

REPORT 1 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (I-16)
Urine Drug Testing
(Reference Committee K)

EXECUTIVE SUMMARY

Objective. The Council on Science and Public Health initiated this report to help promulgate urine drug testing (UDT) as a medical management tool that can be used to better serve patient populations.

Methods. English-language articles were selected from a search of the PubMed database through August 5, 2016 using the search terms “urine drug testing” and “opioids,” and “urine drug testing” and “controlled substances.” Additional articles were identified from a review of the references cited in retrieved publications. Searches of selected medical specialty society websites were conducted to identify clinical guidelines and position statements.

Results. Many urine drug tests (UDTs) utilized in clinical care are grounded in immunoassay (IA) technology. IA UDTs are designed to detect a specific drug or a class of drugs as either present or absent based on a designated threshold concentration. Results based on IAs are considered presumptive and are often used as an initial screening test (i.e., qualitatively positive or negative) in clinical UDT. Point-of-care (POC) tests are typically non-instrumented IA devices (strips, dipcards) that can be used in clinics and are presumptive, qualitative, variable, and have a number of other limitations. The current gold standard and method of confirmatory testing after IA in UDT is separation of a specimen and specific identification of drugs/metabolites using gas or liquid chromatography-mass spectrometry (GC-, LC-MS). Recently, liquid chromatography-tandem mass spectrometry (LC-MS/MS) has been utilized, with success, as screening technique. The detection period for drug exposure varies depending on the disposition characteristics of the drug, dose, and frequency of use. Unexpected findings are common in clinical UDT. Proper interpretation of UDTs can be complex depending on the type of assay, possible adulteration, detection time and thresholds, and therapeutic response.

Conclusion. UDT is an objective means to detect the use of nonprescribed or illicit drugs and to confirm the presence of prescribed drugs. The elements of the drug test such as the composition of the drug test panel and the testing method/technology should be determined by the patient’s physician. Therefore, it is important for physicians to understand the elements of UDT in order to make informed decisions. The value of UDT depends on clinicians appreciating the strengths and weaknesses of the test or the laboratory and their relationship with the laboratory. Understanding the drugs that are detected in IAs and those detectable only via confirmatory methods, cross reactivity, and detection thresholds are critical, as well as the fact that these parameters can change over time. Aberrant UDT results can be used as an objective measure and used to motivate patient change and stimulate healthy physician-directed patient education. Although specific training and application to individual clinical management are outside of the scope of this report, the Council recommends the development of practical guidance to assist clinicians in implementing UDT in their practices and understanding how UDT results may affect patient management.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 1-I-16

Subject: Urine Drug Testing

Presented by: Bobby Mukkamala, MD, Chair

Referred to: Reference Committee K
(Paul A. Friedrichs, MD, Chair)

1 INTRODUCTION

2
3 Over the past two decades, the rate of opioid prescribing, especially for patients with chronic non-
4 cancer pain, has increased dramatically. It is estimated that between 9.6 and 11.5 million
5 Americans are currently being prescribed long-term opioid therapy.¹ The overall increase in
6 prescribing has been associated with a parallel increase in unintentional overdoses and deaths from
7 prescription opioids.² In 2014, a total of 47,055 drug overdose deaths occurred in the United States;
8 61% of these involved some type of opioid, including heroin. Overdose deaths from heroin have
9 quadrupled in recent years, and the majority of past year users of heroin report they used opioids in
10 a nonmedical fashion prior to heroin initiation; hence, the availability of pharmaceutical opioids is
11 relevant to the national heroin use and overdose death epidemics. In the most recent available
12 report, benzodiazepines were involved in 31% of the opioid-related overdoses.³ Despite clinical
13 recommendations to the contrary, the rate of opioid and benzodiazepine co-prescribing also
14 continues to rise.³⁻⁵

15
16 Identifying patients at risk for drug misuse is a challenge. There is no definitive way for physicians
17 to predict which of their patients will develop misuse problems with controlled substances.
18 Because of this, deciding which individual patients to evaluate with drug testing is an arduous task
19 and in its place “universal precautions” have been recommended by some authors so that drug
20 testing becomes a standard process when patients are receiving chronic opioid therapy.⁶

21
22 Urine is the most commonly used biological fluid or specimen used for drug testing. It is non-
23 invasive to collect, a more than adequate volume is usually available, it is easier to process than
24 other matrices,⁷ and the time during which most analytes can be detected after exposure is
25 sufficiently long (1-3 days for most).⁸ This report therefore focuses on urine drug testing (UDT)
26 and not on the testing of alternative specimens such as oral fluid, blood/serum, hair, or other body
27 tissues or fluids (see Appendix). It is important to emphasize that drug testing can identify the
28 presence or absence of a substance in the tissue or body fluids of an individual and can therefore
29 confirm recent substance use (the undesired use of an unauthorized substance or the failure to
30 adhere to use of a prescribed agent). UDT addresses use, but cannot diagnose, rule out, or rule in
31 substance use disorder or addiction. Cases of non-use can indicate diversion but cannot provide
32 proof of such behavior.

33
34 A large national diagnostic laboratory recently published an analysis of more than 3 million urine
35 specimens obtained as part of physician monitoring for prescription drug misuse in 2015.⁴ This
36 analysis revealed a 54% rate of drug misuse based on UDT. Among those patients with abnormal

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Action of the AMA House of Delegates 2016 Interim Meeting: Council on Science and Public Health Report 1 Recommendations Adopted as Amended, and Remainder of Report Filed.

1 findings, 45% had a similar class, non-prescribed, or illicit drug(s) detected; 23% had a different
2 class, non-prescribed, or illicit drug(s) found; and 32% had at least one prescribed drug that was
3 not detected. Benzodiazepines, followed by opioids, were the most common non-prescribed agents
4 found in UDT samples. These results highlight the lack of patient adherence to recommended
5 treatment plans for controlled substances and the potential for harmful drug combinations.⁴ A sub-
6 analysis of more than 150,000 specimens for controlled substances and illicit drugs detected heroin
7 in 1.56% of the samples (age range 18 to 65+), underscoring the increasing threat of heroin use in
8 the United States.⁹ The concurrent use of benzodiazepines among heroin users was nearly 30%,
9 mostly in a nonmedical fashion.

10
11 Accordingly, UDT is currently considered the most objective tool for monitoring and documenting
12 treatment adherence to prescribed controlled substances and signs of drug misuse. When utilized
13 properly, it is an objective indicator clinicians can employ within the confines of a patient-
14 physician relationship along with other risk mitigation tools such as prescription drug monitoring
15 programs (PDMPs) to help guide pain management strategies while balancing patient needs, safety,
16 and reducing risk.¹⁰ UDT in its clinical applications is not intended to stigmatize or penalize
17 patients, but to monitor for signs of misuse, provide clinically useful information, and promote
18 honest dialogue so that a change in therapy or intervention can be introduced if (or when) needed.¹¹

19
20 Outside of pain management practice, and the treatment of anxiety disorders or attention deficit
21 hyperactivity disorder (ADHD), UDT is used in addiction medicine to detect unauthorized use of
22 potentially addictive substances. It is also used in quasi-clinical physician health programs and
23 related programs to monitor the status of continuous abstinence from alcohol and other drugs and
24 the ongoing recovery in health care professionals who are receiving or have received treatment for
25 a substance use disorder.

26
27 Evidence suggests that combining UDT with other risk mitigation strategies such as pill counts,
28 treatment agreements, and patient education can reduce substance misuse by at least 50%.¹⁰ The
29 Council on Science and Public Health initiated this report to promulgate UDT as a medical
30 management tool that can be used to better serve patient populations.

31 32 CURRENT AMA POLICY

33
34 AMA Policy H-95.985, “Drug Screening and Mandatory Drug Testing,” states that physicians
35 should be familiar with the strengths and limitations of drug screening techniques and programs
36 and it lists several other details of drug testing that this report will update and clarify. Policy H-
37 95.984, “Issues in Employee Drug Testing,” advocates for education of physicians and the public
38 regarding drug testing and supports the monitoring of evolving legal issues surrounding the testing
39 of employees. These policies highlight that employment/workplace-related drug testing and clinical
40 drug testing have different aims, ask different questions, and may use different testing
41 methodologies.

42 43 METHODS

44
45 English-language articles were selected from a search of the PubMed database through August 5,
46 2016 using the search terms “urine drug testing” and “opioids,” and “urine drug testing” and
47 “controlled substances.” Additional articles were identified from a review of the references cited in
48 retrieved publications. Searches of selected medical specialty society websites were conducted to
49 identify clinical guidelines and position statements.

1 FORENSIC VERSUS CLINICAL URINARY DRUG TESTING

2
3 Historically drug testing has been forensic in nature and has assumed most donors will provide a
4 negative specimen. In patient-centered UDT in a clinical setting, the majority of specimens
5 provided are expected to be positive for a broad range of drugs that are prescribed for medical
6 purposes which adds to the complexity of the testing and the interpretation of data. Most UDT
7 today that involves drug testing laboratories includes elements of both forensic drug testing and
8 clinical drug testing. Drug testing in clinical settings also includes toxicology testing, usually in
9 hospital emergency departments or emergency psychiatry settings, used to help accurately diagnose
10 possible drug poisoning or overdose. Clinical drug testing is often inaccurately labeled as
11 “toxicology testing” involving “tox screens” when the goal of testing is not to identify a case of
12 acute poisoning but is to assist in treatment planning for a chronic disease, such as chronic non-
13 cancer pain or addiction.

14
15 *Forensic Urine Drug Testing*

16
17 In forensic drug testing, results are meant to stand up to legal challenges and meet the rules of
18 evidence in legal proceedings. Chain-of-custody procedures, secure storage of samples, and
19 stringent method validations are utilized with the aim of minimizing or eliminating false positive
20 results, and rigorous laboratory certification programs are used to assure quality. The personnel
21 running the tests in a forensic UDT laboratory usually have training in chemistry or forensic
22 science and they understand chain-of-custody and medicolegal requirements.

23
24 Federally Regulated UDT. Mandatory guidelines for federal workplace UDT exist and are
25 regulated by the Substance Abuse and Mental Health Services Administration (SAMHSA); only
26 SAMHSA-certified laboratories can perform workplace drug testing on federal employees. The list
27 of drugs tested under the federal program (often referred to as the SAMHSA-5 or federal-5) is
28 limited and includes only five classes of drugs: amphetamines, marijuana, cocaine, opiates (natural
29 opiates such as codeine and morphine, a metabolite of heroin, but not other synthetic opioids such
30 as oxycodone, hydrocodone, buprenorphine and methadone), and phencyclidine (PCP) (see Table
31 1). The SAMHSA-5 derives from Congressional legislation mandating drug testing of interstate
32 truck drivers and other commercial vehicle operators; its finite group of analytes is also referred to
33 as the DOT-5, for the U.S. Department of Transportation which regulates commercial vehicle use
34 across state lines.

35
36 Federally regulated testing follows a screen-and-confirm paradigm in which lower cost, less
37 specific, and often less sensitive screening methodologies are initially used and more costly, more
38 sensitive, and more specific methods are used to confirm positive screening results. Positive test
39 results based on immunoassays (IA) are only considered presumptive because of cross reactivity
40 and differing sensitivity and specificity (see below). Presumptive positive results must be
41 confirmed using definitive chromatography-mass spectrometry methods and all confirmed results
42 must be evaluated by Medical Review Officers (MROs), who serve as a common point of contact
43 between all participants in a UDT. MROs are licensed physicians who have expertise in drug
44 disposition, training in drug collection procedures and the federal program, and have passed a
45 certification exam.¹²

46
47 The concentrations required to generate a positive test result vary for each analyte, but are high (in
48 order to minimize false positive results) compared to clinically-relevant concentrations for the
49 prescription drugs included. The federal UDT program, does, however, set a standard for analytical
50 quality, procedure, and measurement in forensic laboratories as well as in clinical laboratories.

1 Nonregulated Forensic UDT. Many states and private employers have adopted drug-free workplace
2 programs that include UDT similar to the SAMHSA program. A multitude of other UDT
3 applications exist including pre-employment testing, for-cause testing (in response to on the job
4 impairment or after a workplace accident), reasonable suspicion testing, random workplace testing,
5 return to work testing, school testing, sports testing, as well as testing in the criminal justice
6 system, testing in child custody cases, Department of Transportation testing for required
7 occupations, testing in the military (which is the model for the use of drug testing to prevent drug
8 use),⁷ and medical examiner (post-mortem) testing. Most of these testing applications have a
9 testing panel that is broader than the SAMHSA-5 and can therefore include additional analytes
10 such as oxycodone, oxymorphone, and other opioids, benzodiazepines, barbiturates, stimulants,
11 anabolic steroids, emerging designer drugs such as synthetic cannabinoids and cathinones, and
12 others.

13 14 *Clinical Urine Drug Testing*

15
16 Clinical drug testing is part of the medical evaluation within an established patient-clinician
17 relationship. It is used for diagnosis, treatment monitoring, or the promotion of long-term recovery
18 from a substance use disorder and in other clinical settings such as pain management.⁷ The goal of
19 clinical UDT is to meet the standards of medical practice, not the legal requirements of forensic
20 testing. UDT can improve a clinician's ability to manage therapy with controlled substances and
21 assist in, but not make the diagnosis of, a substance use disorder or addiction. Personnel running
22 the testing in a clinical setting have a broad spectrum of laboratory training, often as a medical
23 technologist, but do not usually have chain-of-custody or evidentiary training. Although most
24 dedicated toxicology testing laboratories started as forensic in nature, some now specialize in
25 testing and interpreting clinical and pain management samples and better understand the needs of
26 physicians and their patients.^{13,14}

27 28 URINE DRUG TESTING METHODS

29
30 The U.S. Food and Drug Administration (FDA) classifies laboratory developed tests, including
31 point-of-care (POC) UDT testing devices, as waived, moderate, or high complexity under the
32 Clinical Laboratory Improvement Amendments (CLIA).^{15,16} Waived tests are typically easy to use
33 and pose no reasonable risk if performed incorrectly. Once a CLIA certificate of waiver is
34 obtained, the device or test must be used exactly according to manufacturer's instructions.
35 Moderate and high complexity tests carry a significantly increased risk of inaccurate results,
36 require specialized personnel who have been trained to run the instrumentation, use complex
37 methodologies with multiple steps, and require certification with CLIA.^{15,16}

38 39 *Quality Assurance*

40
41 Laboratory accreditation programs ensure the integrity of analytical results by providing
42 laboratories a set of standards. The standards guarantee that tests are subjected to rigorous quality
43 assurance criteria, are delivered in a manner that promotes proper interpretation, and are performed
44 by qualified individuals. There are several voluntary accreditation programs including CLIA,
45 SAMHSA, the College of American Pathologists (CAP), The American Society of Crime
46 Laboratory Directors (ASCLAD), New York State Department of Health (NYSDOH), and
47 International Organization for Standardization/International Electrotechnical Commission
48 (ISO/IEC). Each accreditation program has requirements specific for the focus of the laboratory
49 services whether it be medical testing, workplace drug testing, or some other application.

1 Laboratories typically develop their own testing methods with rigorous quality controls. Most
2 accreditation programs have proficiency testing that is a peer-based competency evaluation
3 program to ensure accurate and reliable test results. The National Institute of Standards and
4 Technology and the Department of Justice recently established the Organization of Scientific Area
5 Committees (OSAC) in order to support the development and promulgation of forensic science
6 standards and guidelines. The Toxicology Subcommittee focuses on standards and guidelines
7 related to the analysis of biological samples for alcohol, drugs, or poisons, and the interpretation of
8 these results.¹⁷ As clinical UDT is a combination of both forensic and medical requirements, there
9 are currently no standards specifically for its application, but accreditation programs for pain
10 management are likely forthcoming.¹⁸

11
12 Requirements for laboratory directors vary depending on the type of testing and the accreditation
13 body, but most require at a minimum a doctoral degree in a physical science, certification from a
14 major body, and a degree of laboratory experience.¹⁸ The qualifications and competency of
15 individuals in UDT laboratories are evaluated by three major certification bodies: the American
16 Board of Clinical Chemistry, the National Registry of Certified Chemists, and the American Board
17 of Forensic Toxicology. Both personnel at the director level and technical personnel have annual
18 continuing education requirements depending on certification/licensure and laboratory
19 accreditation requirements.

20 21 *Types of Urine Drug Tests*

22
23 Immunoassays. Many UDTs are grounded in IA biology and technology. IAs are based on
24 competitive binding and use antibodies (ABs) to detect the presence of drugs, drug metabolites, or
25 drug classes. In IAs, a known amount of labeled drug/metabolite is added to a specimen. Any
26 drug/metabolite in the specimen will compete with the labeled drug/metabolite for binding with an
27 AB. The amount of labeled antigen-AB complex remaining in the specimen is determined by the
28 amount of drug/metabolite present in the specimen competing for the binding site.¹⁵ IAs can use
29 enzymatic, chemiluminescent, fluorescent, or colorimetric labeling for detection.

30
31 Many IA-based UDTs are designed to detect a specific drug or a class of drugs as either present or
32 absent based on a designated cutoff, or threshold concentration for detection. A negative result
33 could mean that no drug is present, or that the drug concentration is below the threshold. The
34 results of these kinds of tests are considered presumptive; their results can represent either true or
35 false positives, or true or false negatives.

36
37 IA UDTs include waived, moderate, and high complexity laboratory tests under CLIA. Many of
38 these tests are available as commercial kits that contain reagents, calibrators, and controls. Urine
39 samples can be analyzed via IA tests at the POC or can be sent to a laboratory where the IA test is
40 performed by laboratory personnel. Methods and instructions differ in complexity and detail, some
41 with many intricate steps and others with one step. The CLIA-waived IA tests include the POC
42 devices described below. Some moderate and high-complexity IA instrumented devices have been
43 adapted for use in larger medical practices and hospital laboratories, but rigorous and costly CLIA
44 certification requirements have limited the implementation of the instruments in these settings.^{15,18}
45 Some clinical entities such as methadone clinics (federally-licensed Opioid Treatment Programs or
46 OTPs), large pain clinics, and outpatient or residential addiction treatment facilities may have the
47 economies of scale to purchase their own analyzers, obtain CLIA certification, and use these
48 instruments on-site.

49
50 The main advantage of IA UDT is its ability to rapidly detect the presence of substances in urine.
51 One major disadvantage is the limited range of drugs that the assays are able to detect. Because an

1 AB is used for detection, there must be an AB developed specifically for the drug, metabolite, or
2 class of drug. This requirement restricts the number of compounds that can be screened for based
3 on IA. Most commercial IAs include only the SAMHSA-5 panel of drugs, which limits their
4 clinical utility (even if a physician is not aware of this limitation). Some specialized IAs include
5 semisynthetic and synthetic opioids, benzodiazepines, and other drugs. IAs are typically designed
6 to have a high sensitivity (the ability to detect) balanced with lower degrees of specificity (the AB
7 only binds to the target),¹⁵ but the performance characteristics and limitations of the IA UDT vary
8 between tests. Information supplied by the manufacturer should be given appropriate attention; the
9 sensitivity and selectivity can affect the rate of false positive and false negative results and the
10 designated threshold (being too high) could be clinically irrelevant. Home UDT kits available for
11 retail purchase and used by individuals outside of health care settings use IA methods.

12
13 Another confounding variable among IAs is cross-reactivity. Some compounds, despite no
14 structural similarities to the target analyte, may bind to the AB and generate a false positive result.
15 An extensive list of cross-reacting drugs for IAs exists that can cause false positive results (see
16 Table 2).^{15,19-22} Other medications and dietary supplements a patient is taking can significantly
17 impact test results. Additionally, some IAs rely on the ability of an AB to bind to a class of drugs
18 and a lack of cross-reactivity among important members of the class can result in false negative
19 results. For example, many opioid IAs react to the natural opiates codeine and morphine, but may
20 not react with the semisynthetic opioids hydrocodone or oxycodone. In hospital or clinic settings, a
21 physician may order a drug test for opiates, and what is tested for by the IA methodology is only
22 the natural opiates; the clinician may be unaware that in the context of drug-testing, the word
23 “opiates” refers only to the natural compounds such as codeine, morphine, and the metabolites of
24 heroin, without testing for “opioids.” Many primary metabolites may not be reactive with IA UDTs
25 as well. It is essential to understand the limitations of a specific IA test in this regard.

26
27 Unique challenges are associated with IA results for a drug class. IA UDTs do not unequivocally
28 identify which member of a drug class is present in a positive specimen. Even if an IA is labeled
29 “morphine” it may still produce a positive result for any number of opioids, including heroin (and
30 multiple opioids). Conversely, IAs to detect benzodiazepines can have considerable variability in
31 class cross-reactivity depending on which molecule the IA AB is based on. For example, test
32 information may state that the IA will cross-react with alprazolam. A specimen from a patient
33 taking alprazolam containing predominately the major urinary metabolite (α -hydroxyalprazolam)
34 will return a false negative result. Benzodiazepine IAs have very high rate of false negative results
35 and require knowledge of the metabolic pathways of the drugs to properly interpret their results.²³⁻
36 ²⁵ Challenges are also found in the testing of stimulants. Many over the counter products contain
37 sympathomimetics which will generate a false-positive result on an IA for stimulants when the
38 clinician is looking for adherence to psychostimulant therapy or is attempting to detect
39 unauthorized use of methamphetamine or psychostimulants. Prescription drugs such as bupropion,
40 fluoxetine, and others can also produce false-positive IA results for stimulants (see Table 2).

41
42 Physicians and other prescribers typically utilize IA-based tests as an initial screening test (i.e.,
43 qualitatively positive or negative) in opioid-based pain management monitoring programs. Another
44 issue in the clinical use of IA testing is whether confirmation of results is necessary. In some
45 situations the results of an IA UDT may be sufficient, given an understanding of the possible high
46 rates of false positive and false negative results. However, many organizations, including the
47 Federation of State Medical Boards, recommend definitive identification of positive screening
48 results.²⁶ The definitive identification of IA-based presumptive results requires more sophisticated
49 technology for confirmation. Gas or liquid chromatography-mass spectrometry (GC-MS or LC-
50 MS), discussed below, is the standard method of confirming preliminary (screening test) results
51 generated via IA. Without understanding the limitations of testing devices or the laboratories

1 conducting the testing, presumptive UDT testing may not be useful. Testing devices are on a
2 continuum from less expensive/less sensitive and specific (e.g., POC devices) to more
3 expensive/more sensitive and specific (confirmatory testing). Clinicians must be reminded that
4 most drug tests they order are IA tests; actions they take in the care of their patient and treatment
5 plan decisions should not be made based on a non-confirmed result from a presumptive test.

6
7 Point-of-Care Devices. POC tests are typically non-instrumented IA devices (strips, dipcards, cups
8 with imbedded test strips) that can be used in the clinic (at the “point of” care). Testing can
9 therefore occur outside of a laboratory and is not subject to any accreditation standard. These tests
10 are typically granted CLIA-waived status, they lack quality assurance and quality control, and
11 ensuring the integrity of materials following transportation or storage is largely unregulated. Test
12 results are subjective in nature, usually based on a color-changing dye. POC tests are typically
13 performed by health care workers who have many other office-related duties and who are not
14 specifically trained in drug testing. Although POC tests seem simple and are comparatively
15 affordable, they still require proficiency in execution and good laboratory practice is required to
16 obtain reliable results. Product-use instructions and related information accompanying the test
17 device are important to read and understand, and are often not followed.²⁷ Choosing a device that
18 includes reliable customer support is beneficial. Some instrumented benchtop and small floor POC
19 devices have the capability to link with electronic health records. These devices are of moderate
20 complexity and require certification with CLIA,¹⁵ can be expensive, and usually contain the
21 SAMHSA-5 routine drug panel. They do, however, eliminate the visual interpretation and decision-
22 making associated with the use of non-instrumented devices.

23
24 Understanding the limitations of a POC device is important. IA-based POC devices are
25 presumptive, qualitative, variable, have limited sensitivities, offer limited testing menus, cannot
26 distinguish between members of a drug class, and cannot differentiate a drug from its
27 metabolite.^{7,28} The possibility of cross-reactivity with other prescription, over-the-counter, and
28 dietary supplement medications exists, which increases the probability of false positive and false
29 negative results. Many POC IA products have not been optimized for use in a medical setting and
30 are designed with federally-regulated UDT in mind.¹⁵ Threshold concentrations and the drug
31 targets may provide inadequate results for clinicians. The device information provided by the
32 manufacturer includes often-unread advice that presumptive positive IA results must be confirmed
33 with definitive testing, which is not a requirement for clinical UDT, but could be required based on
34 the conditions of the CLIA waiver.¹³ IA-based POC devices do, however, offer rapid results within
35 minutes and can allow physicians to make presumptive in-office clinical decisions, if needed,
36 before results are confirmed. This type of POC test can be useful as long as clinicians are well
37 informed of the limitations.

38
39 Analytical Methods (GC-MS, LC-MS, LC-MS/MS). The current gold standard in UDT is
40 separation of a specimen using GC-MS, LC-MS, or LC tandem mass spectrometry (LC-MS/MS).
41 Separation via chromatography allows each compound in the specimen to be isolated and enter the
42 mass spectrometer individually. The mass spectrometer provides a unique identifying fingerprint
43 for each molecule. The use of GC- or LC-MS depends on the compounds being detected; volatile,
44 nonpolar compounds are more suited for GC (often parent drugs). Chromatography-mass
45 spectrometry is considered high complexity testing, is subject to FDA guidelines, and requires
46 CLIA certification to operate.

47
48 GC- or LC-MS can be used for confirmatory testing after IA. Recently, LC-MS/MS has been used
49 as a screening method⁷ to identify many unique drugs and/or metabolites from different classes of
50 drugs (see Table 1), for example opioids (natural, semi-synthetic, and synthetic), benzodiazepines,
51 and stimulants in lieu of IA. Although LC-MS/MS is a more sophisticated technique than GC- or

1 LC-MS, it can separate and identify many drugs from many classes in a single analysis from a
 2 single specimen. With this advantage, a test profile or panel can include many different analytes
 3 and detect relatively low concentrations of drug or metabolite from low volumes of starting
 4 material and be ideal for an analytical qualitative screening method. More sensitive quantitative
 5 GC-MS and LC-MS analytical methods that are drug class specific can then be used for
 6 confirmatory testing if desired. There are limitations, however, with MS technology; the greater the
 7 number of analytes included in an analysis, the lower the sensitivity of the assay; and not all
 8 substances are capable of detection—the structure of the drug or its metabolites must be known,
 9 therefore, some emerging drugs of abuse and designer drugs remain a challenge for MS detection.

10
 11 Other reasons that these analytical methods may be necessary include the specific identification of
 12 a drug; IA can provide information about the class of a drug only. Additionally, a number of drugs,
 13 such as tramadol, carisoprodol, and designer drugs such as synthetic cathinones and cannabinoids,
 14 are not readily detected using IA and require chromatography testing. Sometimes specialty
 15 analytical testing is necessary, for example only GC-MS with a chiral column will be able to
 16 distinguish between d-methamphetamine (the illicit drug of abuse) and l-methamphetamine (the
 17 compound in Vick’s inhalers). Chromatography-MS tests also can aid in validating disputed test
 18 results. Analytical methods also are quantitative methods, allowing the amount of drug excreted in
 19 urine to be quantified with the use of calibration curves and reference standards. Although this can
 20 be useful for gauging adherence, quantitative GC-MS, LC-MS, or LC-MS/MS data cannot be used
 21 to verify dosage exposure.⁷ POC testing has a high rate of false positive and negative results, which
 22 is not a concern with GC-MS, LC-MS, or LC-MS/MS. Chromatography-MS instrumentation is
 23 relatively expensive, reading and interpreting mass spectrum data requires expertise, and the cost
 24 for a test is variable depending on the testing panel chosen.

25
 26 **TESTING: WHY, WHO, WHEN, AND WHAT**

27
 28 While UDT is an objective means to detect the use of nonprescribed or illicit drugs, the design of
 29 the testing program (including the clinical questions to ask and answer), the patient population to
 30 test, the frequency of testing, and the drug test panel are all determined by the ordering clinician
 31 and should be patient-centered.²⁹ One of the most common failings of UDT in clinical practice is
 32 its application only to high risk patients or those who are suspected of drug misuse.³⁰ Despite the
 33 objective evidence UDT can provide as a clinical tool and recommendations for its use as a risk
 34 mitigation strategy, UDT is underutilized and misapplied, and a lack of understanding exists that
 35 functions as a barrier for introducing successful testing programs into clinical care.³¹⁻³⁸

36
 37 *Why Test?*

38
 39 Standard methods of adherence monitoring for prescribed substances, for example, self-
 40 reporting^{8,39-41} and monitoring of symptoms or patient behaviors,⁴² are unreliable for controlled
 41 substances. As noted above, a high rate of substance misuse occurs in the patients receiving
 42 prescriptions for controlled substances. Seminal studies⁴³⁻⁴⁵ evaluating the use of UDT in patients
 43 with chronic pain revealed that approximately 50% of UDTs yielded appropriate results; the others
 44 showed illicit drugs and/or nonprescribed medications, absence of prescribed opioid(s), and/or
 45 specimen adulteration. In many cases, abnormal test results are not accompanied by behavioral
 46 clues or differences in other demographic or clinical variables.⁴⁴ UDT is objective and an abnormal
 47 result is the most frequently detected signal of opioid misuse. It is similarly useful in managing
 48 patients prescribed benzodiazepines or psychostimulants. UDT plays an important role in providing
 49 a more complete diagnostic picture for clinicians.⁴⁶ As noted earlier, the identification of a drug or
 50 metabolite in a UDT provides evidence of exposure to that drug and information about recent use
 51 of drugs, but it can only provide this information if the substance is present in the urine at levels

1 above the threshold of detection. UDTs cannot identify the presence of a substance use disorder or
 2 the presence of physical dependence.⁷ Before implementing UDT, physicians should understand
 3 the question they want to answer, understand the advantages and limitations of the testing
 4 technology and the interpretation of data, and ensure that the cost of testing aligns with the
 5 expected benefits for their patients.

6 7 *Whom to Test?*

8
9 Practice guidelines on pain management intended to promote safe and competent opioid
 10 prescribing recommend various measures to mitigate risk including UDT, but some disagreement
 11 persists on who should be subjected to routine UDT and its frequency.^{7,26,29,47-51}

12
13 UDT can be useful in many medical specialty practices including but not limited to palliative
 14 medicine,⁵² psychiatry,⁷ geriatrics,⁵³ adolescent medicine,⁵⁴ addiction medicine,²⁹ and primary
 15 care.^{55,56} The routine use of UDT in pain medicine⁵⁷ is recommended in several clinical
 16 guidelines.^{21,26,48,58-60} As stated previously, UDT utilized in emergency settings is typically intended
 17 to diagnose acute drug poisonings or make immediate treatment decisions as opposed to chronic
 18 care situations. An American College of Emergency Physicians policy does address the use of
 19 UDT in the context of psychiatric patients.⁶¹ Although medically appropriate opioid use in
 20 pregnancy is not uncommon, there has been a renewed focus on maternal opioid dependence,
 21 opioid exposure during pregnancy, and the increase in infants born with neonatal abstinence
 22 syndrome.⁶²⁻⁶⁹ UDT can aid in obtaining a complete picture of drug exposure. Two studies in the
 23 Kaiser Health System involving nearly 50,000 obstetric patients demonstrated improved maternal
 24 and fetal outcomes when treatment for substance use disorders were linked with prenatal visits and
 25 UDT allowing for resources to be appropriately allocated for postnatal care.^{70,71} The American
 26 Society of Addiction Medicine (ASAM) supports the use of UDT during pregnancy.^{7,66} The
 27 American Congress of Obstetricians and Gynecologists (ACOG) also supports the use of UDT
 28 during pregnancy when substance use is suspected, but not during routine well care visits.⁷²⁻⁷⁴

29
30 Given the challenges inherent in deciding whom to test and the issues described in the paragraphs
 31 above on why to test, many clinicians have adopted recommendations to utilize “universal
 32 precautions” in opioid prescribing. This approach informs patients at the onset of a plan of care that
 33 the standard procedure for the clinician’s practice is to test *every* patient at the initiation of opioid
 34 therapy, and periodically on a random basis during the course of care. This avoids any patient
 35 feeling singled out and reduces the potential for stigma, discrimination, and clinical errors based on
 36 incomplete clinical information.

37 38 *When to Test?*

39
40 Although uniform agreement is lacking, an evolving consensus recommends testing new patients
 41 before prescribing controlled substances for a chronic disorder, in those seeking increased doses, in
 42 patients who resist a full evaluation, in those requesting specific controlled substances, in patients
 43 displaying aberrant behaviors, in pain management patients recovering from addiction, and special
 44 populations.^{8,47,48} It is recommended that tests be administered at unscheduled and unpredictable
 45 times (random testing) so specimen donors are less likely to try to circumvent the test (see below).⁷
 46 Considerations about how often to test are influenced by concerns about cost and the proper
 47 stewardship of health care resources; both underutilization and overutilization of clinical drug
 48 testing are concerns. The recommended periodicity of testing in given clinical situations continues
 49 to be addressed. Currently, ASAM is developing a guideline for addiction medicine specialists
 50 engaged in varying levels of care (outpatient, intensive outpatient/partial hospitalization,
 51 residential) and within various special populations (for example, health professionals or others in

1 safety-sensitive occupations who are receiving addiction care). Other specialty societies have been
2 encouraged to develop similar guidelines for their physician members and the populations they
3 serve.

4 *What to Test For?*

5
6
7 Clinical drug testing should be individualized and not determined from a device, kit, or forced
8 panel of drugs. It is important to know the clinical question to be answered to properly utilize UDT
9 as a management tool. Although no device or testing panel may be ideal, any testing should be
10 patient-centered. Testing should not be limited to only prescribed controlled substances; it is
11 advantageous to include substances that have been problematic for that patient in the past if a
12 history of drug misuse exists. Local patterns of substance misuse should be considered when
13 designing the testing panel as well.⁷

14
15 The choice of drugs to include on a testing panel is complicated by the fact that many drugs and
16 illicit substances are subject to misuse based on their “rewarding” properties and they may not be
17 included in or detected on a standard drug test. Internet-based and other sources exist that are
18 dedicated to informing users about chemistry, laws, laboratory tests, and how to evade detection of
19 the most commonly tested substances. Additionally, there is a new and ever-evolving drug industry
20 based on “designer drugs” which are being synthesized to evade existing drug tests and laws.⁷⁵

21 22 INTERPRETATION OF UDT RESULTS

23
24 The valid detection period for drug exposure varies depending on the disposition characteristics of
25 the drug, dose, and frequency of use. Specific characteristics of a urine sample include its
26 appearance, temperature within 4 minutes of voiding, pH, creatinine concentration, and specific
27 gravity.⁸ The color of urine is based on the concentration of its constituents^{8,76} and can vary based
28 on medications, foods, or disease states; excess hydration can cause it to appear colorless.
29 Concentrated urine specimens are usually more reliable than dilute specimens.

30 31 *Manipulation/Adulteration, Specimen Validity Testing, Normalization, and Collection*

32
33 One drawback of a urine specimen is that it is easy to tamper with. Collection in a medical setting
34 is typically unmonitored and the potential for manipulation exists and should be considered.
35 Dilution is usually done in an attempt to lower the concentration of illicit substance(s) below
36 detection levels. Specimens that are excessively dilute will have low creatinine levels. Commercial
37 “cleansing” beverages exist that when consumed in large volumes dilute urine and contain B
38 vitamins to restore urine color.

39
40 Urine spiking with a specific substance is done to simulate adherence to medication taking and is
41 not uncommon. For example, patients who know they will be subjected to adherence testing but
42 who have not been taking the prescribed medication per instructions can add crushed drugs hidden
43 under a fingernail to a urine specimen to generate a positive test result.²⁸ Diversion is sale or
44 distribution of a prescribed medication to an unintended recipient. UDT cannot detect diversion,
45 but a negative specimen may indicate diversion or some other maladaptive drug-taking behavior
46 (i.e., periods of reduced medication use or abstinence followed by binging).⁸ These behaviors can
47 occur with buprenorphine prescribed for the treatment of opioid addiction, though the patient’s
48 aberrant behavior can be easily recognized when confirmatory testing data is interpreted and the
49 relative amounts of parent compound and the primary metabolite, norbuprenorphine (if present) are
50 evaluated.

1 Substitution is the switching of donor urine with drug-free synthetic urine, urine from another
2 individual, or urine from an animal.⁷⁷ This is easily detected in many cases because house pets
3 produce urine that has a very different pH from human urine. Test results are typically reported as
4 “specimen incompatible with human urine” (or similar) when testing procedures include pH
5 analysis.

6
7 Adulteration is the addition of oxidizing chemicals or other substances directly to the specimen that
8 may interfere with the UDT. Some adulterants can be other drugs such as dextromethorphan or
9 salicylates, which are known to cause false negative results with some IA UDTs; other adulterants
10 are common household products or substances that are otherwise easily obtainable including salt,
11 vinegar, bleach, soap, Visine®, glutaraldehydes, chromate-containing compounds, and sodium
12 nitrate.¹⁴ Being aware of this, many clinicians will not utilize any drug testing methodology that
13 does not include testing for common commercially-available adulterants.

14
15 Most testing laboratories will perform specimen validity testing (SVT) on urine specimens.⁷⁸ SVT
16 includes testing the specimen for creatinine, specific gravity, pH, nitrates, chromates, and other
17 easy-to-obtain over-the-counter adulterant products, and assuring that values are consistent with
18 those of normal human urine. Values outside of typical ranges may indicate the specimen has been
19 tampered with or adulterants have been added.¹⁴ Many laboratories will also normalize urine
20 samples since urine drug concentrations vary significantly between individuals and can have an
21 effect on UDT; if a urine specimen is dilute, a drug may be present, but below a measurable level.
22 Normalization is a mathematical method using specific gravity or creatinine concentrations to
23 adjust for dilution, thereby allowing the UDT results to be interpreted or compared. Often this can
24 be useful when comparing serial analyte measurements or to minimize false negative results.^{8,14}

25
26 To minimize specimen tampering many collection protocols require patients to leave outerwear and
27 personal belongings in exam rooms, and to show pocket contents. Some relatively inexpensive
28 POC collection devices (cups) incorporate validity testing such as temperature, pH, specific
29 gravity, and oxidation and add an extra layer of assurance to specimen collection. Some testing
30 laboratories will provide staff to physicians’ offices to facilitate collections; third party collectors
31 exist as well. Some third party vendors will send a single collector to a location and many third-
32 party specimen collection sites exist for the employment drug testing market, for use by
33 professional sports leagues for their testing protocols, or for monitoring programs for licensed
34 health professionals, rather than for clinical drug testing. Once the specimen is collected, it should
35 be refrigerated to minimize drug degradation, especially if testing is delayed. As noted, chain-of-
36 custody handling of specimens between the site of collection and the laboratory bench are
37 components of forensic and some employment-related testing, rather than clinical drug testing.

38 39 *Interpretation of Results*

40
41 Clinicians’ predictions of UDT results are often inaccurate²¹ and evidence suggests a majority of
42 physicians have a poor understanding of how to interpret UDT results. Others may have a false
43 sense of confidence about interpreting their patients’ UDT results because they lack specific
44 knowledge or don’t fully understand the breadth of abnormal or unexpected toxicology findings
45 that are possible.^{10,33,79-81}

46
47 Unexpected findings are common in clinical UDT; results are much more than just a positive or
48 negative result. There are complexities to consider in order to properly interpret UDT such as the
49 type of assay, possible adulteration, detection time, detection thresholds, and therapeutic response.
50 Therapeutic response can be variable and can be affected by drug potency, chemical properties,
51 metabolism, dose, preparation, drug-drug or drug-herbal interactions, and the patient (diet, drug

1 ingestion, weight, genetic makeup, disease state).^{82,83} Appropriate interpretation of toxicology
2 testing results requires a working knowledge of drug metabolism; although beyond the scope of
3 this report, there are many intricate details involved in opioid pharmacokinetics and
4 pharmacodynamics to consider.^{82,83}

5
6 If POC devices are being utilized, consultation of product inserts is recommended and choosing
7 devices with readily available customer support is advantageous. If a laboratory is used for UDT,
8 then contacting the professionals at the laboratory, such as a toxicologists or laboratory director, is
9 recommended whenever the clinician feels a need for guidance on interpretation of reported results.
10 Additionally, physicians should be sure to obtain a full prescription and over-the-counter
11 medication history (including dietary and herbal supplements), and use this information in the
12 context of the UDT or provide this information to the testing laboratory since it could be relevant to
13 interpreting UDT results.

14 15 CONCLUSIONS

16
17 UDT is an objective means to detect the use of nonprescribed or illicit drugs and to confirm the
18 presence of prescribed drugs. The elements of the drug test such as the composition of the drug test
19 panel (the list of analytes in a given test) and the testing method/technology should be determined
20 by the ordering clinician. Therefore, it is important for physicians to understand the elements of
21 UDT in order to make informed decisions. The value of UDT depends on clinicians appreciating
22 the strengths and weaknesses of the test or the laboratory and their relationship with the laboratory.
23 Understanding the drugs that are detected in IAs and those detectable only via confirmatory
24 methods, cross-reactivity, and detection thresholds is critical, as is the fact that these parameters
25 can change over time. Some clinicians have adapted the SAMHSA workplace drug testing model
26 for clinical drug testing with success (IA screen with MS confirmation), but the range of analytes in
27 the SAMSHA-5 itself is likely too narrow to be of use in most clinical scenarios. Some laboratories
28 offer LC-MS/MS UDT without IA and have been successful; other labs rely only on IA and find
29 that acceptable for their clientele. Just as clinicians use HbA1c as an objective measure for the
30 diagnosis of pre-diabetes, aberrant UDT results can be used as an objective measure³⁰ and used to
31 motivate patient change and stimulate healthy physician-directed patient education. Although
32 specific training and application to individual clinical management are outside of the scope of this
33 report, the Council recommends the development of practical guidance to assist clinicians in
34 implementing UDT in their practice and understanding how UDT results may affect patient
35 management.

36 37 RECOMMENDATIONS

38
39 The Council on Science and Public Health recommends the following recommendations be
40 adopted and the remainder of the report be filed:

- 41
42 1. That Policy H-95.985, "Drug Screening and Mandatory Drug Testing," be amended by
43 addition and deletion as follows:

44 45 ~~Drug Screening and Mandatory Drug Testing~~

46
47 The AMA believes that physicians should be familiar with the strengths and limitations of drug
48 ~~screening~~ testing techniques and programs:

- 49
50 1. Due to the limited specificity of the inexpensive and widely available non-instrumented
51 devices such as point-of-care drug testing devices ~~screening techniques, forensically~~

1 acceptable clinical drug testing programs ~~must~~ should include the ability to access highly
2 specific, analytically acceptable ~~technically more complicated and more expensive~~
3 confirmation techniques, which unequivocally definitively establishes the identities and
4 quantities of drugs, in order to further analyze results from presumptive testing
5 methodologies. Physicians should consider the value of data from non-confirmed
6 preliminary test results, and should not make major clinical decisions without using
7 confirmatory methods to provide assurance about the accuracy of the clinical data.
8

9 2. Results from ~~such~~ drug testing programs can yield accurate evidence of prior exposure to
10 drugs. Drug testing does not provide any information about pattern of use of drugs, dose of
11 drugs taken, ~~abuse of or physical~~ dependence on drugs, the presence or absence of a
12 substance use disorder, or about mental or physical impairments that may result from drug
13 use ~~nor does it provide valid or reliable information about harm or potential risk of harm to~~
14 children or, by itself, provide indication or proof of child abuse, or neglect or proof of
15 inadequate parenting.
16

17 3. Before implementing a drug testing program, physicians should: (a) understand the
18 objectives and questions they want to answer with testing; (b) understand the advantages
19 and limitations of the testing technology; (c) be aware of and educated about the drugs
20 chosen for inclusion in the drug test; and (d) ensure that the cost of testing aligns with the
21 expected benefits for their patients. ~~and~~ Physicians also should be satisfied that the
22 selection of drugs (analytes) and subjects to be tested as well as ~~and~~ the screening and
23 confirming confirmatory techniques that are used meet the stated objectives.
24

25 4. Since physicians often are called upon to interpret results, they should be familiar with the
26 disposition characteristics ~~pharmacokinetic properties~~ of the drugs to be tested before
27 interpreting any results, and the use to which the results will be put. If interpretation of any
28 given result is outside of the expertise of the physician, assistance from appropriate
29 experts, such as a certified Medical Review Officer, should be pursued. (Modify Current
30 HOD Policy)
31

32 2. That our AMA, in conjunction with the AMA Opioid Task Force, develop practical guidance
33 and educational materials to assist physicians with implementing urine drug testing as part of a
34 risk mitigation strategy when opioid analgesics are prescribed for chronic use. (Directive to
35 Take Action)

Fiscal note: \$30,000

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Table 1. Drugs often included in urine drug testing (UDT) (adapted from⁸).

Drug/Drug Class	Drug or Metabolite Included in Testing
Amphetamines	Amphetamine ^a
	Methamphetamine ^a
	MDA ^a
	MDEA ^a
	MDMA ^a
	Phentermine
Barbiturates	Butalbital
	Phenobarbital
Benzodiazepines	Alprazolam
	Clonazepam
	Diazepam
	Flurazepam
	Lorazepam
	Nordiazepam
	Oxazepam
	Temazepam
Cocaine^a	Benzoyllecgonine ^a
Heroin	Heroin (diacetylmorphine)
	6-AM ^a
	6-acetylcodeine
Marijuana^a	THCA ^a
Opioids	Buprenorphine
	Norbuprenorphine
	Codeine ^a
	Norcodeine
	Dihydrocodeine
	Fentanyl
	Hydrocodone
	Norhydrocodone
	Hydromorphone
	Meperidine
	Normeperidine
	Methodone
	EDDP
	Morphine ^a
	Oxycodone
	Noroxycodone
	Oxymorphone
	Tapentadol
	Tramadol
	O-desmethyl-tramadol
N-desmethyl-tramadol	
PCP^a	PCP ^a
Carisoprodol	Carisoprodol
	Meprobamate
Anticonvulsants	Gabapentin
	Pregabalin

^aDrugs/metabolites included in federally regulated SAMHSA UDT
 6-AM=6-monoacetylmorphine; EDDP=2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine;
 MDA=3,4-methylenedioxyamphetamine; MDEA=3,4-methylenedioxyethylamphetamine;
 MDMA=3,4-methylenedioxymethamphetamine; PCP=phencyclidine;
 THCA=delta-9-tetrahydrocannabinol-9-carboxylic acid

Table 2. Compounds causing potential false positive results with immunoassay testing.

IA Test	Compound Causing a Potential False Positive		
Amphetamines	Amantadine	Isometheptene	Phenylephrine
	Aripiprazole	Isoxsuprine	Phenylethylamine
	Benzphetamine	Labetalol	Phenylpropanolamine
	Brompheniramine	m-Chlorophenylpiperazine	Promethazine
	Bupropion	(mCPP)	Propranolol
	Cathine	MDA	Propylhexedrine
	Cloroquine	MDMA	Pseudoephedrine
	Chlorpromazine	MDPV	Pyrovalerone
	Ciprofloxacin	Mefenamic acid	Ranitidine
	Clobenzorex	Mephentermine	Ritodrine
	Desipramine	Metformin	Salbutamol
	Dimethylamylamine	Methamphetamine ^a	Selegiline
	Doxepin	l-methamphetamine (Vick's	Sodium Cyclamate
	Ephedra	Inhaler)	Thioridazine
	Ephedrine	Methylphenidate	Tolmetin
	Fenfluramine	Metronidazole	Trazadone
	Fenproporex	Ofloxacin	Trimethobenzamide
	Fluorescein	Phenmetrazine	Trimipramine
	Fluoxetine	Phenothiazines	Tyramine
Ginkgo	Phentermine		
Barbiturates	NSAIDS (ibuprofen, naproxen)	Phenytoin	Tolmetin
Benzodiazepines	Chlorpromazine	Flurbiprofen	Oxaprozin
	Efavirenz	Indomethacin	Sertraline
	Fenoprofen	Ketoprofen	Tolmetin
Buprenorphine	Codeine	Morphine	Tramadol
	Dihydrocodeine	Methadone	
Cocaine	Coca leaf tea ^a	Ecgonine methyl ester	Topical anesthetics
	Ecgonine	Tolmetin	containing cocaine ^a
Fentanyl	Trazadone	Risperidone	
Marijuana (THC)	Acetylsalicylic acid	Efavirenz	Proton pump inhibitors
	Baby wash/Soap	Hemp-containing foods ^a	(pantoprazole)
	Dronabinol ^a	NSAIDs (ibuprofen, naproxen)	Rifampin
			Tolmetin
Methadone	Chlorpromazine	Doxylamine	Quetiapine
	Clomipramine	Phenothiazine compounds	Tapentadol
	Cyamemazine	Olanzapine	Thioridazine
	Diphenhydramine		Verapamil
Opiates	Dextromethorphan	Procaine	Ranitidine
	Diphenhydramine	Quinine (tonic water)	Rifampin
	Doxylamine	Fluoroquinolones	Tolmetin
	Heroin ^a	(ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin)	Verapamil
Poppy seeds ^a			
Phencyclidine	Dextromethorphan	Imipramine	Mesoridazine
	Diphenhydramine	Ketamine	Thioridazine
	Doxylamine	Lamotrigine	Tramadol
	Ibuprofen	Meperidine	Venlafaxine, O-desmethyl-venlafaxine
Tricyclic Antidepressants	Carbamazepine	Diphenhydramine	Promethazine
	Cyclobenzaprine	Hydroxyzine	Quetiapine
	Cyproheptadine		

^aContain or metabolize to target analyteTable information from^{15,19-22}

MDA=3,4-methylenedioxyamphetamine; MDMA=3,4-methylenedioxymethamphetamine;

MDPV= Methylenedioxypropylvalerone; NSAIDS=non-steroidal anti-inflammatory drugs

Table 3. Common causes of false negative results with immunoassay testing.

Potential Causes of False Negative IA Test	Example
Lack of cross reactivity for the desired tested drug class	An IA targeted for natural opiates does not readily detect semisynthetic opioids such as oxycodone.
Drug metabolites do not cross react with IA	An IA detects alprazolam but does not reliably detect the predominant metabolite, α -hydroxyalprazolam. Opioid normetabolites are also a concern (e.g., norhydrocodone).
Threshold of IA is too high	Many IAs were developed for workplace UDT and have thresholds > 300 ng/mL (and as high as 2,000 ng/mL). A more appropriate threshold for clinical UDT is \leq 100 ng/mL.
Specimen is dilute	Fluid intake can cause drug concentration to fall below the threshold concentration.
Adulterated or substituted specimen	Added adulterants can mask the presence of some drugs. Substituted specimens can contain urine from another person, animal, synthetic urine, or some other fluid.
Desired drugs not included in testing	Many commonly abused prescription drugs require separate IAs to detect and could be overlooked in a POC device (e.g., natural opiates, oxycodone, synthetic opioids, methadone, tapentadol, buprenorphine) and others may not be included in IA presumptive testing (e.g., carisoprodol).

IA=immunoassay; UDT=urine drug testing; POC=point-of-care testing

Appendix: Alternative Specimens for Drug Testing

Although urine is the most common matrix used for drug testing, other matrices are available including oral fluid, blood/serum, breath, hair, nails, and sweat. Differences in the collection and interpretation for each specimen type as well as some strengths and weaknesses are associated with each matrix.^{8,14}

Matrix	Detection Window	Collection	Interpretation	Strengths	Weaknesses
Oral Fluid	Acute use: ~4 hrs Chronic use: 24-48 hrs	Non-invasive; observed; non-standardized procedures; use of collection device highly recommended	Disposition of parent drug exceeds metabolites; drug concentrations 10-100x lower than urine	Harder to adulterate; use for shy bladder, renal impairment, suspected urine tampering	Some drugs a challenge (e.g. transdermal buprenorphine); sample volume could be hard to obtain; POC devices developed for forensic use and not recommended for clinical testing
Blood/Serum	Limited to current drug use (hours)	Invasive; difficult to properly store and transport	Disposition of parent drug exceeds metabolites	Can detect low levels of drug (usually in a legal context)	Generally requires lengthy testing procedures; expensive
Breath	Limited to current drug use (hours)	Non-invasive	Limited to the evaluation of alcohol	Well correlated with blood alcohol levels	Most other drugs not sufficiently volatile for breath analysis
Hair	Weeks, months, years (depending on hair length)	Non-invasive; easy to collect; difficult to cheat; easy to store	External contamination possible; color bias; hair treatments may alter drug disposition; drugs may not be detectable for weeks following exposure; segmental analysis variable	Possible use for past drug use	Not all drugs equally incorporated; labor intensive sample preparation; low drug concentrations; expensive; not recommended for clinical testing
Nails⁸⁴	Fingernails: 3-5 months Toenails: 8-14 months	Non-invasive; nail clippings	Disposition of parent drug usually exceeds metabolites	Possible use for past drug use	Mechanisms of incorporation not fully understood
Sweat^{85,86}	~1 week	Non-invasive; adherent patch	Less sensitive than urine	Extended detection time	Unreliable adherence so limited utility; rash; external contamination