Clinical Drug Testing in Primary Care

Technical Assistance Publication Series

TAP 32

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TAP

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Center for Substance Abuse Treatment

1 Choke Cherry Road
Rockville, MD 20857

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Audience for the TAP

This Technical Assistance Publication (TAP), *Clinical Drug Testing in Primary Care*, is for clinical practitioners—physicians, nurse practitioners, and physician assistants—who provide primary care in office settings and community health centers. The publication provides information that practitioners need when deciding whether to introduce drug testing in their practices and gives guidance on implementing drug testing.

The TAP does not address drug testing for law enforcement or legal purposes, nor does it include testing for the use of anabolic steroids or performance-enhancing substances. This TAP describes some of the ways that drug testing can contribute to the assessment, diagnosis, and treatment of patients seen in primary care, the management of the treatment of chronic pain, and the identification and treatment of substance use disorders.

Organization of the TAP

This chapter briefly describes the role of drug testing in primary care settings and its historical roots in workplace testing. Chapter 2 defines the terms and practices used in drug testing. Chapter 3 presents the mechanics of testing and describes the steps that primary care practitioners can take to prepare themselves, their staffs, and their office spaces for drug testing. Chapter 4 provides information about implementing testing in clinical practice. Important aspects of urine drug testing for specific drugs are presented in Chapter 5. Appendices A–H include the bibliography; overviews of technical information on specific tests used for initial or screening tests, confirmatory tests, and specimen validity tests; a glossary of terms; the members of the expert panel, consultants, and field reviewers; and acknowledgments.

Reasons To Use Clinical Drug Testing in Primary Care

The term *drug testing* can be confusing because it implies that the test will detect the presence of all drugs. However, drug tests target only specific drugs or drug classes and can detect substances only when they are present above predetermined thresholds (cutoff levels). The term *drug screening* can also be deceptive because it is often used to describe all types of drug testing. However, *drug screening* is usually used in forensic drug testing to refer to the use of immunoassay tests to distinguish specimens that test negative for a drug and/or metabolite from positive specimens. For the purpose of this TAP, the term *drug testing* is used.

When used appropriately, drug testing can be an important clinical tool in patient care. The types of clinical situations in which clinical drug testing can be used include pain management with opioid medications, office-based opioid treatment, primary care, psychiatry, and other situations when healthcare providers need to determine alcohol or other substance use in patients. Drug testing is also used to monitor patients' prescribed medications with addictive potential. Patients sometimes underreport drug use to medical professionals (Chen, Fang, Shyu, & Lin, 2006), making some patients' self-reports unreliable. Drug test results may provide more accurate information than patient self-report. Although drug testing can be a useful tool for making clinical decisions, it should not be the only tool. When combined with a patient's history, collateral information from a spouse or other family member (obtained with permission of the patient), questionnaires, biological markers, and a practitioner's clinical judgment, drug testing provides information that:

- Can affect clinical decisions on a patient's substance use that affects other medical conditions.
- Can affect clinical decisions about pharmacotherapy, especially with controlled substances.
- Increases the safety of prescribing medications by identifying the potential for overdose or serious drug interactions.
- Helps clinicians assess patient use of opioids for chronic pain management or compliance with pharmacotherapy for opioid maintenance treatment for opioid use disorders.
- Helps the clinician assess the efficacy of the treatment plan and the current level of care for chronic pain management and substance use disorders (SUDs).
- Prevents dangerous medication interactions during surgery or other medical procedures.
- Aids in screening, assessing, and diagnosing an SUD, although drug testing is not a definitive indication of an SUD.
- Identifies women who are pregnant, or who want to become pregnant, and are using drugs or alcohol.
- Identifies at-risk neonates.
- Monitors abstinence in a patient with a known SUD.
- Verifies, contradicts, or adds to a patient's self-report or family member's report of substance use.
- Identifies a relapse to substance use.

Primary Care and Substance Use Disorders

Practitioners can use drug testing to help monitor patients' use of prescribed scheduled medications, as part of pharmacovigilance, and to help identify patients who may need an intervention for SUDs.

For the purpose of this TAP, *substances* refers to alcohol and drugs that can be abused. As defined by the *Diagnostic and Statistical Manual of Mental Disorders,*

Fourth Edition, Text Revision (DSM-IV-TR; American Psychiatric Association [APA], 2000), a *substance-related disorder* is a disorder related to the consumption of alcohol or of a drug of abuse (APA, 2000). *Substance use disorders* (SUDs) includes both substance dependence and substance abuse (APA, 2000). *Substance dependence* refers to "a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues use of the substance despite significant substance-related problems. There is a pattern of repeated self-administration that can result in tolerance, withdrawal, and compulsive drug-taking behavior" (APA, 2000). *Substance abuse* refers to "a maladaptive pattern of substance use manifested by recurrent and significant adverse consequences related to the repeated use of substances" (APA, 2000). In this TAP, the term *substance abuse* is sometimes used to denote both *substance abuse* and *substance dependence* as they are defined in the DSM-IV-TR (APA, 2000).

SUDs can have serious medical complications and serious psychosocial consequences and can be fatal. Treatment of other medical disorders (e.g., HIV/AIDs, pancreatitis, hypertension, diabetes, liver disorders) may be complicated by the presence of an SUD. As the front line in health care, medical practitioners are ideally situated to identify substance use problems. The 2009 National Survey on Drug Use and Health (Substance Abuse and Mental Health Services Administration [SAMHSA], 2010a) found that 23.5 million (9.3 percent) persons ages 12 or older needed treatment for an illicit drug[1] or alcohol use problem. Of this population, only 2.6 million (1.0 percent) persons ages 12 or older (11.2 percent of those who needed treatment) received treatment at a specialty facility. Thus, 20.9 million (8.3 percent) of the population age 12 or older needed substance abuse treatment but did not receive it in the past year (SAMHSA, 2010a). Therefore, a visit to a primary care practitioner may be an excellent opportunity for such people to be diagnosed with SUDs. Moreover, the number of people ages 12 or older seeking help for SUDs from a doctor in private practice increased from 460,000 in 2005 to 672,000 in 2008 (SAMHSA, 2006; SAMHSA, 2009).

Despite the potential benefits of drug testing (such as monitoring pain medication) to patient care, few primary care practitioners use it. For example, a small study conducted on the medical management of patients with chronic pain in family practices found that only 8 percent of physicians surveyed used drug testing (Adams et al., 2001).

Development of Drug Testing

Drug testing performed for clinical reasons differs substantially from workplace drug testing programs. However, clinical drug testing draws on the experience of Federal Mandatory Workplace Drug Testing and, to understand drug testing, a review of workplace drug testing may be helpful. An important reason for clinical practitioners to become familiar with Federal Mandatory Workplace Drug Testing is that the majority of drug testing is done for workplace purposes. For this reason, most laboratories and many point-of-care tests (POCTs) use the cutoff concentrations established by the Mandatory Guidelines for Federal Workplace Drug Testing Programs, discussed in Chapter 2.

There are three categories of drug testing: (1) federally regulated for selected Federal employees (including military personnel and those in safety-sensitive positions); (2) federally regulated for non-Federal employees in safety-sensitive positions (i.e., airline and railroad personnel, commercial truckers, school bus drivers); and (3) nonregulated for non-Federal employees. Commercial truck drivers, railroad employees and airline personnel make up the largest group of individuals being drug tested.

The purpose of both Federal (always regulated) and non-Federal (may be nonregulated) workplace drug testing is to ensure safety in the workplace by preventing

[1] Includes the nonmedical use of prescription-type pain relievers, tranquilizers, stimulants, and sedatives.

the hiring of individuals who use illicit drugs and identifying employees who use illicit drugs.

Workplace Drug Testing

Drug-testing methods have been available for approximately 50 years (Reynolds, 2005). Because of drug use in the U.S. military, by 1984, the military established standards for laboratories and testing methods and created the first system for processing large numbers of drug tests under strict forensic conditions that could be defended in a court of law.

In 1986, an Executive Order initiated the Federal Drug-Free Workplace Program that defined responsibilities for establishing a plan to achieve drug-free workplaces. In 1987, Public Law 100-71 outlined provisions for drug testing programs in the Federal sector. In 1988, Federal mandatory guidelines set scientific and technical standards for testing Federal employees. In 1989, the U.S. Department of Transportation (DOT) issued regulations requiring the testing of nearly 7 million private-sector transportation workers in industries regulated by DOT.

The Federal mandatory guidelines included procedures, regulations, and certification requirements for laboratories; outlined the drugs for which testing was to be performed; set cutoff concentrations; and stated reporting requirements that included mandatory medical reviews by a specially trained physician Medical Review Officer (MRO). Because a positive result does not automatically identify an employee or job applicant as a person who uses illicit drugs, the MRO interviews the donor to determine whether there is an alternative medical explanation for the drug found in the specimen. The Federal mandatory guidelines recommended that the initial screening test identify the presence of the following commonly abused drugs or their metabolites (SAMHSA, 2008):

- Amphetamines (amphetamine, methamphetamine)
- Cocaine metabolites
- Marijuana metabolites
- Opiate metabolites (codeine, morphine)
- Phencyclidine (PCP)

These substances are generally called the "Federal 5," but over the years they have also been called the "NIDA 5" and "SAMHSA 5." The Federal mandatory guidelines have been updated and revised over the years to reflect technological and process changes (Exhibit 1-1). The guidelines, last updated in 2008 (effective May 1, 2010), are available at http://dwp.samhsa.gov/DrugTesting/Level_1_Pages/mandatory_guidelines5_1_10.html.

Revisions for testing of other matrixes (e.g., hair, oral fluid, sweat) and the use of POCTs were proposed in 2004 (SAMHSA, 2008), but have not been finalized.

Although Federal agencies are required to have drug-free workplace programs for their employees, private-sector employers that do not fall under Federal regulations can establish their own drug-free workplace programs and establish their own regulations, testing matrices, and testing methods. Non-Federal employees can be tested for a broader range of drugs than the federally mandated drugs. Many States have laws and regulations that affect when, where, and how employers can implement drug-free workplace programs (search in http://www.dol.gov).

Laboratories are accredited by the National Laboratory Certification Program (NLCP) to meet the minimum requirements of the Federal mandatory guidelines. This program resides in SAMHSA in the Department of Health and Human Services (HHS).

Exhibit 1-1. U.S. Department of Health and Human Services Federal Mandatory Workplace Guidelines Cutoff Concentrations for Initial and Confirmatory Drug Tests in Urine

Initial Test Analyte	Federal Cutoff Concentrations (ng/mL)
Marijuana metabolites	50
Cocaine metabolites	150
Opiate metabolites (codeine/morphine[1])	2,000
6-Acetylmorphine (6-AM)	10
Amphetamines[2] (Amphetamine /methamphetamine)	500
Phencyclidine (PCP)	25
Methylenedioxymethamphetamine (MDMA)	500
Confirmatory Test Analyte	**Federal Cutoff Concentrations (ng/mL)**
Amphetamine	250
Methamphetamine[3]	250
MDMA	250
Methylenedioxyamphetamine (MDA)	250
Methylenedioxyethylamphetamine (MDEA)	250
Cannabinoid metabolite (delta-9-tetrahydrocannabinol-9-carboxylic acid)	15
Cocaine metabolite (benzoylecgonine)	100
Codeine	2,000
Morphine	2000
6-Acetylmorphine (6-AM)	10
PCP	25

Source: SAMHSA (2008).
[1] Morphine is the target analyte for codeine/morphine testing.
[2] Methamphetamine is the target analyte for amphetamine/methamphetamine testing.
[3] To be reported positive for methamphetamine, a specimen must also contain amphetamine at a concentration equal to, or greater than, 100 ng/mL.

Drug Testing in Substance Abuse Treatment and Healthcare Settings

Substance abuse treatment programs use drug testing extensively. Drug testing for patient monitoring in SUD treatment programs began considerably before workplace drug testing and has become an integral part of many drug treatment programs for patient evaluation and monitoring. By 1970, the Federal Government implemented specific mandatory testing requirements for treatment programs that were licensed by the U.S. Food and Drug Administration to dispense methadone or that received Federal funds. During the 1970s, Federal agencies developed a program to monitor laboratories performing drug testing for drug treatment programs under Federal mandates.

Drug testing in SUD treatment is:

- Part of the initial assessment of a patient being evaluated for a diagnosis of an SUD;
- A screen to prevent potential adverse effects of pharmacotherapy (e.g., opioid screen prior to starting naltrexone);
- A component of the treatment plan for an SUD;
- A way to monitor the patient's use of illicit substances or adherence to pharmacotherapy treatment for SUDs; and
- A way to assess the efficacy of the treatment plan (i.e., level of care).

Drug testing can also be used to document abstinence for legal matters, disability determinations, custody disputes, or reinstatement in certain professions (e.g., lawyers, healthcare providers, airline pilots).

Drug testing is also useful in healthcare settings:

- For determining or refuting perinatal maternal drug use;
- As an adjunct to psychiatric care and counseling;
- For monitoring medication compliance during pain treatment with opioids;
- For monitoring other medications that could be abused or diverted; and
- To detect drug use or abuse where it may have a negative impact on patient care in other medical specialties.

See Chapter 4 for more information about the use of drug testing in clinical situations.

Differences Between Federal Workplace Drug Testing and Clinical Drug Testing

Important distinctions exist between drug testing in Federal workplace settings and drug testing in clinical settings (Exhibit 1-2). Despite the differences, Federal workplace drug-testing guidelines and cutoff concentrations continue to influence clinical drug testing. For example, many laboratories and POCT devices test either for the federally mandated drugs or for the same drugs, but using modified cutoff concentrations as the default drug-testing panel. These panels are not suitable for clinical drug testing because these panels do not detect some of the most commonly prescribed pain medications, such as synthetic opioids (e.g., hydrocodone) and anxiolytics (e.g., benzodiazepines, such as alprazolam), or other drugs of abuse. Initial screening test cutoffs may not be low enough for clinical practice in some instances (e.g., cannabinoids, opiates, amphetamines).

Caution

Trends in drug use and abuse change over time and can necessitate a change in drug testing panels. The technology for drug testing evolves quickly, new drug-testing devices become available, and old tests are refined. Although this TAP presents current information, readers are encouraged to continue to consult recent sources. Wherever possible, the TAP refers readers to resources that provide up-to-date information.

Exhibit 1-2. Comparison of Federal Workplace Drug Testing and Clinical Drug Testing

Component	Federal Workplace Testing	Clinical Testing
Specimen	• Urine	• Primarily urine, some oral fluid tests
Collection Procedures	• Federal regulations stipulate specimen collection procedures. • Policies minimize mistaken identity of specimens and specimen adulteration. For example, in criminal cases, chain-of-custody policies require identification of all persons handling specimen packages. In administrative cases (e.g., workplace testing), specimen packages may be handled without individual identification. Only those persons handling the specimen itself need to be identified.	• Practitioners and clinical staff (hospital or clinical laboratory) follow procedures for properly identifying and tracking specimens. • In general, rigorous protocols are not used. Chain of custody usually is not required; however, laboratories under College of American Pathologists accreditation and/or State licensure should have specimen collection, handling, and storage protocols in place.
Specimen Validity Testing	• Extensive testing verifies that specimen substitution or adulteration has not occurred.	• In general, laboratories do not conduct the same validity testing as is required for Federal workplace testing. • Validation often is not required with clinical use of POCT. • Some laboratories record the temperature of the specimen and test for creatinine and specific gravity of urine specimens. • Pain management laboratories may have specimen validity testing protocols that involve creatinine with reflexive specific gravity, pH, and/or oxidants in place.
Confirmatory Methods	• Gas chromatography/mass spectrometry (GC/MS)	• GC/MS, liquid chromatography/mass spectrometry (LC/MS), liquid chromatography/mass spectrometry/mass spectrometry LC/MS/MS.
Testing for Predetermined Substances	• Testing is for the federally mandated drugs.	• No set drug testing panel. • Drugs tested vary by laboratory and within laboratories. • Clinicians may specify which drugs are tested for and usually select panels (menus) that test for more than the federally mandated drugs. Various panels exist (e.g., pain).
Cutoff Concentrations	• Cutoff concentrations have been established for each drug. • A test detecting a concentration at or above the cutoff is considered to be a positive result; a test detecting nothing, or a concentration below the cutoff, is considered to be a negative result.	• Cutoff concentrations vary. • In some circumstances, test results below the cutoff concentration may be clinically significant. • Urine and oral fluid drug concentrations are usually not well correlated with impairment or intoxication, but may be consistent with observed effects.
Laboratory Certification	• Testing must be conducted at an HHS, SAMHSA-certified laboratory.	• Laboratories do not need HHS certification. However, clinical laboratories in the United States and its territories must be registered with Clinical Laboratory Improvement Amendments (CLIA) and comply with all State and local regulations concerning specimen collection, clinical laboratory testing, and reporting. • POCT using kits calibrated and validated by manufacturers does not require CLIA certification.
Medical Review	• A physician trained as an MRO must interpret and report results.	• MRO review is not required.

Chapter 2—Terminology and Essential Concepts in Drug Testing

In This Chapter

- Drug Screening and Confirmatory Testing
- Testing Methods
- Test Reliability
- Window of Detection
- Cutoff Concentrations
- Cross-Reactivity
- Drug Test Panels
- Test Matrix
- Point-of-Care Tests
- Adulterants
- Specimen Validity Tests

Drug Screening and Confirmatory Testing

Traditionally, drug testing usually, but not always, involves a two-step process: an initial drug screen that identifies potentially or presumptively positive and negative specimens, followed by a confirmatory test of any screened positive assays.

Screening tests (the initial tests) indicate the presence or absence of a substance or its metabolite, but also can indicate the presence of a cross-reacting, chemically similar substance. These are qualitative analyses—the drug (or drug metabolite) is either present or absent. The tests generally do not measure the quantity of the drug or alcohol or its metabolite present in the specimen (a quantitative analysis). Screening tests can be done in a laboratory or onsite (point-of-care test [POCT]) and usually use an immunoassay technique. Laboratory immunoassay screening tests are inexpensive, are easily automated, and produce results quickly. Screening POCT immunoassay testing devices are available for urine and oral fluids (saliva). Most screening tests use antigen–antibody interactions (using enzymes, microparticles, or fluorescent compounds as markers) to compare the specimen with a calibrated quantity of the substance being tested for (Center for Substance Abuse Treatment, 2006b).

Confirmatory tests either verify or refute the result of the screening assay. With recent improvements in confirmation technology, some laboratories may bypass screening tests and submit all specimens for analysis by confirmatory tests. It is the second analytical procedure performed on a different aliquot, or on part, of the original specimen to identify and quantify the presence of a specific drug or drug metabolite (Substance Abuse and Mental Health Services Administration [SAMHSA], 2008). Confirmatory tests use a more specific, and usually more sensitive, method than do screening tests and are usually performed in a laboratory. Confirmatory tests usually:

- Provide quantitative concentrations (e.g., ng/mL) of specific substances or their metabolites in the specimen.
- Have high specificity and sensitivity.

- Require a trained technician to perform the test and interpret the results.
- Can identify specific drugs within drug classes.

In clinical situations, confirmation is not always necessary. Clinical correlation is appropriate. For example, if the patient or a family member affirms that drug use occurred, a confirmation drug test is not usually needed.

A POCT, performed where the specimen is collected, is a screening test. A confirmatory drug test is usually more technically complex and provides definitive information about the quantitative concentrations (e.g., ng/mL) of specific drugs or their metabolites in the specimen tested. However, the term *drug screening* or *testing* is misleading in that it implies that all drugs will be identified by tests, whereas the drug or drug metabolites detected by a test depend on the testing method and the cutoff concentration.

In Federal workplace testing, all positive initial screening test results must be followed by a confirmatory test (SAMHSA, 2008). In clinical settings, however, confirmatory testing is at the practitioner's discretion. Laboratories do not automatically perform confirmatory tests. When a patient's screening test (either a POCT or laboratory test) yields unexpected results (positive when in substance use disorder (SUD) treatment, or negative if in pain management treatment), the practitioner decides whether to request a confirmatory test. In addition, a confirmatory test may not be needed; patients may admit to drug use or not taking scheduled medications when told of the drug test results, negating the necessity of a confirmatory test. However, if the patient disputes the unexpected findings, a confirmatory test should be done. Chapter 4 provides information that can be helpful in deciding whether to request a confirmatory test.

Testing Methods

Conventional scientific techniques are used to test specimens for drugs or drug metabolites. Most commonly, immunoassay testing technology is used to perform the initial screening test (Meeker, Mount, & Ross, 2003). Appendix B, Laboratory Initial Drug-Testing Methods, briefly describes these methods.

The most common technologies used to perform the confirmatory test are gas chromatography/mass spectrometry, liquid chromatography/mass spectrometry, and various forms of tandem mass spectrometry. Information about these methods and other confirmatory testing methods are in Appendix C, Laboratory Confirmatory Drug-Testing Methods. Other testing methods are used to detect adulteration or substitution. Appendix D, Laboratory Specimen Validity-Testing Methods, provides a short explanation of methods for specimen validity testing.

Test Reliability

Both POCTs and laboratory tests are evaluated for reliability. Two measures of test reliability are *sensitivity* and *specificity*, which are statistical measures of the performance of a test. The *sensitivity* indicates the proportion of positive results that a testing method or device correctly identifies. For drug testing, it is the test's ability to reliably detect the presence of a drug or metabolite at or above the designated cutoff concentration (the true-positive rate). *Specificity* is the test's ability to exclude substances other than the analyte of interest or its ability not to detect the analyte of interest when it is below the cutoff concentration (the true-negative rate). It indicates the proportion of negative results that a testing method or device correctly identifies.

Tests are designed to detect whether a specimen is positive or negative for the substance. Four results are possible:

- True positive: The test correctly detects the presence of the drug or metabolites.
- False positive: The test incorrectly detects the presence of the drug when none is present.
- True negative: The test correctly confirms the absence of the drug or metabolites.
- False negative: The test fails to detect the presence of the drug or metabolites.

Confirmatory tests must have high specificity. Generally, screening tests have relatively low specificity. Screening tests are manufactured to be as sensitive as possible, while minimizing the possibility of a false-positive result (Dolan, Rouen, & Kimber, 2004). Notable exceptions from common manufacturers of laboratory-based or point-of-care immunoassay kits are cannabinoids, cocaine metabolite, oxycodone/oxymorphone, methadone, and methadone metabolite (EDDP, or 2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine). Other examples may exist. With the exceptions noted previously, they cannot reliably exclude substances other than the substance of interest (the analyte), and they cannot reliably discriminate among drugs of the same class. For example, a low-specificity test may reliably detect morphine, but be unable to determine whether the drug used was heroin, codeine, or morphine.

Generally, the cutoff level for initial screening tests is set to identify 95–98 percent of true-negative results, and 100 percent of true-positive results. Confirmatory test cutoff concentrations are set to ensure that more than 95 percent of all specimens with screened positive results are confirmed as true positives (Reynolds, 2005). However, confirmation rates are highly dependent upon the analyte. For cannabinoids and cocaine metabolite, the confirmatory rate usually exceeds 99 percent. The clinically important point is that false positives are rare for cocaine metabolite or cannabinoids.

Window of Detection

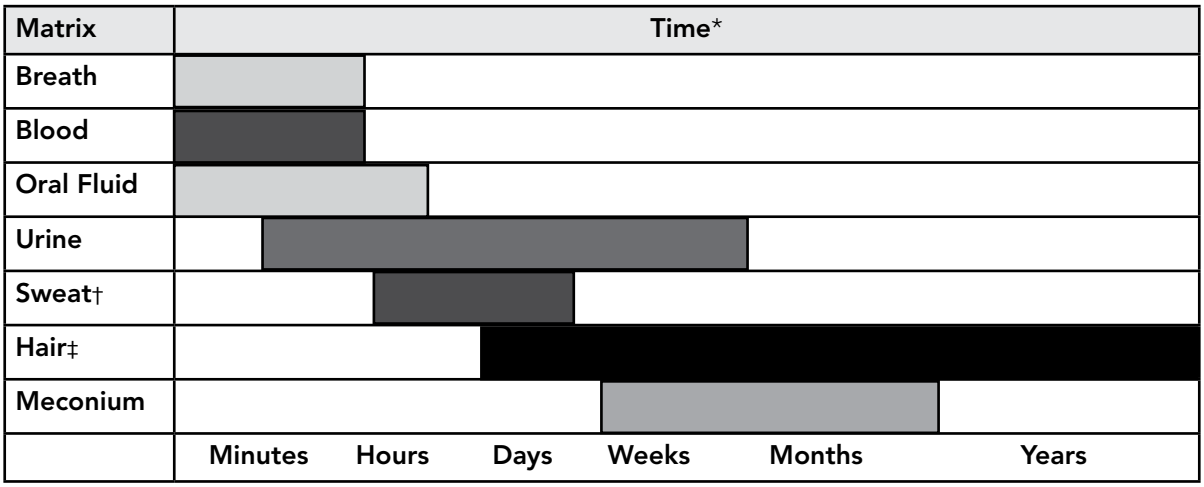
The *window of detection*, also called the detection time, is the length of time the substances or their metabolites can be detected in a biological matrix. It part, it depends on:

- Chemical properties of the substances for which the test is being performed;
- Individual metabolism rates and excretion routes;
- Route of administration, frequency of use, and amount of the substance ingested;
- Sensitivity and specificity of the test;
- Selected cutoff concentration;
- The individual's health, diet, weight, gender, fluid intake, and pharmacogenomic profile; and
- The biological specimen tested.

All biological matrices may show the presence of both parent drugs and their metabolites (Warner, 2003). Drug metabolites usually remain in the body longer than do the parent drugs. Blood and oral fluid are better suited for detecting the parent drug; urine is most likely to contain the drug's metabolites. Exhibit 2-1 provides a comparison of detection periods used for various matrices.

Many factors influence the window of detection for a substance. Factors include, but are not limited to, the frequency of drug use (chronic or acute), the amount taken, the rate at which the substance is metabolized (including pharmacogenomic abnormalities, such as mutations of CYP2D6 and other drug-metabolizing enzymes [White & Black, 2007]), the cutoff concentration of the test, the patient's physical condition and, in many cases, the amount of body fat.

Exhibit 2-1. Window of Detection for Various Matrices



*Very broad estimates that also depend on the substance, the amount and frequency of the substance taken, and other factors previously listed.
†As long as the patch is worn, usually 7 days.
‡7–10 days after use to the time passed to grow the length of hair, but may be limited to 6 months hair growth. However, most laboratories analyze the amount of hair equivalent to 3 months of growth.

Sources: Adapted from Cone (1997); Dasgupta (2008).

Cutoff Concentrations

The administrative *cutoff* (or *threshold*) of a drug test is the point of measurement at or above which a result is considered positive and below which a result is considered negative. This level is established on the basis of the reliability and accuracy of the test and its ability to detect a drug or metabolite for a reasonable period after drug use (see Test Reliability).

Before the establishment of the Federal mandatory guidelines, cutoff concentrations for screening tests were determined by the manufacturer of the test or the laboratory. Because the majority of drug testing is done for workplace purposes, most laboratories and many POCTs use the Federal mandatory guidelines for workplace testing cutoff concentrations. However, Federal cutoff concentrations are **not** appropriate for clinical use. Practitioners need to know the cutoff concentrations used in the POCTs, or by the laboratory testing their patients' specimens, and should understand which analyte and at what cutoff the test is designed to detect.

Detection thresholds for Federal, employer, and forensic drug testing panels are set high enough to detect concentrations suggesting drug abuse, but they do not always detect therapeutic concentrations of medications. For example, the threshold for opiates in federally mandated workplace urine drug screening is 2000 ng/mL. The usual screening threshold for opiates in clinical monitoring is much lower, at 300 ng/mL for morphine, hydrocodone, and codeine (Christo et al., 2011) to detect appropriate use of opioid pain medication.

For laboratory tests, practitioners can request lower cutoff concentrations than are commonly used in workplace testing. However, in some cases, the error rate increases as the cutoff concentration decreases.

Cross-Reactivity

Cross-reactivity occurs when a test cannot distinguish between the substances being tested for and substances that are chemically similar. This is a very important concept when interpreting test results.

Drug class-specific immunoassay tests compare the structural similarity of a drug or its metabolites with specially engineered antibodies. The ability to detect the presence of a specific drug varies with different immunoassay tests, depending on the cross-reactivity of the drug with an antibody. For example, a test for opioids may be very sensitive to natural opioids, such as morphine, but may not cross-react with synthetic or semisynthetic opioids, such as oxycodone.

Substances other than the drug to be detected may also cross-react with the antibody and produce a false-positive result. Some over-the-counter (OTC) decongestants (e.g., pseudoephedrine) register a positive drug test result for amphetamine. Phentermine, an anorectic agent, commonly yields a false-positive initial amphetamines test. Dextromethorphan can produce false-positive results for phencyclidine (PCP) in some assays. Cross-reactivity can be beneficial in clinical testing. As an example, a urine test that is specific for morphine will detect only morphine in a patient's urine. The morphine-specific test will miss opioids, such as hydrocodone and hydromorphone. A urine drug test or panel that is reactive to a wide variety of opioids would be a better choice for a clinician when looking for opioid use by a patient. Conversely, the lack of sensitivity to the common semisynthetic opioid, oxycodone, is detrimental to patient care when a clinician is reviewing the results of a "urine drug screen" and sees "opiates negative" when oxycodone abuse is suspected. Thus, cross-reactivity can be a double-edged sword in clinical practice.

To avoid false-positive results caused by cross-reactivity, practitioners should be familiar with the potential for cross-reactivity and ask patients about prescription and OTC medication use.

Drug-testing accuracy continues to improve. For example, newer drug tests may correct for interactions that have been formerly associated with false-positive results. Practitioners can find some of this information in the instructions in the POCT packaging material, or they can talk with laboratory personnel to know exactly what a laboratory's tests will and will not detect.

Drug Test Panels

A *drug test panel* is a list (or menu) of drugs or drug classes that can be tested for in a specimen. These can be ordered to identify drugs of abuse or in pain management. No single drug panel is suitable for all clinical uses; many testing options exist that can be adapted to clinical needs. These panels are designed to monitor adherence to pain treatment plans, to detect use of nonprescribed pain medications, and to screen for use of illicit drugs. Clinical practitioners can order more comprehensive drug test panels to identify drugs or classes of drugs that go beyond the federally mandated drugs for testing. Which drugs are included in the testing menu vary greatly between and within laboratories; laboratories differ in the drugs or metabolites included in their comprehensive panel and have more than one type of panel. Therefore, practitioners should contact their laboratory to determine the capabilities and usual practices of the laboratory. It is just as important for a clinical practitioner to know what a "urine drug screen" will not detect as it is to know what it will detect. Some laboratories have a comprehensive pain management panel for people prescribed opioids for pain (Cone, Caplan, Black, Robert, & Moser, 2008). Panels can be customized for individual practices or patients, but using existing test panels from the laboratory is generally less expensive for patients and less time-consuming for practitioners than ordering tests for many individual substances. However, these panels vary by laboratory and are not standardized. However, it should be noted that laboratories may default to the federally mandated drug tests if a practitioner does not order a different test panel.

Panels are available in various configurations. The more drugs on a panel, the more expensive the test. Substances typically on these panels include, but are not limited to:

- Amphetamine, methamphetamine.
- Barbiturates (amobarbital, butabarbital, butalbital, pentobarbital, phenobarbital, secobarbital).
- Benzodiazepines (alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam).
- Illicit drugs (cocaine, methylenedioxyamphetamine [MDA], methylenedioxymethamphetamine [MDMA], methylenedioxyethylamphetamine [MDEA], marijuana).
- Opiates/opioids (codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, meperedine, methadone, morphine, oxycodone, oxymorphone, propoxyphene).

The practitioner should consult with the laboratory when determining the preferred test panels.

The test menu for POCTs differs per the manufacturer and the device. Most POCTs screen for drugs included in the federally mandated test panel and other drugs or metabolites. Different devices and manufacturers offer various configurations of drugs tested for in devices.

Test Matrix

A *test matrix* is the biological specimen used for testing for the presence of drugs or drug metabolites. Almost any biological specimen can be tested for drugs or metabolites, but the more common matrices include breath (alcohol), blood (plasma, serum), urine, sweat, oral fluid, hair, and meconium. Depending on its biological properties, each matrix can provide different information about a patient's drug use. For example, the ratio of parent drug to metabolite in each matrix can be decidedly different, and each matrix has a different window of detection. Urine is the most widely used test matrix (Watson et al., 2006). Detailed information about test matrices is in Chapter 3.

Point-of-Care Tests

A *POCT* is conducted where the specimen is collected, such as in the practitioner's office. POCTs use well-established immunoassay technologies for drug detection (Watson et al., 2006).

POCTs:

- Reveal results quickly;
- Are relatively inexpensive ($5–$20, depending on the POCT, the drugs or drug metabolites tested for, and the number of tests purchased);
- Are relatively simple to perform; and
- Are usually limited to indicating only positive or negative results (qualitative, not quantitative).

When reading the test results, it is important to know that how quickly the test becomes positive or the depth of the color do not indicate quantitative results.

A comparison of POCTs and laboratory tests is in Chapter 3.

Adulterants

An *adulterant* is a substance patients can add to a specimen to mask the presence of a drug or drug metabolite in the specimen, creating an incorrect result to hide their drug use. Methods to detect adulterants exist, and most laboratories and some POCTs can detect common adulterants. No one adulterant (with the exception of strong acids, bases, oxidizers, and reducing agents) can mask the presence of all drugs. The effectiveness of an adulterant depends on the amount of the adulterant and the concentration of the drug in the specimen. A specimen validity

test can detect many adulterants. Numerous adulterants are available, especially for urine (see Chapter 5).

Specimen Validity Tests

Specimen validity tests determine whether a urine specimen has been diluted, adulterated, or substituted to obtain a negative result. A specimen validity test can compare urine specimen characteristics with acceptable density and composition ranges for human urine, detect many adulterants (e.g., oxidizing compounds), or test for a specific compound (e.g., nitrite, chromium VI) at concentrations indicative of adulteration. Many laboratories perform creatinine and pH analyses of all specimens submitted for drug testing. An adulteration panel can be ordered that determines the characteristics of the urine sample (e.g., creatinine level with reflexive specific gravity when a low creatinine is encountered) and checks for the presence of common adulterants. POCT devices are available that test for specimen validity, as well.

Although validity testing is not required in clinical settings, it is sometimes advisable if the patient denies drug use. For example, a physician treating a patient for an SUD may want to request validity testing if the patient exhibits signs of relapse, but has negative test results. Point-of-care validity tests are available, and some POCT devices also test for validity at the same time they test for the drug analyte.

Additional information on validity follows:

- The pH for normal urine fluctuates throughout the day, but usually ranges between approximately 4.5 and 9.0. Specimens outside this range are usually reported by the laboratory as invalid. Specimen adulteration should be suspected if the pH level is less than 3.0 or greater than 11.0.
- Creatinine is a normal constituent in urine at concentrations greater than or equal to 20 mg/dL. If the creatinine is less than 20 mg/dL, the specimen is tested for specific gravity.
- *Specific gravity* of urine is a measure of the concentration of particles in the urine. Only specimens whose creatinine is less than 20 mg/dL need to be reflexively tested for specific gravity, although specific gravity may be an integral part of a POCT device's specific validity testing panel. Specimens with a low creatinine and an abnormal specific gravity may be reported as dilute, invalid, or substituted, depending on the laboratory's reporting policies (SAMHSA, 2008).

If the laboratory finds the specimen is dilute, it will report the specimen as dilute. However, the laboratory will also report the positive or negative test results. Depending on the degree of dilution, an analyte may still be detected.

Appendix D provides more information on laboratory specimen validity tests.

Chapter 3—Preparing for Drug Testing

In This Chapter

- Deciding Which Drugs To Screen and Test For
- Choosing a Matrix
- Selecting the Initial Testing Site: Laboratory or Point-of-Care
- Preparing a Specimen Collection Site

Deciding Which Drugs To Screen and Test For

When using drug tests to screen a patient for substance use disorders, the practitioner should test for a broad range of drugs. Decisions about which substances to screen for can be based on:

- The patient, including history, physical examination, and laboratory findings;
- The substance suspected of being used;
- The substances used locally (the Substance Abuse and Mental Health Services Administration's [SAMHSA's] Drug Abuse Warning Network compiles prevalence data on drug-related emergency department visits and deaths; information is available at http://www.samhsa.gov/data/DAWN.aspx);
- The substances commonly abused in the practitioners' patient population; and
- Substances that may present high risk for additive or synergistic interactions with prescribed medication (e.g., benzodiazepines, alcohol).

Choosing a Matrix

Practitioners can choose among several matrices for drug and alcohol testing for adults: urine, oral fluid, sweat, blood, hair, and breath (alcohol only). Neonates can be tested using meconium. Urine is the most commonly used matrix for drug testing and has been the most rigorously evaluated (Watson et al., 2006); it is discussed at length in Chapter 5. Exhibit 3-1 provides a brief comparison of the advantages and disadvantages of the seven matrices.

Exhibit 3-1. Advantages and Disadvantages of Different Matrices for Drug Testing

Matrix	Advantages	Disadvantages
Urine	• Available in sufficient quantities • Higher concentrations of parent drugs and/or metabolites than in blood • Availability of point-of-care tests (POCTs) • Well-researched testing techniques	• Short to intermediate window of detection • Easy to adulterate or substitute • May require observed collection • Some individuals experience "shy bladder" syndrome and cannot produce a specimen
Oral Fluid	• Noninvasive specimen collection • Easy to collect • Reduced risk of adulteration • Directly observed specimen collection • Parent drug rather than metabolite can be the target of the assay • Able to detect same-day use, in some cases • Availability of POCTs • Detect residual drug in the mouth	• Limited specimen volume • Possibility of contamination from residual drug in mouth that cannot be correlated with blood concentrations • Short window of detection • Requires supervision of patient for 10–30 minutes before sampling • Salivation reduced by stimulant use • Need for elution solvent to efficiently remove drugs adsorbed to collection device • Cannabinoids in oral fluid have been shown to arise from contamination of the oral cavity rather than excretion in saliva from blood
Sweat	• Detects recent use (fewer than 24 hours with a sweat swipe) or allows for cumulative testing with the sweat patch (worn for up to 7–14 days) • Noninvasive specimen collection • Difficult to adulterate • Requires little training to collect specimen • May be an economical alternative to urine	• Few facilities and limited expertise for testing • Risk of accidental or deliberate removal of the sweat patch collection device • Unknown effects of variable sweat excretion among individuals • Only a single sweat collection patch available so multiple analyses cannot be done if needed (i.e., more than one positive initial test) • May be affected by external contaminants • Requires two visits, one for patch placement and one for patch removal
Blood	• Generally detects recent use • Established laboratory test method	• Expensive, except to detect ethanol • Limited window of detection • Invasive specimen collection (venipuncture) • Risk of infection • Requires training to collect specimen • May not be an option for individual with poor venous access

Exhibit 3-1. Advantages and Disadvantages of Different Matrices for Drug Testing, continued

Matrix	Advantages	Disadvantages
Hair	• Longest window of detection • May be able to detect changes in drug use over time (from 7–10 days after drug use to 3 months, depending on length of hair tested) • Directly observed specimen collection • Noninvasive specimen collection • Four tests will cover 1 year • Easy storage and transport • Difficult to adulterate or substitute • Readily available sample, depending on length of hair tested	• Cannot detect use within the previous 7–10 days • Difficult to interpret results • Costly and time consuming to prepare specimen for testing • Few laboratories available to perform testing • No POCTs currently available • Difficult to detect low-level use (e.g., single-use episode) • May be biased with hair color (dark hair contains more of some basic drugs [cocaine, methamphetamine, opioids] due to enhanced binding to melanin in hair) • Possibility of environmental contamination • Specimen can be removed by shaving
Breath	• Well-established method for alcohol testing • Readily available	• Used only for alcohol and other volatiles • Short window of detection • May be difficult to obtain adequate sample, especially with patients who are very intoxicated or uncooperative • Uncommon in clinical setting
Meconium	• Can detect maternal drug abuse and fetal or infant exposure • Wide window of drug detection (third trimester of gestation) • Noninvasive collection from diaper • Generally, adequate specimen amount	• Narrow collection window that can be missed, especially in babies with low birth weight • Testing not available in all laboratories • Requires extra steps (weighing and extraction) • Confirmation assays more difficult than for urine

Sources: Center for Substance Abuse Treatment (2006a); Dolan, Rouen, & Kimber (2004); Kwong & Ryan (1997); Warner (2003).

Once ingested, drugs of abuse are rapidly distributed via the blood to all parts of the body. Abused drugs are generally lipid soluble and are mainly metabolized by the liver to more water-soluble metabolites. These metabolites are removed from blood by the kidneys and excreted in urine. Because many drugs are cleared from the blood rapidly, testing of blood or its components (serum) has short periods of detection, as does breath for testing for alcohol consumption and oral fluids because the drug passes quickly into, and is eliminated from, breath and oral fluids. Depending on the drug itself and previously listed factors that affect metabolism, urine usually has a window of detection that is slightly longer than oral fluid. Urine detection times vary from less than 1 day after ingestion to several weeks. Hair has a longer window of detection, but is best suited for detection of heavy drug use. The cells that generate hair absorb the metabolites that are circulating in the blood at the time the hair is produced; therefore, hair has the longest window of detection, depending on the length of the hair. It is notable that drugs may be incorporated into hair from external sources, such as mechanical contact between the hair and the drug. In utero drug exposure also can be monitored with maternal and neonatal urine and/or hair testing.

Specimen Availability

Some specimens are more easily collected than others. Collection of blood samples requires trained personnel to perform venipuncture and is more invasive than collection of urine, oral fluid, or hair specimens. Collections of oral fluid and hair are less intrusive than urine collection.

Oral Fluid

During the past decade, the use of oral fluid for drug testing has been validated by a large body of scientific literature (Bosker & Huestis, 2009; Cone & Huestis, 2007). The parent drug is usually found in oral fluids, although the metabolite(s) may be present and quite useful. The parent drug is generally found in higher concentrations in oral fluids than are drug metabolites. Compared with urine specimens, oral fluid specimens present fewer opportunities for adulteration or substitution (Dams, Choo, Lambert, Jones, & Huestis, 2007). Use of commercial adulterants or mouthwashes were not found to interfere with the immunoassay (Bosker & Huestis, 2009), or they did not affect test results if the products are used more than 30 minutes before specimen collection (Drummer, 2006; Niedbala, Kardos, & Fries, et al., 2001; Niedbala, Kardos, Fritch, Cannon & Davis, 2001). The window of detection for oral fluid is narrower than it is for urine, and drug concentrations are generally lower (Warner, 2003). In general, drug testing of oral fluids detects drug use during the previous 24–48 hours, regardless of the route of administration (Cone, 2006), although the selection of cutoffs plays an important role in the length of the detection window.

Oral fluid collection devices vary, but the most common version is a swab or absorbent pad on a stick that is placed between the lower cheek and gums to collect fluid and is left in place for a few minutes. It is then inserted into a vial containing a buffer solution for shipment to the laboratory. POCTs are also available for oral fluid testing.

On occasion, dry mouth syndrome can slow oral fluid collection, often requiring several minutes to collect an adequate sample (Drummer, 2006). Some medications and illegal drugs cause a dry mouth, and some oral fluid collection devices assist collection by stimulating oral fluid flow. Patients should not eat immediately before testing because some food tends to inhibit oral fluid production. If blood is present in the patient's oral fluid, collection of an alternative specimen, such as blood or urine, would be needed. Oral fluid limits the number of repeat or confirmatory tests on the specimen because of the small amount of the sample, compared with a urine sample.

Sweat

Several collection devices have been manufactured for collecting sweat specimens. The two most common are the patch and the swipe; however, the sweat patch is the only device approved by the U.S. Food and Drug Administration (FDA). The quantity of sweat collected is determined by the length of time the patch is worn and the physiology of the person wearing the patch. The patch should be worn for at least 3 days, but no longer than 7 days, although most drugs will have been excreted within the first 48 hours (Barnes et al., 2009; Huestis et al., 2008; Kacinko et al., 2005; Schwilke et al., 2006). This ensures that a sufficient amount of sweat is collected for testing. The sweat collected with the patch detects drug use that occurred shortly before the patch was applied and while the device remains on the skin.

The skin should be thoroughly cleaned with soap and water and then swabbed well with alcohol. The patch should then be applied to the skin by a staff member, not the patient (Watson et al., 2006). After 7 days, the patch is removed by the practitioner and sent to the laboratory for analysis.

Mainly the parent drug is found in sweat; however, some drug metabolites also may be detected (Dasgupta, 2008). Drugs and drug metabolites that have been detected

in sweat include tetrahydrocannabinol (THC), amphetamine, methamphetamine, methylenedioxymethamphetamine (MDMA, or "Ecstasy"), codeine, morphine, heroin metabolite, phencyclidine (PCP), and cocaine and its metabolites (e.g., benzoylecgonine, ecgonine methyl ester) (Barnes et al., 2009; Dasgupta, 2008).

Because sweat can be collected only in limited quantities, there may not be sufficient specimen for repeat or confirmatory testing. Sweat is less susceptible to tampering or adulteration than is urine. The accuracy of sweat testing is not standardized. Its accuracy remains somewhat controversial (Chawarski, Fiellin, O'Connor, Bernard, & Schottenfeld, 2007; Watson et al., 2006) and more research is needed (Barnes et al., 2009; Huestis et al., 2008; Kacinko et al., 2005; Schwilke et al., 2006). However, the sweat patch is used extensively in the criminal justice system, and its use to identify relapse or violations of conditions of probation has been upheld by the courts.

Blood

Blood testing detects alcohol or drug use starting shortly after use, depending on the substance and the route of administration. In general, blood has a shorter detection period than urine (Warner, 2003). Blood collection is more invasive than other procedures and requires trained personnel to collect the specimen and perform laboratory testing. For people who inject drugs, or those with poor venous access, drawing blood may be difficult.

Hair

In theory, the presence of drugs in hair is based on a simple principle: Drugs or their metabolites circulate in a person's bloodstream, and the hair follicles absorb the drug and/or metabolites from the bloodstream and from secretions of the sebaceous and sweat glands in the scalp (Cone, 1996; Musshoff & Madea, 2006). Trace amounts of drug become entrapped in the core of the hair as it grows, at a rate of approximately 1 cm per month (Dolan et al., 2004). Drug metabolites can be detected in the hair shaft approximately 7–10 days after drug ingestion. Hair is unique in that it may provide retrospective information on drug use, versus the point-of-time information provided by urine, blood, and breath. (Kintz, Villain, & Ludes, 2004). In some cases, drugs were found to move down the hair shaft via sweat (Henderson, Harkey, Zhou, Jones, & Jacob, 1996), which would disrupt the use of hair testing's ability to determine the historical use. Another unfortunate aspect of interpreting hair test results of drugs and their metabolites is that drugs may be incorporated into hair by simple environmental drug exposure (Ropero-Miller & Stout, 2008; Wang & Cone, 1995).

The hair sample is usually taken from the back of the head, cut with scissors as close to the skin as possible (Wong & Tse, 2005). Hair can be collected from other parts of the body (e.g., face, armpit) of patients who are bald or have shaved heads.

Hair testing appears to be most reliable for detecting prior frequent, heavy use of cocaine, opioids, amphetamine, PCP, and Ecstasy, but is not suited for detection of very recent use, or occasional drug use. Musshoff and Madea (2006) report that hair tests can detect the presence of the THC metabolite, tetrahydrocannabinol carboxylic acid. Hair analysis can often distinguish between heroin and morphine use—a distinction that is sometimes difficult to make with blood or urine analysis (Dolan et al., 2004) because of the short half-life of heroin metabolite in these matrices. Hair testing for alcohol is inappropriate; alcohol does not incorporate into hair. However, the minor metabolites of ethanol, ethyl glucuronide, and ethyl sulfate in hair show promise as markers of alcohol use (Wurst, Skipper, & Weinmann, 2003).

Hair testing is suited to:

- Detecting chronic drug use (Dolan et al., 2004; Warner, 2003);
- Providing a view of the patient's long-term substance use pattern; and
- Indicating periods of abstinence (Pragst & Balikova, 2006).

An advantage of drug testing with hair is the longer window of detection compared with other matrices (Boumba, Ziavrou, & Vougiouklakis, 2006). The detection period for hair is limited only by the length of the hair sample and the degree of deposition in the hair. Cannabinoids have been shown to deposit less readily than basic drugs in hair (Huestis et al., 2007). Some laboratories typically restrict analysis to a hair segment representing about 3 months of growth. However, this long window period is also a disadvantage; hair testing is not useful in substance abuse treatment or monitoring opioid pain or other addictive medications when frequent (weekly or monthly) drug testing is desired. Because the timing of the drug use is difficult to determine by testing hair, it is not very useful clinically.

Disadvantages for testing for drugs in hair are the high costs and the longer time needed to obtain results, compared with the time required by other matrices. Analysis of the hair specimen is a complex process that involves breaking down the hair to free the drugs trapped in it. This chemical process requires a longer time of analyses than other matrixes. It can be done only in a laboratory; no POCTs are available for testing hair samples.

Some questions remain about environmental contamination; a person may claim that the drug is present in the hair because the individual was in a room where others were smoking drugs. Therefore, in preparation for analysis at the laboratory, the hair sample is washed, which may remove the contamination. Unfortunately, this environmental contamination cannot always be differentiated from actual drug use, even if drug metabolites are measured quantitatively in hair (Ropero-Miller & Stout, 2008).

Additional controversies exist about whether biophysical attributes affect hair analysis. Studies have shown that concentrations of drugs in hair can be affected by variations in hair structure, growth rate, melanin content, hygiene, and cosmetic hair treatments, such as bleaching (Dasgupta, 2008). Although there have been a limited number of human clinical controlled studies, data show that higher concentrations of some drugs (e.g., codeine, cocaine, amphetamine) are found in dark hair compared with concentrations found in blond or red hair (SAMHSA, 2004). Cone and Joseph (1996) reviewed several articles and found that hair testing may be biased toward some hair types. Drugs of abuse bind more readily to Africoid and Mongoloid types of hair compared with Caucasoid hair. Cosmetic hair treatments also affect the binding of drugs to hair. For example, bleaching of the hair can reduce drug content, but it also can damage the hair to the extent that bleaching may increase binding of the drug to the hair (Skopp, Pötsch, & Moeller, 1997). Some drugs (i.e., THC) do not differentially distribute into hair based on melanin content (Smeal, 2007). Therefore, hair testing may not be the most equitable drug testing matrix. Hair rinses, bleaches, and shampoos that claim to interfere with drug tests are advertised on the Internet and in magazines.

Breath

Several simple-to-use, but accurate, breath-testing devices are available for detecting very recent alcohol use. Breath also may be employed for the identification and quantitation of a variety of other volatiles, especially in industrial hygiene situations. However, breath testing is commonly used in alcohol treatment programs, but not in primary care.

The body metabolizes alcohol rapidly, but alcohol will be detectable in breath as long as it is present in blood. The detection period for ethyl alcohol itself is hours (not days) after the last alcohol use. The metabolism of alcohol varies considerably by the person's gender, age, physical condition (especially the condition of the liver), and weight.

Easily administered breath alcohol tests are available to confirm alcohol ingestion within the past several hours. When a breath alcohol analyzer test is conducted properly, it gives an accurate measurement of breath alcohol content (BrAC). The BrAC gives an estimate of blood alcohol level (BAL) (Watson et al., 2006). Body temperature and breathing patterns can affect breath alcohol test results. Compared with blood and urine tests, breath tests are less precise. Some evidence suggests that breath tests may underestimate BALs by approximately 8.5 percent (Garriott, 2008).

The breath alcohol analyzer (such as the best-known version, Breathalyzer) is a device that gives an accurate BrAC. The benefits of breath alcohol analyzers are that they:

- Are simple to use;
- Are inexpensive;
- Give instant results; and
- Are noninvasive.

The National Highway Traffic Safety Administration provides a list of breath alcohol analyzer devices that have been tested for accuracy and reliability. The list is available through http://www.dot.gov/odapc.

Meconium

Meconium is the first few bowel movements of a neonate. Research shows that meconium provides a record of neonate exposure and maternal substance use in the third trimester of gestation (Concheiro et al., 2010; Gray & Huestis, 2007; Kacinko, Jones, Johnson, Choo, & Huestis, 2008). Meconium offers a wide window of drug detection, monitoring drug use primarily over the third trimester of gestation. Because collection of meconium is noninvasive (requiring only the transfer of the specimen or meconium from diaper to specimen container), it is usually easier to collect than urine. Collection of a specimen must be made before the neonate passes the first formed stool; for full-term babies, this generally occurs within 3 days (Gareri, Klein, & Koren, 2006).

However, this is a highly subspecialized area that may be used in connection with a maternal urine drug test. The testing of meconium should be recognized as having potential medicolegal ramifications (i.e., a positive test may result in the State removing the newborn from the new mother's custody).

Potential disadvantages to using meconium exist. Test results vary greatly by substances used and cutoff concentrations because of the unique qualities of meconium. Moreover, laboratory methods of preparing the specimen can affect the test results greatly (Gray & Huestis, 2007). Urine contamination may skew results (Gray et al., 2010).

Selecting the Initial Testing Site: Laboratory or Point-of-Care

Many factors should be considered when deciding to test onsite with a POCT for the initial test or offsite by a laboratory. Exhibit 3-2 compares POCTs and laboratory tests. The sections below explain each method.

Collection Devices

The collection device must be single use. It will normally be individually packaged with collection aids and a tamper-evident security seal. The collection device must not alter or affect the specimen. The device should have the following features for each specimen matrix:

- **Blood**. Sterile tubes that usually contain sodium fluoride to inhibit breakdown of drugs. The use of "gel" or "serum separator

Exhibit 3-2. Comparison of Laboratory Tests and POCTs

Criterion	Laboratory Test	POCT
Time to Results	Initial test can be available within hours, but the confirmatory test takes days	Minutes
Ease of Use	Requires complex equipment	Relatively simple to use
Training	Requires trained technicians or technologists	Minimal training required
Breadth of Tests	Wide range of test menus	Limited test menu
Interpretation	Objective quantitative results; variations in laboratory cutoff concentrations may influence interpretation	Subjective results; requires interpretation, not quantitative

Sources: Melanson (2005); Watson et al. (2006).

tubes" for specimen collection for any type of drug analysis is highly discouraged.

- **Hair**. Foil or a plastic bag to store the sample with an indication of proximal and distal ends.
- **Oral fluid**. Device that allows accurate determination of the volume collected (usually 1.0±0.1 mL) and that contains an elution solvent to efficiently elute the adsorbed drugs.
- **Sweat**. A patch, placed on the skin, typically composed of an adhesive layer, release liner, and sweat-collection pad.
- **Urine**. A plastic collection container typically with a temperature strip outside the container to determine specimen temperature.

Shipping materials, documentation, and order forms will be needed if the specimen is to be sent to a laboratory.

Laboratory Tests

Laboratories perform screening, confirmatory, and validity tests, using instrumented devices that are operated by trained technical personnel. Laboratory testing is more accurate than POCT and provides quantitative information on what drugs and/or metabolites were detected. Laboratories use high-volume immunoassay tests to separate negative specimens from those that require confirmation testing. Confirmation tests use either liquid chromatography (LC) or gas chromatography (GC) in combination with mass spectrometry (MS) for detection and measurement of drugs and metabolites. Tandem mass spectrometry (MS/MS) is a more sensitive form of MS. These tests provide a laboratory with the ability to identify and measure drugs and/or metabolites in biological fluids at low concentrations. Technical details about these tests and their strengths and limitations are in Appendixes B–D.

Most laboratories usually perform initial drug tests for commonly abused drugs, including 6-acetylmorphine (heroin metabolite), opioids, cocaine, amphetamines, barbiturates, PCP, and THC. Some laboratories offer extended opioid panels; these laboratory tests can detect and confirm several opioids including morphine, codeine, hydrocodone, hydromorphone, oxycodone, and oxymorphone. Some laboratories offer, upon request, panels that will differentiate individual benzodiazepines and their metabolites. Other extended panels include buprenorphine, carisoprodol, methadone, fentanyl, meperidine, and propoxyphene, among others. Not all laboratories are capable of identifying all known benzodiazepines and, where necessary or appropriate, their metabolites. The requirement for additional testing depends in large part on the patient population

served by the facilities using the laboratory (e.g., a methadone clinic or a detoxification facility might require methadone, EDDP [methadone metabolite], burprenorphine/norbuprenorphine, and/or other drug or metabolite analyses). POCTs or laboratory-based tests may be used for the initial testing, but only laboratories can perform confirmatory testing.

Advantages and Disadvantages of Testing in a Laboratory

Advantages. Laboratory tests have several important advantages over POCTs. Laboratory tests:

- Generally have a higher degree of precision.
- May offer quantitation of drugs and/or metabolites and a reasonable estimate of the timeframe in which the drug was used.
- Can provide information on specific drugs used.
- Can be directly sent for confirmatory GC/MS on the same sample.
- Are performed by trained laboratory professionals.

Disadvantages. The disadvantage of laboratory-based tests is turnaround time. The time required for laboratory-based testing may include transportation of the specimen to the laboratory, specimen aliquot preparation, and instrument analysis time—steps that are not required for POCTs. Results from POCT can be available while the patient is still in the office, so the practitioner can immediately discuss them with the patient. Depending on the laboratory, clinical screening results may be available in less than 1 hour after receipt or the next day, unless further testing, such as confirmation or reflexive testing, is required.

Considerations for Selecting a Laboratory

Before selecting a laboratory, practitioners should contact the laboratory and speak directly to the director or toxicologist to (White & Black, 2007):

- Determine the laboratory's analytic capabilities (laboratories may use the Federal Five as the testing menu for drug screens, which may or may not include the clinical drugs of interest);
- Inquire about other panels that test for drugs and drug classes of clinical interest;
- Confirm that the laboratory follows established Federal and State regulations (Exhibit 3-3);
- Determine whether the laboratory's testing procedures are appropriate for clinical use; and
- Ensure that the laboratory provides technical assistance so the practitioner can obtain help with interpreting test results or determining which panel to order.

Exhibit 3-3. Federal and State Regulations

- The Clinical Laboratory Improvement Amendments (CLIA) of 1967 and of 1988 set forth conditions that all laboratories must meet to be certified to perform testing on biological specimens (http://www.cms.gov).
- The U.S. Department of Health and Human Services (HHS) Mandatory Guidelines for Federal Workplace Drug Testing Programs specify the requirements for a laboratory to be certified by the HHS National Laboratory Certification Program. Information is available at http://workplace.samhsa.gov/Dtesting.html
- Private and professional organizations (e.g., College of American Pathologists) have established voluntary laboratory accreditation programs. The American Association of Bioanalysts has private personnel standards.
- State clinical laboratory programs operate under individual State laws; State programs are usually authorized through the Centers for Medicare & Medicaid Services.

Practitioners need to talk to laboratory personnel about:

- Appropriate in-office specimen collection, handling, and storage procedures for each matrix used;
- Each test ordered, at least until the practitioner is thoroughly familiar with the tests and drug panels the laboratory offers (practitioners need to be sure they know exactly what they are ordering and the limitations of any particular test);
- Test results (practitioners should contact the laboratory about unexpected results, whether positive or negative); and
- Referral testing for drugs not offered by the primary testing clinical laboratory.

Point-of-Care Tests

Several different types of POCTs are available. Generally, POCTs:

- Use well-established immunoassay technologies for drug detection;
- Determine the presence of parent drugs or their metabolites;
- Sometimes can determine the validity of a specimen, which is to be highly recommended as an integral part of the testing process;
- Identify drug classes (e.g., opioids, benzodiazepines, barbiturates), single drugs, or metabolites (e.g., benzoylecgonine, a cocaine metabolite); and
- Require a few drops of a specimen.

FDA has approved POCT devices for urine, breath, and oral fluid testing, but devices for urine drug testing are most widely used. Advances are being made in developing POCTs for other matrices, and these may be available in the future.

Various POCTs are available:

- Breath-testing devices, which are rare in primary care practice (the patient blows into the device)
- Cards or cassettes (drops of urine are placed on a card or in wells on a cassette)
- Dipsticks (an absorbent strip is dipped into the specimen)
- Combination collection/test cups (the testing strip is integrated into the collection cup, and results can be read on the outside of the cup)

A few devices double as both collection and testing devices. After the specimen is collected, the tester initiates the test, carefully times the test, and interprets and records the results. The test component of noninstrumented POCTs is an absorbent strip with an antibody-dye complex. The test is done by inserting the absorbent strip, card, or cassette into the specimen or adding the specimen to the testing device. When the strip or cassette comes into contact with the specimen, it reacts to the drug or drug class that the POCT can detect. Generally, a line or dot appears in the zone labeled for a specific drug if the drug is not present (negative test result); no line or dot appears when a specific drug is present (positive test result). A photocopy of the portion of the POCT device that is read can be made and placed in the patient's chart. Enough fluid (urine or oral fluid) should be retained for any reflexive or confirmatory testing that may be required.

It is critical that practitioners read package inserts carefully to know how to perform the test and read the results. Positive POCT results should usually be followed by a laboratory confirmatory test if the patient denies drug use when confronted with the positive results. A confirmatory test must be done if legal or employment ramifications for the patient will result.

Advantages and Disadvantages of POCTs

The principal advantage of POCTs is that the results are available in approximately 10 minutes. This fast turnaround allows practitioners to discuss the results with the patient during that office visit and make clinical decisions and act appropriately that day. This early intervention may prevent other health problems, hospitalization, or treatment episodes. It is also in keeping with behavioral principles: the immediacy of the intervention in relation to a behavior makes reinforcement more useful. Several manufacturers have developed drug-of-abuse assays for POCT that offer similar, but not exact, sensitivity and specificity to the methodologies used by central laboratories (Melanson, 2009). A variety of testing panels with different cutoff concentrations is available for these testing devices, but they are not as varied as laboratory testing. Increasingly, vendors are offering point-of-care devices that test for a wider range of drugs and with more sensitivity and specificity. POCTs are available to test for amphetamine, methamphetamine, barbiturates, benzodiazepines, cocaine, methadone, opioids, PCP, propoxyphene, Ecstasy, oxycodone, tricyclic antidepressants, buprenorphine, and THC acid metabolite (Melanson, 2005).

A survey of five POCT immunoassay devices for urine testing found that each had a false-negative rate for opioids of less that 1 percent and a false-positive rate less than 0.25 percent for testing for pain management (Crouch, Hersch, Cook, Frank, & Walsh, 2002). Melanson's (2009) review of the literature reviewed studies looking at the analytical performance (sensitivity, specificity, precision, and accuracy) of POCTs for drugs of abuse. Generally, most studies suggested that POCTs are a reliable method to screen for drugs of abuse and that the results are comparable to those from automated immunoassays and GC/MS. However, Melanson (2009) also noted that some studies found inconsistencies, such as:

- Several devices were found to have discrepancies between the claims of the manufacturer and the devices' product performance.
- Some devices deviated from their stated cutoffs showing positive results below the cutoff or negative results above the cutoffs.

However, no POCT device yields perfect agreement with more sophisticated testing, such as GC/MS or high-performance liquid chromatography (Watson et al., 2006). Disagreement between methods was highest for samples near the cutoffs.

Cross-reactivity differs among POCT devices because of differing antibody specificity. The manufacturer provides a list of compounds tested and their degree of cross-reactivity, including those medications outside the drug class, which may cause false-positive results (Melanson, 2009).

George and Braithwaite (2002) caution that the apparent benefit of POCTs—rapid assessment of a patient's drug use—can be detrimental if treatment decisions are based on these rapid, but unconfirmed, results. A disadvantage of noninstrumented POCTs is that most test only for drug classes, not for specific drugs within a class (Gourlay, Caplan, & Heit, 2010), which is what is needed more often in clinical applications. Many POCTs have a limited test menu, compared with laboratory testing and in clinical settings; practitioners may need a more complete panel, or separate tests, to assess for specific drugs. POCT devices do not provide quantitative drug or metabolite information. POCT devices provide presumptive results only; a sample needs to be sent for confirmatory testing at a laboratory. Cutoffs employed by some POCT devices may not provide adequate sensitivity. Result interpretation may also be subjective, making performance operator-dependent (Melanson, 2009).

Considerations for Selecting POCT Devices

Matrices. POCT devices should be FDA approved and usually CLIA-waived to test urine, breath (for alcohol), and oral fluid for substances of abuse. None are available yet for hair, sweat, or blood for drugs of abuse, although some POCT devices do exist for therapeutic drugs in blood or blood products. POCTs for urine remain the most commonly used, despite advances in testing of other matrices. Cutoff levels, cross-reactivity, and other possible interferences have been studied more for POCT urinalysis than for any other matrix (Watson et al., 2006). Most POCT devices are used in an environment that is external to a clinical laboratory.

Regulatory Issues. The use of POCTs is covered by two Federal regulations. The Medical Devices Act requires that all in vitro medical diagnostic devices be evaluated and cleared for use by FDA for commercial distribution before use with patients. CLIA regulates the use of POCTs and requires that medical diagnostic tests and devices be used only in laboratories that meet CLIA standards and are certified to perform those specific tests. However, tests may be waived from CLIA regulatory oversight if they meet certain requirements, primarily if they are simple to use and interpret and have a low error risk.

Practitioners should be aware of the following specific requirements when considering using a POCT device:

- **FDA approval**. FDA has cleared several point-of-care devices for testing drugs of abuse. The FDA Center for Devices and Radiological Health provides information on test categorization and approval or clearance of testing devices (http://www.fda.gov/MedicalDevices/default.htm).
- **Waived tests.** A testing device may have been cleared by FDA for commercial distribution, but may not have been CLIA waived. FDA maintains a list of currently waived tests (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/testswaived.cfm). POCT manufacturers will also state whether a test is waived by CLIA.
- **Certificate of waiver**. All sites performing waived tests must have a CLIA-waiver certificate and adhere to the manufacturer's instructions for performing the test. Facilities or physicians' offices performing waived tests must enroll in CLIA, pay the applicable fee, and follow the manufacturer's instructions. An explanation of the procedures to obtain a CLIA certificate is available at https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/downloads/HowObtainCertificateofWaiver.pdf.
- **State regulatory issues**. Many States have their own regulations regarding POCTs that practitioners or their designees must learn before they start to test.

Cost. The information on the economics of POCT for drugs and ethanol is limited, although cost issues should be important in deciding to initiate a point-of-care drug-testing program. The fixed unit price of POCTs often exceeds those of laboratory-based test methods. However, the cost of devices also depends in large part on the number of drugs included in the test panel, the difficulty in identifying the substances included in the panel, the number of devices ordered, and the volume of testing. Costs may vary according to location. In general, as the demand for POCTs grows, the cost per device decreases. In addition, the extra staff time and space to perform the test, staff training, quality assurance procedures, and documentation need to be taken into account when considering the cost. Then again, staff already collect specimens and perform POCTs to test for other conditions in many physician practices. These costs should be carefully reviewed prior to initiating POCT for drug testing.

Other Considerations. Practitioners should research the point-of-care devices being considered for use in terms of (Melanson, 2005):

- **Analytic performance**. Seemingly minor differences in sensitivity, specificity, and accuracy among the available POCT devices may or may not be clinically important and must be evaluated.
- **Cross-reactivity**. Some devices may not be able to distinguish between the substance being tested for and other chemically similar substances.
- **Validation studies**. Lot-specific evaluation information is usually summarized in package inserts, with more extensive verification documentation available on request. A POCT manufacturer may have additional credentials documenting that the testing device and the manufacturing processes meet quality control and quality assurance standards (e.g., certification by the International Organization for Standardization).
- **Ease of use**. Most POCT devices can be operated by an individual with little laboratory experience. However, some devices may entail following fairly complex instructions for use, which can contribute to human errors that will affect test results. Even test operators with technical or scientific backgrounds can make errors using these devices because of lack of training or unfamiliarity with new devices.
- **Ease of reading and interpreting the results**. Most devices require visual interpretation of a color response. Clear, distinguishable results are necessary for accurate interpretation. It is also necessary to know which substances will cross-react and produce a false-positive result (e.g., pseudoephedrine giving an "amphetamines" positive) or a false negative result (e.g., oxycodone and its active metabolite oxymorphone, both of which are opiates, giving a negative opiates result when either or both are present in the patient's specimen).
- **Quality assurance and control procedures**. Devices differ in the amount of time needed for staff to learn quality control procedures, such as completing documentation to ensure adherence to the manufacturer's instructions for maintenance (if any) and assay of the appropriate control specimens at the required intervals. Maintenance and quality control procedures also must meet CLIA, State, and local regulations. Positive and negative quality control samples must be included to verify accurate testing, but the frequency of analysis of quality control is dependent upon State regulations or regulatory agency.
- **Laboratory testing for verification**. It is suggested that a percentage (i.e., 5 percent) of specimens that screen negative or positive be sent to a laboratory to verify accurate performance of POCT results, and that all positive results that are contested by patients be submitted to a laboratory for confirmation testing.

Implementing Point-of-Care Testing

Based on surveys of sites holding CLIA waivers, Howerton, Anderson, Bosse, Granade, and Westbrook (2005) suggest that practitioners consider the following questions when deciding whether to use any type of POCT device:

- Who will manage and be accountable for testing oversight? Can this person receive the appropriate training?
- Are there sufficient personnel to conduct testing?
- How will testing affect workflow?
- How will staff be trained to conduct a POCT?
- Can the site adequately comply with Federal, State, and local regulations regarding the POCT?
- What are the safety considerations for both personnel and patients?

- Can personnel reasonably follow quality control procedures?
- Does the site meet physical requirements for testing (e.g., space for collection, testing, storage, security)?
- What are the benefits and costs of POCTs to the practitioner?
- How will testing records be maintained? What written documentation is needed?
- What are the plans for quality control testing and quality assurance?

Preparing Clinical and Office Staffs for Testing

Once a practitioner has decided which matrices and types of tests to use, the clinical and office staffs need to be prepared to begin testing. Preparation may include:

- Obtaining a CLIA waiver;
- Developing written policies and procedures for testing, including ongoing staff training, and establishing quality control procedures;
- Developing and implementing testing protocols, including guidelines for specimen collection, use of POCT, confirmatory testing, and laboratory technical assistance;
- Establishing confidentiality safeguards;
- Training staff in use of the selected POCT devices and in collecting specimens for laboratory testing;
- Establishing recordkeeping procedures;
- Preparing appropriate storage sites for completed POCTs and laboratory tests; and
- Arranging pickup or transportation for laboratory tests.

Preparing a Specimen Collection Site

The collection site is a designated area where a patient provides the specimen for a drug test. Collection of most specimen matrices does not require special arrangements. Urine collection in primary care settings needs to be configured for privacy while a patient provides a specimen if direct observations are not required. Water for drinking needs to be available in the event the patient cannot provide sufficient urine (shy bladder). In substance abuse treatment and workplace testing, measures need to be taken to prevent adulteration or substitution, such as putting a bluing agent in the toilet, not providing access to soap and water in the collection room, and directly observing specimen provision. These actions are needed in clinical situations only if adulteration or substitution is suspected. Once specimens are collected and labeled, there must be space and proper conditions for securely and appropriately storing them. A refrigerator is a convenient, appropriate storage place, especially when samples are picked up by a laboratory courier on a daily or less frequent basis.

Chapter 4—Drug Testing in Primary Care

In This Chapter

- Uses of Drug Testing in Primary Care
- Talking With Patients About Drug Testing
- Cultural Competency and Diversity
- Monitoring Patients
- Ensuring Confidentiality and 42 CFR Part 2
- Preparing for Implementing Drug Testing
- Interpreting Drug Test Results
- Frequency of Testing
- Documentation and Reimbursement

Uses of Drug Testing in Primary Care

Primary care providers order a wide array of laboratory tests as part of routine physicals and to determine the cause of symptoms, adjust medication dosages, monitor treatment effectiveness, and diagnose. Drug tests can be ordered and used for these same reasons.

Discussing substance use with patients can be time-consuming and may upset some patients. However, if a drug test is indicated, talking with patients before, after, and even if drug testing is refused can yield information that may improve many aspects of primary care. Some examples of when the use of drug testing or discussing substance use could improve patient care include:

- Evaluating unexplained symptoms or unexpected responses to treatment and identifying substance use that has contributed to, caused, or is complicating the patient's treatment;
- Evaluating patients in psychiatric care for substance abuse issues, or before prescribing psychoactive medications;
- Identifying potential substance use problems in women who are pregnant, or planning on becoming pregnant, and identifying at-risk neonates;
- Identifying patients with possible substance abuse issues;
- Monitoring patients in substance abuse treatment: to assess the efficacy of the treatment plan and the level of care, to monitor abstinence before administering medications to treat substance use disorders (SUDs), and to help identify a relapse to substance use;
- Ensuring patient safety prior to surgery or other invasive procedures to prevent medication interactions;
- Managing patients prescribed opioids for chronic pain control; and
- Monitoring potentially addictive prescription use (e.g., sedatives, tranquilizers, medications to treat attention-deficit/hyperactivity disorder [ADHD]).

Monitoring Prescription Medication Use

Drug testing is useful for monitoring patient treatment compliance with prescribed medications that have addictive properties (e.g., opioid pain medication, sedatives, ADHD medication). Test results can reveal whether patients have recently taken their prescribed medication and if non-prescribed or illicit drugs have been used. Drug testing can help practitioners identify and reduce diversion of scheduled drugs by patients.

Management of Chronic Pain With Opioids

Primary care practitioners often provide medical management for patients taking opioids for chronic pain. Long-term pain treatment with opioids requires monitoring for continuing effectiveness for pain relief and the potential for misuse, addiction, or diversion. Current clinical guidelines recommend the use of drug tests for pain management with opioids to help guide decisions about prescribing scheduled medications, revising treatment regimens, and when to initiate or refer for substance abuse treatment (Chou et al., 2009; Fishman, 2007).

Gourlay, Caplan, and Heit (2010) suggest that drug testing may be useful for:

- New patients as part of regular care to indentify the use of illicit or nonprescribed drugs;
- Patients being prescribed a controlled substance;
- Patients who present with a condition that warrants a prescription for a controlled substance and who resist a full evaluation or who request a specific medication with addictive potential;
- Patients with aberrant behavior (e.g., patients who consistently want appointments toward the end of office hours, arrive after office hours, insist on being seen immediately, repeatedly report losing prescriptions or medications, are reluctant to change medication, do not adhere to the treatment plan);
- Patients who are suspected of diversion;
- Patients who need advocacy to verify their abstinence;
- Patients in recovery from SUDs; and
- Patients who need a change in their treatment.

Katz and colleagues (2003) conducted a 3-year study on behavioral monitoring and urine drug testing in patients receiving long-term opioid therapy for pain. Their findings suggest that random drug testing of all patients receiving opioids for pain may be warranted. The researchers found that urine drug testing was much more effective than behavioral monitoring alone in identifying patients who were taking drugs other than the prescribed opioid. For example, 72 percent of patients with a positive test result did not have any behavioral indicators considered useful for screening.

Evaluation of Unexplained Symptoms or Unexpected Responses to Treatment

The results of drug tests can clarify situations in which substance use contributes to, causes, or complicates diagnosis or treatment, but the substance use is not apparent to the clinician. Patients may not disclose:

- All the medications prescribed by other providers or over-the-counter (OTC) medications and herbal products;
- That they take medications prescribed for other people;
- Use of illicit drugs or how much alcohol they consume; or
- If they have stopped taking their medications.

Following are some clinical examples of when or where drug testing might explain the cause of symptoms or unexpected response to treatment:

- A man whose hypertension remains uncontrolled, despite adhering to a low-salt diet and several antihypertensive medication changes, who does not inform the clinician that he drinks more than four drinks almost every evening and more on weekends.
- A college student who complains of heart palpitations, but does not mention using her roommate's medication for ADHD to help her study.
- An elderly woman who is increasingly confused and somnolent and has a normal physical, tests, and laboratory results, but does not state that she self-medicates with her friend's prescribed benzodiazepines to help her "nerves."
- A patient with pancreatitis who repeatedly denies alcohol use and is negative for any other causes.

In clinical situations, such as these and others, practitioners can order drug tests and use the results to gain a better understanding of the true clinical picture, determine the diagnosis, talk to the patient, and then work more effectively with the patient.

Patient Safety

In some cases, ensuring patient safety is the primary reason for testing in clinical situations. For example:

- **Preoperative or preprocedure evaluations**. Primary care providers often do evaluations for their patients prior to planned surgery or other invasive procedures. Drug tests may identify medication or illicit drug use not disclosed during the practitioner–patient interview. Drug testing can be used if the practitioner suspects that the patient is using drugs, or if the patient has a history of drug use. The primary care physician can alert the anesthesiologists or radiologists to the possible presence of substances that could cause adverse drug reactions, interfere with anesthesia, prevent possible cardiac complications or respiratory depression, prevent the patient from experiencing withdrawal if hospitalized, or experience poor pain management if the patient has been taking high doses of opioids and has developed tolerance.
- **Preventing toxic drug interactions.** Drug testing may reveal a patient's use of multiple substances, both legal (prescribed and OTC medications) and illicit drugs. A practitioner needs this information before prescribing a new medication or starting pharmacotherapy for SUDs, psychiatric conditions, and other health problems. For example, a toxic interaction can occur if a patient uses other central nervous system depressants while taking buprenorphine or methadone.

Pregnancy

Drug and alcohol testing of women who are pregnant or who want to become pregnant is an opportunity to prevent damage to the woman and the fetus. During preconception counseling, women should be advised about the risks of alcohol, tobacco, and drug use to the fetus. Screening for substance use should be done so that the patient can be assessed and referred to treatment before becoming pregnant. SUD screening and assessment of a pregnant woman can identify an SUD early enough for intervention and for preventing, minimizing, or at the very least preparing for serious problems for the fetus or neonate. Pregnant women should be strongly urged to abstain from alcohol and drugs, and, if necessary, referred to treatment as soon as possible. Drug testing can be used to monitor abstinence.

A difficult dilemma is created by State laws that require the reporting of nonmedical use of controlled substances by a pregnant woman or that require drug testing after delivery if illicit drug use is suspected. These laws can have the unintended effect

of women not seeking prenatal care. Drug testing during pregnancy, or postnatally, can have severe consequences. In many States, pregnant and parenting women can be reported to child protective services, even though the courts have struck down criminal charges against women who are pregnant and use drugs. Women have the right to refuse drug testing (American College of Obstetricians and Gynecologists, 2008); however, if drug abuse is suspected that is contributing to child abuse, reporting to child protective services is necessary.

Psychiatric Care

Drug testing is uncommon for patients who are primarily being treated for mental disorders, but should be considered when assessing a patient presenting with mood or behavior changes (Black & Andreasen, 2011). Drug tests could be used with patients with possible mental disorders to aid in diagnosis, help determine whether the psychiatric symptoms are substance use or withdrawal related, or to identify a co-occurring SUD.

Controlled substances are prescribed for some psychiatric conditions (e.g., benzodiazepines for chronic anxiety disorder or stimulants for ADHD). Drug test monitoring for adherence to controlled medications may be indicated for some patients.

Monitoring Office-Based Pharmacotherapy for Opioid Use Disorders

The Drug Addiction Treatment Act of 2000 (DATA 2000) permits office-based substance abuse treatment by allowing certified physicians to prescribe Schedule III, IV, and V medications to treat opioid dependence. To prescribe buprenorphine, a Schedule III opioid medication, physicians must qualify for a DATA 2000 waiver. Physicians providing office-based pharmacotherapy use drug testing to monitor compliance with pharmacotherapy and abstinence from illicit opioids. For more information, visit http://buprenorphine.samhsa.gov/index.html and see Treatment Improvement Protocol (TIP) 40: *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction* (Center for Substance Abuse Treatment [CSAT], 2004).

Detection of Substance Use Disorders

Many patients seeing primary care providers have an undiagnosed SUD and providers can play important, preventive roles in detecting and addressing SUDs in the primary care setting. Drug testing can aid the provider in identifying those patients using illicit substances and screen them further for a possible SUD. It must be noted that a positive drug screen is not diagnostic in itself of an SUD.

The practitioner can find clues for a possible SUD in a patient's laboratory findings, physical examination, and medical history. For example, liver enzyme abnormalities may suggest current or past alcohol misuse or dependence, and hepatitis B and C antibodies can suggest current or past drug use. A physical examination may reveal track marks or abscesses, or a patient may have a history of medical conditions that suggests an SUD (e.g., cirrhosis, pancreatitis). Other physical signs include frequent falls or injuries, bruises the patient cannot explain, physical complaints without corresponding physical findings, deterioration in personal hygiene, and disheveled appearance.

Physical signs of SUDs may not appear until late in the progression of the disorder. Nonphysical or behavioral signs could include:

- Reports of marital, academic, or employment problems;
- Chaotic lifestyle;
- Deterioration in grooming or hygiene;
- Unusual mood swings or outbursts;
- Money or other valuable items missing from the home;

- Requests for specific potentially addictive medications; and
- Frequent reports of losing prescriptions for potentially addictive medications.

Initial Assessment of a Person With a Suspected SUD

A positive drug test does not necessarily indicate a diagnosis of an SUD. The drug use could be sporadic and not meet the diagnostic criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (American Psychiatric Association, 2000). These patients will need screening and assessment. When informing a patient about the test results of an initial assessment, the practitioner can:

- Inform the patient about the health and medical consequences (Fleming, 1995). Once screening results are explained, describe the health risks and medical consequences of use of the substance in question. For some (e.g., people with chronic hepatitis) any consumption of a substance, such as ethanol, may be unsafe. Likewise, the use of stimulants, such as cocaine and amphetamines, could have disastrous consequences for a patient with compromised cardiac function or hypertension. Women who are pregnant or who want to become pregnant should be told of the dangers an SUD poses to the fetus and the mother, receive further assessment, or be referred to SUD treatment.
- Pay careful attention to semantics. Avoid pejorative labels of "alcoholic" or "addict." Use neutral, nonstigmatizing language (e.g., "people with substance use problems"). Do not use humiliating or confrontational approaches to try to force the patient to agree to treatment.
- Recognize that a positive test result may trigger patient resistance or feelings of guilt, shame, or anger. Avoid arguing with the patient. Negative reactions can often be countered by focusing on the relationship between the original health complaint and the patient's use of drugs or alcohol.
- Demonstrate an understanding and acceptance of the patient and communicate that the clinician will help the client help himself or herself.
- Address goals and strategies for change. Assess the patient's readiness for change. Help the client clarify the nature of his or her difficulties. Express empathy and a willingness to listen to the client. Use motivational counseling approaches to encourage further screening or assessment or treatment options. Foster hope for positive change. Resources for more information about motivational approaches are in Exhibit 4-1.

A positive test result for illicit drugs or nonprescribed licit medications does not necessarily mean that the patient has an SUD; it means that the SUD may exist and the patient needs further screening to rule out an SUD or determine whether an SUD assessment is needed. The practitioner can do brief office-based screening, using the test result to start a discussion. The practitioner can also use a screening instrument; the simplest and quickest screening instrument is CAGE-AID (Exhibit 4-2). CAGE-AID is a tool that has been tested with primary care patients (Brown & Rounds, 1995).

Exhibit 4-1. Motivational Interviewing Resources

- TIP 35: *Enhancing Motivation for Change in Substance Abuse Treatment* (CSAT, 1999b)
- *KAP Keys for Clinicians Based on TIP 35* (CSAT, 2001a)
- *Quick Guide for Clinicians Based on TIP 35* (CSAT, 2001b)
- *Motivational Interviewing: Preparing People for Change* (Miller & Rollnick, 2002)
- The Motivational Interviewing Page (http://www.motivationalinterview.org)
- *Helping Patients Who Drink Too Much: A Clinician's Guide, Updated 2005 Edition* (National Institute on Alcohol Abuse and Alcoholism, 2007)

Exhibit 4-2. The CAGE-AID Questions

1. Have you felt you ought to **C**ut down on your drinking or drug use?
2. Have people **A**nnoyed you by criticizing your drinking or drug use?
3. Have you felt bad or **G**uilty about your drinking or drug use?
4. Have you ever had a drink or used drugs first thing in the morning to steady your nerves or to get rid of a hangover (**E**ye-opener)?

The National Institute of Drug Abuse's (NIDA's) NIDAMED provides resources for health professionals and is available at http://www.nida.nih.gov/nidamed/screening/.

The NIDAMED Web site includes a number of resources, such as:

- NIDA's Clinician's Screening Tool, NIDA-Modified Alcohol, Smoking, and Substance Involvement Screening Test (NMASSIST), is available online and in hard copy.
- Resource Guide: Screening for Drug Use in General Medical Settings provides information on using the 5As–Ask, Advise, Assess, Assist, and Arrange.

NMASSIST is a well-validated tool in general medical settings. The empirical evidence is good for screening and brief intervention for alcohol use disorders in a primary care setting, but it is more limited for the treatment of drug use disorders, which might require a more intensive care setting.

Several screening and assessment tools are listed in Appendix C—Screening and Assessment Instruments in TIP 24: *A Guide to Substance Abuse Services for Primary Care Clinicians* (CSAT, 1997).

When screening or a brief assessment indicates a problem with substance use, the practitioner may want to try brief office-based interventions. A brief intervention is a pretreatment tool or prevention technique that involves office-based, practitioner-patient contacts of 10–15 minutes for a limited number of sessions. The number and frequency of sessions depend on the severity of the problem and the patient's response. A brief intervention can be useful before or after an indepth assessment and both during and after specialized treatment as part of followup and relapse prevention. Exhibit 4-3 lists basic elements of brief interventions using FRAMES. More indepth information can be found in TIP 34: *Brief Interventions and Brief Therapies for Substance Abuse* (CSAT, 1999a); TIP 24: *A Guide to Substance Abuse Services for Primary Care Clinicians* (CSAT, 1997); *Brief Intervention for Hazardous and Harmful Drinking: A Manual for Use in Primary Care* (Babor & Higgins-Biddle, 2001); and at the Substance Abuse and Mental Health Services Administration's (SAMHSA's) Web site on screening, brief intervention, and referral to treatment http://www.samhsa.gov/prevention/SBIRT/index.aspx.

Exhibit 4-3. Brief Intervention Elements: FRAMES

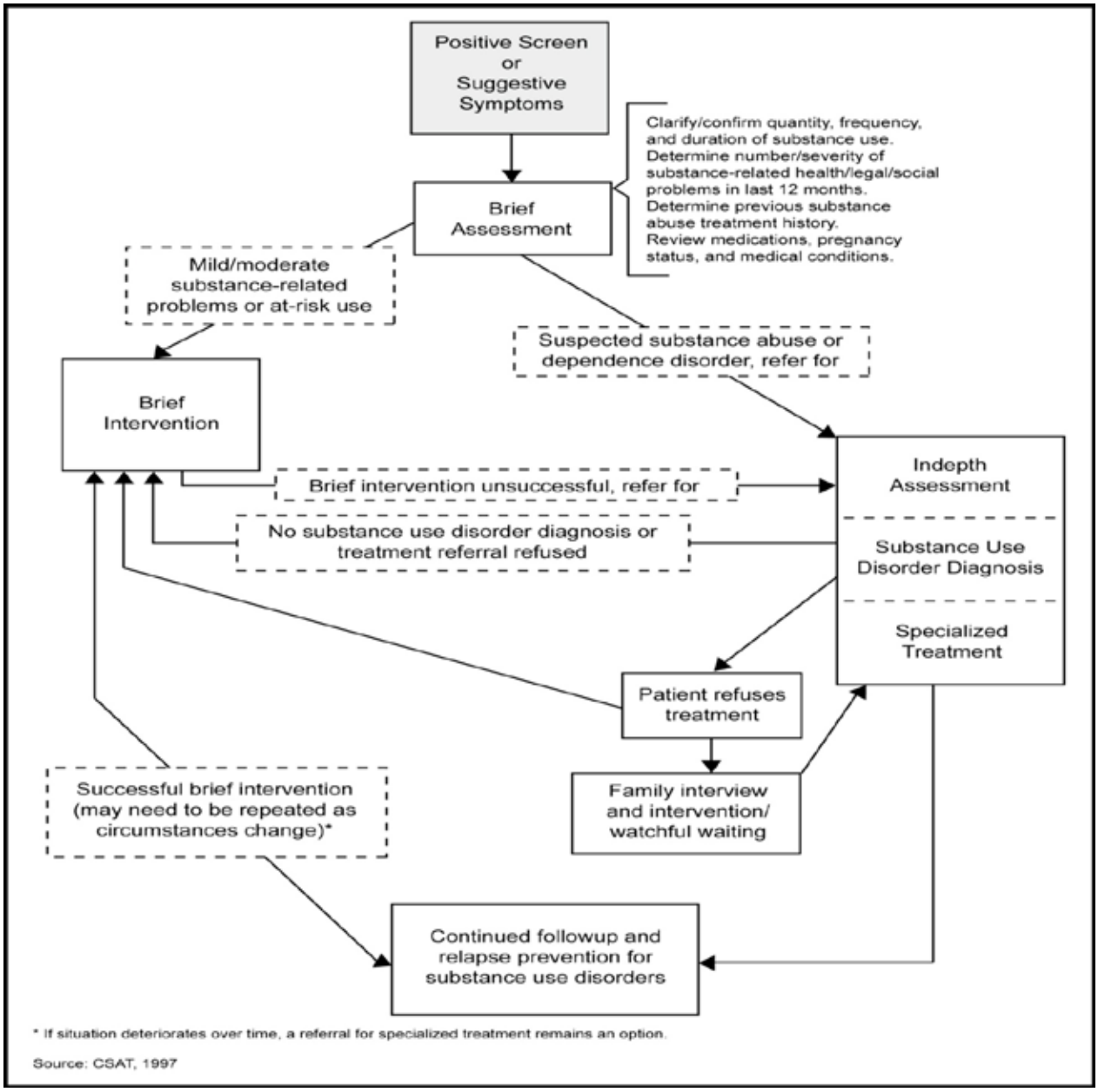
Feedback—The practitioner gives patients personalized feedback relevant to their individual situation.
Responsibility—The practitioner lets patients know that they are ultimately responsible for their recovery.
Advice—Studies have proved that even brief sessions providing information or advice about substance use can lead to behavior changes (Rollnick, Heather, & Bell, 1992).
Menu—Giving patients a menu of strategies (as appropriate to the treatment situation) adds to the sense of responsibility patients feel.
Empathy—An empathetic approach to treatment has been positively linked to positive treatment outcomes.
Self-Efficacy—The feeling of self-efficacy (e.g., I can change) is critical to promoting behavioral changes in patients. Patients' belief that they are capable of changing their behavior can help them through challenging parts of recovery.

SOURCE: Miller & Sanchez (1994)

If a practitioner suspects an SUD, he or she can refer the patient to appropriate psychosocial or medication-assisted treatment services. Often, making a telephone call to a treatment facility while the patient is in the office is the best way to get a patient to treatment. Substance abuse treatment providers will do a thorough assessment and recommend the least intensive environment that is safe and effective for the patient.

The practitioner should follow the patient's progress in treatment and request evidence of the patient's adherence to prescribed psychosocial services. Brief interventions can be successful. The patient could also have drug tests during subsequent visits to assess progress. Exhibit 4-4 provides a flowchart of the screening, assessment, brief intervention, and referral processes in primary care settings.

Exhibit 4-4. Patient Flow Through Screening and Referral in Primary Care



For more information, refer to the following publications:

- TIP 24: *A Guide to Substance Abuse Services for Primary Care Clinicians* (CSAT, 1997)
- TIP 40: *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction* (CSAT, 2004)
- TIP 49: *Incorporating Alcohol Pharmacotherapies Into Medical Practice* (CSAT, 2009)
- *Screening for Drug Use in General Medical Settings, Quick Reference Guide* (NIDA, 2009)
- *Helping Patients Who Drink Too Much: A Clinician's Guide* (National Institute on Alcohol Abuse and Alcoholism, 2007)

Talking With Patients About Drug Testing

Prior to testing, important tasks for the practitioner are to explain to patients: (1) the reasons for performing drug testing, (2) use of the test results, and (3) the practitioner's duty to maintain confidentiality. It should also be explained to the patient that the drug tests and the results will become part of the patient's record. Establishing a trusting relationship in which patients feel comfortable about confiding substance use helps address any questions or negative reactions to testing or test results. If the patient has language, hearing, or vision-related challenges, accommodations may need to be made with the use of a translator or assist technologies. Key practitioner actions that contribute to such a relationship include:

- Communicating openly;
- Having an understanding attitude;
- Listening actively;
- Treating the patient with dignity and respect;
- Reassuring the patient regarding confidentiality of medical records;
- Having a straightforward, but nonjudgmental attitude; and
- Using a matter-of-fact, nonconfrontational approach in explaining the reasons for drug testing and any subsequent treatment.

Explicit consent for drug testing is not required in primary care settings. However, there are reasons why practitioners should inform patients before drug testing:

- **The practitioner–patient relationship**. Although patients may assume they will be tested for cholesterol or glucose levels, most do not expect to be tested for drug use. Patients confronted with results of tests that they did not realize were being performed may feel betrayed by the practitioner, possibly eliminating the chance for discussion about substance use problems and harming the practitioner–patient relationship.
- **Privacy**. If the practitioner orders a test and the cost is submitted to the insurance company, the patient's health insurance company will know about it. Patients should have the choice of deciding whether they are willing to have their insurance carrier learn this information.
- **Reimbursement**. Patients' third-party payers may not cover drug tests. If insurance companies do not pay for the test, patients should decide whether they are willing to self-pay; this decision should be made before the test is done. The patient may want to pay out of pocket to keep the drug test out of his or her insurance record.

Before testing, the practitioner needs to emphasize to patients the importance of revealing all prescription and nonprescription drugs (including OTC medications and herbal preparations) they are taking. Patients may not realize that OTC or herbal products can affect drug test results.

Even if a patient refuses to consent to a drug test, the conversation between the practitioner and patient may facilitate a discussion about possible substance use problems. The practitioner could begin by asking why the patient does not want to have a drug test, or agree to re-visit the issue during another visit. A patient may be willing to examine his or her behavior after refusing the test.

Discussing drug testing results can be difficult. Patients need clear and thoughtful explanations of the test results and the terms positive, negative, adulterated, dilute, or substituted. They need to understand why the test was positive or negative and what that means for the patient and any treatment. All results should be presented in a straightforward, nonjudgmental manner using terms the patient understands. Effective communication is essential for the practitioner–patient relationship to be successful in these circumstances.

Cultural Competency and Diversity

The ease or difficulty in establishing and maintaining a therapeutic alliance is affected by many factors, including the amount of time the practitioner can spend with the patient, the backgrounds of both the practitioner and the patient, the patient's ability to speak English, and acculturation levels (if the patient is from another country). Drug testing with some patients from diverse groups can be challenging due to their cultural beliefs, history, and heritage. Some patients may distrust the medical profession because of past abuses by the medical community. They might feel additional shame about SUDs because of the strong stigma in their community, they might fear disclosure to law enforcement, or they might possess a different idea of what constitutes normal drinking versus problematic drinking.

Some approaches to help improve communication in these circumstances include:

- Providing an explanation of the practitioner's perceptions of the problem and listening, with sympathy and understanding, to the patient's perception of the problem.
- Acknowledging and discussing the differences and similarities in beliefs about treatment.
- Recommending treatment and then negotiating a treatment agreement (Berlin & Fowkes, 1983).

Following are some ideas for the practitioner to consider when treating patients from diverse backgrounds:

- Culture is important in every patient's identity.
- Communication of cultural understanding and respect is essential for establishing rapport.
- Culture-related stresses and tensions can induce illness.
- Culture-related behaviors or beliefs (e.g., religion, family structure and influence, health practices, traditional health beliefs) affect patients' acceptance of and compliance with prescribed therapy.
- Nonverbal and verbal communication may differ from culture to culture.
- Customs and attitudes surrounding SUDs may differ from the accepted medical definition.
- Awareness of prevailing cross-cultural tensions and psychosocial issues may help the practitioner understand patients from that culture (Bobo, Womeodu, & Knox, 1991).

Intercultural skills need to be as specific as possible for each culture. For example, the practitioner should:

- Attempt to understand how the patient's background and culture can affect treatment.
- Elicit the patient's understanding of drug testing.
- Negotiate a culturally relevant care plan with the patient as partner.
- Interpret verbal and nonverbal behaviors in a culturally relevant manner.
- Acknowledge the patient's role as an active participant in his or her own care (Bobo et al., 1991).

Monitoring Patients

Patients With an SUD

If the practitioner is providing substance abuse treatment, drug testing can:

- Objectively monitor abstinence from drugs or alcohol;
- Monitor response to treatment;
- Corroborate self-reports;
- Help address denials of substance use; and
- Identify relapse to substance use.

For example, an increasing number of physicians provide medications for alcohol use disorders (e.g., disulfiram, naltrexone). Drug testing can be used to help monitor patients' use of drugs, if necessary, and is needed before starting naltrexone. The patient and practitioner need to negotiate a plan of action to address the patient's substance use and monitor progress. Any medical problem other than substance use (e.g., hypertension) should also be monitored, as should any abnormal biological markers (e.g., elevated gamma-glutamyl transpeptidase levels in patients who abuse alcohol).

A practitioner using drug tests may seem intrusive to some patients, whereas other patients welcome the discipline imposed. The practitioner and patient should negotiate the use of any form of objective monitoring beyond self-reports of substance use. Biological monitoring should be viewed as an informative measure, not cause for punitive action against the patient. Repeated positive urine drug test results mean that the treatment plan is not working and that another approach should be considered. Efforts to reduce the patient's substance use by monitoring drug test results work best in conjunction with open communication between the practitioner and the patient.

Monitoring treatment compliance is a trust issue, and trust is important for the development of the therapeutic alliance. The practitioner needs to create an environment in which the patient feels safe to report honestly how he or she is progressing in recovery. Relapses are a normal part of the natural history of recovery, and how the practitioner responds to them is essential to building a therapeutic alliance and trust. Getting honest with oneself and others about one's substance use and its impact on one's life is essential to lasting recovery, so honesty is an important ground rule for establishing the patient–practitioner relationship. That said, the practitioner should be clear early on that addiction leads some patients to be dishonest about their drug use, so a policy of "trust yet verify" is used—drug testing and corroboration from family can help verify the patient's reports. The practitioner should express trust in the patient; then, if the patient is not honest about reporting substance use, the practitioner must address the lack of honesty as a therapeutic issue that impedes recovery. If a patient tries to deceive the practitioner, the practitioner should be direct yet empathic: "I know it is hard to stop using. What do you think might help?"

The response to a positive drug screen in patients being treated for an SUD depends on more than one factor, including the types of drugs found in the test. If positive results

continue and the patient is not progressing, the patient may need referral to more intensive treatment. However, if the patient readily admits to a relapse and seems fully committed to continuing treatment, the practitioner should support the patient's recommitment to recovery. Each patient needs to be assessed as an individual. If the patient is receiving medication-assisted treatment, the dosage may need to be increased.

An important concept of substance abuse treatment is that one failure (e.g., relapse, leaving treatment), or even multiple treatment failures, is not a reason to deny further treatment to a patient. The practitioner should expect relapses and be prepared to respond in a therapeutically appropriate manner. The patient may not be able to achieve recovery after one, or even several, treatment periods. SUDs are chronic, relapsing conditions that often need repeated interventions or treatments before a patient is stabilized. The practitioner should not expect that patients with problems related to alcohol and drug use will have any less difficulty than other patients in making significant lifestyle changes.

Unless a practitioner is testing for all substances (which is virtually impossible), heavy reliance on drug tests can be misleading in monitoring abstinence. Patients can abstain from their substance of choice while using other substances that may not be part of a particular drug test panel. Practitioners should test not only for the patient's substance of choice, but also other commonly abused drugs. In general, the practitioner should avoid using drug testing as a punitive measure. A cooperative practitioner–patient relationship includes trusting the patient's self-report of substance use, with drug testing used to verify reports.

If a patient is currently in treatment for substance abuse at a treatment center, he or she is likely being tested for drug use. In this case, it is cost effective—and in the patient's best interest—for the practitioner to ask the treatment program (with permission from the patient) for drug test results rather than to repeat a drug test.

Monitoring Patients Receiving Opioids for Chronic Noncancer Pain

Urine drug tests are becoming more common to monitor patients receiving chronic opioid analgesics. In pain management, drug tests can be useful, but they need to be used thoughtfully. The plan and reasoning for drug testing for these patients needs to be discussed thoroughly with the patient. Some patients may find drug tests intrusive; others accept the practice. Drug tests tend to be associated with drug abuse treatment and some patients may be offended when asked to participate in drug testing as part of pain treatment.

Drug tests do not monitor therapeutic drug levels; they provide information regarding medication adherence to the prescribed medication and/or the ingestion of illicit drugs. The only exception is the use of serum methadone levels. If the drug test shows the use of illicit drugs in addition to the prescribed medications, the patient needs to be educated regarding the danger of using illicit substances and opioid pain medications and that substance abuse is not helpful to long-term pain management. Some patients may need to be referred to specialists in both addiction and pain management.

To properly interpret urine drug screens, a detailed understanding of the pharmacology of the prescribed opioid and its relationship to the urine-testing technique must be understood by the prescribing provider. A negative test result when a positive one was expected (e.g., pain medication) may also trigger patient resistance or feelings of guilt, shame, or anger. In these cases, it is important that the practitioner avoid arguing with the patient and remain nonjudgmental. For more information, see TIP 54: *Managing Chronic Pain in Adults With or in Recovery From Substance Use Disorders* (SAMHSA, 2012).

Ensuring Confidentiality and 42 CFR Part 2

The concern about the adverse effects that negative attitudes about SUDs and discrimination have on patients in recovery—and how those adverse effects might deter people from entering treatment—led the U.S. Congress to pass legislation and the Department of Health and Human Services (HHS) to issue a set of regulations to protect information about patients' substance abuse. The law is codified at 42 United States Code §290dd-2. The implementing Federal regulations, "Confidentiality of Alcohol and Drug Abuse Patient Records," are contained in 42 CFR Part 2 (Vol. 42 of the Code of Federal Regulations, Part 2). The law and regulations severely restrict communications about identifiable patients by "programs" providing substance use diagnosis, treatment, or referral for treatment (42 CFR §2.11). These rules are stricter than the general Health Insurance Portability and Accountability Act of 1996 (HIPAA) rules about disclosure of personal health information. Under HIPAA, information can be disclosed without written consent for the purposes of routine clinical care and most administrative functions. Written permission from the patients for these disclosures is generally required by 42 CFR Part 2.

In most primary care settings, 42 CFR Part 2 does not apply. Confusion persists about whether general medical care settings (e.g., primary care clinics, hospital emergency rooms) are subject to the law and related regulations because they provide substance abuse diagnosis, referral, and treatment as part of their services. In 1995, HHS revised the definition of the kinds of programs subject to the regulations, clarifying that the regulations do not *usually* apply to a general medical care facility unless that facility (or person) "holds itself out as providing, and provides, alcohol or drug abuse diagnosis, treatment or referral for treatment" (42 CFR §2.11).

Practitioners should be aware that if a healthcare practice includes someone whose primary function is to provide substance abuse assessment or treatment, and if the practice benefits from Federal assistance (including Medicare or Medicaid payments), that practice must comply with the 42 CFR Part 2 law and regulations and implement special rules for handling information about patients who may have substance abuse problems (CSAT, 1997). Clinicians who use a controlled substance (e.g., benzodiazepines, methadone, buprenorphine) for detoxification or maintenance treatment of an SUD are also subject to this regulation. However, physicians who do not use a controlled substance for treatment (e.g., naltrexone) are not subject to the regulation (SAMHSA, n.d.).

In practices subject to 42 CFR Part 2, the results of a patient's drug test and substance use history are confidential and may not be revealed to a third party without the patient's consent, except in certain circumstances (e.g., if the patient was mandated to treatment). Patients must be told before being tested whether the test results must be reported. In addition, any releases of information must specify that the information cannot be shared with a third party without specific consent of the patient.

Many States offer additional protection to medical information about patients that is as strict or stricter than 42 CFR Part 2. However, each State has its own set of rules, which means that the scope of protection offered by State law varies. Whether a laboratory test result is privileged or protected information may depend upon several factors:

- The type of professional holding the information and whether he or she is licensed or certified by the State;
- The context in which the information was communicated;
- The context in which the information will be or was disclosed; and
- Exceptions to any general rule protecting information.

Which practitioners are covered depends on the State within which the clinician practices. Practitioners should consult with their State medical or substance abuse treatment authorities to ascertain the requirements and regulations in their State. SAMHSA provides a directory of State agencies for substance abuse services located at http://www.samhsa.gov/Grants/ssadirectory.pdf.

For more information, see Appendix B of TIP 24: *A Guide to Substance Abuse Services for Primary Care Clinicians* (CSAT, 1997), and *Confidentiality of Alcohol and Drug Abuse Patient Records Regulation and the HIPAA Privacy Rule: Implications for Alcohol and Substance Abuse Programs* (CSAT, 2005).

Preparing for Implementing Drug Testing

Before starting a drug testing program, it is recommended that the practitioner discuss the needs of the program with the laboratory toxicologist or other knowledgeable laboratory staff. Some important areas to obtain information about and to understand include:

- The strengths and limitations of the different tests;
- Standard collection procedures;
- Possible cross-reactivities with the targeted drugs that could affect test results;
- Limitations of the tests offered by the laboratory;
- Windows of detection for different specimens;
- Confirmatory testing, which can be done automatically, or only with specific request of the practitioner;
- Cutoff levels and whether they are appropriate for clinical purposes; and
- Cost of clinical drug test panels.

When ordering a laboratory test to detect substances of abuse, practitioners and staff need to order the correct test for the substances of interest and complete the required forms accurately. The practitioner needs to know exactly what a test is—and is not—measuring. For example:

- The specific drugs or metabolites that can be detected by the test
- The cutoff concentration used by the laboratory or the point-of-care test (POCT)
- The specific substance, class of substances, cross-reacting drugs, and/or metabolites that may yield a positive test result
- The drugs, drug classes, and/or their metabolites for which the test is being done
- The drugs/drug classes that will not be detected by the test

Collecting Specimens

No matter what the reason for drug testing, collections of specimens have more similarities than differences. As in workplace drug testing, which has specific requirements for collecting samples, clinical drug testing should have established collection procedures for that facility or office that follow the College of American Pathologists, Clinical Laboratory Improvement Amendments, and local and State regulations. A properly collected specimen is essential to a obtaining an accurate test result, whether for a POCT or for a test performed at a laboratory. The person responsible for specimen collection needs proper training. His or her duties include:

- Establishing the identity of the patient;
- Explaining clearly the collection procedure to the patient;
- Ensuring that the collection container is appropriate for the specimen matrix;
- Labeling the specimen properly;
- Collecting a sufficient amount of the specimen;
- Ensuring that the specimen collection method prevents substitution, dilution, or adulteration;

- Preventing contamination from environmental sources when collecting specimens;
- Storing the specimen according to the manufacturer's or laboratory's recommendations (e.g., proper temperature) to maintain specimen integrity;
- Preventing loss of or tampering with specimen by storing it in a secure area;
- Properly recording information; and
- Following universal precautions (e.g., wearing gloves and a mask, proper disposal of contaminated materials).

Collection procedures for drug testing should be conducted in ways that preserve patients' dignity. The procedures should be written and explained to patients before collection. Product inserts should be the basis for written protocols and not used as directions when actually collecting and testing specimens or reporting results.

The results of a drug test will not provide a diagnosis of an SUD.

Conducting POCTs

Personnel assigned to conduct the POCTs need to:

- Have access to current product inserts for the laboratory collection device and for the POCT device, if it is a combined collection and testing device;
- Pay close attention to the instructions provided with the test, particularly regarding timing and reading the results accurately;
- Understand possible cross-reactivities with other substances, especially if they are interpreting the results;
- Assay appropriate positive and negative quality control samples;
- Decide under what circumstances laboratory confirmatory tests will be ordered; and
- Record test results according to the protocols established by the practice.

If a practitioner is giving immediate feedback to a patient—a major benefit of using POCTs— the practitioner needs to be confident about what the test is measuring, its results, and the limitations of the test. POCT manufacturers generally have a technical assistance telephone line to answer questions. Chapter 5 provides details about using urine drug tests for specific drugs, including windows of detection, cross-reactivities, limitations, and special considerations for interpreting results.

Interpreting Drug Test Results

A drug test indicates whether a substance or a prescribed medication is present at levels below (negative) or above (positive) the test cutoff concentration. A test result can reveal that a specimen is negative, positive, adulterated, substituted, or dilute. Generally, drug testing cannot tell the practitioner the amount of drug ingested by the patient, whether a therapeutic level has been achieved (e.g., opioids for pain relief), or frequency of use, nor can it indicate the patient's level of intoxication, impairment, or severity of abuse, when trying to determine whether a patient may have an SUD. The results of a drug test will not provide a diagnosis of an SUD.

When interpreting drug test results, the practitioner must know exactly what a test is—and is not—measuring. The practitioner must consider:

- The purpose of the drug test;
- The limitations of the test used;
- The drugs or drug metabolites being detected and those not being detected;
- Potential cross-reactivities; and
- The limitations of the selected matrix.

Many other factors need to be considered when interpreting drug test results (e.g., specific substance, class of substances, cross-reacting drugs and/or metabolites that may yield a positive result). Drug test results may raise clinical concerns for practitioners, or provide reassurance about patient adherence to treatment. Testing may provide unexpected information, but should never be the sole basis for diagnosis and treatment decisionmaking. Test results should be used to supplement the information obtained from a comprehensive patient interview, the physical examination, and consideration of the patient's overall health.

To appropriately respond clinically, it is important that there be thoughtful consideration of drug test results, especially those that seem unusual for a particular patient or possibly incorrect. Other clinical findings must also be considered as well as drug test results.

Result: Negative Specimen

A negative test result means that a particular substance was not detected at or above the cutoff concentration in the specimen. A negative screening test result is rarely followed by a confirmatory test, but can be done if requested by the practitioner. Laboratories perform confirmatory tests on positive results, either routinely or only for certain drug/drug class positives (e.g., amphetamines, opiates) (White & Black, 2007), depending on the laboratory. It is imperative that the clinician is familiar with the laboratory's practices and procedures for testing.

The practitioner's response to a negative drug test result is based on the patient's diagnosis and reason for testing:

- If the patient is being treated for an SUD, consistently negative results—along with improvement in other areas of the person's life—may warrant a change in level of treatment (e.g., decreased frequency of visits, decreased testing frequency, changing from observed to nonobserved urine collection).
- If the patient is being prescribed medications with addictive potential (e.g., opioids, sedatives), a negative drug test warrants a reassessment that may lead to more frequent drug testing and office visits.

A negative drug test does not necessarily mean the patient has not used a particular substance or taken the prescribed medication. Negative test results can occur if:

- Errors were made in interpretation of the test.
- The patient has induced enzyme levels from smoking or liver disease and eliminates the medication more rapidly than usual (e.g., methadone).
- The patient has a shortened gastrointestinal tract from surgery and does not absorb the drug sufficiently for detection.
- The patient ran out of medication.
- The patient took the medication but not when expected or during the window of detection for the ordered test.
- The patient was thirsty and drank sufficient water to dilute the specimen.
- The patient may have consumed an excessive amount of fluids to deliberately dilute a urine specimen.
- The appropriate test for a particular medication or substance was not performed.
- The cutoff concentration used in the test was set too high, so small amounts of the drug/drug metabolites were missed.
- The parent drug and/or its metabolites were excreted before specimen collection (e.g., outside the detection window).
- The specimen may have been adulterated or substituted.

If a negative confirmatory test result is a surprise based on the patient's self-report, collateral report (e.g., from a spouse or partner, from a parent stating that he or she has found drugs or drug paraphernalia in a child's room), or other evidence, the practitioner should reconsider the testing procedures and assessing the patient's behavior. The practitioner could contact the laboratory and discuss the results with laboratory personnel, especially to see whether the negative report came from values that were just below the laboratory's cutoff concentration. Repeated urine testing could be done, or oral fluid could be tested.

The practitioner could also consider:

- Changing or including additional drugs for which testing is performed based on the information received.
- Adding specimen validity testing or testing the original negative specimen for validity.
- Changing the matrix tested (e.g., test urine instead of oral fluid for a longer detection window), if possible (e.g., based on drug detection period, sensitivity, ease of adulteration/substitution of the specimen).
- Testing repeated serial urines.
- Changing the drug-testing methods (i.e., change from POCT to laboratory test).
- Determining whether the testing occurred outside of the detectable window for the substance.

A confirmed negative test result for a patient receiving a prescribed medication, such as in pain treatment, is of concern. Again, the practitioner should first check with the laboratory about the validity of the test: Was the cutoff concentration low enough to measure therapeutic levels of the medication? In this case, retesting may be appropriate. Was the correct test performed to detect the prescribed substance (e.g., oxycodone is not detected in a standard 5-drug panel)?

If the negative test result is valid for prescribed scheduled medications, the practitioner must decide how to proceed with the patient who is, at best, not adhering to his or her prescribed medication regimen or, at worst, diverting the medication. For many reasons, a negative test should not be used to blame the patient for "diversion" unless there is other credible, incriminating information (e.g., witnessed attempts to sell the medication, drug-seeking documentation from prescription monitoring programs).

Result: Positive Specimen

A positive screening test result means that a particular substance was detected at or above the administrative cutoff concentration in the specimen. Confirmatory tests are frequently performed for specimens with positive screening results. If the patient admits drug use when informed of positive results from a POCT, a confirmatory test is not needed.

False-positive results are possible with screening (initial) tests. If a presumptive positive is confirmed by a second methodology, such as gas chromatography/mass spectrometry (GC/MS) or liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS), a false positive is highly unlikely if the test is performed correctly. If a positive result is surprising and the patient vehemently denies recent or current use, the practitioner should order a laboratory confirmatory test if such a test is not already part of the laboratory's testing agreement.

Interpretation of positive tests can sometimes be complex, especially if a patient is being monitored for abstinence following heavy drug use. With frequent use, significant bodily accumulation of drugs can occur with the consequence that drug metabolite(s) may be excreted for extended periods. This is especially true for highly lipid soluble drugs, such as marijuana (tetrahydrocannabinol) and phencyclidine, but it also applies to other drugs, such as cocaine and heroin. A patient who is recently abstinent may continue to test positive for days to weeks depending upon the drug and pattern of use. Distinguishing this normal pattern of body elimination of

drugs from new drug use can be difficult. Huestis and Cone (1998) have published methods for evaluating creatinine-normalized cannabinoid urine results between two specimens collected at least 24 hours apart to predict new marijuana use. These models were more recently updated and improved to take into account the specific times between two urine collections (Smith, Barnes, & Huestis, 2009). In a similar vein, Preston, Silverman, Schuster, and Cone (1997) developed a model for differentiating new cocaine use from residual cocaine metabolite excretion during abstinence. These criteria are based on established pharmacokinetics of benzoylecgonine and include urine creatinine normalization for control of variations in water intake and excretion.

If the confirmatory test result is positive for nonprescribed substances, the practitioner should review the patient's use of prescribed medications, OTC products, and herbal products to determine whether any of these may be the source of the positive result (e.g., poppy seeds causing a positive for codeine or morphine; high doses of morphine causing a positive for hydromorphone). The practitioner may also retest using a different matrix. However, it is worth noting that changing matrices makes interpretation difficult. Hair provides a longer detection window than do other matrices. If a hair specimen was used for testing, a patient could test positive for drug use, even if he or she has not used the substance for weeks. Segmenting a hair specimen is useful to narrow the window in which a positive is observed. However, hair testing is expensive. A urine or oral fluid drug test could provide a more accurate picture of very recent use. However, if the second specimen using the same or a different matrix is negative, it does not refute the scientific validity of the first test.

Clearly, drug test results should never be the sole criteria used for diagnosis of an SUD or making treatment decisions. The practitioner should not take action based solely on drug test results, but should consider them along with behavioral and physical assessments and any collateral information obtained (with permission of the patient) from a spouse, partner, or family member.

Other possible changes in drug-testing procedures include:

- Increasing the testing frequency to discourage illicit drug use by the patient, or possible diversion of prescribed medications;
- Changing the drugs tested for (e.g., test for another class of drugs) to detect the full scope of the patient's drug use; and
- Changing the drug-testing methods (e.g., use a laboratory test instead of a POCT or request a confirmatory test for all initial tests) to rule out false-positive results.

Other changes to treatment are discussed in the section on monitoring patients in Chapter 4.

Result: Adulterated or Substituted Specimen

Urine is the easiest specimen to adulterate, and commercial formulas of synthetic urine are available for substitution. Other fluids, including water, also have been used for substitution. If the test result indicates that the specimen has been adulterated or substituted, the practitioner collects another specimen and reviews procedures to determine whether the temperature and pH of specimens are being checked immediately after collection. For patients who seem to have several test results of adulterated or substituted urine, stricter collection procedures could be instituted for that patient. These could include:

- Ensuring that adulterants, such as soap, ammonia, or bleach are not readily available in the collection area when that patient provides specimens;
- Prohibiting personal belongings in the bathroom;

- Turning off the source of running water during collection and putting blue dye in the toilet; and
- Observing specimen collection.

The practitioner should review the patient's history, interview the patient, and observe the patient's behavior during the interview. The patient may need to be referred to a more intensive level of care. The drug-testing program can also be modified by adding a specimen validity test to the POCT or laboratory test, and changing the specimen matrix (e.g., oral fluid is least likely to be adulterated).

Result: Dilute Specimen

A dilute urine specimen can be negative or positive, depending upon the degree of dilution and amount of drug excreted. If the test result shows that the specimen has been diluted, the practitioner should discuss both the dilution and the negative or positive test result with the patient. In addition, the practitioner could:

- Test a different matrix, if possible;
- Collect and test a new specimen;
- Review the specimen collection site and ensure that bluing has been added to the toilet, that the water is turned off to the taps, and that patients are not allowed to take personal effects into the bathroom; or
- Consider medical reasons for diluted urine (e.g., conditions, such as routinely receiving diuretics, resulting in polyuria).

Result: Invalid Urine Specimen

An invalid result is one in which scientifically supportable analytical test results cannot be established for a specimen. An invalid laboratory test result for urine can be caused by many factors, such as:

- A physiological inconsistency between the patient's urine creatinine and specific gravity;
- An interference in the screening or initial test analysis;
- An interference in the confirmatory assay;
- The presence of oxidizing compounds at or above a cutoff set by the laboratory;
- A urine pH greater than or equal to 3.0 but less than 4.5 or outside other range set by the laboratory or POCT manufacturer;
- A urine pH greater than or equal to 9.0, but less than 11.0 or outside other range set by the laboratory or POCT manufacturer;
- The presence of nitrites in urine at or greater than 200 µg/mL but less than 500 µg/mL, or above a level set by the laboratory or POCT manufacturer;
- The possible presence of chromium (VI);
- The possible presence of a halogen (e.g., bleach, iodine, fluoride);
- The possible presence of surfactant (e.g., soap);
- The physical appearance of a specimen is such that the laboratory feels analysis of the specimen might damage its instruments; and
- Other factors determined by the laboratory for an invalid specimen.

An invalid test result is not definitive proof of specimen tampering. The practitioner should consider other possible causes before assuming that the patient has attempted to subvert the test. The practitioner could try to determine the reason for the report or discuss possible causes with the laboratory (e.g., Was an unidentified adulterant suspected? Were the specimen's physical characteristics inconsistent with human urine?). A review of the patient's history may reveal a medical explanation (e.g., a medication that could have interfered with the test).

The practitioner could also have another specimen collected and tested and ensure that the collector follows proper procedures, including restricting patient access to

materials that could be used to adulterate or substitute the specimen.

Results are also reported as indeterminate or inconclusive. The practitioner should consider the possible causes, including storage and transport irregularities, and potential medical explanations (e.g., a medication that could have interfered with the test). If this happens often, the practitioner may want to ask the patient to return for further discussion and repeat the test.

Frequency of Testing

Drug testing can be done when conducting an assessment when an SUD is suspected, or as a baseline when prescribing medications with addictive potential. The subsequent frequency of drug testing depends on the practitioner, the individual patient, the diagnosis, and the reason for drug testing.

In opioid pain management, testing can be done both to ensure compliance with prescribed medications and to identify abuse of illicit substances. Drugs of interest in this instance include benzodiazepines and opioids (e.g., oxycodone, methadone, fentanyl, hydrocodone, hydromorphone, morphine). Drug tests can be done before providing initial prescriptions or refills (White & Black, 2007) or for other medications with addictive potential. Testing can also be done if the patient exhibits aberrant behavior, if diversion of prescribed medications is suspected, or randomly to monitor treatment.

For the patient being treated for an SUD, drug tests can be done:

- With changing frequency as the patient progresses (less often as the patient progresses, or more often with lack of progress);
- If relapse is suspected;
- If the patient exhibits aberrant behavior; or
- Randomly to monitor treatment.

For the patients receiving medications, particularly opioids, with abuse potential, drug tests can be done during every visit, randomly, before providing prescription refills, or if the patient exhibits aberrant behavior. The frequency can also change with several drug tests that show that the patient is taking the medication as prescribed and is not positive for illicit drugs.

A drug test may not be needed if the patient admits illicit drug use or treatment noncompliance for prescribed medications when coming to his or her appointment.

Documentation and Reimbursement

Proper documentation is needed for both patient record keeping and to obtain reimbursement.

Documentation

In addition to keeping accurate patient medical records, practitioners must ensure proper documentation of the use of POCTs. This includes (Howerton et al., 2005):

- Written procedures for performing POCTs;
- Inventory control—lot numbers and expiration dates for POCTs;
- Documentation of staff training and reassessment;
- Quality assurance test results;
- Documentation of problems and problem resolution; and
- Copies of laboratory test orders and results.

Patient medical records should document:

- The medical necessity for drug testing;
- Tests performed and test results;
- Changes made to the treatment plan based on test results; and
- Referrals made.

Reimbursement

Testing for alcohol or drugs is billed by the specific biological tests conducted according to the Current Procedural Terminology (CPT) codebook (American Medical Association, 2006). Insurance coverage for alcohol or drug testing varies by carrier. Careful documentation of the need for testing assists with obtaining reimbursement. The current issue of the CPT codebook should be consulted to obtain proper reimbursement.

Some CPT codes that are used for testing include:

- 80100: For qualitative screening tests used to detect the presence of *multiple* drug classes.
- 80101: For qualitative screening tests used to detect the presence of *one* drug class.
- 80102: For each *confirmatory* test.
- 82055: Alcohol testing (any method other than breath).
- 82075: Alcohol testing (breath).

Centers for Medicare & Medicaid Services uses different codes:

- G0430-QW: When multiple drug classes are tested and the testing methodology does not use the chromatographic method
- 80100-QW: When testing for multiple drug classes that do use the chromatographic method
- G0431: Used, per drug class, when performing a test for a single drug class

The medical necessity for testing can be documented by using International Classification of Diseases codes (i.e., harmful use or dependence syndrome) from the *International Statistical Classification of Diseases and Related Health Problems, Volume 1: 10th Revision* (World Health Organization, 1992). However, the patient may want to pay for a drug test and not submit the cost to the health insurance company. This should be discussed with the patient.

Chapter 5—Urine Drug Testing for Specific Substances

In This Chapter

- Window of Detection
- Specimen Collection
- Adulteration, Substitution, and Dilution
- Cross-Reactivity
- Alcohol
- Amphetamines
- Barbiturates
- Benzodiazepines
- Cocaine
- Marijuana/Cannabis
- Opioids
- Other Substances of Abuse

Urine is the most rigorously evaluated and most commonly used matrix for drug testing (Watson et al., 2006). All results are affected by laboratory test or point-of-care test (POCT) cutoff concentrations. Therefore, practitioners should always consult with laboratory staff when ordering laboratory tests or carefully read POCT package inserts before using the test. Numerous POCTs are available for urine drug testing.

Window of Detection

The window of detection for urine falls in the intermediate range, compared with the detection period or window for other matrices. Many factors influence the window of detection for a substance. Factors include, but are not limited to, the frequency of use (chronic or acute), amount taken, rate at which the substance is metabolized, cutoff concentration of the test, patient's physical condition and, in many cases, body fat. Some hepatic, renal, endocrine, and other pathologies may extend the detection window.

Drugs are present in urine from within minutes of use to several days after, depending on the substance; quantity ingested; the degree to which the bladder was filled with drug-free urine at the start of drug use; the patient's hepatic, cardiac, and renal function; the patient's state of hydration; and drug type. Drugs that are smoked or injected are detectable in urine samples almost immediately. Detection rates for drugs taken orally are slower, taking up to several hours and peaking at about 6 hours (Dolan et al., 2004).

The window-of-detection estimates used in this chapter are from several sources: Cone (1997), Dasgupta (2008), Verstraete (2004), Warner (2003), White and Black (2007), Wolff et al. (1999), and Wong and Tse (2005).

Many urine drug tests detect the drug metabolite, rather than the drug itself. As a general rule, drug metabolites remain in the body for a longer period than does the parent drug, allowing for a longer detection period. For example, when the test is for cocaine using urine, the target compound is usually the metabolite, benzoylecgonine, rather than the parent cocaine molecule.

It may be difficult to detect illegal substances in urine specimens of patients who stop use for several days before providing a specimen. Most substances of abuse are detectable in urine for approximately 2–4 days (Center for Substance Abuse Treatment [CSAT], 2006b; Cone, 1997). However, the detection time may be prolonged when large, frequent doses are taken over a long period (CSAT, 2006b). For example, one dose of intranasal cocaine may be detectable in urine for 3–5 days using a cutoff of 300 ng/mL after ingestion, but daily, heavy cocaine use may be detected for additional days following discontinuation of use (Verstraete, 2004). Chronic use of marijuana may be detectable for up to 30 days after use is stopped.

Specimen Collection

Urine collection usually is easier than collecting blood, and samples are available in sufficient quantities (Warner, 2003). Urine sample collection is not usually observed in primary care settings. Clinical drug testing usually does not warrant direct observation that may be necessary in forensic or substance abuse treatment program testing. However, if it is suspected that a patient is tampering, diluting, or adulterating urine specimens, some measures used in forensic or workplace testing can be used to prevent this, including:

- Directly observing specimen provision;
- Turning the water off to the taps and adding a bluing agent to the toilet tank to avoid sample dilution;
- Not providing hand soap in the restroom where the sample is being done;
- Not storing cleaning agents in the restroom (e.g., ammonia-containing products, bleach, toilet cleaning products); and
- Not allowing coats, purses, or bags into the restroom with the patient.

Patients who exhibit "shy bladder syndrome" (inability to void) may need to consume liquids to provide a specimen (e.g., 8 oz. of water every 30 minutes, but not to exceed a maximum of 40 oz. over a period of 3 hours, or until the patient has provided a sufficient urine specimen).

Once the specimen is collected and labeled:

- The appearance and color of the urine sample should be documented.
- The use of primary collection containers with a temperature-sensitive strip on the outside is recommended, rather than placing a thermometer or temperature strip into the urine.
- The urine specimen temperature should be recorded within 4 minutes of collection; the temperature should be between 90°F and 100°F.

Additional clinical testing, such as a routine urinalysis (e.g., pH and tests to detect the presence of oxidizing components and adulterants) can be conducted on an aliquot separate from that used for urine drug testing to avoid any argument that a positive was the result of a foreign object being placed in the patient's urine specimen.

Adulteration, Substitution, and Dilution

Urine tests can be reported as adulterated, substituted, or dilute.

Adulteration

An adulterated urine specimen is one containing a substance that is not normally found in urine or that is normally found, but is in abnormal concentrations. In vitro adulterants are foreign substances added to the urine specimen after voiding. Adulterants work by interfering with immunoassay and/or confirmatory assay function, or they convert the target drug to compounds not

detected by the test (Jaffee, Trucco, Levy, & Weiss, 2007). Ordinary household products (e.g., laundry bleach, toilet bowl cleaner, hand soap, vinegar, ammonia, eye drops) have been used for many years to adulterate urine specimens to obtain a negative drug test result (Dasgupta, 2007). Household products that alter the pH of urine to a value outside the physiologic range can be easily detected by determining the pH of the sample (Dasgupta, 2007). Products such as bleach and other oxidizing agents can be detected with a general oxidants assay.

Numerous types of commercial adulterants are available via the Internet. The following list is a summary of such products by active ingredient (Jaffee et al., 2007):

- Glutaraldehyde (e.g., "Clean X") can interfere with absorbance rates on immunoassay tests, masking the presence of substances such as the marijuana metabolite, 11-nor-9-carboxy-THC (THCCOOH), opioids, cocaine metabolites, morphine, amphetamine, phencyclidine (PCP), and most other immunoassay tests. The presence of glutaraldehyde usually is detected by observing abnormal immunoassay results; however, other substances can also cause an abnormal immunoassay result.
- Sodium or potassium nitrite (e.g., "Klear," "Whizzies") can mask the presence of marijuana metabolite in immunoassay tests and the presence of THCCOOH in confirmatory tests. Abnormal nitrites in urine can be detected by a specific nitrites assay or in a general oxidants assay.
- Pyridinium chlorochromate (PCC, commercially known as "Urine Luck") is an oxidizing agent that masks the presence of THCCOOH and, depending on the pH of the urine, can affect test results for morphine. Cocaine metabolites, amphetamine, and PCP are not affected by PCC (Dasgupta, 2007). Chlorochromate and other oxidizers, such as dichromate, can be detected in urine using a general oxidants assay.
- Peroxide/peroxidase (e.g., "Stealth") can oxidize drugs and their metabolites, making THCCOOH and lysergic acid diethylamide (LSD) undetectable by immunoassay tests. The peroxide/peroxidase combination may be difficult to detect in urine that is not fresh because both hydrogen peroxide and peroxidase tend to degrade with time.

The effectiveness of an adulterant depends on the amount of the adulterant added and, in some instances, the concentration of the drug in the sample. Specimen validity tests can detect many adulterants in addition to those described above.

Substitution

Synthetic urine products can be submitted when collection of a urine specimen is not observed. These products are premixed liquids with the characteristics of natural urine (i.e., correct pH, specific gravity, and creatinine levels). To achieve the temperature of recently voided urine, synthetic urine products can be heated in a microwave or taped next to a heating pad in a pocket. Sometimes, another person's urine is submitted.

More commonly, water or a saline solution is substituted for urine. Thus, a urine specimen is considered substituted when the creatinine concentration on both the initial and the confirmatory tests is less than 2.0 mg/dL and the specific gravity is less than or equal to 1.0010 or greater than or equal to 1.0200 (Substance Abuse and Mental Health Service Administration [SAMHSA], 2010b).

Dilute Specimens

Diluting the urine sample to the point where the targeted drug is below the cutoff concentration is another way to obtain a negative test result. For instance, consuming water in more-than-normal quantity and taking diuretics can dilute the urine sample. Individuals may also add water from the tap or toilet bowl to dilute specimens if tap

water is available in the restroom and/or bluing has not been added to the commode water. Commercial products are available that promise to "cleanse the urine." These products advocate consuming large amounts of tea or other fluids, increasing urine volume, thereby diluting drugs in the urine. Reducing the amount of time between notice that a specimen will be collected and the time of collection reduces the potential for the patient to consume enough fluids to dilute the urine.

A laboratory will report a urine specimen as dilute in conjunction with a positive or negative drug test when the creatinine concentration is greater than or equal to 2 mg/dL and less than 20 mg/dL, and the specific gravity is greater than 1.0010 and less than 1.0030 (SAMHSA, 2010b). Dilution may raise suspicion of tampering, but does not necessarily confirm tampering. Other factors need to be considered, such as whether the patient is taking a diuretic, eating a strict vegetarian diet, or maintaining a high state of hydration. Other factors include whether the patient was working in hot weather conditions and drank large amounts of fluid or drank fluids immediately before providing the specimen.

Cross-Reactivity

The cross-reactivity of urine immunoassay tests varies by drug class. For example, tests for cocaine measuring its principal metabolite, benzoylecgonine, have low cross-reactivity with other substances. However, tests for amphetamine/methamphetamine usually are extremely cross-reactive, and further laboratory testing using a method different in principle from immunoassay (i.e., not a second immunoassay) is required to confirm amphetamine use (Gourlay et al., 2010). As stated above, cross-reactivity is many times viewed as a negative aspect of immunoassay. However, cross-reactivity does have a positive side. An immunoassay that is specific for morphine will detect only morphine and will miss other opiates (e.g., hydrocodone) that a patient might be using without the treating physician's knowledge. Thus, a general opiates screen is preferred over a specific test when looking for opiate-type drugs. Lack of cross-reactivity also may affect testing, such as that performed for oxycodone, as discussed under "opioids."

Alcohol

The window of detection for alcohol is 7–12 hours. The frequency of alcohol use minimally affects the window of detection; however, ingestion of large amounts results in a longer detection time in body fluids than ingestion of a small amount of alcohol. The metabolism of ethanol may be accelerated in people who use chronically or binge. Approximately 90–95 percent of alcohol is oxidized in the liver before elimination in the urine, and only 1–2 percent of ingested alcohol is excreted unchanged in the urine (Moeller, Lee, & Kissack, 2008). Because of this rapid metabolization, blood tests or the standard hand-held breath devices (breathalyzers) are often used, and in clinical settings, urine alcohol tests are used far less frequently than are blood tests.

Urine can be analyzed for alcohol through chemical assays, enzyme immunoassays, or gas-liquid chromatography (GLC), with the most accurate reading produced by GLC. Urine drug tests for alcohol indicate only recent ingestion; they cannot identify long-term abuse. Furthermore, a urine ethanol can show use prior to the collection of the urine specimen only within a reasonable timeframe. Alcohol in blood or a blood product (e.g., serum, plasma) or a breath alcohol is required to show impairment and the degree of impairment.

Biomarkers, such as the gamma-glutamyl-peptidase, carbohydrate-deficient transferrin, aspartate amino transferase (measured in serum), and erythrocyte mean cell volume tests may confirm a suspicion of long-term alcohol abuse or dependence. Ethyl glucuronide EtG) and ethyl sulfate are direct metabolites

of ethanol that can be measured in urine. Testing for EtG is becoming more common to monitor alcohol consumption for people who have been ordered to abstain. However, more research is needed to establish standards to rule out possible exposure to alcohol in commercial products, such as mouthwash and hand sanitizers, versus drinking of alcoholic beverages (CSAT, 2006a). More information about biomarkers for alcohol use disorders is in *The Role of Biomarkers in the Treatment of Alcohol Use Disorders, 2012 Revision*.

Amphetamines

The SAMHSA workplace cutoff concentration for amphetamines is 500 ng/mL for initial testing, and 250 ng/mL for confirmatory testing. To be reported positive for methamphetamine, a specimen must also contain amphetamine at a concentration equal to or greater than 100 ng/mL (SAMHSA, 2008).

The window of detection varies. A single dose of amphetamine or methamphetamine can be detected in the urine for approximately 24 hours, depending upon urine pH and individual metabolic differences. People who use chronically and at high doses may continue to have positive urine specimens for 2–4 days after last use (SAMHSA, 2010b). Methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA), and methylenedioxyethylamphetamine (MDEA) can be detected for 1–2 days (Moeller et al., 2008; SAMHSA, 2010b).

Drug tests for the presence of amphetamine are among the hardest to interpret. Methamphetamine is the target analyte for amphetamine/methamphetamine testing. Immunoassay tests are highly cross-reactive and may detect other sympathomimetic amines, such as pseudoephedrine, readily available as over-the-counter (OTC) products. Structural similarities of many OTC products—including diet agents; decongestants; and several prescription medications, such as those to treat attention deficit/hyperactivity disorder, narcolepsy, and Parkinson's disease, or to suppress appetite—can cause initial positive test results. Adderall is an amphetamine and will result in a positive test for amphetamine.

Methamphetamine exists as two optical isomers (stereoisomers) that are designated *d*- and *l*-. The *d*-form has high abuse potential. The *l*-form in therapeutic doses has a primarily peripheral action and is found in some OTC products (Kwong, 2008a, 2008b). Immunoassay tests for amphetamine and methamphetamine can be divided into two types: (1) those designed to detect amphetamine and methamphetamine, only; and (2) those that also have variable cross-reactivities with "designer amphetamines," such as MDA, MDMA, and MDEA, as well as with sympathomimetic amines (e.g., ephedrine, phentermine, pseudoephedrine, phenylpropanolamine) (Kwong, 2008a, 2008b).

Typical immunoassay tests do not distinguish methamphetamine and/or amphetamine use from use of OTC products containing sympathomimetic amines. All presumptively positive urine "amphetamines" results should be confirmed by an alternate methodology different in principle from the immunoassay used to produce the screening result (White & Black, 2007). A confirmed test by gas chromatography/mass spectrometry (GC/MS) for methamphetamine can either be *d*-methamphetamine (licit or illicit) or OTC nasal spray. A confirmed test for methamphetamine is insufficient to distinguish illicit drug use from use of an OTC product. A separate test is available that is offered by most laboratories that distinguishes illicit methamphetamine (*d*-methamphetamine) from OTC nasal inhaler (*l*-methamphetamine). This specialized confirmatory test, stereospecific chromatography, is necessary to distinguish methamphetamine, amphetamine, and their isomers from legitimate sympathomimetic agents (Gourlay et al., 2010). However, a result confirmed by a second methodology, such as GC/MS, is definitively amphetamine

and/or methamphetamine. Cross-reactivity with MDMA, MDA, and/or MDEA is beneficial in that, once confirmed by an alternate methodology, it may uncover a previously unsuspected substance abuse problem.

Patients should be advised to avoid the use of this type of OTC nasal spray when being tested. A confirmed test for amphetamines or methamphetamines can occur because a number of other prescription medications metabolize to these isomers. The patient needs to be questioned regarding the reasons for taking the medication to determine whether it is by prescription or is being misused.

Tests for amphetamine cross-react with several other substances and are too numerous to present a comprehensive list. A confirmed test for amphetamine or methamphetamine can occur because a number of other medications metabolize to these. The product inserts should be consulted for the current list of cross-reacting drugs. Substances known to metabolize to methamphetamine and amphetamine include benzphetamine, dimethylamphetamine, famprofazone, fencamine, furfenorex, and selegiline (SAMHSA, 2010b). Substances known to metabolize to amphetamine include amphetaminil, clobenzorex, ethylamphetamine, fenethylline, fenproporex, mefenorex, mesocarb, and prenylamine (SAMHSA, 2010b).

Barbiturates

The incidence of barbiturate abuse is low compared with abuse of other drugs or alcohol (SAMHSA, 2009). Barbiturates (sans phenobarbital) are detected easily using a variety of immunoassays, even though only a small amount of the parent drug is found in the urine. The use of barbiturates may be confirmed readily using several different methods including, but is not limited to, GC/MS and liquid chromatography/tandem mass spectrometry (LC/MS/MS) due primarily to the high doses commonly administered or taken (Levine, 2010). Most urine immunoassay tests use secobarbital as the calibrator, at a cutoff concentration of 200 ng/mL or 300 ng/mL. Cross-reactivity with other barbiturates varies with this assay, and the detection window is dose dependent. Several commonly used assays generally cross-react with and detect butabarbital and amobarbital (Kwong, 2008b). The window of detection depends on the type of barbiturate (see Exhibit 5-1).

Benzodiazepines

The results of urine drug tests for benzodiazepines may be challenging to interpret without a basic knowledge of the pharmacokinetics of the different benzodiazepines. Like barbiturates, benzodiazepines are classified by their elimination half-lives. It is important to know a test's sensitivity and specificity for the benzodiazepine in question. False-negative results can occur if a test is set to detect only one benzodiazepine or its primary metabolite(s), and the clinician is trying to monitor a non-cross-reacting benzodiazepine. Because the parent drug in the benzodiazepine class is usually undetectable in urine drug tests, drug-screening immunoassay tests are usually designed to detect a specific metabolite,

Exhibit 5-1. Barbiturates—Window of Detection

Selected Barbiturates	Window of Detection
Short acting (e.g., pentobarbital, secobarbital)	4–6 days after the last use (cutoff of 300 ng/ml)
Intermediate acting (e.g., amobarbital, butabarbital)	3–8 days (cutoff of 300 ng/mL)
Long acting (e.g., phenobarbital)	10–30 days (cutoff of 300 ng/mL)

Sources: Baselt (2008); White & Black (2007).

either unconjugated oxazepam or its glucuronide conjugates. Immunoassay tests are more likely to detect benzodiazepines that are metabolized to the targeted compound and may miss the other non-cross-reacting compounds.

Benzodiazepines can be divided into several groups, based on their metabolites:

- Some benzodiazepines (e.g., chlordiazepoxide, diazepam, temazepam) are metabolized to oxazepam. Oxazepam is conjugated into an inactive glucuronide metabolite.
- Nitrobenzodiazepines (e.g., clonazepam which is primarily reduced to 7-aminoclonazepam, which is further metabolized) are usually reduced to the corresponding amino compound, but are not converted into oxazepam or its conjugate.
- The triazolobenzodiazepines such alorazepam, estazolam, and triazolam tend to form hydroxyl derivatives that are separate and distinct from oxazepam.
- Other benzodiazepines (e.g., lorazepam, flurazepam) have a unique metabolism that does not result in the formation of oxazepam.

Clinical laboratories usually use cutoff concentrations of 200 ng/mL or 300 ng/mL, which can detect use of a benzodiazepine, but may not necessarily detect a low therapeutic dose (e.g., triazolam) (Warner, 2003).

Flunitrazepam (Rohypnol), commonly known as "Roofies," is a Schedule I substance. Flunitrazepam is one of the so-called "date-rape" drugs and shows good to excellent cross-reactivity in most commercial urine benzodiazepine assays except the Neogen, Immunalysis, and Randox assays. If ingested, flunitrazepam and/or its metabolites may be detected for approximately 4–12.5 days at higher doses (White & Black, 2007). See Exhibit 5-2 for estimated windows of detection of some of the most commonly prescribed benzodiazepines.

Cocaine

The Federal workplace cutoff concentration for initial testing for cocaine is 150 ng/mL, and confirmatory testing for cocaine metabolite (benzoylecgonine) is 100 ng/mL (SAMHSA, 2008).

Urine drug tests for cocaine detect cocaine's major metabolite, benzoylecgonine. The body quickly metabolizes cocaine to its major metabolite, benzoylecgonine, and neither is stored in the body. Therefore, even with chronic use, the window of detection is 1–3 days (Jufer, Walsh, Cone, & Sampson-Cone, 2006), with the clinical test cutoff of 300 ng/mL. The detection window may be longer using the federally mandated cutoffs.

Urine immunoassay tests for cocaine are highly specific and detect use of powder (snorting or insufflation), parenteral use, oral ingestion, smoked, or use of crack cocaine. Among the possibilities of products they

Exhibit 5-2. Benzodiazepines—Window of Detection*

Benzodiazepines	Estimated Window of Detection
Short acting (e.g., triazolam)	Up to 24 hours
Intermediate acting (e.g., alprazolam, clonazepam, lorazepam, temazepam)	1–12.5 days
Long acting (diazepam)	5–8 days for diazepam 6–24 days for the active metabolite, nordiazepam
Chronic abuse of benzodiazepines	Up to 30 days after the last dose

*Higher doses and some pathologies may extend the window of detection.

Source: White & Black (2007).

cannot distinguish is "Inca" tea or "coca" tea—made from coca leaves—because they contain cocaine. Ingestion of tea prepared from coca leaves produces positive urine tests for benzoylecgonine (Jenkins, Llosa, Montoya, & Cone, 1996).

Immunoassay tests are highly specific for the cocaine metabolite (benzoylecgonine) and do not cross-react with other substances.

Marijuana/Cannabis

The SAMHSA workplace cutoff concentration for cannabinoid metabolites is 50 ng/mL for initial testing. The confirmatory testing cutoff for cannabinoid metabolite (delta-9-tetrahydrocannabinol-9-carboxylic acid) is 15 ng/mL.

Marijuana, the most commonly used illicit drug, can be detected for prolonged periods after regular use. The active principle of marijuana, tetrahydrocannabinol (or THC) has high lipid solubility. The THC that is stored in fatty tissue gradually reenters the bloodstream at very low levels, permitting metabolism and eventual excretion. THC is metabolized extensively in the liver.

The window of detection is highly dependent on the quality of the marijuana, the individual's body fat content and metabolism, chronicity of use, the individual's state of hydration when the urine sample is collected, and the cutoff used by the laboratory (White & Black, 2007). Approximate window of detection times are as follows:

- Up to 3 days for single use
- Up to 4 days for moderate use
- Up to 10 days for heavy use
- 30–36 days for chronic, heavy use

Marijuana is easily detected by immunoassay. Generally, laboratory tests for marijuana use are designed to detect THC-COOH (11-nor-Δ9-tetrahydrocannabinol-9-carboxylic acid; commonly referenced as THC acid or THCA), the major inactive metabolite of THC. Laboratory tests are available with cutoff concentrations of 20 ng/mL, 50 ng/mL, or 100 ng/mL, although the majority of laboratories employ 50 ng/mL. The 20 ng/mL cutoff is commonly used clinically (White & Black, 2007). The 100 ng/mL cutoff is rarely used due to its lack of sensitivity.

Confirmation by GC/MS tests should be performed if the positive screening test results have legal or other serious implications for the patient. Some legal food products are made from hemp seeds (e.g., hemp seed oil, flour, liquor, ale). These products do not appear to be psychoactive, but, after a person has ingested these food products, THC metabolites have been detected in urine specimens. However, usually the THC concentrations in the food products are too low to produce a positive urine drug test result (Bosy & Cole, 2000). Some proton-pump inhibitors have caused positive tests on immunoassay (Gourlay et al., 2010).

The literature is mixed on the test results of passive exposure to marijuana. Under extreme conditions (e.g., the person rides in a closed car with people smoking marijuana), passive exposure can lead to positive results with a screening cutoff of 20 ng/mL. However, the levels of marijuana metabolites found in urine under less extreme passive exposure conditions are below the 50 ng/mL (employment-related) cutoff concentrations and would not be detected (Cone et al., 1987; Perez-Reyes, Di Guiseppi, & Davis, 1983). Marinol and Sativex cause positive results because they contain THC.

Opioids

Clinical urine opioid drug testing is done to detect illicit opioid use, monitor adherence to pain treatment with opioids (especially in pain management clinics), and monitor adherence to methadone treatment. Practitioners need to be particularly careful when interpreting urine drug test results

for opioids. It is essential to understand the metabolism of this class of drugs to interpret drug tests.

The term *opioids* includes both opiates and opioids. Opioids are a group of compounds that have pharmacological properties similar to morphine and have affinity toward the opiate receptors in the brain (Dasgupta, 2008). The term *opiates* refers to naturally occurring alkaloids (morphine and codeine) obtained from the opium poppy and semisynthetic alkaloids that are partially derived from the opium poppy (i.e., buprenorphine, dihydrocodeine, heroin, hydrocodone, hydromorphone, levorphanol, oxycodone, and oxymorphone) (Dasgupta, 2008). Opioids include the synthetic compounds that are structurally unrelated to morphine (i.e., fentanyl, meperidine, methadone, pentazocine, propoxyphene, tramadol) (Dasgupta, 2008).

Opiate immunoassay tests were originally designed to detect morphine and codeine as target analytes to identify heroin use (Kwong, 2008a, 2008b). Morphine is a metabolite of heroin (Warner, 2003). Many laboratories use SAMHSA's Federal workplace cutoff concentrations for opiates and test for morphine, codeine, and 6-acetylmorphone (6-AM). However, for opiates, a cutoff of 300 ng/mL is commonly preferred clinically (White & Black, 2007). As heroin is metabolized, 6-AM is produced, which is then hydrolyzed to morphine. Thus, the detection of 6-AM in the urine proves heroin use, but 6-AM is eliminated quickly from the body, making detection in urine possible for only a few hours (Gourlay et al., 2010). A typical opiate screen reports the presence of only codeine and morphine. An expanded opiate panel may also include hydrocodone and hydromorphone and/or oxycodone and oxymorphone (see Exhibit 5-3).

Distinguishing between illicit opioid use and the use of prescribed opioid medications can be difficult. Immunoassay tests have variable cross-reactivity with semisynthetic opioids (i.e., hydrocodone, hydromorphone) and may or may not detect their use. The synthetic opioids (e.g., meperidine, fentanyl, methadone) are structurally dissimilar enough from morphine that they are not detected in standard opioid urine immunoassay tests, although some cross-reactivity—especially with the metabolites—may exist. Separate immunoassay tests specifically designed for their detection must be used. Oxycodone and its active metabolite, oxymorphone, require a drug-specific test. Specific assays for oxycodone are available as both POCTs and laboratory tests. Specialized tests for synthetic opioids must be ordered when

Exhibit 5-3. Opioids—Window of Detection*

Opioid	Window of Detection	Cutoffs
Buprenorphine	Up to 4 days	0.5 ng/mL
Codeine	1–2 days	300 ng/mL
Heroin metabolite (6-acetylmorphine [6-AM])	1–3 days	10 ng/mL
Hydrocodone	1–2 days	100 ng/mL
Hydromorphone	1–2 days	300 ng/mL
Methadone (maintenance dose)	3–11 days	300 ng/mL
Morphine	1–2 days	300 ng/mL
Oxycodone (immediate-release formulation)	1–1.5 days	100 ng/mL
Oxycodone (controlled-release formulation)	1.5–3 days	100 ng/mL
Oxymorphone (immediate-release formulation)	1.5–2.5 days	100 ng/mL
Oxymorphone (extended-release formulation)	1–4 days	100 ng/mL

*Higher doses and some pathologies may extend the window of detection.

Sources: Kronstrand et al. (2008); White & Black (2007).

concerns exist about abuse or diversion of synthetic opioid pain medications or to monitor patients' use of buprenorphine or methadone. Many laboratories have specific pain medication panels that test for codeine, morphine, hydrocodone, hydromorphone, oxycodone, fentanyl, and buprenorphine (Gourlay et al., 2010). Buprenorphine has potential for abuse, especially in the stand-alone preparation—Subutex (Smith, Bailey, Woody, & Kleber, 2007).

Poppy seeds can contain morphine and codeine. Ingesting large amounts of poppy seed or products containing poppy seeds can cause a positive urine drug test result. The urine drug test result will show that morphine and, possibly, codeine are present, and the practitioner needs to determine whether poppy seeds are the source. The original employment-related and clinical cutoff concentration for morphine and codeine was 300 ng/mL, but was increased to 2,000 ng/mL to avoid positive test from poppy seed consumption (often cited as the "poppy seed defense"). This higher cutoff minimized opioid-positive test results from poppy seeds, but also reduced the likelihood that opioid use would be detected.

Methadone is a synthetic opioid used for treatment of opioid dependence and chronic pain and is not detected in standard opioid drug tests. Specific tests for methadone and its major metabolite EDDP (or 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine) exist and are used to monitor adherence to medication-assisted treatment and to check for illicit drug use. These methadone immunoassay tests have little cross-reactivity with other opioids. Therefore, a positive opioid drug test result for a patient on methadone suggests the use of other opioids. The cutoff concentration is generally set at 300 ng/mL and can detect methadone in urine for several days after the last therapeutic dose. To confirm that the patient has taken methadone and is not simply adding it to a urine specimen, the test for the methadone metabolite, EDDP, can be ordered. If a practitioner is caring for a patient on methadone maintenance treatment for opioid dependence, the practitioner can ask the patient to sign a release of information to obtain the patient's urine test results from the opioid treatment program.

Other Substances of Abuse

Testing information for other substances is presented below.

PCP

The SAMHSA revised workplace cutoff concentration for PCP is 25 ng/mL for initial testing. The confirmatory testing cutoff for PCP is 25 ng/mL. This cutoff is often used for clinical purposes, as well. Federally regulated laboratories are required to test for PCP; other laboratories are not. Directors of clinical laboratories may add PCP to their screening drug panel if PCP use is prevalent in the community. The window of detection for PCP from casual use is 1.5–10 days (urine pH-dependent) and for up to several weeks with chronic use. The metabolite of dextromethorphan can cross-react with PCP and could cause a false positive.

When used to adulterate urine specimens, table salt, sodium hypochlorite, sodium hydroxide, detergent, and soap cause false-negative test results (Jaffee et al., 2007). However, these adulterants can be detected if the pH and specific gravity of the urine samples are checked.

Club Drugs

Club drugs generally include gamma-hydroxybutyrate (GHB), ketamine, flunitrazepam (Rohypnol, or "Roofies"), MDMA, MDA, and MDEA. Urine drug screening tests do not generally screen for club drugs. However, please see the section above on amphetamines for information about MDMA, MDA, and MDEA, and the section on benzodiazepines for information on flunitrazepam (Rohypnol, or "Roofies"). New drug tests may screen for some club drugs,

but routine drug tests cannot detect ketamine or GHB. Testing for GHB can be done by using GC or high-performance LC (LeBeau et al., 2006). The window of detection for GHB is generally less than 12 hours. Two commercial enzyme-linked immunosorbent assays (ELISAs) that test for ketamine are available (Huang et al., 2007). For a single dose of ketamine, detection is possible for about 3 days at a cutoff of 50 ng/mL (Baselt, 2004; Cone & Huestis, 2007).

LSD

Very little of the parent drug, LSD, is excreted in urine and it can be detected for only approximately 4 hours. The most abundant metabolite is nor-LSD (N-desmethyl-LSD), which is generally detected at a cutoff level of 0.5 ng/mL. Confirmatory testing is usually done with LC/MS or LC/MS/MS.

Inhalants

No standard drug test can detect inhalant use. Most inhalants contain many compounds, and no single assay can test for all of them. Some laboratories can test for inhalants using specially ordered tests, primarily with GC. Collection of a specimen for inhalants requires that the specimen be appropriately and rapidly sealed to ensure that the volatile inhalants are not lost.

Toluene is the main substance in many inhalants. It is cleared from the body quickly, leaving a short period to detect exposure. Most laboratories are unable to test for this substance. Urinary hippuric acid (UHA) measurements can be adapted to detect toluene inhalation, but they should be used cautiously because a person's metabolism can raise the levels of UHA. Thiesen, Noto, and Barros (2007) report that UHA levels higher than 3.0 g/g creatinine indicate intentional exposure.

Appendix A—Bibliography

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Appendix B—Laboratory Initial Drug-Testing Methods

Testing Method	Description	Advantages	Disadvantages/ Cautions
Cloned Enzyme Donor Immunoassay (CEDIA)	• An immunoassay using enzyme (ß-glucuronidase) fragments engineered by recombinant DNA techniques. • Two fragments, the enzyme donor and enzyme acceptor, are inactive when separated. • Based on competition for antibody binding sites between drug conjugated with enzyme donor (ED) and drug in the specimen. • Enzyme activity decreases when the ED drug fragment is bound, so the drug concentration in the specimen can be measured by an increase of enzyme activity.	• Same reliability as EMIT in screening for barbiturate use.	• May produce false-positive results for amphetamines and lysergic acid diethylamide when bupropion is used.
Enzyme-Multiplied Immunoassay Technique (EMIT)	• An immunoassay based on competition for antibody binding sites between drug in the specimen and drug labeled with an enzyme. • Enzyme activity decreases on binding to the antibody, so the drug when present in the specimen can be measured by an increase in terms of enzyme activity.	• Widely used. • Simple to conduct (same as CEDIA or KIMS).	• Poor performance record (high rate of false-positive results in some studies). Many over-the-counter (OTC) preparations can cause false-positive results for amphetamines and phencyclidine (PCP) assays.
Enzyme-Linked Immunosorbent Assay (ELISA)	• A competitive binding enzyme immunoassay using drug-specific antibodies immobilized on the sides of a microplate well.	• The most versatile and commonly used immunoassay. • Customized tests developed for different settings, substances, purposes, and matrices.	• Labor intensive. • Poorly suited for automation.

Testing Method	Description	Advantages	Disadvantages/ Cautions
Fluorescence Polarization Immunoassay (FPIA)	• An immunoassay based on competition between the drug in the specimen and drug labeled with a fluorophore. • Light emitted by the fluorescently labeled drug/antibody complex is more polarized. • The specimen's fluorescence polarization value is inversely related to the drug concentration.	• Sensitive. • Specific.	• Cannot be automated conveniently.
Kinetic Interaction of Micro-particulates in Solution (KIMS)	• An immunoassay based on the principle of the kinetic interaction of microparticles in a solution where the drug content of the urine is directly proportional to the inhibition of the microparticle aggregation.	• May be used to test a wide variety of drugs of abuse.	• Cross-reacts with some OTC preparations when testing for amphetamines.

Sources: Armbruster, Hubster, Kaufman, & Ramon (1995); Center for Substance Abuse Treatment (2006b); Neerman (2006); Verebey, Meenan, & Buchan (2005); Vidal & Skripuletz (2007).

Appendix C—Laboratory Confirmatory Drug-Testing Methods

Testing Method	Description
Gas Chromatography (GC)	• A technique for separating and analyzing compounds that can be vaporized without chemicals.
High-Performance Liquid Chromatography (LC)	• A chromatographic technique for separating and analyzing chemical substances in solution. • Separation is based on absorption, partition, ion exchange, and/or size exclusion.
GC/Mass Spectrometry (GC/MS)	• A combined technique coupling an MS (mass spectrometer or mass selective detector) with a GC instrument. • After the GC has separated the analytes in a specimen, the components enter the MS, which identifies and quantifies the separated analytes. • The MS creates charged particles (ions) and separates them according to their mass-to-charge ratio. • The ions form unique mass spectra, which are used to identify analytes. • Most common method of confirmation.
GC With Tandem MS (GC/MS/MS)	• The same principles, as described above. • The MS produces and isolates the ion of interest, which is then reacted with a reagent gas to produce fragments. • The MS scans the fragments (called the "productions") to obtain structural information. • This method is more sensitive than GC/MS.
LC With MS (LC/MS)	• LC can accommodate nonvolatile compounds. • Separation is based on distribution of the solutes between a liquid mobile phase and a stationary phase. • MS phase is the same as described above. • Widely used for pain management.
LC With Tandem MS (LC/MS/MS)	• Described above, with two MS phases. • Also used in pain management.

Appendix D—Laboratory Specimen Validity-Testing Methods

Testing Method	Analytes	Description
Colorimetry	Specific gravity, pH, creatinine, adulterants (general or specific tests)	• A technique that compares the color developed in a solution of a test material with that in a standard solution, quantitated on the basis of the absorption of light. • The concentration of the analyte is determined by visually noting the color or electronically measuring the intensity of light at selected wavelengths (i.e., spectrophotometry).
Refractometry	Urine-specific gravity	• A method for determining the amount of solute (i.e., urinary total solids) in the urine by measuring the index of refraction. • A urine specific gravity refractometer displays specific gravity values converted from refractive indices.
Potentiometry	pH	• An instrument (e.g., pH meter) that measures hydronium ion activity and converts it into the negative logarithm (base 10), which is the displayed pH.
Atomic Absorption Spectrophotometry	Adulterants	• A method in which the specimen atoms in the vapor phase absorb ultraviolet or visible light and transition to higher electronic energy levels. • The analyte concentration is determined from the amount of absorption of specific wavelengths.
Capillary Electrophoresis (CE)	Adulterants	• A technique based on the mobility of ions in an electric field. • Positively charged ions migrate toward a negative electrode, and negatively charged ions migrate toward a positive electrode. • Ions have different migration rates depending on their total charge, size, and shape and can therefore be separated. • CE is an electrophoretic method using a small-bore, fused silica capillary tube.
Gas Chromatography/ Mass Spectrometry (GC/MS)	Adulterants	• Full-scan MS or selected ion monitoring identifies unknown analytes. • The identification of the analyte of interest relies on a comparison with the mass spectra of an analyzed reference standard or reference library spectra.
Inductively Coupled Plasma/MS	Adulterants	• A combined analytical method in which a vaporized sample is introduced into a radio frequency-induced plasma, is ionized, and then enters an MS for identification and quantification.

Testing Method	Analytes	Description
Multi-Wavelength Spectrometry	Adulterants	• A method that uses multiple wavelengths of light (or other electronic transmissions) to identify an analyte. • The method generates corrected absorbance values that are related to the analyte concentration.
Ion Chromatography	Adulterants	• A form of liquid chromatography that uses ion-exchange resins to separate atomic or molecular ions based on their interaction with the resin.

Appendix E—Glossary

adulterated specimen. A specimen containing either a substance that is not a normal constituent for that type of specimen or containing an endogenous substance at a concentration that is not a normal physiological concentration.

adulteration panel. Testing a specimen for substances that mask the presence of illegal drugs in that specimen.

aliquot. A fractional part of a specimen.

analyte. Any material or substance subjected to analysis (testing).

chain of custody. Procedures to account for the integrity of each specimen or aliquot by tracking its handling and storage from point of specimen collection to final disposition of the specimen and its aliquots.

concentration. Amount of a drug in a unit volume of biological fluid expressed as weight/volume. Urine concentrations are usually expressed as nanograms per milliliter (ng/mL), micrograms per milliliter (ug/mL), or milligrams per liter (mg/L).

confirmatory drug test. A second analytical procedure performed on a different aliquot of the original specimen to identify and quantify the presence of a specific drug or drug metabolite.

confirmatory validity test. A second test performed on a different aliquot of the original specimen to support or deny the initial validity test result.

conjugate. A compound produced by the chemical joining of at least two other compounds.

creatinine. An endogenous substance appearing in the urine, commonly used to estimate kidney functioning.

cutoff concentration or level. The measurement used to establish and report a specimen as negative or positive.

deconjugate. The breaking down of a substance into the original compounds.

dilute specimen. A urine specimen whose creatinine is less than 20.0 mg/dL, but equal to or greater than 2.0 mg/dL and whose specific gravity is less than 1.0030, but equal to or greater than 1.0010.

diversion (of prescribed medications). The act of selling or giving away prescribed medications instead of taking them as prescribed.

initial drug test. A test to differentiate a negative specimen from one that requires further testing for drugs or drug metabolites. Also called a *screening test*.

invalid result. The result reported when a scientifically supportable analytical test result cannot be established for a specimen.

matrix. The biological medium tested for the presence of drugs or drug metabolites.

Medical Review Officer (MRO). A licensed physician who reviews, verifies, and reports a specimen test result in regulated workplace programs.

metabolite. A compound produced by enzymatic or chemical means while in the body, usually to a more water soluble form for easy excretion.

negative test result. The result reported by a laboratory when a specimen contains a drug or drug metabolite less than a prespecified cutoff level or concentration.

pharmacogenomic. The genetic factors that influence an organism's response to or metabolism of a drug or a medication.

point-of-care test (POCT). A drug or validity test conducted at the collection site to obtain an initial or screening result on whether a specimen contains a drug or drug metabolite or is not a valid specimen. Also called onsite, point-of-service, or point-of-collection test.

positive test result. The result reported by a laboratory when a specimen contains a drug or drug metabolite greater than or equal to a prespecified cutoff level or concentration.

sample. A representative portion of a specimen or quality control material used for testing.

specimen. Fluid or tissue derived from the body collected for testing.

substituted specimen. A specimen that has been submitted in place of the patient's urine, either as evidenced by creatinine and specific gravity values that are outside the physiologically producible ranges of human urine or is another person's urine.

Appendix F—Expert Panel

Louis Baxter, M.D., Chair
Executive Medical Director
Professional Assistance Program of New Jersey
Princeton, New Jersey

Lawrence S. Brown, Jr., M.D., M.P.H.
Senior Vice President
Addiction Research and Treatment
Brooklyn, New York

Paula Satterly Childs, Ph.D., D-ABFT
Director of Toxicology
Laboratory Corporation of America
Research Triangle Park, North Carolina

Edward Cone, Ph.D.
President
ConeChem Research LLC
Severna Park, Maryland

Dennis J. Crouch, M.B.A.
Associate Director for Sports Testing Services
Aegis Sciences Corporation
Nashville, Tennessee

Martin Doot, M.D. (Deceased)
Medical Director
Illinois Professionals Health Program
Des Plaines, Illinois

Mahmoud A. ElSohly, Ph.D., BCFE, BCFM
President
ElSohly Laboratories, Inc.
Oxford, Mississippi

M. P. George, M.S.
Laboratory Operations Director
Quest Diagnostics, Inc.
Schaumburg, Illinois

Barbara L. Johnson, Esq.
Partner, Employment Department
Paul Hastings
Washington, D.C.

Donald Ian Macdonald, M.D., FASAM
Chief Medical Officer
Integrated Laboratory Services
Chestertown, Maryland

Susan McCall, M.D., M.P.H.
Medical Director
Oregon Health Professionals Program
Tigard, Oregon

Susan Neshin, M.D.
Medical Director
Jersey Shore Addiction Services
Asbury Park, New Jersey

Kent Peterson, M.D.
President
Occupational Health Strategies, Inc.
Charlottesville, Virginia

Gregory Rokosz, D.O., J.D.
Senior Vice President
Medical and Academic Affairs
St. Barnabas Medical Center
Livingston, New Jersey

Michel A. Sucher, M.D., FACEP, FASAM
Greenberg and Sucher, PC
Scottsdale, Arizona

Robert E. Willette, Ph.D.
President
Duo Research, Inc.
Eagle, Colorado

Appendix G—Consultants and Field Reviewers

Consultants

Peter David Friedmann, M.D., M.P.H.
Assistant Professor
Brown Medical School
Departments of Medicine and Community Health
Rhode Island Hospital
Providence, Rhode Island

Elizabeth A. Warner, M.D.
Medical Director
Ambulatory Services
Associate Professor
Department of Internal Medicine
University of South Florida
Tampa, Florida

Field Reviewers

Paul L. Cary, M.S.
Director
Toxicology and Drug Monitoring Laboratory
University of Missouri
Columbia, Missouri

Nancy L. Hamilton, M.P.A., CAP, CCJAP
Chief Executive Officer
Operation PAR
Pinellas Park, Florida

Carolyn Hardin, M.P.A.
Director
National Drug Court Institute
Alexandria, Virginia

Jim Heit, M.T.
Sterling Reference Laboratories
Tacoma, Washington

Ron Jackson, M.S.W.
Director
Evergreen Treatment Services
Seattle, Washington

Jason Kletter, Ph.D.
President
Bay Area Addiction Research and Treatment (BAART)
San Francisco, California

Appendix H—Acknowledgments

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Lynne MacArthur, M.A., A.M.L.S., served as the JBS KAP Executive Project Co-Director, and Barbara Fink, RN, M.P.H., served as the JBS KAP Managing Project Co-Director. Other JBS KAP personnel included Wendy Caron, Editorial Quality Assurance Manager; and Frances Nebesky, M.A., Copy Editor.

Technical Assistance Publications (TAPs) include:

TAPs 1–9, 25* These TAPs have been archived and are no longer available.

TAP 10 *Rural Issues in Alcohol and Other Drug Abuse Treatment*

TAP 11 *Treatment for Alcohol and Other Drug Abuse: Opportunities for Coordination**

TAP 12 *Approval and Monitoring of Narcotic Treatment Programs: A Guide on the Roles of Federal and State Agencies**

TAP 13 *Confidentiality of Patient Records for Alcohol and Other Drug Treatment* **BKD156**

TAP 14 *Siting Drug and Alcohol Treatment Programs: Legal Challenges to the NIMBY Syndrome* **BKD175**

TAP 15 *Forecasting the Cost of Chemical Dependency Treatment Under Managed Care: The Washington State Study**

TAP 16 *Purchasing Managed Care Services for Alcohol and Other Drug Abuse Treatment: Essential Elements and Policy Issues**

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