaO₂, glucose, and potassium. change the most rapidly attract and demand our attention, data become available. Certainly, physiologic parameters that the laboratory data can be acted upon as soon as the result divided by the TAT (Equation 1). This assumes the value of a test result can be conceptualized as the quality of the result. Figure 31.1 depicts a theoretical curve for the relationship of quality to turnaround time (TAT). The central laboratory’s ability to provide both quality results and a short TAT are often at odds with one another; more accurate and precise complex assays are usually more time consuming, and such tests may not be available on POCT devices. Figure 31.1 expresses this concept with quality results as the y-axis and TAT as the x-axis. If assay time is reduced below a certain limit, the quality of the assay will be reduced. On the other hand, significant delays in making critical clinical decisions can adversely affect patient outcome. We must also acknowledge that POC tests rarely, if ever, will be as accurate or precise as tests accomplished in the central laboratory.

Equation 1:

\[
\text{Value of a test} = \text{quality of the result} \times \text{turnaround time}^{-1}
\]

Note: Higher-quality results and lower turnaround times can provide higher-value tests.

Equation 2:

\[
\text{Quality of the result} = \text{bias}^{-1} \times \text{coefficient of variation}^{-1}
\]

Note: Reduced bias (e.g., higher accuracy) and reduced coefficients of variation (e.g., higher precision) improve the quality of the test result.

Desirable intrinsic characteristics of the assay for the diagnosis, management, or prediction of disease are a high sensitivity and specificity. In epidemiologic terms, sensitivity is the number of true positive results divided by the number of observations in a diseased population. Specificity is the number of true negative results divided by the number of observations undertaken in a nondiseased population.

Specificity = true negatives + (true negatives + false positives)

In its broadest sense, TAT is the “vein to brain” time: The time it takes between sample acquisition (e.g., venipuncture: the vein time) to result recognition by the treating physician (i.e., the brain time). Usually TAT is defined as the duration of time between sample acquisition and result reporting. Unfortunately, the laboratory often has little control over factors that determine when a sample is delivered to the central laboratory after acquisition. Similarly, preanalytical problems frequently develop because the sample is not properly drawn, labeled, or preserved prior to delivery to the laboratory. To be of value, the correct sample must be drawn from the correct patient at the correct time in the correct volume and placed in the correct tube.

If the analysis produces the most accurate result possible, but the TAT is unacceptably long, the value of the result in patient management is significantly degraded. TAT is most important in the ICU setting when the test results are used to immediately alter the patient’s care. Examples of such tests include ABG analysis for ventilated patients and glucose measurements in glycemic control protocols. There are many instances, however, where a TAT of several hours or more may be appropriate when the test is not used for immediate patient management (e.g., a karyotype result in a patient with suspected Down syndrome). Thus, the required TAT for any test result is relative. On the other hand, an instantaneous result that is not sufficiently accurate will not help—and may even hurt—the patient. It is wise to remember that bad data are worse than no data at all; physicians using bad data are misled.

Assay Performance: Precision

Precision is synonymous with reproducibility; for example, if aliquots of the original sample are retested, will the same result as the original result be observed? Precision can be defined in terms of the assay’s standard deviation (SD) and coefficient of variation (CV). When aliquots of a single sample are measured repeatedly, the histogramic distribution of results will represent a bell-shaped curve. Other descriptions for such a distribution include a Gaussian distribution or parametric distribution.

The SD for an assay is the square root of the variance. The variance is calculated as follows: The difference between each individual value and the mean is squared, these values are summed, and the sum of the squares is then divided by the number of repeats minus one. Sixty-eight percentage of the repeats will fall within ±1 SD of the mean. Approximately 95% of the repeats will fall within ±2 SD of the mean, and approximately 99% of the repeats will fall within ±3 SD of the mean. This concept will be used in developing rules that will help us determine when an analysis and analyzer are or are not working properly.

CV is expressed as a percentage: The SD is divided by the mean multiplied by 100. While SDs have values with units—mg/dL for glucose or mmHg for PO₂—and are difficult to remember, CVs are unitless and allow easy comparisons among various analyses without needing to recall the specific SD or units. For example, electrolyte measurements using
ion-selective electrodes usually display CVs of 1% to 2%. By way of comparison, analyses that use chemical reactions with spectrophotometric or electrical detection typically have CVs of 4% to 5%. As a consequence of their complex nature involving antigen–antibody interactions, immunoassays can show even greater variability, with CVs of 5% to 10%.

Precision can be further described as intra-assay or interassay reproducibility. Intra-assay precision is assessed when the same sample is run 10, 20, or more times in a single run. A “run” is the series of same analyses that are accomplished in a single day, shift, or other period of time during which the analyzer is believed to be analytically stable (e.g., does not require recalibration; many modern analyses are so stable that calibration may not be required for many days or longer). Intra-assay comparisons would not exceed 1 day.

Intra-assay precision is almost always superior to interassay precision; interassay precision is determined by measuring the same sample serially on different days (e.g., measuring the same sample once per day for 20 or more workdays in a row). For a typical chemical analysis, the intra-assay CV might be 5% and the interassay CV might be 7%. Clinicians do need to know the total imprecision—the combined intra-assay (e.g., same-day or same-shift reproducibility) and interassay (e.g., reproducibility over several days) imprecision—because some patients may be, for example, on ventilatory support for days or weeks with various degrees of pulmonary failure. While CVs (or SDs) cannot be added together to determine total imprecision, the intra-assay and interassay variances can be added together. The square root of the total variance then provides the SD, and the SD divided by the sample mean (multiplied by 100) provides the percentage CV.

**Assay Performance: Accuracy**

Accuracy is a measure of bias. Bias is the difference between the “real” (or “true”) result and the measured result; bias can be positive or negative. A positive bias is present when the measured result exceeds the true result. A negative bias is found when the measured result is less than the true result. Bias must not be excessive; the bias that does exist must not lead to incorrect diagnosis, management, or disease prediction.

The true result of an assay may be difficult to define or determine. This is especially true when there is only one basic method available for the measurement of an analyte. For many measurements, the only method of analysis is the field method (i.e., the analytical procedure that is used in the central laboratories or at the POC). For example, pO2 can only be measured using an oxygen-sensitive electrode. Reference methods, by definition, are more specific for the measurement of the analyte in question than the field method. Definitive methods are the best available methods of measurement with the highest specificity. Ideally, reference and definitive methods also have better precision than field methods. Because reference intervals (i.e., the “normal” ranges) are dependent on proper calibration, if there is a significant bias in calibration between the method used to establish the reference interval and the method in real-time use in the care of the patient, errors may be made in the interpretation of the result as to whether or not it falls within the reference interval, and to what degree the result may exceed or fall below the reference interval. On the other hand, relative change (i.e., the present result compared to a previous result) will not be affected by bias if instrument calibration is stable and the assay is precise. However, a lack of precision can have a major misleading effect on the interpretation of serial results. A lack of precision (i.e., imprecision) implies that larger absolute differences occur between serial measurements. With a highly precise assay, small serial differences are more likely to represent a true difference in the patient’s condition. With a highly imprecise assay, larger serial differences are required to indicate a true difference in the patient’s condition. To further complicate the consideration of a normal versus an abnormal result, we must consider biologic variation: The normal variation in a biologic measurement that can represent minute-to-minute or hour-to-hour fluctuations: Ultradian rhythms (e.g., luteinizing hormone [LH] or follicle-stimulating hormone [FSH] secretion); daily variations: Circadian rhythms (e.g., am vs. pm levels of cortisol); or variations greater than a day: Infra- dian rhythm (e.g., the menstrual period).

**Analytical Sensitivity and Specificity**

In analytical terms, sensitivity is the lowest concentration of an analyte that can reliably be measured. As measurements approach zero concentration of the analyte, the uncertainty of the measurement increases. At a certain point with a progressive decline in analyte concentration, the uncertainty of the measurement is so great that to report a lower number becomes meaningless. Analyzer manufacturers should define their lower limit of detection (LLD) to inform the user of the analyzer’s expected analytical sensitivity. In addition, it is routine policy for laboratories to define their own LLD or, at a minimum, to confirm the manufacturer’s stated LLD. In the ICU setting, LLD is most probably important in the measurement of glucose: “How low a glucose concentration can our POCT analyzer reliably report?” There are two forms of LLD. It is important to define which one the laboratory is using. One is the Limit of Detection (LOD) while the other is the Limit of Quantitation (LOQ). The LOD is the lowest concentration of an analyte that can reliably be distinguished from zero; the LOQ (also called the functional sensitivity) is the lowest concentration of an analyte that gives a reasonable precision, usually a CV of not more than 20%.

Analytical specificity is the certainty that the assay only measures the analyte of interest and does not measure other unintended substances in solution (e.g., “What is the assay’s cross-reactivity to other analytes?”). Cross-reactivity is not usually an issue for POCT in ICUs based on the types of assays run in such situations. However, in the central laboratory, cross-reactivity can be a significant issue. For example, cardiac troponin-T or troponin-I measurements should not cross-react with skeletal muscle troponin-T or troponin-I. On the other hand, assay cross-reactivity is desirable if one wishes to test for a class of drugs (e.g., drug abuse testing for benzodiazepines, opiates, sympathomimetics, or barbiturates).

**Quality Control Testing**

For all inpatient testing, whether waived-regulated testing, moderate complexity testing, or high-complexity testing (see below), quality control must be assessed at least daily for all analytes measured on the device. For certain types of testing, such as radioimmunoassays or enzyme-linked immunosorbent
assays (ELISAs), control testing may need to be performed with each run of patient samples.

To perform quality control testing, a sample of known concentration is measured with the device in question (5). This is the “control material” or, simply, the “control.” The control material is usually available in a large volume and is prepared in many aliquots (e.g., >100) in a stable (e.g., frozen) form, so that the control material can be used over the course of many months to even longer than 1 year. If the control result for a run of samples falls within previously defined limits, the device and run are said to be “in control,” and patient results can be reported. If the control result is outside defined limits, the device and run are said to be “out of control,” meaning an analytical error has occurred and patient results cannot be reported. Another way to express an out-of-control run is to state that the run was “rejected” or “failed.” Thus, before any patient results can be reported, the operator must ensure that the analyzer is functioning correctly. Clearly, the control material must be measured prior to the release of any patient results. For moderate- and high-complexity testing, at least two levels of control are usually assessed. For example, the mean value of one control can be near a clinical decision point, while the mean value of the other control value can be considerably above the clinical decision point.

If the assay is out of control, the operator must troubleshoot the problem. Possible causes of out-of-control runs include:

- Machine mechanical errors (e.g., pipetting too little or too much liquid)
- Outdated reagents
- Reagents that have lost potency due to heating or lack of refrigeration
- Degraded control materials
- Operator error (e.g., mislabeled or switched controls, as in reversing the low-level and high-level controls)
- Spectrophotometric error (e.g., bulb loss or degraded function)
- Detector error

Fortunately, most POCT devices, even if moderately complex, are self-contained, are fairly robust, and can be simply “fixed” by replacing the reagent cartridge. If nothing else, another POCT analyzer can be used.

James Westgard created a series of rules that can be used to determine if a run or device is in control or is out of control (5). These “Westgard rules,” or their variations, are used essentially universally throughout the laboratory community. For each control material, the performance of the material is initially established by running this sample daily over the course of 20 to 30 days when the assay is otherwise known to be in control by using previously characterized control materials. From these data, the mean and the SD for the sample’s concentration is measured with the device in question (5). This is the control material’s “performance” on the device in question can be calculated.

Once the performance of the control material is known (i.e., its mean value and SD are established), this material can then be used to determine if subsequent runs are in control. If a single control value is 3 or fewer SDs away from the mean, the assay is in control and the results can be released. While, strictly speaking, being in control—a control result of +2 to +3 SDs above or –2 to –3 SDs below the mean—is a “warning,” the operator should review previous control data and confirm that other instrument parameters are functioning normally.

### Table 31.3 Westgard Quality Control Rules for a Single Level of Control

<table>
<thead>
<tr>
<th>Rule Name</th>
<th>Rule Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1s</td>
<td>One control result is between 2 and 3 standard deviations (SDs) above or below the mean (warning only; all other rules are rejection rules)</td>
</tr>
<tr>
<td>2s</td>
<td>One control result greater than 3 SDs above or below the mean (random error)</td>
</tr>
<tr>
<td>2x</td>
<td>Two sequential control results between 2 and 3 SDs both above or both below the mean</td>
</tr>
<tr>
<td>4x</td>
<td>Two sequential control results with a total range of greater than 4 SDs (random error)</td>
</tr>
<tr>
<td>10x</td>
<td>Four sequential control results greater than 1 SD above or below the mean (systematic error)</td>
</tr>
</tbody>
</table>

If the control result exceeds the mean value ±3 SDs, this is such an unlikely event (e.g., this should occur at random no more than in ~1% of all runs) as to suggest that the run is “out of control.” A single out-of-control run represents the consequence of a random error. On the other hand, if in two sequential runs a control displays a warning result each time (on the same side of the mean), the second run is out of control. This is the 2s rule and demonstrates a probable systematic (i.e., nonrandom) error. The Westgard quality control errors are summarized in Table 31.3; systematic errors reflect recurrent errors such as short sampling and a degraded reagent, a constant interference, or loss of calibration.

For many POCT assays, the mechanics of the measuring device (e.g., electrodes) are designed into a single-use, disposable cartridge. In such cases, individual cartridges cannot be quality controlled, as measurement of a control material in the cartridge expends the cartridge. However, when such cartridges are manufactured using highly automated and monitored systems, the reproducibility of the manufacturing process can be so highly regulated that minimal variation exists among cartridges within a single manufacturing run, batch, or lot. While individual cartridges cannot be tested for quality control, the batch of cartridges can be assessed upon receipt by the health care institution by measuring a control material in one or more cartridges chosen at random from the batch received. Devices that use disposable cartridges can have their electronics or optics checked daily or more often via electronic quality control. In electronic quality control, a cartridge simulator is placed into the instrument to test if the instrument reports the proper result as defined for the simulator.

### Regulatory Issues in Point-of-Care Testing

Laboratory testing, both at the POC and in satellite or central laboratories, is highly regulated by the Clinical Laboratory Improvement Amendments (CLIA) passed by the U.S. Congress in 1988. The shorthand term for the subsequent regulations is “CLIA 88” or, more simply, “CLIA.” Laboratories that perform ex vivo tests on any human tissue or body fluid must be certified by the Secretary of Health and Human Services (HHS).

Analyses where a biologic sample is not intentionally removed from the body does not fall under CLIA regulations.
These types of analyses reflect *monitoring* and not *testing* according to CLIA. Examples of such analyses include measurement of the partial pressure of exhaled carbon dioxide, alcohol breathalyzers, exhalation of $^{13}$CO$_2$ after oral administration of $^{13}$C-Urea in search of *Helicobacter pylori* infection, transcutaneous bilirubinometers, pulse oximetry, and intermittent arterial sampling via indwelling cannula for blood gases when the blood is returned to the patient’s body. Incidentally, workplace drug abuse testing does not fall under the CLIA regulations.

The CLIA laboratory certification program is operated by the Centers for Medicare and Medicaid Services (CMS), the Food and Drug Administration (FDA), and the Centers for Disease Control and Prevention (CDC). Specific information on CLIA can be found at [http://www.fda.gov/medicaldeviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm](http://www.fda.gov/medicaldeviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm) (the FDA CLIA website that addresses complexity test categorizations and waivers); [http://www.cms.hhs.gov/clia/](http://www.cms.hhs.gov/clia/) (the CMS CLIA website concerning program information, statistics, etc.); and [http://www.cdc.gov/clia/](http://www.cdc.gov/clia/) (the CDC CLIA website regarding regulations).

Currently the FDA determines whether an in vitro diagnostic test (including the test system) is waived or nonwaived; nonwaived tests are further classified as moderate complexity or high complexity. Therefore, there are three major CLIA regulatory categories: waived testing, moderate-complexity testing, and high-complexity testing. The location of testing—POC versus satellite or central laboratory—does not define the complexity of the testing. Moderate-complexity testing can be performed immediately adjacent to the OR or ICU in a satellite laboratory, while, alternatively, a waived test (e.g., BNP) can be performed in a central laboratory.

The main differences between waived and nonwaived testing (from the regulatory perspective) are as follows.

- **Method validation** is needed for all nonwaived tests. For all FDA-approved nonwaived tests, the key principle is one of verification: verification of accuracy by comparing the results of the POC test with an assay for the same analyte either in the same laboratory or elsewhere, verification of precision (both within-run and run-to-run), and verification of the limit of detection (LOD) or limit of quantitation (LOQ) of the assay.
- **All nonwaived tests require proficiency testing otherwise known as external quality assurance (EQA).** This is the means by which externally provided specimens are analyzed by the laboratory and the results are graded by an independent agency.
- **Nonwaived tests, in some states, can only be performed by licensed personnel.**

### Waived Testing

Waived tests are defined as determinations that can be performed at any site by any operator following the manufacturer’s recommendations. Theoretically, a waived test is a test that is so simple to perform that it is believed to carry little risk of error. CLIA describes waived tests as “simple procedures with little chance of negative outcomes if performed inaccurately.” However in the real world, experience teaches us that even waived tests can be performed improperly and erroneous results from certain waived tests in various situations can undoubtedly lead to potentially serious or fatal adverse outcomes (e.g., underestimation or overestimation of the PT/INR in patients being treated with warfarin for anticoagulation).

A common misconception in the hospital setting is that waived POC tests can be plugged in, switched on, and used immediately by any and all operators, with perhaps an occasional glance at the instructions. There are however major differences in process between waived POC tests performed by the patient at home (e.g., SMBG, HbA1c testing, pregnancy testing etc.) and waived POC tests run in the hospital setting.

Any waived hospital-based POC test will require that:

- The manufacturer’s instructions need to be followed exactly as written.
- An SOP must be on file and readily available to all operators.
- Reagents need to be stored correctly.
- Controls need to be analyzed as recommended by the manufacturer.
- Results need to be documented in the electronic medical record.
- Documentation of operator competency needs to be performed.
- Failure to comply with these requirements may shift the test category from a waived to a nonwaived high-complexity category; this is especially so if the manufacturer’s instructions are not followed and the method is modified. High-complexity testing for practical purposes cannot be implemented in the POC setting.

Hospitals must develop procedures and policies that specify the circumstances in which waived test results are employed in patient management, services, and treatment. To achieve this, waived test results must be placed in the clinical record, along with the appropriate reference interval (i.e., the “normal range”).

The need for confirmatory testing must be defined; for example, if the PCT blood glucose is less than 60 mg/dL or greater than 500 mg/dL, a blood sample is sent to the central laboratory for confirmation (note: the specific cutoffs depend upon the POCT analyzer). For inpatient waived testing to be performed properly, CLIA mandates that the staff executing the test must be identified, supervised, and qualified to perform the test. This requires adequate specific training and orientation to test performance and documentation of a satisfactory level of competence. This applies to all health care providers, including physicians. Competency must be demonstrated at the time of orientation training and yearly thereafter. Determination of competency must include at least two of the following four assessments.

- Performing a test on an unknown specimen
- Observation by a supervisor or qualified delegate
- Monitoring the user’s quality control performance
- Written testing relevant to the waived test method

Other CLIA standards for inpatient waived testing include that written policies and procedures are readily available and kept up to date; quality control checks are defined and conducted on each procedure; and the quality control results are recorded and maintained for review.

Examples of waived tests are given in Table 31.4. Presently, there are at least 40 waived tests; the current list of waived tests and devices can be found at [http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfClia/testswaived.cfm](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfClia/testswaived.cfm).
It is important to recognize that CLIA approval of a test as being waived is device specific: The test and the device are together approved as being waived for a specific analysis. For example, just because one manufacturer’s test for blood glucose is waived does not mean that all single-use strip measurements of glucose by all manufacturers are waived.

A laboratory or health care unit performing only waived tests must obtain a certificate of waiver (COW). COW laboratories are required to follow manufacturers’ test instructions, participate in the CLIA program, and pay applicable biennial certificate fees. This is relevant outside the formal boundaries of the hospital and ICU setting.

### Moderate- and High-Complexity Testing

CLIA defines moderate-complexity tests as being more intricate than waived tests. Moderate-complexity testing is typically carried out on automated analyzers. Examples of such tests include blood counts and routine chemistries. High-complexity tests are still more complicated, usually involving nonautomated or complicated analyses requiring considerable technologist or laboratory professional judgment, such as cross-matching of blood, electrophoresis, or microbiology testing.

Seven categories are considered when classifying the complexity of a nonwaived test:

- Required operator knowledge
- Operator training and experience
- Preparation of reagents and materials
- Characteristics of the operational steps
- Calibration, quality control, and proficiency testing
- Test system troubleshooting and equipment maintenance
- Test result interpretation and judgment

For each category, the complexity of the test is scored: A score of 1 indicates the lowest level of complexity, and a score of 3 indicates the highest level. A score of 2 indicates complexity intermediate between 1 and 3. If the total score for the seven criteria is 12 or less, the test/device system is categorized as moderate complexity, whereas those test/device systems receiving scores above 12 are codified as high complexity.

Moderate- and high-complexity tests require quality control, proficiency testing, a QA program, and so forth. There are also specific and detailed requirements regarding personnel qualifications and, as an aside, the experienced laboratory recognizes that their most important resource is a highly skilled staff. Excluding provider-performed microscopy (PPM), which is a subset of moderate-complexity testing, all nonwaived tests are generally the purview of the pathologist and the clinical laboratory, or supervised by the pathologist and the clinical laboratory. Similar to waived, but regulated, POC tests, all moderate-complexity tests performed at the POC are regulated and, at a minimum, require similar training, supervision, quality control, and proficiency testing as waived inpatient tests.

Many POC testing devices applicable to ICUs are of moderate complexity. Some POC devices applicable to ICUs perform only blood gas measurements (pH, pO₂, pCO₂), while the option to perform co-oximetry may also be available. Other devices will measure Na⁺, K⁺, glucose, ionized Ca²⁺, and/or lactate, in addition to blood gases. At least one device on the market has the capacity to measure cardiac markers and PT-INR in addition to the above parameters. Some devices can perform a wide battery of non–blood gas analyses and may not even be of moderate complexity (e.g., the Abaxis Piccolo POC Chemistry Analyzer [Abaxis North America, Union City, CA] performs 11 chemistry panels that are CLIA waived and regulated). While not attempting to provide an exhaustive list of all available blood gas analyzers, robust blood gas analyzers are available from a variety of manufacturers, including the following:

- Abbott Point of Care Inc., Princeton, NJ: iStat
- Siemens RAPIDPoint 500 Blood Gas System, Siemens Healthcare Diagnostics, Inc., Tarrytown, NY
- Accriva Diagnostics, San Diego, CA: Avoximeter 1000E
- Siemens RAPIDPoint 500 Blood Gas System, Siemens Healthcare Diagnostics, Inc., Tarrytown, NY
- Nova Biomedical, Waltham, MA: Stat Profile pHox Series
- Radiometer America Inc., Westlake, OH: ABL90 FLEX, ABL80 FLEX CO-OX and ABL80 FLEX

Some of these devices are completely mobile and hand-held (e.g., iStat), while other analyzers can be pole-mounted (Radiometer ABL80 and ABL90) or only require a small amount of bench space (e.g., they have a small “footprint”).

There are important financial considerations in providing ICU POC testing. Which cost center is going to be responsible for NIH and other expenses that are related to this testing?
for financing the new equipment? Is the equipment going to be a capital purchase, a reagent rental, or an equipment lease? Will a service contract be needed (most likely “yes”) and how much does this cost? Will the equipment require a laboratory information system (LIS) interface, and how much will that cost?

Intensivists should work closely with their hospital’s clinical pathologists and POCT coordinators in determining what type of acute testing should be available in their ICU. With the emergence of improved glycemic control as a general principle of inpatient care, blood glucose testing must be available at the POC in ICUs. Such testing should be robust, accurate, and precise, and suffer from few, if any, critical interferences. These characteristics must also be sought in any POCT device that is brought into the ICU or OR. Likewise, the device must be FDA-approved approved for use in the care of critically ill patients.

The need for POCT for blood gas analysis and other tests depends on the ease of sample delivery to a satellite or central hospital laboratory and result TAT. In our satellite “STAT” laboratory located immediately outside the operating room complex and adjacent to many of the ICUs, 90% of blood gas results are reported in 10 minutes or less.

If blood gas analyses are performed in the ICU, unless personnel are added to the ICU staff, the work load is transferred, to some extent, to the ICU nursing or respiratory care staff from the laboratory staff. However, there may be time savings in the ICU if a sample does not need to be prepared for transit to the satellite or central laboratory, and it is this immediacy of the test result that may improve patient care. Nevertheless, it is very difficult to find evidence-based medicine studies that clearly demonstrate better patient outcomes that result from reduced laboratory TATs. Even if patient care is not markedly improved, reduced TATs may aid in transferring patients to the floor or home more quickly. Patients may be more rapidly weaned from ventilation, which may decrease the use of resources. After improving patient outcomes, the next most important outcome variable for most hospital administrators is the expense of care and the need to reduce those costs (6).

If the decision has been made to proceed with POCT in the ICU, the analyzer and the support system must be carefully chosen. Ideally, the POCT device should have the ability to easily interface with the LIS to enable laboratory data transfer, billing, quality control data management, and tracking of operator competency (7). The nursing staff or respiratory care staff who perform the testing should have a voice in the analyzer choice. The device’s reproducibility must be examined (i.e., the precision of the device) (5), and the device results should be correlated with those of the central laboratory in search of biases (i.e., the accuracy of the device) (5).

Just as important as the analyzer is the quality of the blood sample that will be used for testing. For example, blood for a glucose measurement that is drawn through a line through which glucose has been infused may give falsely elevated values unless a sufficient “blank” sample is drawn through the line—in other words, “clearing the line” beforehand. Recall that D5 has a glucose concentration of 5,000 mg/dL (50 times greater than normal) and D10 has a glucose concentration of 10,000 mg/dL (100 times greater than normal). Another example of such a preanalytical error is the exposure of blood to room air when blood gas testing is warranted. Blood samples exposed to room air can exhibit an increased pO2, decreased pCO2, and increased pH. When POCT devices that require cartridges are used, proper filling of the cartridge is essential to obtain a valid result. Wasting cartridges is expensive; in some systems, individual cartridges may cost several dollars, as opposed to pennies per test in a central laboratory.

Analytical interferences must be considered in the choice of ICU POCT instruments. An interference can bias a result. Examples of interferences affecting certain central laboratory tests include hyperlipidemia, hyperbilirubinemia, and hemolysis. At the POC, some blood glucose testing devices that use glucose dehydrogenase and the PQQ reagent (pyrroloquinoline) display positive interferences when maltose is present in the patient’s bloodstream. Maltose is used as a stabilizer in drugs such as intravenous immunoglobulin, and icodextrin that is used in dialysis is metabolized to maltose. This positive interference can lead to an overestimate of the blood glucose and subsequent overtreatment of “hyperglycemia,” with severe or even fatal hypoglycemia as the consequence. Such devices have now been modified by the manufacturers to improve the analytical specificity and eliminate the maltose interference (Roche Accucheck Inform II). Glucose oxidase devices that use the patient’s blood as a source of oxygen exhibit negative biases in the glucose measurement in cases of hypoxia or where the elevation is over approximately 5,000 ft. On the other hand, glucose oxidase devices that use ferrocene or ferricyanide display positive biases in blood glucose when the patient is hypoxic and negative biases when the patient is hyperoxic, such as a ventilated patient receiving supplemental oxygen.

Quality control for the POCT must be carried out and monitored as part of an overall QA program. All device operators will require initial training and competency testing. Cost per test must also be a consideration. POCT can be 10 or more times as expensive as central laboratory testing. In considering any POCT in the ICU, the pathologist and POCT coordinator must be involved in this process from the start, as this fosters a collegial relationship and best decision for the institution. In the end, the ultimate goal is to provide excellent patient care. New laboratory tests will continue to appear that will influence ICU care such as test panels for stroke and sepsis and improved cardiac risk panels. Prudent review of the medical literature and cooperation between the ICU staff and the laboratory staff will help determine where such testing is best carried out.

Key Points

- Every hospital and ICU is distinctive and has unique laboratory needs.
- The nursing staff, intensivists, POCT coordinators, and clinical pathologists should work together to define the appropriate testing mix for their institution.
- The take-home message for the intensivist and patient care staff is that POCT must be quality controlled to ensure a high reliability of test results.
- Intensivists and patient care staff must ensure that all regulatory rules are followed and enforced. This provides the best environment possible for the provision of accurate and precise laboratory test results.
References


