

A Clinical Guide to Urine Drug Testing

CME Certified Monograph



**AUGMENTING PAIN MANAGEMENT
& ENHANCING PATIENT CARE**

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*University of Medicine & Dentistry of
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PharmaCom Group, Inc.

*An educational activity designed for
primary care physicians, family physicians,
and pain physicians.*

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Educational Overview

Urine drug testing (UDT) has expanded beyond the workplace and now is utilized in a number of contexts. Clinically, UDT is regularly performed in drug treatment centers to monitor abstinence from illicit drugs and to confirm adherence to maintenance drugs, in emergency departments to support both acute treatment decisions and efforts to prevent future events (illicit drug use is considered a marker for future trauma), in pain clinics, and in primary care settings. This monograph will focus on patient-centered UDT used to enhance the management of chronic pain patients. In this context, UDT can serve as a useful tool to help verify patient-reported compliance or demonstrate unreported drug exposure.

Three key elements of UDT must be appreciated to best utilize this tool: the pharmacologic characteristics of the drugs tested, their relationship to the sample, and the analyses performed by the laboratory. Physicians who order UDT should frequently consult with laboratory scientists to select appropriate tests, and keep informed of laboratory changes, such as adoption of new agents or assays. Physicians should consider UDT results in the context of all the clinical information, and contact the laboratory scientist to clarify test results when there is a discrepancy. Unfortunately, in a study among family medicine physicians, only 23% would consult with the laboratory director when confronted with an abnormal or unexpected UDT result.

The purpose of this monograph is to provide the knowledge necessary to interpret most UDT results in the context of pain management.

Target Audience

This activity is designed for primary care, family, and pain medicine practitioners interested in or involved with the clinical management of patients receiving opioid therapy and the utilization of UDT in the clinical setting to aid in treatment.

Learning Objectives

After completing this educational activity, participants should be better able to:

1. Distinguish between the needs of forensic testing and UDT used in clinical practice.
2. Describe the 2 main types of UDT methodologies.
3. Develop a strategy to incorporate UDT into practice and order appropriate tests.
4. Interpret UDT results within the limitations of current technologies.

Method of Instruction

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INTRODUCTION

The technologic advancements that enable laboratories to detect exquisitely low concentrations of drugs in biologic fluids began in the late 1950s with the development of the immunoassay and the coupling of gas chromatography (GC) and mass spectrometry (MS). These technologies serve as the backbone of the 2-tiered testing program that has grown out of the Federal Drug Free Workplace Act established in the 1980s.^{1,2} The majority of urine drug testing (UDT) is still performed in regulated workplace programs as a means to deter and detect illicit drug use.³ Spurred by insurance and injury compensation coverage, many non-federal agencies and companies have adopted the *Mandatory Guidelines for Federal Workplace Drug Testing Programs* into their own employee protocol.³ In these settings, UDT is routinely performed prior to hiring and in response to any accident. Additional testing may occur with or without announcement, depending on the company's policies.

UDT has expanded beyond the workplace and now is performed in a number of contexts, such as in sports organizations, schools, and the criminal justice system, to provide objective data on drug exposure.⁴⁻⁷ Depending on the circumstances, consequences for using illicit substances are quite severe and include incarceration, termination of employment, suspensions, and fines.^{4,7} Clinically, UDT is regularly performed in drug treatment centers to monitor abstinence from illicit drugs and to confirm adherence to maintenance drugs, in emergency departments (EDs) to support both acute treatment decisions and efforts to prevent future events (illicit drug use is considered a marker for future trauma), in pain clinics, and in primary care settings.⁴⁻¹² This monograph will focus primarily on patient-centered UDT used to enhance the management of chronic pain patients. In this context, UDT can serve as a useful tool to help verify patient-reported compliance or demonstrate unreported drug exposure. However, 3 key elements of UDT must be appreciated to best utilize this tool: the pharmacologic characteristics of the drugs tested, their relationship to the sample, and the analyses performed by the laboratory. The purpose of this monograph is to provide the knowledge necessary to interpret most UDT results encountered in the management of patients with pain. ■

OPIOID THERAPY IN PAIN MANAGEMENT

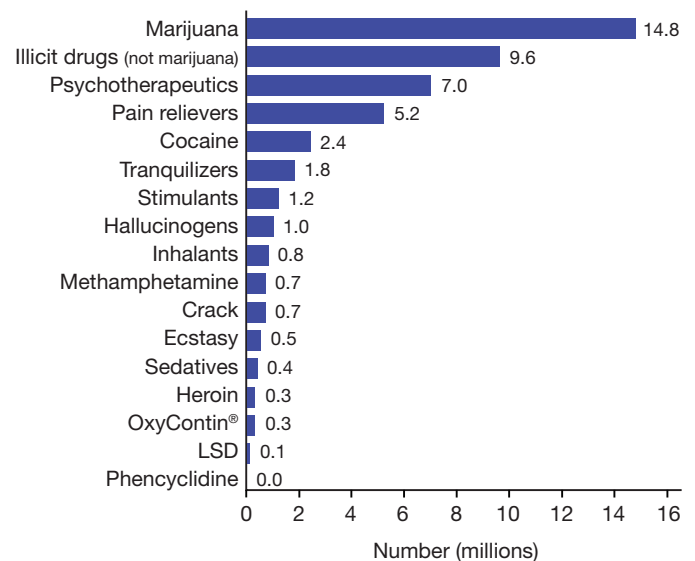
The use of opioids in pain management is a double-edged sword: while they are absolutely necessary to manage the pain and improve the function of many patients, their misuse is a significant national public health problem.¹³⁻¹⁸ Concerns about addiction, drug abuse, and diversion can be major barriers when managing chronic pain patients.¹³⁻¹⁶ In one study, physicians were most reluctant to prescribe opioids due to concerns about drug abuse (84%) and addiction (75%), followed by side effects (68%) and tolerance (61%).¹⁹ In addition, time constraints, skepticism regarding overall benefit for patients, and high-profile legal ramifications have deterred many physicians from prescribing opioids.^{17,20,21}

In order to overcome these barriers to pain management, a practical approach is needed to monitor patient adherence and response to prescribed opioids.^{13,17,18,22} Objective UDT data accompanied by appropriate surveillance and follow-up can contribute to patient management, particularly when there is uncertainty about the pain diagnosis or the patient's level of risk.^{6,14,19}

Scope of Drug Abuse

The *2006 National Survey on Drug Use and Health* estimated that 20.4 million Americans aged 12 years or older (8.3% of the population) were current (past-month) illicit drug users.²³ While it is clear that marijuana was the most commonly used illicit drug (14.8 million current users) (Figure 1), 7.0 million

Figure 1. Past-Month Use of Specific Illicit Drugs: 2006*²³



*Among persons aged 12 years and older
LSD=lysergic acid diethylamide

persons also used prescription-type psychotherapeutic drugs nonmedically*—of these, 5.2 million misused analgesics, an increase from 4.7 million in 2005.²³ The number of people who initiated nonmedical prescription analgesic use in 2006 was similar to the number of new initiates of marijuana use in that year (Figure 2).²³

Source of Opioid Analgesic: Among persons who used analgesics nonmedically in the past year, 56% reported that they obtained their most recent drug from a friend or relative for free, 19% from a single physician, and 4% from a drug dealer or other stranger.²³ Less than 1% reported buying the drug on the Internet, although some sources suggest the volume of online analgesic sales is underreported.^{23,24}

Abuse/Misuse in Chronic Pain Patients

The majority of patients on long-term opioid therapy for chronic pain will not develop opioid-use disorders. However, the rates of opioid abuse are usually somewhat higher in these patients than in the general population. In a sample of patients receiving opioid therapy from their primary care physician (PCP), the frequency of opioid use disorders was 4 times higher compared with general population samples (3.8% vs 0.9%).²⁶ In another primary care sample of chronic pain patients receiving opioids, lifetime drug problems were common—with 17% of men and 10% of women reporting drug abuse treatment at least once in their lifetime.¹⁴

Any departure from medical direction in the consumption of pain medication calls for a clinical intervention. Aberrant drug-related behaviors (ADRBs) should be documented and addressed with the patient to help understand his or her motivation for noncompliance. For example, is he/she suffering from:

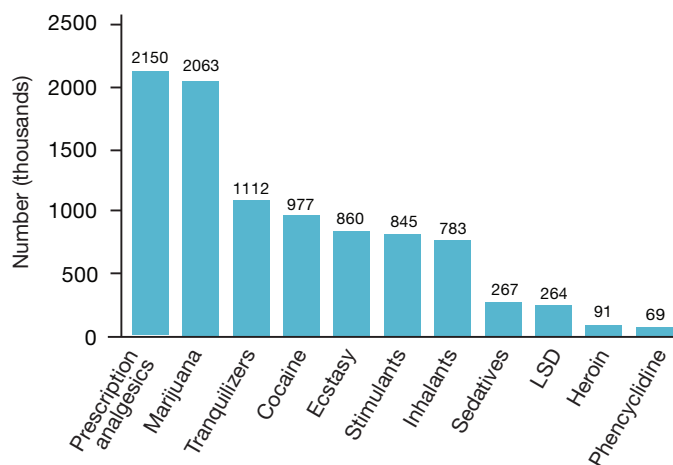
- Undertreated pain?
- Active addiction?
- A comorbid anxiety or depressive disorder?

Rates of psychiatric comorbidity among chronic pain patients are higher than the general population, but similar to those of addiction treatment samples.¹⁴ Because pain management is complicated by alcohol and drug use, stress, depression, and a variety of other comorbid medical and social issues, it is important to deal with these underlying problems in order to optimize treatment.¹⁴ Monitoring measures may need to be increased and referrals to specialists made when appropriate.

Patient Risk of Displaying ADRBs

The basis for selecting, excluding, or terminating chronic pain patients from opioid treatment is not well-defined.^{13,17,22} As a

Figure 2. Past-Year Initiates of Illicit Drugs: 2006*²³



*Among persons aged 12 years and older
LSD=lysergic acid diethylamide

result, physicians frequently rely on demographic information, assumed risk factors, and “gut instinct” to determine whether a patient will misuse opioids prescribed to relieve pain.²⁷ Unfortunately, several reports demonstrate the difficulty in predicting medication misuse and ADRBs based on patient demographics, as well as medical and behavioral variables.^{23,27-30} For example, in 2006, 18.5% of unemployed adults were current illicit drug users, compared with 8.8% of those employed full-time and 9.4% of those employed part-time—however, 74.9% of current illicit drug users were employed full- or part-time.²³ In another study, 45% of chronic pain patients on opioid therapy in an urban pain management center had confirmed abnormal UDT results: 20% were found to have used illicit substances, 14% had used additional prescription drugs, and another 10% had not used the drugs prescribed.²⁷ However, patient gender, pain site, and the number, type, and dose of prescribed opioids were poor predictors of abnormal UDT results.²⁷ At an academic

Table 1. Serious ADRBs Among Chronic Pain Patients (N=196)³¹

ADRB	Number (%)
Positive UDT result for stimulants (cocaine or amphetamines)	25 (40.3%)
Negative UDT result for prescribed opioids	15 (24.2%)
Doctor shopping	10 (16.1%)
Inconsistent UDT result (nonprescribed)	9 (14.5%)
Prescription forgery	2 (3.2%)
Diversion	1 (1.6%)
Total	62 (100%) [31.6% of total]

*Nonmedical use was defined as use without a prescription of the individual's own or simply for the experience or feeling the drugs caused.

pain management program, 62 of 196 patients exhibited ADRBs over 1 year (Table 1): 25 had confirmed positive UDT results for stimulants, 15 had repeated confirmed negative results for prescribed opioids despite being counseled on scheduling of their medication, and 9 had repeated positive results for nonprescribed opioids.³¹

Other investigators have also found that both monitoring behavior and requiring UDT for individuals receiving long-term opioid therapy captures more patients with inappropriate drug-taking behavior than either method alone.²⁸ A total of 43% of patients had a “problem,” identified by either a positive UDT result or an ADRB—21% had positive UDT results alone for either an illicit drug or a nonprescribed controlled substance, 14% had behavioral issues alone, and only 8% had both positive results and behavioral issues (Figure 3).²⁸

Patient Self-Reporting

Although self-report may identify some patients with ADRBs, studies in a number of settings have demonstrated that a significant percentage of chronic pain patients inaccurately report nonadherence and illicit drug abuse.^{6,11,28,32} Therefore, it is unwise to rely on the patient’s word alone that drugs are being taken as prescribed.⁹ Deception is notoriously difficult to detect, and physicians are particularly susceptible because they practice with a “truth bias”—the physician-patient relationship is traditionally based on the physician accepting the veracity of a patient’s self-report.^{28,33} Researchers at Cornell University found that physicians detect a bogus patient only 10% of the time, even when warned of a visit by an actor with a “pain” condition; in addition, physicians were liable to mistakenly identify real patients as actors.³³

In a primary care sample of adults receiving daily opioid therapy for chronic pain, there was a 24% rate of positive UDT results for

Table 2. Opioid Risk Tool^{35,38}

Factor	Male	Female
Family history of substance abuse		
■ Alcohol	<input type="checkbox"/> 3 points	<input type="checkbox"/> 1 point
■ Illegal drugs	<input type="checkbox"/> 3 points	<input type="checkbox"/> 2 points
■ Prescription drugs	<input type="checkbox"/> 4 points	<input type="checkbox"/> 4 points
Personal history of substance abuse		
■ Alcohol	<input type="checkbox"/> 3 points	<input type="checkbox"/> 3 points
■ Illegal drugs	<input type="checkbox"/> 4 points	<input type="checkbox"/> 4 points
■ Prescription drugs	<input type="checkbox"/> 5 points	<input type="checkbox"/> 5 points
Age 16–45 yrs	<input type="checkbox"/> 1 point	<input type="checkbox"/> 1 point
History of preadolescent sexual abuse	<input type="checkbox"/> 0 points	<input type="checkbox"/> 3 points
Psychologic disease		
■ ADD, OCD, bipolar disorder, schizophrenia	<input type="checkbox"/> 2 points	<input type="checkbox"/> 2 points
■ Depression	<input type="checkbox"/> 1 point	<input type="checkbox"/> 1 point
Total Points		
0–3 points=low risk; 4–7 points=moderate risk; ≥8 points=high risk		

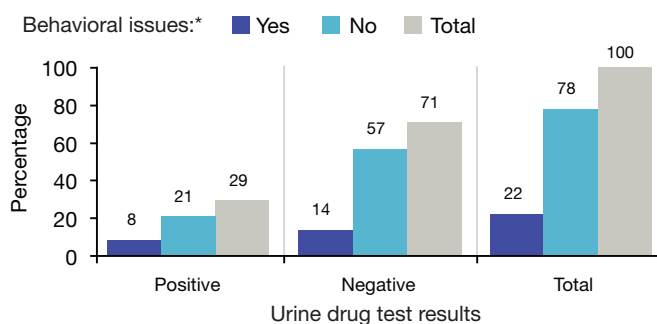
ADD=attention deficit disorder; OCD=obsessive-compulsive disorder

illicit drugs, but significant underreporting—46% of patients with positive results denied illicit drug use even when guaranteed anonymity.²⁶ In some cases, patients may underreport or deny nonmedical use of drugs or alcohol for fear of being taken off their pain medications or jeopardizing their ability to receive future prescriptions.¹⁴ Furthermore, the perceived social stigma associated with some drugs, such as heroin and cocaine, may compound inaccurate self-reported use.^{25,34} Incorrect accounts of drug use may also be the unintentional consequences of impaired memory or misunderstanding instructions or questions.^{32,34}

Screening Instruments

There is growing evidence that the use of risk-assessment instruments may provide a more rational basis for which patients can be selected for treatment.^{15,17,22,27} Stratification of patients based on their risk for opioid misuse and ADRBs can be used to establish appropriate levels of monitoring and/or identify patients who warrant referral.^{22,35–37} Examples of screening instruments include the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP®-R) and the Opioid Risk Tool (ORT).^{17,22,35,38,39} In the ORT, each factor is assigned a point value reflecting its contribution towards an individual’s likelihood of displaying ADRBs if opioids are prescribed—the tallied score is indicative of the patient’s overall risk (Table 2).^{35,38} Systematically collecting such information can help physicians develop a comprehensive treatment plan so that pain patients can receive opioids, when indicated, under controlled conditions based on their risk level.^{14,15,35} ■

Figure 3. Proportion of Chronic Pain Patients With Behavioral Issues or Positive UDT Results²⁸



*Lost/stolen prescriptions, consumption in excess of the prescribed dosage, visits without appointments, multiple drug intolerances, frequent telephone calls

UTILIZING URINE DRUG TESTING IN CLINICAL PRACTICE

Given that self-reporting of substance use is unreliable and that risk-assessment instruments are screening rather than diagnostic tools, a management strategy utilizing UDT in addition to a careful history, appropriately directed physical examination, and observation of patient behavior is useful prior to initiating and during opioid therapy. Data support that adding UDT identifies more nonadherent patients than monitoring behaviors or self-reporting alone.^{6,13,28}

Clinical Versus Forensic/ Workplace UDT

There is a significant difference between the standards and needs of forensic testing for the detection of illicit drug use and clinical testing to monitor adherence to a treatment regimen.^{9-11,40} This basic fact is important to recognize, as many “standard” urine drug tests were designed for or adapted from workplace requirements and are not optimized for clinical applications.^{9,11} Firstly, the drugs for which UDT is conducted in these 2 settings differ. In the workplace, opiate testing is performed to identify heroin, morphine, or codeine use. In the pain management setting, this list is expanded to include other opioids, such as hydrocodone, hydromorphone, or oxycodone. Secondly, in contrast to forensic testing, which generally assumes that most donors will be negative for the substance of abuse, physicians in therapeutic settings often expect to detect the presence of prescribed drugs as evidence of their use. Thirdly, forensic testing is governed by strict requirements for chain of custody that are generally not considered necessary in a clinical setting.^{9,40}

Pain Management

Patients being considered for long-term opioid therapy should understand the likely benefits and risks, and agree to the requirements of such therapy, including intensive monitoring and responsibly managing their medications. UDT can be a valuable tool in the pain management setting (Table 3) to help monitor compliance to an agreed-upon treatment plan, identify possible new or recurrent drug misuse, support medical decisions, and assist in diagnosis, although it does not itself “diagnose” addiction nor abuse.^{9,11,28,40} UDT can also serve as a deterrent to illicit drug use and provide objective evidence of abstinence in high-risk patients.^{10-12,28} In addition, documentation of UDT policies and results can demonstrate to regulatory authorities physicians’ efforts in monitoring patients.⁹ Whatever the reason for testing, the level of understanding of physicians using UDT in a clinical setting must be appropriate, and communication with the testing laboratory is key.^{9,11}

Treatment Agreements

A written opioid treatment agreement that outlines physician and patient responsibilities is often used to clarify the likely benefits and risks, mutually agreed-upon treatment goals, terms of treatment, and the consequences of misuse.^{13,42-45} Some physicians require all patients to sign a written treatment agreement before prescribing opioids for chronic pain as a routine part of care, so as not to stigmatize “at-risk” patients. However, it is unclear if such agreements should be implemented for all patients in all circumstances. The Federation of State Medical Boards of the United States recommends a written treatment agreement for patients “at high risk for medication abuse or with a substance abuse history.”⁴⁶ The most important elements in a written agreement include listing prohibited behaviors and a process for discontinuing treatment, should this become necessary.^{9,13,22,43} An example of a treatment agreement can be found on the American Academy of Pain Medicine Web site: www.painmed.org/pdf/controlled_substances_sample_agrmt.pdf.⁴⁷ Very often, agreements include the provision of a urine specimen when requested to monitor illicit drug use and adherence to treatment.^{29,43,48}

Table 3. Pain Clinic Studies of UDT^{13,27-29,31,32}

Study	Number of patients	Problem UDT result (%)	Findings
Hariharan J, et al. <i>J Gen Intern Med.</i> 2007;22:485-90.	330	53 (38%)	<ul style="list-style-type: none"> Illicit substances (cocaine, THC) No confirmations Did not consider opiates
Michna E, et al. <i>Clin J Pain.</i> 2007;23:173-9.	470	210 (45%)	<ul style="list-style-type: none"> 20.2% illicit substances 14.5% nonprescribed opioid 10.2% missing opioid
Ives TJ, et al. <i>BMC Health Serv Res.</i> 2006;6:46.	196	62 (32%)	<ul style="list-style-type: none"> 38.7% cocaine 1.6% amphetamine 24.2% missing opioid 14.5% nonprescribed opioid
Manchikanti L, et al. <i>Pain Physician.</i> 2006;9:123-9.	500	80 (16%)	<ul style="list-style-type: none"> 11% THC 5% cocaine 2% amphetamine
Katz NP, et al. <i>Anesth Analg.</i> 2003;97:1097-102.	122	36 (29%)	<ul style="list-style-type: none"> 16.7% cocaine 55.6% THC 22.2% nonprescribed opioid
Fishbain DA, et al. <i>Clin J Pain.</i> 1999;15:184-91.	226	105 (46.5%)	<ul style="list-style-type: none"> 6.2% THC 2.2% cocaine 8.8% incorrect self-report of current drug use

THC=11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid

Ongoing Monitoring

Patients should be monitored in accordance with their risk level for displaying ADRBs. Random or scheduled UDT can be utilized along with other measures (eg, contacting pharmacists, querying prescription monitoring programs/pharmacy databases, conducting pill counts) to help determine appropriate intake of prescribed drugs; help identify nonadherence, diversion, or illicit drug abuse; support referral for substance abuse assessment; and facilitate accurate documentation in the medical record.^{9,15,22,48,49}

A structured UDT strategy can be approached as a consensual test that is part of the effort to monitor the clinical efficacy of pain treatment, just as glucose analysis is essential for the evaluation and ongoing management of diabetic patients.^{9,13} Appropriate use of UDT may help overcome barriers to opioid analgesic use for chronic pain.

Appropriate use of UDT may help overcome barriers to opioid analgesic use for chronic pain.

Addressing UDT Results

Clearly established and consistently enforced policies around UDT minimize the potential for legal consequences, and vice versa.⁴⁹⁻⁵¹ For example, if nonprescribed/illicit drugs are present, will:^{9,27,31,49,50}

- Controlled substances be discontinued?
- The patient be referred to drug abuse treatment, a psychologist/psychiatrist, or a pain specialist?
- The patient be discharged from the practice?

It is recommended that all UDT results be promptly reviewed, interpreted, and documented in the medical chart, together with communications to the patient about the results.^{9,50} For physicians working in a group or multipractice setting, or when the patient has been referred to other health care professionals for treatment of comorbid conditions, it is important to indicate a plan for follow-up in the progress notes so that the patient receives a consistent message.⁵⁰ Electronic medical records, or another recordkeeping system that allows multiple physicians within a group practice to access UDT results and prescriptions written for a patient, may help to improve prescribing and monitoring practices. UDT results that are inconsistent with the prescribed medications should prompt the physician to delve more deeply

into the patient's problems by considering the results within the context of the "4 A's":^{9,52}

- Analgesia
- Activities of daily living
- Adverse effects
- ADRBs

This may require a psychological/psychiatric referral, because those who misuse their opioids to self-medicate and relieve symptoms such as anxiety, depression, or insomnia may require different treatment than those who abuse prescription opioids for euphoric effects or who are addicted.^{6,27,28}

Underutilized UDT

An audit of medical records to assess the medical management of chronic pain patients found that only 8% of PCPs utilized UDT.⁵³ Patients had a variety of pain syndromes, but must have been using opioids for the treatment of chronic pain for at least 3 months prior to the audit date.⁵³ In a more recent survey of PCPs, 7% ordered UDT before prescribing opioids, and 15% had—at least once—tested established chronic pain patients already prescribed opioids.¹⁹ The low frequency of UDT is surprising in view of the data indicating that patient self-reporting of current illicit drug use and physician observation alone are not reliable.^{19,26} ■

URINE DRUG TESTING METHODOLOGIES

The classification of UDT methods grew out of their use in the forensic setting according to the type of result they provide. In these programs, methods are designated as either screening or confirmatory, and the use of these terms has carried over into the clinical setting.

Immunoassay Screening

Despite the depiction of laboratories in the media, the term “screening” does not indicate that a test can detect the presence of all drugs in the sample, nor identify all drugs within a class.¹¹ Laboratories use a variety of testing methodologies for screening, but immunoassay is widely employed because the technique is relatively cost-effective, has a rapid analysis time, and is readily available. Similar to the risk-assessment tools discussed previously, immunoassay tests are designed to identify individuals, or samples, that need closer scrutiny. Laboratory screening methods provide a qualitative determination as to the presence or absence of drugs in a sample. They are used within the forensic arena to eliminate negative samples from additional, more costly testing. They are usually relatively sensitive, but may not necessarily be specific. Screening tests are further classified according to the drug or class of drugs the method is designed to detect.

Most of the immunoassays used for UDT are based on a competitive antigen-antibody reaction, where drug molecules in the sample compete with a labeled version of that drug to bind with an antibody. In some cases, the assay is targeted to detect a drug metabolite rather than the parent drug. Enzymes and compounds that fluoresce or chemiluminesce are used to measure the antibody-drug reaction.⁵⁴ There are many types of immunoassays available, from point-of-care testing (POCT) devices to reagents for use on fully automated, large, laboratory-based platforms.¹¹

Laboratory-based methods typically target the compounds required in forensic or workplace settings. These compounds were chosen because they are excreted over a reasonable period of time and therefore provide a good window of opportunity in which to detect prior use. Some are also considered representative of the drug class. For example, cocaine assays do not target cocaine because it has a short period of excretion. Instead, these assays target benzoylecgonine—an inactive metabolite unique to cocaine—because it has a much longer window of excretion (Figure 4).

An immunoassay’s ability to detect a drug or metabolite in a sample is affected by the specificity of the antibody, the assay cutoff, and the drug concentration within the sample. The antibodies employed may be very specific in their recognition of a given drug and fail to recognize similarly structured drugs within the class.^{11,54} Conversely, other antibodies may recognize an antigen site common to many drugs or metabolites within a class or even shared by drugs of other classes. The term cross-reactivity is used to convey an antibody’s reactivity with another compound, including those totally unrelated to the targeted compound. The specificity of an immunoassay and the concept of cross-reactivity partially explain conflicting results between screening and confirmation testing.^{11,54} When the antibody cross-reacts with a compound outside the class of drugs it is designed to detect, a false-positive may result. Cross-reactivity patterns for immunoassays differ between manufacturers and even between lots of reagents from a single manufacturer.^{11,54} For this reason, it cannot be assumed that a cross-reaction documented for one assay will affect another, or that a compound previously not interfering will never interfere (see page 13).

Laboratory-Based Specific Drug Identification

At this time, GC/MS remains the “gold standard” for confirmation testing. This technique uses GC to separate the analytes in a specimen, and the highly specific and sensitive MS to identify the specific molecular structures of the drug and metabolites.⁹ One of the advantages of this technique is that it provides the chemical equivalent of a “fingerprint” of an analyte. Additionally, it can quantify the amount of drug/metabolite present in the sample. In the clinical setting, the technique can not only be used to confirm the results using screening assays, but also to identify the presence of drugs that are not reliably detected by those methods.

Figure 4. Excretion Patterns of Cocaine and Metabolites

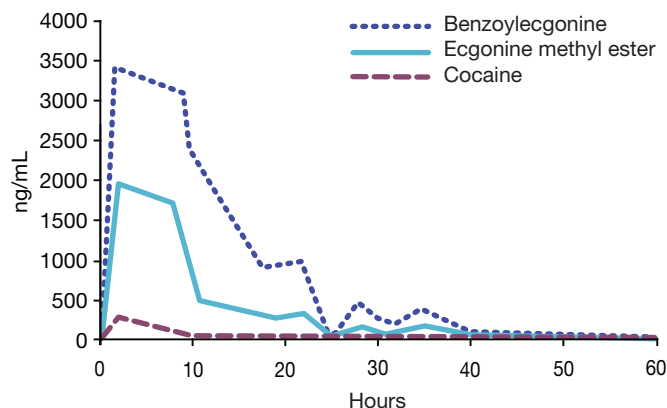


Figure courtesy of Hammett-Stabler CA.

Table 4. Drugs Included in Federally Regulated Testing^{54,64}

Drug/metabolite	Immunoassay screen cutoff concentration (ng/mL)	Confirmation cutoff concentration (ng/mL)
Marijuana metabolites THC	50 -	- 15
Cocaine metabolites Benzoylecgonine	300 -	- 150
Opiates Morphine Codeine 6-MAM*	2000 - - -	- 2000 2000 10
Phencyclidine	25	25
Amphetamines Amphetamine Methamphetamine	1000 - -	- 500 500

THC=11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid

6-MAM=6-monoacetylmorphine

*When morphine concentration is ≥ 2000 ng/mL

GC/MS refers to the technique used for the analysis, but does not describe the method used by the laboratory. There are many methods described in laboratory sciences literature for each drug or metabolite. A laboratory may have adopted or modified one of these or possibly developed its own. These methods detail how samples are prepared for testing on GC/MS, as well as the conditions or settings for the instrumentation, and the criteria used to judge acceptability of the results. Although these methods are not approved by the US Food and Drug Administration, they are regulated and all laboratories follow guidelines to assure the results are accurate and reliable.

Other Confirmatory Testing

Other detection systems are being evaluated for UDT. Most rely on a type of chromatography to separate the various constituents of the sample before identification. Liquid chromatography (LC)/tandem MS (LC/MS/MS) can be a more time-efficient method for the simultaneous quantification of multiple abused and therapeutic drugs and metabolites in urine.^{9,55-59} Another technique gaining interest for the analysis of drugs in biologic samples is ultra-performance liquid chromatography (UPLC). Coupled with the appropriate detection system, such as MS or diode-array ultraviolet spectrophotometry, methods using UPLC have been developed to both screen for large numbers of drugs and for confirmation analysis.⁶⁰ Technologic advances associated with UPLC allow for high-throughput testing compared with classic high performance liquid chromatography (HPLC).⁶¹ UPLC is also being utilized in the development of biomarkers for drug/alcohol abuse.⁶²

Reporting of Results

The cutoff of an assay, whether screening or confirmatory, defines when a result is considered positive or negative and is based upon the analytic capabilities of the method.⁴⁰ Results at or above this level are considered positive; results below are considered negative. How a laboratory reports results varies: some use the terms present or positive, while a few report the result as above or equal to the designated cutoff. Any result below the cutoff is considered negative. These results may be reported as negative, below the cutoff, or, perhaps inaccurately, as absent or none detected. In a forensic setting, positive results from screening methods are considered “presumptive” until verified using a more sensitive and specific confirmatory method.

While federally mandated cutoffs are typically adopted in workplace or forensic settings (Table 4), different cutoffs may be more appropriate in a clinical setting. For example, the 2000 ng/mL immunoassay cutoff for opiates, chosen to minimize the issue of positive results due to poppy seed ingestion, is clearly not useful in the clinical setting. It may be desirable to ask the laboratory to customize the cutoffs it uses or to use other versions of an assay, but keep in mind that they may be limited by the available technology. Only a few immunoassay systems currently allow laboratories to alter cutoffs, although they have greater flexibility to do so when using GC/MS or other similar technologies. A laboratory should never alter cutoffs without carefully and consistently documenting the method’s performance and accuracy at a given level. There is always a concentration below which results are not reliable or accurate, so laboratories should not usually eliminate a cutoff altogether.⁶³

Testing Menu

No single urine drug “screen” is suitable for all clinical uses, but rather a multitude of options exist that can be adapted to clinical needs.¹¹ Which drugs are included in the testing menu vary greatly between and even within laboratories.¹¹ Most menus for automated immunoassays include those desired for workplace drug testing, sometimes referred to as the “NIDA Five” after the original federal agency involved (National Institute of Drug Abuse); ie, amphetamine, cocaine, opiates, marijuana, and phencyclidine.^{9,11,64} Tests for additional drugs or classes, such as benzodiazepines, barbiturates, lysergic acid diethylamide (LSD), propoxyphene, methadone, and semisynthetic/synthetic opioids, are available on automated immunoassay platforms.^{5,9,11} Although this has been an area of great expansion in recent years, with several “new” tests coming to market, immunoassays are still not available for every drug pertinent to pain management or for use with all instruments.

Multidrug panels commonly include an opiate immunoassay screen that is designed to detect heroin, morphine, or codeine use. In most cases, the metabolic pattern of heroin results in morphine, which is therefore the target compound for these assays. How readily an opiate assay detects other opioids varies considerably. Physicians should speak with their laboratories to better understand what is usually detected by the immunoassays they use, but recognize that some manufacturers provide limited data for drugs other than the target compounds. It is also important to understand what is identified and measured by the confirmation assays. Most GC/MS opioid confirmations include morphine, codeine, hydrocodone, hydromorphone, oxycodone, and oxycodone, but not fentanyl or methadone—the latter 2 are available as separate tests.

Efficient use of laboratory resources begins with knowledge of the drugs prescribed for the patient as well as those currently abused in the locality.

Customizing a Pain Management Profile

Pain management clinics commonly test for prescribed drugs and drugs with high abuse potential.⁹ Physicians must decide whether to screen for illegal drugs and, if so, which—some degree of testing is advisable because an abuser of illicit drugs is at increased risk for prescription drug abuse, but selecting everything the laboratory has available is neither cost-effective nor clinically useful.^{9,11} Efficient use of laboratory resources begins with knowledge of the drugs prescribed for the patient as well as those currently abused in the locality.⁹ Several resources are useful in this endeavor, including law enforcement, the medical examiner's office, and clinical laboratories. The next step is to review the drug screening and confirmatory testing menu available through the laboratory and select accordingly. Some laboratories offer groups of drug assays for convenience, but these are also available as single tests; ie, it is not necessary to order a phencyclidine or LSD assay that the laboratory offers to meet ED needs.^{5,9,11} Also consider asking patients what they think will show up in the results—patients may admit to taking drugs that the tests you planned to order do not detect.⁵⁰ Depending on the drug in question, confirmation testing may be necessary to reliably detect it. Another approach is to customize appropriate menus with the laboratory for patient populations; for example, one with a rapid analysis time and another that is more comprehensive.¹¹

Point-of-Care Testing

POCT refers to any testing performed outside the traditional laboratory, typically by personnel whose primary training is not in the laboratory sciences.¹² POCT is available for many tests, and most physicians are familiar with the devices used for glucose or coagulation monitoring. The demand for rapid turnaround time to detect drugs of abuse in certain clinical, employment, and ED settings has increased use of POCT immunoassay devices as an alternative to collection, transport, and subsequent laboratory analysis.^{9,12} Federal workplace drug testing programs are considering allowing the use of POCT devices in order to quickly identify specimens that are negative for drugs.³

There are several issues to consider before implementing a POCT system for UDT in clinical practice. It should be understood that these devices are intended to be used only for screening, and that POCT is not interchangeable with traditional laboratory confirmation tests.^{9,12} The staff chosen to perform the testing must be able to carry out the required steps exactly as described by the manufacturer. Theoretically, POCT can shorten the interval between sample collection, test completion, and therapeutic intervention, but this is not a justification for POCT if the quality of results is compromised.^{9,12,65}

POCT devices are generally noninstrumented immunoassay tests with endpoints that are visually read by the operator. The “device” may be a dipstick, cup, card, or cassette. The amount of urine needed for testing ranges from a few drops to approximately 30 mL.^{3,12} The simplest-to-use POCT devices combine collection and testing, but most require the operator to perform multiple steps, including sample application, timing of reaction, and reading/interpreting the endpoint.¹² Data recording from typical POCT devices is performed manually, in contrast to laboratory testing that both reads results and captures this data on a computer system—although POCT devices are becoming available that are read by a meter and may interface to an information system.¹² One often-cited issue with POCT devices for drugs of abuse testing is that some give a negative visual sign when the drug of interest is at or above the defined threshold; ie, absence of a line or color indicates a drug is above the threshold and vice versa.¹²

These devices have a varied but limited menu in terms of the drugs, drug classes, or groups of drugs detected.^{9,12} The antibodies used in the POCT devices target the same drug and/or metabolites detected by laboratory immunoassays, and a positive result is similarly obtained when the drug(s) or metabolite(s) of interest is present at or above a designated cutoff concentration.¹² These devices are also subject to the same challenges and limitations of laboratory-based immunoassays, but recognition and resolution of these rest in the hands of the POCT operator.¹²

When results may direct or influence treatment, clinical staff using the data should understand the limitations of testing and order a laboratory confirmation test, such as GC/MS, before taking any definitive action.¹²

POCT devices vary in accuracy of analytic performance, cutoff concentrations, cross-reactivity, reproducibility, and ease-of-use.^{9,12,66} The POCT literature contains numerous reports in which devices are compared to laboratory testing. Unfortunately, many of these were conducted using trained laboratory personnel rather than in the field by individuals who were likely to be performing the testing on a routine basis.¹² Under these controlled conditions, the current devices were generally found to agree with comparable laboratory methods, although none were 100% concordant with the comparator methods—disagreement was greatest for samples near the designated cutoffs.¹² In addition, there are anecdotal reports of discrepancies in interpretation of subjective results by nonlaboratory personnel and quality control practices that fall short of laboratory standards.^{12,65,67}

Evaluating POCT

The clinical and economic impact of POCT should be established prior to introduction at a site.¹² The staff should conduct evaluations under conditions in which testing will be performed.¹² Some devices have very rapid color development that must be read soon after application of the specimen. Staff need time to perform POCT without interruptions as the reaction typically continues beyond that point and may be incorrectly interpreted if read 5, 10, or 15 minutes later.⁶⁸

The fixed-unit cost of POCT devices often exceeds that of laboratory-based methods.^{12,68} A significant value-added component needs to be justified for obtaining immediate access to results for patients.⁶⁸ Some clinicians have found performing the test in front of the patient useful, while others have found this can negatively affect the clinician-patient relationship when subsequent, more specific testing reveals a conflicting result.

Specimen Tampering/Validity

In many contexts, particularly in the workplace, school, and within law enforcement, there are significant consequences for illicit drug use, including termination of employment, suspension, expulsion, ineligibility for federal student loans, athletic bans, incarceration, loss of custody, and fines.^{4,7} Theoretically, the greater the negative consequences of substance use, the greater the likelihood of tampering with a sample to produce a false-negative result.⁷ Although the number of pain patients who tamper with their urine samples appears to be low, consequences in the clinical setting include discharge from treatment or change in clinical management.^{7,9,27}

The Internet is a common source of information, providing drug users with broad advice, recipes, and commercial products to circumvent detection.^{7,69,70} Methods to mask illicit drugs in urine fall into 3 categories:^{3,7,71}

- Dilution and cleansing products
- Additives to prevent drug detection
- Urine substitutes

The type of UDT method will determine whether or not an adulterant will successfully produce a false-negative result.^{7,71}

Although the number of pain patients who tamper with their urine samples appears to be low, consequences in the clinical setting include discharge from treatment or change in clinical management.

In Vivo Adulteration

Although many commercial products purport more elaborate mechanisms of action to “flush” the body of toxins and drive the drug concentration below the level of detection, most in vivo adulterants work by excessively hydrating the individual and thus diluting the urine before excretion.^{3,5,7} Ingesting as little as one half to a full liter of water or other fluid prior to micturition will work just as well and be more cost-effective.^{3,5,7,71} The drawback to water alone is that the urine produced is usually pale or colorless. Some products attempt to avoid visual detection by adding ingredients, such as niacin and vitamin B, which produce a yellow color consistent with that of urine.⁷

In Vitro Adulteration

In vitro adulterants are added to urine after micturition into the collection cup to:^{3,5,7,71}

- Drive the concentration of the illicit drug below the threshold detection level of a test
- Interfere with immunoassay detection
- Convert a target drug to compounds that are not detected

The addition of water from the toilet bowl or sink is a common method to dilute the sample, although the use of saline or other medical solution has been documented. Several commercial adulterants, designed to be added to the sample either during or after collection and specifically marketed for the purpose of “passing” UDT, are sold via Web sites, magazines, and shops devoted to recreational drug use.^{7,9} The active ingredients of some

include glutaraldehyde, sodium or potassium nitrate, pyridinium chlorochromate, or peroxide/peroxidase.⁷ Common household products used as in vitro adulterants include bleach, vinegar, eye drops, caustic soda, detergent/soap, ammonia, and sodium chloride.⁷ Formulations constantly change as laboratories implement methods to identify their use.³

Urine Substitution

Urine substitution methods involve obtaining and substituting either commercially available fluids formulated to chemically resemble urine or a “clean” urine specimen from a nonusing acquaintance.^{3,7} Substitute products may include reservoirs, prosthetic devices, and hand warmers or a heating unit strapped to the body to maintain specimen temperature.^{3,7} Some deliver drug-free or synthetic urine through a color-matched artificial penis—the “Whizzinator®” kit received media coverage in 2005, as well as discussion in Congress, after a professional National Football League player caught in possession of one at a US airport was subsequently suspended.⁷² An alternative to external urine storage is urine substitution within the bladder (recatheterization), where an individual voids and uses a catheter to refill the bladder with clean urine via the urethra.⁷

Validity Testing

Many attempts to dilute, substitute, and adulterate urine are detected by a combination of close visual inspection and on-site or laboratory analyses (Table 5).^{7,71} Urine is typically translucent and light yellow in appearance, although color may vary due to diet and other factors.⁷ Household adulterants may create a specimen that is unusually foamy, bubbly, cloudy, clear, or dark, but visual inspection alone is not sufficient to confirm tampering, and samples with these appearances may be caused by pathologic conditions.⁷ A useful on-site test is the recording of urine temperature within 4 minutes of voiding. In this time

period, the temperature of a urine specimen collected from a healthy patient should range from 90°F to 100°F—temperatures outside these values suggest that a substitute specimen was provided.^{3,7,9} Specimen containers that have a temperature strip impregnated within the collection cup provide a convenient way to measure temperature, but again, these are effective only if read within the prescribed time.^{3,7} A sample that is outside of the expected temperature range should be recollected immediately. In addition, urinary creatinine, specific gravity, and pH are 3 clinically useful tests that have been adopted by workplace programs as indicators of specimen integrity or validity.^{3,7,71} Use of the SAMHSA-mandated criteria may be helpful in the decision process when visual inspection suggests tampering. Brief descriptions of the rationale for the use of these 3 tests, as well as the SAMHSA-mandated thresholds for interpretation, are as follows:^{3,7,71}

- Creatinine concentration:** Creatinine is a byproduct of muscle metabolism. Its concentration in the blood is related primarily to muscle mass and, to a smaller degree, diet. Since it is freely filtered by the glomeruli and secreted by the tubules at a relatively constant rate, it serves as a good indicator of hydration. A randomly collected urine sample from an adult should contain 15 to 400 mg/dL creatinine.⁷³ Because of their lower body mass, women tend to excrete less creatinine than men and, as a result, a urinary creatinine in the lower part of the reference range is not unexpected for a small-framed woman. For similar reasons, very low concentrations are common in young pediatric populations; however, by adolescence, excretion usually reaches the adult range. Workplace programs have adopted the finding of a creatinine concentration <20 mg/dL as an indicator of possible dilution, either by excessive fluid ingestion or the physical addition of fluid to the sample. Creatinine <5 mg/dL is usually inconsistent with adult urine, and SAMHSA has designated a creatinine <2 mg/dL as indicative of substitution. Although low creatinine concentrations may be produced by healthy individuals during the course of a day, finding a urinary creatinine <20 mg/dL in the pain management setting raises a “red flag” and should be investigated.
- Specific gravity:** Specific gravity compares the density of a solution to that of pure water. It is routinely used to evaluate the concentration of urine—the specific gravity increases as substances are added to urine and, conversely, decreases if water is added. The expected specific gravity of a randomly collected urine sample from an adult is 1.002 to 1.030, with the caveat that the individual has not restricted or ingested excess fluids.⁷³ As shown in Table 5, SAMHSA has established criteria using specific gravity along with a urinary creatinine measurement to evaluate urine samples for dilution or possible substitution.

Table 5. SAMHSA Criteria for Validity Testing of a Urine Specimen^{3,64}

Urine specimen is reported as:	When:
Dilute	Creatinine concentration ≥ 2 mg/dL, but <20 mg/dL, & specific gravity* >1.001 , but <1.003
Substituted	Creatinine concentration <2 mg/dL & specific gravity* ≤ 1.001 or >1.020
Adulterated	pH [†] <3 or ≥ 11 , nitrite concentration ≥ 500 $\mu\text{g/mL}$; chromium (VI) concentration ≥ 50 $\mu\text{g/mL}$; presence of a halogen (eg, from bleach, iodine, fluoride), glutaraldehyde, pyridine, surfactant

*Using refractometry; [†]using a pH meter

- **pH:** The pH of a freshly collected urine sample is typically in the range of 4.5 to 8.0.⁷³ This measurement is useful to detect the addition of chemicals such as bleach and vinegar. A pH of <3 or ≥11 is suggestive of adulteration.^{3,64}

Finally, testing is available to detect the presence of the aforementioned compounds that are added to a urine sample in an attempt to avoid detection; for example, glutaraldehyde, nitrates, and peroxide. Keep in mind that these tests are not routinely performed by many laboratories—ask if this type of testing is conducted and under what circumstances.

Collecting the Sample

In the workplace setting, the possibility a donor will attempt to alter his or her sample is a concern, and steps are routinely enforced to prevent this from happening. Unfortunately, the clinical setting is not immune to these occurrences—for example, a study of adolescent patients in a primary care setting revealed that the creatinine measurements of 6% of specimens were below 20 mg/dL (ie, dilute).⁵ In a survey of PCPs, only 7% of those who ordered UDT also requested both specific gravity and urinary creatinine to ensure sample validity, and 61% ordered neither.^{7,74} Usually, specific gravity, pH, and urinary creatinine must be ordered separately.

Proper collection procedures can minimize in vitro adulteration and dilution.⁵ Simple steps can be taken to limit access to water that could be used to dilute the specimen:³

- Turn off the water supply to the bathroom sink
- Place a blue dye dispenser in the toilet water tank
- Remove cleaning agents and soaps from the bathroom
- Do not allow the patient to carry unnecessary outer clothing or personal belongings into the bathroom
- Only allow designated staff access to the specimen after collection

However, even rigorous collection procedures cannot prevent determined individuals from adulterating their urine specimens—when suspected, consider collecting another specimen under direct observation.^{3,5} In vivo dilution resulting from the ingestion of excess fluid and/or a diuretic will only be detected if samples are checked for adequate concentration.⁵ Advise patients who provide dilute samples to decrease fluid intake prior to testing, or collect samples in the early morning when urine is most concentrated.^{9,40} ■

INTERPRETATION OF URINE DRUG TESTING RESULTS

As a clinical tool used in conjunction with other monitoring measures, UDT provides significant benefits, and even the knowledge that it will be performed can increase patient adherence.^{5,9} But no test has value—and can even cause harm—if the end user cannot correctly interpret the results. Because the results of UDT often carry possible repercussions, false-negatives and false-positives are a major concern. A false-positive result carries greater consequences in the workplace setting, but in the clinical setting either can cause harm. When using UDT, physicians must recognize issues resulting from collection practices, understand the limitations imposed by the currently available analytic methods, have a sound grasp of the pharmacology of the drugs tested, be able to decide when screening is sufficient or confirmation is needed, and put all of these together for each patient. However, in a 7-question survey assessing UDT interpretation, none of the physicians who employed UDT to monitor patients receiving chronic opioid therapy correctly answered all questions, and only 30% correctly answered more than half (Figure 5).⁷⁵ The questions most frequently answered incorrectly related to what substance(s) would likely be detected in urine following heroin use or following oxycodone use together with the consumption of poppy seeds, and plausible explanations for a negative opiate immunoassay result in a patient on chronic opioid therapy.

False-Negative Results

Analytically, a result is considered false-negative when a drug is present above the cutoff but not detected by the test. A false-negative result may give a physician misplaced confidence that drug abuse is not occurring, delay diagnosis, and reinforce ADRBs by the patient; it may also lead to accusations of diversion.^{5,75} As explained in previous sections of this monograph, UDT methods, whether screening or confirmatory, have a threshold below which results are not accurate or reliable. The threshold is set at a level the laboratory is confident can be achieved routinely. A result below that number is considered negative. A negative UDT result for a patient prescribed an opioid may be due to several factors:^{5,9,75-77}

- Absence of recent use
- A dilute urine sample
- An immunoassay test that does not cross-react with that particular opiate or is not sufficiently sensitive to detect the drug level
- Pharmacogenetic variability in drug metabolism (eg, ultra-rapid metabolizer)

Many immunoassays do not readily detect synthetic/semisynthetic opioids at therapeutic doses; however, in the above-mentioned survey, only 12% of PCPs correctly knew that a test for oxycodone,

a semisynthetic opioid, must be specifically ordered.^{9,25,40,74} Before testing, physicians should take a history of recent use of the prescribed drug to assess the patient for nonadherence—he or she may have missed 1 to 2 days by misunderstanding instructions, but the patient could also be hoarding, bingeing, or diverting the drug, all of which must be addressed.^{9,15}

False-Positive Results

False-positives occur when a drug is detected by UDT but is, in fact, absent. To reduce the possibility of a false-positive result, positive workplace UDT results are evaluated by a medical review officer (MRO) before final interpretation. This physician assesses all of the circumstances that can lead to a positive result to determine if there is a medical reason for it. In the clinical setting, this role is assumed by the ordering provider.

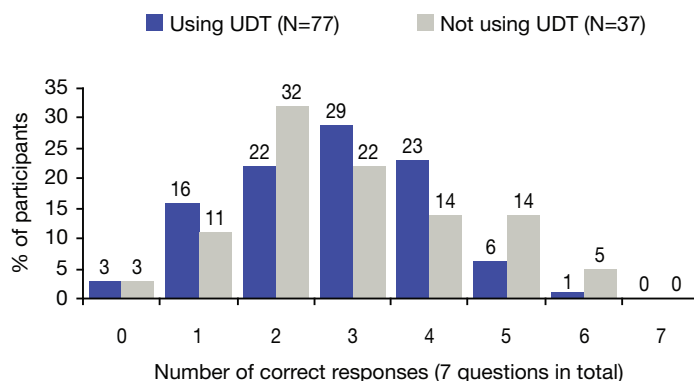
False-positive results can substantially harm patients who are not abusing drugs by placing them under a cloud of unjust suspicion, false accusations of abuse, unjustified cessation of opioid treatment, deterioration of the physician-patient relationship, and/or compromised ability to receive future therapy.^{5,74,75} Immunoassays from different manufacturers have different interference profiles, and laboratories will provide this information when requested.⁷⁸ However, data about false-positive UDT results are often limited to case reports, and not all drugs that cross-react are always included on the immunoassay manufacturer's package insert.^{50,78,79} Examples of drugs previously reported to cause false-positive UDT results with some immunoassays include:

Interfering drug	Immunoassay affected
■ Quinolone antibiotics (eg, levofloxacin, ofloxacin) ^{80,81}	Opiates
■ Antidepressant trazodone ⁸²	Fentanyl
■ Antidepressant venlafaxine ^{79,83,84}	Phencyclidine
■ Atypical antipsychotic quetiapine ⁸⁵	Methadone
■ Antiretroviral efavirenz ⁸⁶	THC
■ Diet pills (eg, clobenzorex, fenproporex) ^{9,40}	Amphetamine
■ Promethazine (for allergies, agitation, nausea, vomiting) ⁷⁸	Amphetamine
■ <i>l</i> -methamphetamine (over-the-counter [OTC] nasal inhaler) ^{9,40}	Amphetamine

Many of the interferences from the drugs listed have been eliminated, but new interferences should be expected to arise as drugs arrive on the market. Physicians can make a valuable contribution within this area by raising the question of false-positives with their laboratory and notifying them of the drugs that a patient is taking.

False-positives due to a prescription or OTC medication cross-reacting with an immunoassay can be avoided by confirming

Figure 5. Physicians' Knowledge Level of UDT by Ordering Status⁷⁵



unexpected results using GC/MS.^{5,78} However, legitimate use of a prescription medication that contains or is metabolized to the target drug can be assessed only by taking an accurate medical history and knowing which medications can account for such results.⁵ Correct interpretation requires a detailed, up-to-date list of prescribed, OTC, and herbal agents that the patient is taking.^{5,40} This should preferably occur before ordering the test, but physicians should conduct a follow-up interview when the patient has an unexpected result.^{5,40} In a primary care study, 21% of confirmed positive UDT results were due to legitimate use of prescription or OTC drugs.⁵ For example, amphetamine and methamphetamine have legitimate medical uses in the treatment of obesity, narcolepsy, and attention deficit/hyperactivity disorder, but can also be diverted from legitimate pharmaceutical sources or manufactured in clandestine laboratories.^{25,40} Medical use of cannabinoids include the orally active synthetic agents dronabinol (Marinol®) and nabilone (Cesamet®), which are both indicated to treat nausea and vomiting associated with cancer chemotherapy.⁸⁷ Dronabinol is also indicated for the treatment of weight loss associated with acquired immune deficiency syndrome. UDT results are likely to be positive after therapy with dronabinol, which is identical to the THC from marijuana, and it is possible that an immunoassay may cross-react with nabilone.^{87,88} The increased availability of cannabinoid-based therapeutics has highlighted the need to identify other biologic markers or metabolites from the mix of cannabinoids in naturally occurring products that will accurately distinguish between ingestion of natural and synthetic cannabinoids.^{88,89} Certain foods can also cause analytically valid results; for example, ingested poppy seeds may cause positive opiate results due to morphine and codeine present on the surface of some seeds. In fact, morphine concentrations as high as 10,000 ng/mL have been found in the urine of volunteers who ingested poppy seed bakery products.⁹⁰ Without an appropriate investigation, this result could be incorrectly interpreted.

Metabolism

All aspects of a drug's pharmacokinetic properties influence its detection in a urine sample. However, in one survey, only 29% of physicians who used UDT knew that the metabolic pathway of codeine includes the formation of morphine, so that both codeine and morphine are ordinarily detected in the urine of patients administered codeine (Figure 6; Table 6).^{5,9,49,75} Similarly, methamphetamine is metabolized to amphetamine, so both drugs may be present in the urine after methamphetamine use.²⁵ Thus, it is important to review drug metabolic pathways when interpreting results. Even apparently straightforward results are not always easy to interpret.^{9,91}

- Codeine is metabolized to morphine—a prescription for codeine may explain the presence of both drugs^{9,40}
- Morphine is not metabolized to codeine, but small amounts of codeine may be a manufacturing by-product^{9,40}
- Codeine is partially metabolized to hydrocodone⁴⁰
- Hydrocodone is metabolized to hydromorphone^{40,92}
- High doses of morphine can sometimes produce very low levels of the minor metabolite hydromorphone^{40,93}
- Heroin is metabolized to 6-monoacetylmorphine (6-MAM) and morphine⁴⁰

Heroin is particularly difficult to detect because it metabolizes to 6-MAM within minutes.^{9,94} Although definitely indicative of heroin use, 6-MAM is rarely detected in urine because it has a 25- to 30-minute half-life and dissipates within hours—the presence of 6-MAM indicates recent heroin use, but morphine may be detected in urine for 2 to 4 days after the last heroin use.^{9,25,40}

Pharmacogenetic Testing

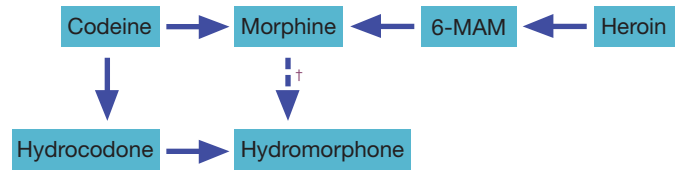
Interindividual differences in metabolism will determine the type and amount of metabolites formed, and increase or decrease the

Table 6. Urinary Analytes of Patients Treated With Opioids⁹

Drug	Urinary analytes
Morphine	Morphine Hydromorphone*† Codeine‡
Codeine	Codeine Morphine* Hydrocodone*
Hydrocodone	Hydrocodone Hydromorphone*
Oxycodone	Oxycodone Oxymorphone* Hydrocodone‡

*Metabolite; †at very low levels, primarily after high-dose morphine; ‡potential impurity of commercial manufacturing

Figure 6. An Example of Opioid Metabolism*⁴⁰



*Not comprehensive pathways, but may explain the presence of apparently un-prescribed drugs; includes the production of some minor metabolites
6-MAM=6-monoacetylmorphine
†At very low levels, primarily after high-dose morphine

detection time.⁹⁴ Because responses to and disposition of many drugs appear to be partly genetically determined, the relationship between genotype, drug metabolism, and response may have diagnostic value.⁹⁵ Pharmacogenetic testing is being developed to identify and characterize the genetic polymorphisms that affect drug-metabolizing enzymes and drug transporters.⁹⁵

Drug-Class-Specific Windows of Detection

When interpreting UDT, an important consideration is the window of detection for drugs and their metabolites in urine (Table 7), which are affected by physiologic and analytic factors. Most windows of detection using immunoassays are about 1 to 3 days. However, these detection times are often determined following administration of a single drug dose and may underestimate the window following multiple administrations or use over an extended period.⁴ For example, urine typically

Table 7. Examples of Detection Time of Illicit Drugs in Urine^{25,94,97-99}

Drug/metabolite	Cutoff (ng/mL)	Detection time in urine
Amphetamine (multidrug misusers, dose unknown)	1000	<5 days
Methamphetamine (oral administration of multiple controlled 20 mg doses) ⁹⁷	500	<4 days
THC after marijuana: ²⁵ ■ Casual use ■ Moderate use ■ Heavy use	30	1-3 days ≥7 days ≥30 days
Morphine from heroin: ⁹⁸ ■ Low dose (3 mg IV) ■ Higher dose (6-12 mg IV)	300	0.5 days 1-2 days
Benzoyllecgonine after: ^{94,99} ■ 20 mg IV cocaine* ■ Chronic cocaine use	300	<1.5 days 2-3 days; <7 days at higher doses

*Detection times are generally shorter following smoking and longer following intranasal administration¹⁰⁰

remains positive for THC for 1 to 3 days after a single use of marijuana and for 7 days after moderate use—however, this lipophilic metabolite significantly accumulates in fat stores so urine may remain positive for a longer time.⁹⁴ Some studies suggest that this may be up to 30 days in chronic users depending on the quality of the marijuana smoked.⁹⁴ Some benzodiazepines can also take weeks to eliminate from the body depending on the amount and type ingested.^{9,11,25}

Analytic factors that can influence UDT results include the characteristics of the test method used for screening and confirmation (eg, accuracy, sensitivity, specificity), the laboratory’s procedures for sample preparation and analysis, and the cutoff concentration used to distinguish positive and negative samples.^{4,7,25,49,94,96} The appearance of an ingested drug or metabolite in urine ends a series of complex events involving absorption, distribution, and metabolism, which can be affected by a number of factors:^{4,7,9,11,25,49,94,96}

- Urine pH
- Urine volume
- Diet
- Urinary frequency
- Body weight
- Presence/absence of malabsorption
- Concurrent medications
- Pharmacokinetic drug properties
- Amount of drug ingested
- Route of administration
- Dosage intervals
- Patient ability to metabolize drug
- Time since ingestion
- State of hydration
- Duration of use
- Disease state

Caveats to Interpretation

As well as having negative consequences for patients, it has been suggested that false accusations of drug abuse or diversion based on misinterpreted UDT results have potential medicolegal ramifications for physicians.⁷⁵ To avoid this, physicians who employ UDT should understand the pharmacology of illicit and prescribed drugs, and work closely with laboratory professionals when ordering and interpreting these tests.^{3,5,75} This includes having accurate knowledge of alternative medical explanations for positive results, reasons why a specimen may be reported as invalid, and the need for confirmatory testing.^{3,75}

Before ordering UDT, ensure that the medical record accurately reflects all medications that the patient is currently taking.⁹ A thorough history provides an opportunity to order more specific tests if the patient’s drug of choice or prescribed medication is not detected reliably by a routine panel or if he or she is taking a prescribed or OTC drug that might cross-react with an assay.^{5,9} Problematic results are cues to counsel the patient, tighten treatment boundaries, and possibly refer that individual for drug abuse treatment, but physicians should discuss results with the laboratory and the patient before making major treatment

changes.^{9,40} Concurrent use of illegal drugs is clearly abuse, but a test that fails to detect a prescribed opioid in the urine cannot differentiate whether the patient took the medication early because of uncontrolled pain (pseudoaddiction), to treat psychologic symptoms (“chemical coping”), is addicted, sold some or all of the medication, or whether other factors influenced the results.^{6,9,27,28}

Predicting Dose Compliance

A positive UDT result does not provide enough information on drug use to establish exposure time, dose, and frequency of drug use, nor does it provide enough information to diagnose drug addiction or current impairment.^{9,40} Algorithms are under investigation to help determine whether patients are taking their opioid medication as prescribed by comparing a patient’s UDT value to an expected range.^{40,101} However, at this time there is no scientifically validated relationship between the amount of drug taken and the concentration of the drug in urine, and attempts to calculate a normalized value are hampered by a large degree of variability in opioid metabolism and elimination.^{40,101} Even protocols that calculate a normalized value based on patient characteristics and specimen properties (eg, pH, specific gravity, creatinine level) cannot account for the numerous other factors that may influence the absorption, distribution, metabolism, and elimination of a drug.⁴⁰ These include genetic polymorphisms, renal and hepatic function, disease states, drug-drug interactions, drug-food interactions, body surface area and muscle mass, and age.⁴⁰ However, developing methods to help assess compliance with prescribed medications through UDT is an area of intense research.

Consultation With Laboratory Scientists

Physicians who order UDT should frequently consult with laboratory scientists to select appropriate tests, ensure proper results interpretation, and keep informed of changes in the laboratory, such as adoption of new agents or assays.⁵ Physicians should consider UDT results in the context of all the clinical information, and contact the laboratory scientist whenever there is a discrepancy to review the laboratory procedures that were used and clarify test results.⁵ Unfortunately, in a study among family medicine physicians, only 23% indicated that they would consult with the laboratory director when confronted with an abnormal or unexpected UDT result.¹⁰² ■

EMERGING TECHNOLOGIES FOR DRUG TESTING

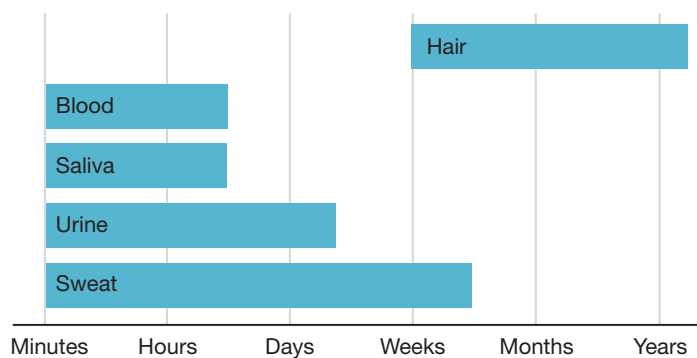
Urine is the most extensively used specimen for drug testing and remains the standard for drug-use monitoring. It requires minimal preparation for analysis, and many drugs of interest or their primary metabolites concentrate in this matrix.^{9,11} Collecting an adequate volume of urine for analytic purposes is not usually a problem unless the patient is in renal failure or incontinent, although it has been suggested that UDT discriminates against patients who suffer from shy bladder (paruresis), and some patients complain that it is invasive and embarrassing.^{11,51,103} UDT has good sensitivity and specificity for detection of recent drug use, although a very recently ingested drug may not be detected in urine, and the presence of a drug in urine reflects prior exposure only and does not correlate with clinical status.^{11,103}

The major specimens being assessed as alternatives to urine for drug testing are blood, oral fluid, hair, and sweat.

Alternative Specimens

Drugs can be detected in other biologic specimens, including hair, oral fluid, blood, sweat, nails, and semen.²⁵ Of these, the major specimens being assessed as alternatives to urine for drug testing are blood, oral fluid, hair, and sweat.^{9,11} Each biologic specimen offers a unique pattern of information regarding drug use over time and has particular strengths and weaknesses regarding the type of information that may be obtained for each drug class, ease of use, degree of invasiveness, and cost.^{9,25} The window of drug

Figure 7. Relative Detection Times of Drugs in Biologic Specimens¹⁰⁴



detection for urine, hair, blood, oral fluid, and sweat are not identical, but the results from each specimen can complement each other (Figure 7).^{3,9,104} Characterization of the disposition of different drug classes in these biologic matrices and the effect of chemical, physiologic, and pharmacologic factors are important for accurate interpretation of results.^{4,105,106} Some drug classes are more difficult to detect than others for a given type of specimen.^{3,11}

Blood/Serum/Plasma

Low levels of substances can be effectively detected in blood, serum, or plasma and, theoretically, these samples provide the optimal measure for the assessment of an intoxicated patient.¹¹ Their use in the workplace setting is limited because the invasiveness of collection requires a trained individual. This is less of an issue in a pain clinic where skilled personnel are available to properly collect samples. In this setting, blood, serum, or plasma samples may be occasionally useful for an individual who is anuric, but this type of testing is generally more expensive than UDT.^{9,11} As seen in Figure 7, the window of detection for many drugs in this matrix is short and reflects current or very recent drug use.^{9,11} Although the benefits of therapeutic drug monitoring (TDM) using serum drug concentrations is well documented for many drugs—antiepileptics for example—very few studies have been conducted to demonstrate utility of TDM in the management of pain medications.¹⁰⁷

Oral Fluid

Oral fluid testing is increasing in popularity since it overcomes some of the problems of urine—it offers accessible collection in almost any location, less embarrassment, observable conditions, and limited invasiveness.^{4,9,12,68,108,109} Researchers comparing the effectiveness of oral fluid testing with UDT found a similar pattern and frequency of positive drug test results in the general workforce over the same time period.^{9,110} In 2004, the US Department of Health and Human Services (DHHS) proposed developing scientific and technical guidelines, based on the current UDT National Laboratory Certification Program, to include oral fluid analysis in federal workplace drug testing.^{3,4,111}

Oral fluid is composed of saliva mixed with gingival crevicular fluid, buccal and mucosal transudates, cellular debris, bacteria, and residue of ingested products.⁴ Oral fluid specimens reflect circulating drug concentrations because salivary glands are highly perfused, allowing rapid transfer of a drug from blood.⁴ Thus, it can be stated that drugs are detected earlier in saliva than in urine, but for shorter time periods.¹² Oral fluid is generally useful for detecting drugs in the range of less than 1 hour up to 4 hours, but some drugs can be detected for up to 24 hours.^{3,9}

A drug is transferred from blood to saliva primarily by passive diffusion, which depends on chemical properties of the drug, salivary pH, concentration of nonionized drugs, and drug-protein binding (only free nonionized drugs can passively diffuse across biologic membranes; hence, protein-bound drugs are generally present in lower concentrations in oral fluid than in plasma).⁴ Basic drugs (eg, amphetamine and cocaine) tend to accumulate in oral fluid compared to plasma because of the lower pH of saliva, but the dynamic pH of oral fluid can substantially affect their concentration (basal pH of saliva is 6.5, whereas stimulated flow has a pH around 8.0).^{4,9,12}

Oral fluid as a test matrix shows promise for detection of recent drug use.

Collection procedures are not standardized and can affect drug concentrations.¹² Specimens are collected by having the patient expectorate—with or without stimulation—into a clean container, or by using a commercial collection device. Absorption of the drug by the material of a collection device also introduces issues of drug recovery compared with neat oral fluid.^{4,12,51} The sample volume of saliva necessary for laboratory testing is difficult to obtain, and considerably lower drug concentrations compared with urine present an analytic challenge.¹²

Oral fluid as a test matrix shows promise for detection of recent drug use, and a significant body of scientific literature documents aspects such as drug disposition and detection times.^{4,12} However, it has not yet been determined whether adulterants exist that can be safely placed in the mouth to produce false-negative results, and evidence on interference of common compounds present in the mouth, residual drug in the oral cavity, and other issues of manipulation is still lacking.^{4,12,51}

Hair

The disposition of drugs in the body includes incorporation into growing hair.¹¹² Hair may be useful to objectively document past drug use, but it is usually inefficient for clinical testing.^{9,112} Testing hair can extend the window of detection for a drug to weeks, months, or even years depending on the length of the hair tested.^{3,9,113} However, dose and time relationships for drugs in hair are not clear—some studies support that segmental hair analysis can provide a chronologic record of drug use, but others have found high variability in such results.^{25,114,115}

Several mechanisms for incorporation of drugs into hair have been proposed.¹¹² Drugs diffuse from arterial capillaries near the root into hair matrix cells at the base of hair follicles, but drugs in sweat and sebum on the skin's surface contact hair and contribute to drug incorporation.^{105,112} The ability of hair testing to distinguish drug use from external contamination (eg, drugs in smoke or the environment) remains controversial.^{25,112} Typically, measuring metabolites and washing hair samples in solvents can help prevent false-positive results from external contamination.¹¹²

Darkly pigmented hair has a greater capacity to bind a drug than hair that is light or gray, leading to the claim that hair analysis might have a color or racial bias.^{9,25,114–116} Other disadvantages of hair analysis to validate drug use include irregular growth, labor-intensive sample preparation, low analyte concentrations, and excessive cost.^{25,115,116} Differences in hairstyle lengths may affect ability to analyze hair specimens, and hair treatments such as bleaching, dyeing, and permanent waves can alter drug concentrations in hair.²⁵ However, methods for evading UDT do not affect hair analysis, and collection may be achieved under close supervision.¹¹³

Sweat

Sweat could provide a convenient, less invasive collection method and a longer detection window than urine for most drugs.^{103,105} The window of drug detection for a sweat patch is a cumulative measure of drug use from shortly before the patch is applied until it is removed, which may be from several days to weeks.^{3,9,105} Sweat testing may be most useful to deter future drug use in patients participating in drug abuse treatment programs, but is not ideal to monitor drug use for pain management.^{3,9,105}

Criteria for reporting hair, oral fluid, and sweat-patch specimens as invalid, adulterated, or substituted have yet to be defined.

The mechanisms by which drugs are incorporated into sweat are not fully understood.¹⁰⁶ Drugs primarily passively diffuse from blood to the sweat gland, but also dissolve in sweat on the skin's surface after passing through the stratum corneum.^{103,106} Deposition of drugs in sweat depends on molecular mass, pKa, extent of protein binding, and lipophilicity.¹⁰⁵ Nonionized basic drugs (eg, codeine) in blood diffuse into sweat and become ionized, leading to ion trapping and accumulation in the

lower pH of sweat.¹⁰⁵ Lipophilic drugs may also deposit in sweat from sources other than passive diffusion from blood (eg, adipose depots), so the possibility of residual excretion of drug into sweat should be considered when interpreting test results.^{105,106}

Sources of drug-concentration variability include the site of patch application, intra- and intersubject variability in sweat production, loss or dynamic exchange of drug between the patch and skin, and possible environmental contamination.^{103,105,106} Early sweat patches occluded the skin, causing irritation and altering the skin's steady-state pH.¹⁰³ Although newer nonocclusive patches use a transparent film that allows oxygen, carbon dioxide, and water vapor to escape, researchers have demonstrated low acceptability by patients (only half of applied patches were brought back attached to the skin) and a low sensitivity for detecting illicit opioid use (sweat patches detected one-third of illicit opioid-use instances detected by weekly UDT).¹⁰³

It is premature to replace UDT in clinical settings, despite limitations and inconveniences associated with urine collection and testing.

Alternative Specimens Summary

New diagnostic tests are developed in an attempt to increase clinical utility, accuracy, convenience for the patient and/or clinician, and revenue; or to decrease expense and turnaround time.⁶⁸ Different biologic matrices have varying cutoff concentrations depending on the drug, but criteria for reporting hair, oral fluid, and sweat-patch specimens as invalid, adulterated, or substituted have yet to be defined.³ At present, much of the available knowledge on drug disposition in biologic matrices has been generated from single- or multiple-dose studies, but information is limited in chronic users.⁴ Ethical issues exist in the study of many licit and illicit drugs that preclude their study under conditions that simulate “real-world use,” and relevant information may never be available.⁴ It is premature to replace UDT in clinical settings, despite limitations and inconveniences associated with urine collection and testing.¹⁰³

Testing for Alcohol Abstinence

Some physicians test for alcohol abuse, which can compromise the safety of opioid treatment by accelerating the release of certain sustained-delivery formulations.⁹ More than half of Americans aged 12 years and older reported being current alcohol users in 2006—23% participated in binge drinking at least once and 7% reported heavy drinking in the month prior to the survey.²⁵ Ethanol concentrations in breath parallel those in blood and relate to impairment. Ethanol, however, has a short duration in the body and is generally detected for less than 12 hours following use.¹¹⁷ While ethanol is excreted in urine, this is not the optimal sample for assessing alcohol use.

Alcohol biomarkers can serve as measures for possible alcohol problems in individuals unwilling to accurately self-report their drinking, and as evidence of abstinence in individuals prohibited from drinking.¹¹⁸ A recently available laboratory test is for ethyl glucuronide (EtG), a minor but stable ethanol metabolite that can persist in urine for up to 80 hours, providing an extended window to assess drinking status.¹¹⁸⁻¹²¹ The test is a specific marker for alcohol exposure that may help motivate patients to remain or become abstinent from alcohol, but is not useful to measure reduced alcohol intake.⁴⁰ However, the marker does not distinguish between alcoholic beverage consumption and incidental exposure to alcohol in daily use products such as mouthwash, cough medication, “nonalcoholic” beer, and cleaning products.^{118,121,122} The US DHHS issued the following warning:¹¹⁸

Currently, the use of an EtG test in determining abstinence lacks sufficient proven specificity for use as primary or sole evidence that an individual prohibited from drinking, in a criminal justice or a regulatory compliance context, has truly been drinking. Legal or disciplinary action based solely on a positive EtG, or other test discussed in this Advisory, is inappropriate and scientifically unsupported at this time. These tests should be considered as potential valuable clinical tools, but their use in forensic settings is premature.

While promising, much remains to be learned about this marker and the potential causes of false-positive or -negative EtG results; for example, false-negative EtG results have been documented for individuals due to bacterial urinary tract infections.^{117,123} Other investigators have found that urine samples collected more than 26 hours after alcohol ingestion had false-negative results.¹²⁴ It is not known how disease, ethnicity, gender, time, or other drug use might affect results.^{118,122} ■

PRACTICE MANAGEMENT

Selecting a Testing Laboratory: Questions to Ask

- How are urine collection kits provided?
 - What is included?
 - Are there any out-of-pocket charges to the clinician?
- How are the samples sent to the laboratory?
 - Is there a preferred courier for specimen shipping?
 - Can routine pickups be scheduled?
 - Who provides and pays for shipping supplies?
 - Who pays for shipping charges?
- What is the normal time frame for results reporting?
 - Can expedited reporting be provided?
- How are results reported?
 - Is there secure Internet access for data transmission?
 - During what hours are laboratory scientists available to consult with and review results?
 - What qualifications do they have?
- Can customized testing panels be ordered?
 - Are there any customized pain management panels?
 - Is a laboratory scientist available for consultation about appropriate tests to order?
 - What kinds of technology are available for initial screening and confirmatory testing?
 - Is confirmatory testing performed in-house?
 - What testing is performed to assess specimen integrity or validity?
 - Under what circumstances?
- Does the laboratory handle billing through third-party insurance carriers?
 - If not, how is billing handled? ■

CASE STUDIES

Case 1

TF is a 35-year-old female with a history of depression, anxiety, migraine, constipation, and chronic low back pain related to multiple motor vehicle accidents. Her medications include baclofen 10 mg 2 to 3 times per day, clonazepam 1 mg 3 times per day, diazepam 5 mg 3 times per day, venlafaxine extended release 75 mg once daily, hydrocodone/acetaminophen (APAP) 7.5/750 mg 2 times per day, hydroxyzine 50 mg at bedtime, propranolol hydrochloride 20 mg daily, and polyethylene glycol 17 g daily.

Immunoassay results showed benzodiazepines in urine as expected, but were also positive for opiates, suggesting codeine, morphine, or heroin use. Confirmation testing with GC/MS revealed the presence of codeine and morphine in addition to the expected hydrocodone and hydromorphone (metabolite of hydrocodone). Further investigation is required to determine the reason for the unauthorized use of nonprescribed opioids.

Case 2

AC, a 52-year-old male, is transferred to a university hospital from a small outside facility in response to a positive urine drug screen for phencyclidine. The history accompanying the emergent urine drug screen indicated that on arrival, the patient was difficult to arouse, with no history or report of violent or unusual behavior. The immunoassay screen obtained at transfer was negative for all classes tested (opiates, barbiturates, cocaine, methadone, benzodiazepines, phencyclidine, amphetamines). When these results were obtained, the admitting team contacted the laboratory toxicologist to determine what could be interfering with testing. Because the history and admission presentation made the ingestion of phencyclidine unlikely, the toxicologist suggested that another drug may have caused a false-positive result. On questioning, an accompanying family member indicated finding an empty bottle of zolpidem that had been filled 2 days earlier. On day 2 of hospitalization, AC admitted to having ingested 8 tablets of 10 mg zolpidem. Subsequent investigation determined that the phencyclidine immunoassay screening method used in the referring facility exhibited significant cross-reactivity with zolpidem. This is an example of cross-reactivity and emphasizes why it is important to communicate with the testing laboratory.

Case 3

JB is a 24-year-old male with a history of low back pain that started after a motocross accident 4 years ago. During that time, he underwent trigger-point and steroid injections and tried a variety of alternative and medication regimens, including opioids, all of which afforded him only partial relief. He continued to experience persistent and intermittent, sharp, shooting pain that worsened his emotional state and lessened his ability to concentrate on work or to enjoy recreational activities. He admitted to once using a friend's methadone, but stated that he obtained little pain relief from doing so. He exhibited no personal history of drug abuse and did not use alcohol or tobacco. At the time of his initial visit, the patient was prescribed only ibuprofen 800 mg 3 to 4 times daily. His stated goal was for pain therapy that would allow him to fully resume the life he had led before the accident.

Most assays used to detect opiates do not reliably detect synthetic/semisynthetic opioids.

JB was administered a urine immunoassay as part of routine screening, which revealed the presence of opiates. The positive opiate immunoassay result suggested that the patient had ingested morphine, codeine, or heroin because most assays used to detect opiates do not reliably detect synthetic/semisynthetic opioids; however, cross-reactivity can occur. A request was made to the laboratory to test specifically for the presence of several common opioids. This GC/MS confirmation testing detected methadone, methadone metabolite, and oxycodone. It appears this patient was ingesting unauthorized, unprescribed opioids. This behavior may be a sign of undertreated pain or could be a form of prescription drug abuse and requires further investigation.

Case 4

MT is a 44-year-old male with a 10-year history of low back pain that started with a series of work-related injuries involving his back and fractures of his right foot, ankle, and scapula. He had significant neck and back pain that he described as sharp, shooting, and, at times, burning. Because he was unable to lift his right arm, bend over, or walk for long distances, he switched his former labor-intensive occupation to the less physical job of part-time building supervisor, but was still unable to work for more than a couple of hours before the pain forced him to lie down. Sleep disturbance, sexual dysfunction, curtailed social activities, and depression followed.

Interventions that included medication, surgeries, counseling, and occupational therapy were only partially helpful. To combat sexual dysfunction, plans were made to slowly wean MT from paroxetine while initiating duloxetine for depression. The patient reported good prior pain relief from oxycodone/APAP, which was therefore started at 10 mg/325 mg 4 times daily, along with ramelteon 8 mg at bedtime to assist with sleep. Though this patient revealed no prior indications of illicit drug abuse, a routine immunoassay drug test revealed the presence of cocaine.

Significant and ongoing life stresses heighten the potential for abuse of illicit drugs.

Significant and ongoing life stresses heighten the potential for abuse of illicit drugs, even in people who appear to demonstrate low risk for abuse, and abnormal UDT results may appear when least expected. Patients can have chronic pain that warrants opioid therapy concurrent with abuse of illicit substances, but comorbid conditions such as depression and drug abuse must be managed simultaneously with pain therapy.

Case 5

DR is a 45-year-old male referred by his PCP for pain management resulting from a job-related injury 3 years ago. As part of the treatment agreement, UDT is performed at the conclusion of the first visit. Immunoassay results are positive for cannabinoids and benzodiazepines. Confirmation testing with GC/MS confirms the presence of THC and a previously prescribed benzodiazepine. When you discuss these results with the patient during a telephone follow-up the next day, he admits to using marijuana regularly, but states that he understands the terms of the agreement and has not used since signing it.

Three days later, he returns to the clinic for physical therapy and counseling. At the conclusion of the visit he is asked to provide another urine sample. He appears stressed about the request but agrees to do so. UDT reveals the presence of the prescribed benzodiazepine, a newly prescribed opioid, and THC. You contact the laboratory to discuss if there is a way to determine whether this result represents new or continued use.

After cessation of marijuana use, cannabinoids are released from the tissue over several days to weeks.

Most laboratories that perform confirmation testing report both the compound detected as well as its concentration. Using these data in conjunction with urinary creatinine concentration can help in interpreting the results. THC has a long half-life, and, in general, cannabinoids are lipid-soluble compounds that are taken up by and stored in adipose tissue. After cessation of marijuana use, cannabinoids are released from the tissue over several days to weeks and excreted into the urine where they are detected by UDT. This means patients who have used marijuana for some time may have positive UDT results for several weeks after stopping. How long this lasts varies and is related to the marijuana's quality and quantity, in addition to the individual's physiology. Studies have shown that most individuals' results are negative within 3 weeks.

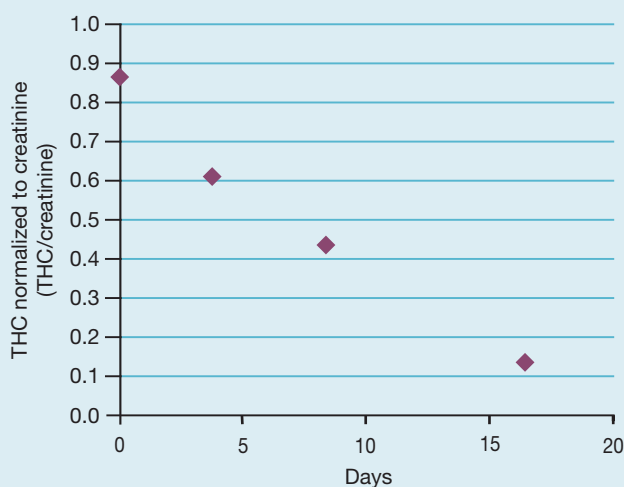
During this time, one can monitor this clearance by following the concentration of THC normalized to the

urinary creatinine. This takes into account varying urine concentration. If the patient is compliant and has not relapsed to or continued marijuana use, normalized levels will steadily decline. Over the next 6 weeks, several urine samples from DR are tested via GC/MS. The concentration of THC is shown below along with the accompanying creatinine:

Visit	THC (ng/mL)	Creatinine (mg/dL)	THC/creatinine
1 (day 0)	97	110	0.88
2 (day 4)	75	121	0.61
3 (day 9)	90	210	0.43
4 (day 17)	15	115	0.13
5 (day 28)	0	122	–
6 (day 40)	0	110	–

There is an initial decline in THC concentration, but on visit 3 (day 9) there is a sharp increase, which could cause one to conclude that DR has resumed marijuana use. However, by normalizing the results to the creatinine excretion, you see this rise was likely the result of a concentrated sample and dehydration. When the normalized values are graphed over time (see figure below), the results show a steady decline. From these data, one should conclude that DR has not relapsed to drug use.

Graph of normalized THC results for DR:



SUMMARY: GUIDELINES FOR TESTING

UDT can be an effective tool in clinical practice for the assessment and ongoing management of patients being considered for or currently managed with opioid analgesics for chronic pain.^{9,40} However, such testing should never be substituted for good diagnostic skills.¹¹

Whether UDT is cost-effective and of clinical value depends upon the ordering physician's interactions with the testing laboratory.

Whether UDT is cost-effective and of clinical value depends upon the ordering physician's interactions with the testing laboratory, so that he or she can:¹¹

- Clarify the purpose of UDT
- Identify a clear testing strategy: why, who, and when to test
- Understand the limits of what is actually being measured
 - Under what circumstances a false-positive result might be reported
 - The probability of cross-reactivity with other substances
 - What confirmatory testing to order
- Understand the terminology the laboratory uses to report its results
- Distinguish between the needs and cutoffs used in workplace testing and clinical settings
- Use strategies to improve analysis and interpretation of results ■

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