

Chapter 2

On-Site Tests for Therapeutic Drugs

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1. RATIONALE FOR THERAPEUTIC MONITORING AND NEED FOR ON-SITE DRUG TESTING

There are thousands of therapeutic drugs approved by the United States Food and Drug Administration (FDA) available today for clinical use. These medications are widely used by patients for the acute treatment of illnesses or disease, or for the proper maintenance of health. In addition to approved drugs, there are hundreds of herbal medications that are gaining in popularity, and are not regulated by the FDA. For the vast majority of these drugs regular therapeutic monitoring of blood concentrations is unnecessary because they are safe, and have a low incidence of toxicity and side effects. There are a few drugs for which monitoring is effective for improving the pharmaceutical efficacy of the medication, or for reducing the incidence of unwanted effects.

The criteria utilized to determine whether or not a particular therapeutic drug warrants routine monitoring of blood concentrations are tabulated in Table 1. Therapeutic drug monitoring is the most objective manner to determine if patients are taking their medications. This is particularly true for elderly outpatients on oral prescriptions as they may not remember when or if they took their last dose. Drugs that have a low therapeutic index and therefore will have a narrow target blood concentration range, also warrant therapeutic

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Table 1
Rationale for Therapeutic Drug Monitoring

Monitoring patient compliance
Drug has a narrow therapeutic index
Individual variation in drug absorption, distribution, metabolism, and excretion
Alterations in predicted drug concentrations because of disease
Alterations in predicted drug concentrations because of interactions with other medications

monitoring. For example, the therapeutic range for the slow acting barbiturates is only 2–3 fold lower than concentrations that produce coma. Other physiologic, pathologic, and pharmacologic factors have the potential for altering predicted drug concentrations. An individual’s genetic makeup may dictate the rate by which drugs are metabolized or cleared (pharmacogenetics) and may also determine if a patient will respond to the medication or not. Coexisting diseases will have variable and unpredictable effects on drug concentrations. Poor cardiac or thyroid function, or the presence of liver or renal failure will reduce the rate of metabolism and clearance of therapeutic drugs, and may therefore, increase the likelihood of toxic reactions. Moreover, because multiple drug regimens are commonly used today, the potential for drug interactions is high. Medications that are potent displacers of plasma protein binding, or those that increase or decrease rates of hepatic metabolism, will alter the blood concentrations of co-administered drugs, thereby warranting therapeutic monitoring. Among the classes of medications that fulfill one or more of these criteria (and therefore are routinely monitored) include the anticonvulsants, antibiotics, antiarrhythmics, and antiasthmatics (e.g. theophylline).

2. ON-SITE AND POINT-OF-CARE (POC) DRUG TESTING

The clinical need and commercial interest for on-site testing for therapeutic drug monitoring is not in high demand compared with the demand in the workplace drugs-of-abuse testing arena. Quantitative measurement of drug concentrations for routine drug monitoring in serum or plasma is largely conducted by a central hospital or clinic laboratory. Drug concentrations that are outside the desired therapeutic range may affect the quantity and frequency of subsequent dosing. In the majority of cases, a rapid turnaround time (TAT)

for results (e.g., <1 h) is not needed for emergencies. The exceptions might be the urgent need to receive rapid results of analgesic (salicylates and acetaminophen), theophylline (especially in children), digoxin, and antidepressant drug concentrations in blood of emergency department patients who have symptoms of toxicity. A quantitative on-site assay for digoxin would be useful for effective patient management, as overdoses can be treated with digoxin antibodies (Digibind) (1). Although there are no FDA-approved POC assays for digoxin at present, one manufacturer has indicated plans to develop this assay (Response Biomedical Corp., Burnaby, Canada) (2). Measurement of digoxin will be difficult due to the low concentration expected, even after overdoses (>2.0 ng/mL).

The development of on-site testing for individual tricyclic antidepressants (TCA) is problematic due to the difficulty of raising antibodies that recognize the target drug, and not metabolites or other structurally-related drugs such as the muscle relaxant, cyclobenzaprine (3). Although there is one point-of-care testing device for the tricyclic antidepressants (Triage, Biosite Diagnostics, San Jose, CA), this assay for TCAs was designed for use in urine for overdose detection (>1,000 ng/mL), and cannot be used for routine quantitative therapeutic drug monitoring in blood. The laboratory-based Syva EMIT tricyclic antidepressant assay (San Diego, CA) has a lower cutoff of 200–400 ng/mL. The clinical utility of the Triage assay was examined in several clinical trials. In separate studies, Poklis et al. and Schwartz et al. found a 95 and 89% agreement of positive results with the Triage Plus compared with thin-layer chromatography (4,5). Baskin et al. found a 85% agreement between Triage and a high-pressure rapid UV-scanning liquid chromatographic assay (Remedi, BioRad Labs., Hercules, CA) (6). In terms of specificity, the Triage assay is superior to EMIT. While both assays produce positive results in the presence of cyclobenzaprine, the Triage assay is not sensitive to phenothiazines such as chlorpromazine and thioridazine (Table 2).

In addition to acute clinical needs, a rapid TAT for drug results may also be useful in routine patient management. On-site testing conducted in physicians' offices may enable a doctor to adjust drug doses while the patient is still in the office (7). Despite this potential for improved medical management, there is very little on-site drug testing currently conducted.

3. DIRECT ON-SITE TESTING INSTRUMENTS AND DEVICES FOR THERAPEUTIC DRUGS

There have been a few on-site drug testing instruments and devices developed and studied for therapeutic monitoring that directly measured the

Table 2
*Cross-Reactivities of Nontricyclic Antidepressant Drugs
 for EMIT vs Triage^a*

Drug	EMIT	Triage
Chlorpromazine	200–300	50,000
Cyclobenzaprine	>200	1,500
Thioridazine	>1,500	>100,000
Orphenadrine	>6,000	250,000
Diphenhydramine	>12,000	>1,000,000
Cyprohepatidine	>420	250,000

^aConcentration of drug resulting in positive results

drug concentrations of interest. The initial use of on-site testing used small chemistry analyzers located in physicians office laboratories (POL) (8). For example, the DT60 analyzer (Ortho-Clinical Diagnostics, Raritan, NJ) was widely used for POL testing. The only therapeutic drug available on the menu, however, was theophylline. Unlike most assays for therapeutic drugs, the DT-60 assay is not antibody-based. Instead, it is based on the ability of theophylline to inhibit beef-liver alkaline phosphatase. The DT-60 requires testing on serum or plasma and cannot use whole blood, therefore a centrifuge is necessary. The Vision analyzer (Abbott Laboratories, Abbott Park, IL) uses serum, plasma, or whole blood, making it more practical for routine POL testing. The instrument uses disposable cartridges and has an on-board centrifuge for separation of serum and plasma from red cells. The only assays for therapeutic drugs available, however, are theophylline and phenytoin. Both of these tests are immunoassay-based. The newest general POL testing analyzer is the Piccolo Portable Blood Analyzer (Abaxis, Inc., Sunnyvale, CA). Multi-analyte reagents are configured in a disposable reagent disk and can test whole blood, serum, or plasma for routine clinical chemistry analytes. Although there are no therapeutic drugs currently available, the manufacturer is considering adding a few to the menu.

The first POC testing device for measuring therapeutic drugs was the AccuLevel (Syntex, Palo Alto CA), a quantitative enzyme immunochromatography assay. AccuLevel assays were available for theophylline (9), carbamazepine, phenobarbital, and phenytoin (10). In an Emergency Department study, use of the AccuLevel theophylline assay at the bedside reduced the length of stay and time required to achieve a therapeutic drug concentration in the acute treatment of asthmatic children as compared with testing

from a central laboratory (11). Unfortunately, the AccuLevel assays were discontinued by the manufacturer.

The AccuMeter is an improved POC theophylline test cartridge device that is commercially available (AccuTech, Vista, CA). Figure 1 illustrates the schematic diagram for this device. AccuMeter has been evaluated against a laboratory-based analyzer (TDx, Abbott Labs) using capillary, serum, and heparinized blood samples (12). The analytical correlation of results was good with coefficients of $r = 0.96$, 0.96 , and 0.99 , respectively. The precision (%CV) for low (8–12 mg/L) and high (19–25 mg/L) controls was 7.4 and 6.6%, acceptable for routine drug monitoring. However, the TAT for this assay is 20 min, which is fairly long for a POC testing assay.

The only other direct POC assay for therapeutic drugs that has received commercial interest is a test for whole blood cyclosporine A. This drug is widely for immunosuppression in patients who have received organ transplants, especially kidney transplants. On-site testing for cyclosporine A may be useful for real time management of transplant patients. A quantitative commercial device is in the development stage.

Further development of POC TDM devices will likely be diminished due to the incorporation of TDM assays onto general chemistry analyzers that have large on-board menu capacities. Most laboratories have the capability to deliver results of TDM assays with the same TAT and convenience as general chemistry analytes. Other than those discussed above, there are unlikely to be additional therapeutic drugs that have a clinical need for a turnaround time of <1 h. On the other hand, there may be a market for POL or at-home testing for therapeutic drugs if compact, rapid, and inexpensive assays can be developed.

4. INDIRECT ON-SITE TESTING FOR THERAPEUTIC DRUGS

In contrast to direct testing, there is considerable interest in the indirect monitoring of a select few therapeutic drugs. For example, in a patient with insulin-dependent diabetes (Type 1), the direct quantitative measurement of glucose in blood provides an indirect means for determining if the proper insulin doses are being used. Quantitative on-site blood glucose concentrations are routinely used to make dosage adjustments. A discussion of glucometers is beyond the scope of this chapter. However, the next section describes other indirect on-site assays that monitor the efficacy and toxicity of therapeutic drugs.

4.1. Monitoring of Lipid Lowering Medications

Coronary artery disease (CAD) continues to be the major cause of morbidity and mortality in the US and throughout the western world. The risk

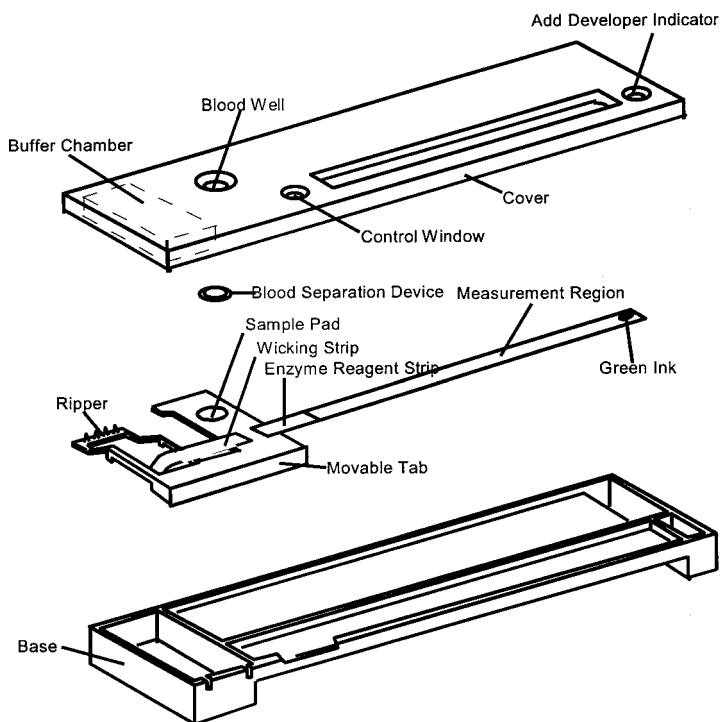


Fig. 1. The AccuMeter for theophylline and cholesterol. The cassette contains a paper strip coated with immobilized antibodies to the target analyte. The sample volume is 3 drops. When whole blood is used, a filter separates the red cells from the plasma. After a 2-min incubation, a cassette "tab" is pulled to initiate the migration onto the paper strip of the sample, and a fixed amount of labeled analyte (with horseradish peroxidase). This sets up a competition for antibody binding sites between the unlabeled (sample) and labeled analytes. The higher the sample analyte concentration, the higher the labeled analyte will migrate on the paper strip. The migration distance of the labeled antigen is determined by the addition of the peroxidase reagent, 4-chloro-1-naphthol, which produces a purple chromophore, which is read off a calibrated scale and converted to the analyte concentration. Used with permission from AccuTech, Carlsbad, CA.

factors for CAD are well established and include a family history of premature heart disease, diabetes, hypertension, cigarette smoking, and high blood concentrations of lipids and lipoproteins. Landmark studies conducted in Framingham, Massachusetts have established an exponential relationship between blood cholesterol concentrations and risk for CAD (13). Guidelines

for the interpretation of cholesterol and lipoprotein concentrations in blood have been established by the US National Cholesterol Education Program (NCEP) (14). The NCEP has determined that a desirable total and low density lipoprotein (LDL) cholesterol should be <200 and <130 mg/dL, respectively. Subjects with values between 200 and 240 mg/dL for cholesterol, and 130 and 160 mg/dL for LDL cholesterol are considered at borderline risk. Those with values exceeding 240 and 160 mg/dL, respectively, are designated high risk.

The NCEP guidelines recommend that patients, who are at high risk or borderline risk with two or more CAD risk factors, are treated with a lipid lowering drug. The most effective drugs for lowering cholesterol and LDL are the inhibitors of HMG CoA reductase, collectively known as the "statins." HMG CoA reductase is the rate-limiting enzyme in the hepatic synthesis of cholesterol. In large placebo-controlled clinical trials, statins have been effective in reducing blood concentrations of total and LDL cholesterol, and reducing the incidence of CAD death or nonfatal acute myocardial infarction (AMI) (15). For example, in the West of Scotland Coronary Prevention Study of 6,595 subjects, use of pravastatin led to a reduction of 20% in total cholesterol, 26% in LDL cholesterol, and a 33% reduction in definite and suspected CAD deaths, compared with placebo (16). While the initial studies have focused on high risk groups, more recent trials have shown that the statins such as fluvastatin, are also useful for subjects who have moderate or borderline cholesterol concentrations (17). There are six statins approved by the US FDA for clinical use in the U.S. lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and cerivastatin. More drugs will likely be approved in the future.

Blood concentrations of total and high density lipoprotein (HDL) cholesterol, and triglycerides, may be accurately measured using POL instruments and on-site devices. The earliest commercial instruments for lipids and lipoproteins were the DT-60, Vision, and the Reflotron (Roche Diagnostics). These instruments have been used for many years for on-site testing such as POLs, and in unconventional laboratory testing areas such in shopping malls, grocery stores, and health fairs for mass cholesterol screening programs. More recently, other manufacturers have developed improved on-site lipid and lipoprotein analyzers (e.g., L•D•X, Cholestech, Hayward, CA). Accurate results may be obtained on a nonfasting blood specimen for measurement of total cholesterol and HDL. For calculation of LDL cholesterol from the Friedewald equation, a fasting blood specimen is needed because this calculation uses triglyceride concentrations, which increase shortly after eating.

POC testing devices are becoming available for cholesterol determination. The first device was the AccuMeter. The performance of this assay was compared against the L•D•X analyzer, and a US Centers for Disease Control

standardized reference laboratory (18), using goals established by the NCEP (19). Both devices met the NCEP accuracy goal of <3%. However, neither device met the 3% precision goal, and both had a significant number of results that exceeded the 8.9% total error allowance. Based on this study, the author concluded that neither device was suitable for therapeutic monitoring for patients being treated for hypercholesterolemia. The results of this study were particularly disturbing considering all comparative assays were performed in duplicate, which is not the current standard of practice. Other investigators have reached the same conclusion for the Cholestech analyzer (20,21), but the opposite conclusion for the AccuMeter (22).

A POC testing device designed for at-home use was recently announced by Lifestream (Sandpoint, ID). The Cholestroon measures cholesterol concentration from capillary blood in 3 min, and is projected to sell for \$130–\$300 (depending on optional features). This device is approved by the FDA.

4.2. Monitoring of Antithrombotic Medications

4.2.1. Heparin

The clotting of blood is a complex system of biochemical reactions. Initiation of the coagulation cascade by either the intrinsic or extrinsic pathways, leads to the conversion of prothrombin to thrombin, which in turn, catalyzes the conversion of fibrinogen to an insoluble fibrin clot. Systemic anticoagulation is widely used to prevent clot formation in patients with AMI and unstable angina, arterial and venous thrombotic diseases, and those undergoing procedures such as coronary artery bypass graft surgery (CABG), angioplasty, and hemodialysis. The most commonly used anticoagulant is unfractionated heparin, an acid mucopolysaccharide of varying molecular weights (10,000 to 30,000 daltons). Unfractionated heparin prevents fibrin formation by accelerating the natural interaction of antithrombin III and thrombin, thereby inhibiting other activated proteases that are involved with hemostasis (e.g., Factor IIa, IXa, and Xa). Because heparin is not well absorbed after oral administration, it is mainly administered intravenously either as a bolus injection or continuous infusion. Relative to use in other patients, very high doses are administered to patients undergoing CABG. The plasma half life of heparin is between 1–2 h. In cases of heparin overdose, protamine sulfate may be administered. This compound binds heparin to inactivate the anticoagulant property (23).

A new anticoagulant widely used in Europe and gaining more acceptance in the US is low molecular weight heparin. This form of heparin is produced from enzymatic degradation of unfractionated heparin to produce polymers

that range from 3000–5000 Daltons. Low molecular weight heparin has different pharmacological properties compared with unfractionated heparin. It is a less potent activator of platelets, may lead to a reduced incidence of clinical bleeding, and does not alter prothrombin, thrombin, or activated partial thromboplastin (aPPT) times. However, its effects are not as easily reversed with protamine.

The clinical use of heparin is routinely monitored by measurement of the activated clotting time (ACT), aPPT, and serum heparin concentrations. Because heparin concentrations cannot be directly measured using on-site testing devices, this will not be discussed any further in this chapter. Both ACT and aPTT are measures of the intrinsic coagulation pathway. The tests are performed by measuring the time needed for whole blood or plasma to form a fibrin clot following the addition of a contact reagent such as kaolin, used to accelerate clot formation. ACT is performed on whole blood collected without an anticoagulant. The expected ACT is about 2 min. The ACT requires on-site testing, as the sample begins to clot soon immediately after collection; it therefore cannot be sent to an off-site laboratory. The ACT is most widely used assay in the operating rooms for patients undergoing CABG, where a fast TAT for results is needed. The higher heparin concentration used in these patients makes it more appropriate to use ACT rather than aPTT. The target ACT time for CABG patients is 400–480 s (24). Conditions that limit the accuracy of ACT measurements include hemodilution, platelet lysis, and hypothermia.

The aPPT is performed on citrated whole blood or plasma to which calcium, a thromboplastin reagent, and the clot activator are added. aPPT monitoring is more convenient and universally used than ACT for heparin monitoring, because plasma samples do not have to be tested immediately. Expected values range from 25–35 s. The target therapeutic concentration for heparin monitoring is an aPTT of approx 1.5–2.5 times the upper limit of normal.

4.2.2. Oral Antithrombotic Therapy

Oral anticoagulants such as warfarin, are ideal for outpatient use because these medications have a delayed onset of action, and a prolonged half-life of 2–3 d. Warfarin blocks the reductase enzyme in the vitamin K pathway, thereby producing structurally incomplete clotting factors such as prothrombin, VII, IX, and X. The drug is indicated for treatment of patients with venous and arterial thromboembolic diseases such as deep vein thrombosis, pulmonary embolism, and in survivors of AMI to prevent subsequent thrombosis in these patients.

The clinical use of oral antithrombotic therapy is routinely monitored by measurement of the prothrombin time (PT). This test involves measuring the

time needed for plasma to clot after adding calcium and tissue factor (thromboplastin), and is a measure of the extrinsic coagulation pathway. There is great variability in reference values for these assays because different thromboplastin reagents have different sensitivities towards clotting factors. Although thromboplastin reagents originating from the human brain are the most sensitive, most reagents used in the US originate from rabbit brain or combination of brain and lung. In order to normalize values between different laboratories, the International Normalized Ratio (INR) was created:

$$(\text{patient PT value} \div \text{mean normal PT})^{\text{ISI}},$$

where the ISI is the International Sensitivity Index (25). The ISI value is dependent on the sensitivity of the thromboplastin reagent used. This calculation enables standardization of PT results from different laboratories. Expected PT values are between 10–14 s, and the INR from 0.9–1.1. The target INR ratios for patients on oral anticoagulant therapy is between 1.3 and 1.6.

4.2.3. *On-Site Testing for Anticoagulant Drugs*

Therapeutic monitoring of patients on heparin or oral anticoagulants using either ACT or aPTT, and PT, respectively, is well established. There are numerous on-site testing devices for the coagulation markers, including Hemochron (International Technidyne, Edison, NJ), CoaguChek Plus (Roche Diagnostics, Indianapolis, IN), Thrombolytic Assessment System (Dade International, Miami, FL), and proTime (International Technidyne, Edison, NJ).

For the monitoring of heparin, controversy exists as to whether or not ACT testing is superior to aPTT, and studies comparing the two have been conducted. Using quantitative heparin concentrations as a gold standard or reference, some investigators have concluded that measurement of the aPTT is superior to ACT (26,27). Others have suggested that aPTT has the same limitations of hemodilution and hypothermia as ACT (28). While most agree on the need for delivering a rapid TAT, the costs for delivering on-site testing are likely to be higher and therefore need to be justified. There are also issues regarding governmental regulations for on-site testing. Outcome studies have been conducted that compare POC vs central laboratory testing. In the GUSTO-I trial, aPTT monitoring was used to adjust heparin dosing in AMI patients who were treated with thrombolytic agents (29). Figure 2 illustrates the decrease in the incidence of moderate to severe bleeding, blood transfusions, and decreases in hematocrit. Moreover, there were fewer bedside-monitored patients who had subtherapeutic concentrations. Bedside testing did have a slight increase in the incidence of recurrent ischemia. In another study, investiga-

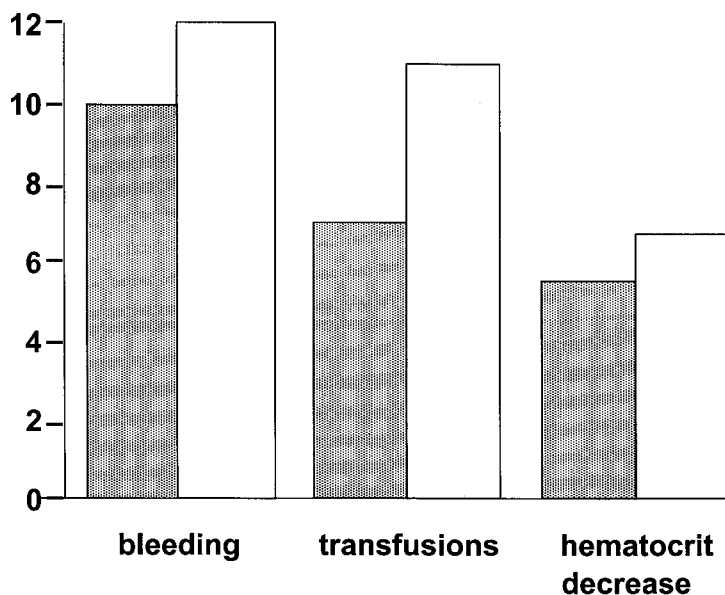


Fig. 2. Comparison of on-site testing for aPTT (shaded bars) vs central laboratory testing (open bars) for monitoring heparin therapy. The rate of complications for bleeding and need for blood transfusions, and % drop in hematocrit are compared. Data from ref. 29.

tors compared on-site vs central laboratory testing for aPTT in the adjustment of heparin therapy (30). On-site testing significantly reduced the time from when the blood sample was collected to a heparin infusion adjustment (0.4 vs 1.6 h), and the time to reach the therapeutic aPTT range (16.1 vs 19.4 h). These studies illustrate that rapid aPTT testing can be justified when overall hospital costs and improvements in clinical outcomes are taken into consideration.

Equivalent studies demonstrating the clinical advantages of delivering results with a rapid TAT using on-site testing for PT monitoring of oral anti-coagulants have not been conducted to date. Published studies have focused on analytical correlation to determine how well POC devices agree with results obtained from the central laboratory. In one study, the CoaguCheck significantly underestimated the INR relative to a central laboratory result, while the TAS was more comparable (31). Use of different thromboplastin reagents may have contributed to the differences in analytical correlations. Despite the lack of evidence-based outcome studies, these devices are being extensively used in physician offices, and are being considered for at-home testing (32).

5. CONCLUSION

Beyond the markers described in this chapter, the commercial potential for point-of-care therapeutic drug monitoring devices is not extensive. The majority of therapeutic drugs do not need to be measured in an acute manner. Therefore the additional expense to deliver results with a fast turnaround time may not be warranted. Even though the list of drugs approved by the US FDA increases each year, demands for therapeutic drug monitoring have actually declined over recent years. The development of safer drugs to replace those that are more toxic is one reason for this decline. The overall reduction in reimbursement for laboratory tests is another important factor. Each site must consider a multitude of factors before deciding if on-site testing for therapeutic drugs is warranted.

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