CHAPTER 8
LABORATORY DATA

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8.1. Introduction

Historically, drug testing in America has been construed as an adversarial game of cat and mouse between the testers and those persons required to provide these sometimes-incriminating samples. This does not need to be the case, and in fact should not be in OTPs. The clinician's aim for testing is to help diagnose and treat patients; this is entirely different than of, say, law enforcement, workplaces, or airlines. Patient-Centered Urine Drug Testing (UDT) should be the basis for all clinical encounters involving patient care.

Unsanctioned drug use in a largely negative testing population is relatively easy to detect. However, when monitoring for compliance with prescribed medications (i.e. where the absence of the analyte causes concern), the challenges for urine drug testing are greater. Unfortunately, a lab report of "not detected" with a cutoff of 299 ng/dL vs. a "detected" reported with the same cutoff of 300 ng/dL is, from a scientific perspective, identical. Compliance testing using UDT results should be explored with caution.

Addiction specialists rely on urine drug tests to verify that drugs of abuse or street drugs are absent, and the therapeutic drugs such as buprenorphine or methadone and their metabolite are present. Federal and State of California regulations require certain levels of monitoring drug screens to help ensure that patients are complying with the directives of the treatment program. All drugs fall in one of two categories: medications (prescribed or unprescribed) and illicit substances. The former has a specified dose, and the latter an unknown amount of a pure drug or a mixture of components containing the drug. If a patient is taking a prescription that is part of the drug-testing panel while in a treatment program, this is usually a strong indicator of the source of the positive result. However, since urine drug screens are often reported as positive or negative, it is not clear whether a positive test is the result of ingestion of a low therapeutic dose, a high illicit dose, or some combination of these. Owing to the concentrating effects of the kidneys, no meaningful relationship can be drawn between amounts of drug taken and the amount of drug extracted from a donor sample. This means that a monitored individual can abuse a prescribed medication with relative impunity. Patients seeking treatment for OUDs involving street methadone, street buprenorphine or opioids prescrived for pain present UDT challenges. Most drug testing is conducted using a twostep process. The first step is a quick and inexpensive screening test. This test identifies whether any drugs in a variety of classes are present or absent. It is not very specific. Most of the opioids are lumped together in one class, excluding some like methadone and gentanyl. Most of the benzodiazepines are grouped together in another class, again excluding some, like clonazepam and lorazepam. The second step is the confirmatory process, which is used to identify the specific drug(s) present in the class that had a positive screen. A positive screen for opioids may confirm positive for hydrocodone or for codeine, morphine or 6MAM, the metabolite of heroin. There is a quantity associated with each specific drug that is identified.

Attempts by the patient to mask drugs in the urine by adding chemicals or diluting the urine by liquid loading or addition of water further complicate the interpretation. The number and types of drugs in the screen along with the amount of the specific marker creatinine and the temperature of the urine sample will aid in ensuring that a reliable specimen is being tested. Adding methadone

directly to the urine sample in an effort to appear compliant has a specific result that requires interpretation. Understanding the detailed information in the laboratory report is a necessary requirement for treatment specialists to insure the integrity of the program and the safety of the patient. A good working relationship with the laboratory will help in these interpretations.

All clinic treatment personnel interpreting toxicology results must understand the benefits and the limitations of toxicological testing procedures. In order for the laboratory results to be an effective diagnostic tool, the details of the testing parameters that define a positive or negative value such as sensitivity (cut-off values) and specificity (cross-reactivity) should be well understood. This is an important issue in choosing a laboratory and knowing how to act on screened values and when to request a confirmation. For example, a positive screen for cocaine or fentanyl will indicate to a high degree of reliability that the drug is present. However, a positive screen for opiates must be confirmed to identify the specific drug in the opiate class that is present due to a lack of specificity in the screening assay. Furthermore, the interpreting healthcare personnel must have a working knowledge of the various factors that affect the adsorption, metabolism, and elimination of the drugs in question.

8.2. Regulations

8.2.1. Federal Regulations

Federal regulations require eight drug tests per calendar year and specify which drug categories are included in a general drug screen to include methadone and its metabolite. The federal regulations state that the drug screen typically includes opioids, benzodiazepines, barbiturates, cocaine, marijuana, methadone, methadone metabolite, buprenorphine, amphetamine, and alcohol (as the metabolite ethyl glucuronide). However, there is no mandated testing panel. Confirmation of the drugs in each screening class is left to the discretion of clinic personnel. In abnormal UDT results, all contested screen results should be confirmed by more advanced combination techniques. Uncontested results typically do not need further testing.

8.2.2. California State Regulations

Under current California regulations, random toxicology screens are required once a month for most OTP patients and are required once a week for pregnant patients. In California, drug testing performed to comply with state regulation must be sent to a state-approved laboratory. Under Title 17, the required drug-screening panel must include amphetamines, cocaine, opioids, barbiturates, methadone and methadone metabolite. Confirmation of all screening presumptive positives must be done before reporting, and the methadone and methadone metabolite must be confirmed if either one or both screen negative. The amphetamines screening positives must be confirmed for both methamphetamine and amphetamine, and opioids must be reported for morphine and codeine. Secobarbital, pentobarbital and phenobarbital must be confirmed for the barbiturates class. This can create problems and misinterpretation for the drugs that are not specifically listed in the State of California's confirmation requirement.

The certified laboratory is usually not in the same geographical area as the clinic, so the specimen must be transported to the laboratory for testing. An off-site laboratory can delay the availability of the laboratory results and may not facilitate immediate clinical intervention with the patient. To compensate for this, some OTPs utilize additional on-site testing which allows prompt evaluation of acute clinical situations, even if they do so with some reduction in reliability and accuracy. This "non-Title 9" testing is used for in-house decisions and for medical-exception take-home decisions, but not for the state specified 'regular' take-home criteria. When using this "non-Title 9 (on-site, dip stick) testing" it is always preferable to check with the clinic referral lab with regards to the cross-reactivities and the cut-offs of the on-site test method. This will minimize the generation of conflicting results between the two different testing methods.

Urine is the best and preferred sample type for California drug testing under Title 9. There is a time-honored history in the published data with this type of testing. Urine as a matrix, will give a concentrated sample that represent the metabolism and excretion of drugs from the current collection to the previous void over a reasonable period of time (window of detection). Urine can offer only a semi-quantitative result because of the variations in water intake. Saliva and blood tests are also available. The serum values for drugs represent the effective amount of drug in the body. This quantitative value will represent the patient values for a given dose and it may be useful as a peak and trough comparison for split dosing or compliance issues involved with changing the patient's dose. Although these values may be of interest academically, their utility in clinical care has yet to be proven.

Many state-approved laboratories have a standard panel of drugs for which they routinely screen. This list is based on the tests required by OTP regulation, and panels often do not include tests for alcohol, marijuana, some benzodiazepines (notably clonazepam (Klonopin®) and lorazepam (Ativan®), and other sedatives such as muscle relaxants. Fentanyl, a synthetic opioid, is never detected by an opiate immunoassay screen, whereas oxycodone, a semisynthetic opioid, is not reliably detected in the opiate screening assay and must be ordered as a specific oxycodone screen if use is suspected. Additional tests should be ordered as needed on a case-by-case basis to assist in the medical management of the individual patient.

Periodic breathalyzer testing for alcohol may be needed for patients with a history of alcohol abuse or dependence; alternatively an ethyl glucuronide laboratory test will give results that correspond to past usage for three to five days (although interpretation of absolute levels remains under debate). Strategic breathalyzer screening for alcohol (after holidays or on weekends) may be particularly helpful to ensure that the patient is safe to dose on a given day. At times, daily breathalyzer testing may be needed to clarify the frequency and extent of a patient's alcohol use and

Table 8.2.1

Urine Drug Testing Requirements: Federal vs. State

Drug Class/ Analytes	Federal Regulations			California Regulations		
	No Requirements			Certified Laboratory		
	8 drug tests per year			1 drug test per month		
	Screen	**Confirm**	**POCT***	**Screen**	**Confirm**	**POCT***
Opioids**	R	O	O	R	R	O
Morphine				R	R	O
Codeine				R	R	O
Hydrocodone						
Hydromorphone						
Fentanyl						
Oxycodone						
Benzodiazepines	R	O	O	O	O	O
Oxazepam						
Nordiazepam						
Temazepam						
α-hydroxy-Alprazolam						
Clonazepam						
Lorazepam						
Desalkylflurazepam						
α-hydroxy-Triazolam						
Nitrazepam						
Barbiturates	R			R	R	O
Phenobarbital				R	R	O
Pentobarbital				R	R	O
Secobarbital				R	R	O
Butalbital						
Cocaine	R			R	R	O
Benzoylecgonine				R	R	O
Cannabinoids	R					
Delta-9-THC						
Methadone	R			R	R	O
Methadone				R	R	O
EDDP (Methadone Metabolite)				R	R	O
Buprenorphine***	R					
Buprenorphine						
Norbuprenorphine						
Amphetamines	R			R	R	O
Amphetamine				R	R	O
Methamphetamine				R	R	O
Alcohol	R					
Ethanol (Alcohol)	R					
Ethylglucuronide (EtG)	R					

*POCT= Point of Care Testing
**6-MAM = 6-monoacetyl morphine is the relatively short lived but definitive marker for recent heroin use
*** a negative buprenorphine report may not accurately reflect use of this drug
R = required test; O = optional test; Blank = discretion of medical staff

to identify patients who may not be able to stop drinking without medical assistance. At the present time, there is no evidence that safety is improved by withholding a methadone dose from an MMT patient who is otherwise clinically stable but has provided an incidental positive Breath Alcohol Reading. However, they certainly should be identified as higher risk and referred on for further evaluation and treatment.

8.3. Laboratory Practices

8.3.1. Urine Specimen Collection: Improving Sample Reliability

Urine specimen collection should be done in a therapeutic setting that respects patient privacy. This process should both minimize falsification and show respect and trust for the patient. Usually reliance on direct observation is not required, nor is it appropriate for most patients. Where direct sample collection is felt to be necessary, the witness observing the collection must be gender appropriate.

8.3.2. Substitution, Adulteration and Sample Tampering

Some patients may attempt to avoid testing positive for drugs of abuse by tampering with the urine sample. Many methods have been used, including adding various substances to the urine, diluting the specimen, substituting someone else's urine or submitting a sample of their own urine collected earlier. Some patients will consume copious quantities of water (volume loading) to decrease the concentration of drug in their urine. To discourage tampering, programs are required to test on a random schedule; patients are not informed in advance of the date/time of the next test. In addition, programs may require patients to remain in the clinic once they have been asked to test until testing is complete. Most laboratories offer a test for creatinine in the urine screening procedure, typically offered as a test in the point of care testing devices (POCT). This allows the programs to monitor the creatinine levels in the urine to screen for dilution. If the urine creatinine level is below 20, the specimen is considered to be dilute urine, and the sensitivity of the test is diminished. If the creatinine is below 5, the specimen is considered to be substituted, meaning it is not consistent with human urine. In the event that a patient is consistently providing dilute urines, he/she should be counseled and encouraged to regulate fluid intake to ensure that the creatinine will be above 20. In general, samples collected in the early morning are going to be more concentrated and so, more accurate in terms of drug detection.

The clinic staff conducting the collection procedure can also make observations regarding the urine color, clarity, viscosity and noting any foreign substances in the urine sample. If a provided sample is suspected of being tampered with or substituted, a second sample should immediately be requested. Both samples, appropriately labeled, should be sent in for testing.

There are also temperature recording devices that can determine the urine temperature very accurately. However, sample volume and any time delay of temperature testing can play key roles in assessment of sample integrity (see MRO Standards – www.udtmonograph6.com). Some Point of Collection (POC) testing strips are available that can give an indication of pH, creatinine, specific gravity, as well as common adulterants such as oxidizers, nitrites and bleach. Laboratory validity testing is often more sophisticated. These test strips are very inexpensive and can be used on suspected urines. If patients are diabetic, they may spill sugar in their urine sample. The sugar may ferment in the sample collection container, converting the sugar to alcohol. This alcohol may result in a positive test. The laboratory can supply sodium fluoride tablets (10 mg NaF) which when added to the collected sample will inhibit the fermentation process (glycolysis). Again, it is important to emphasize that the presence of ethyl glucuronide (EtG) is a totally independent marker of ethanol exposure.

8.3.3. Testing Methodologies

There are different drug testing technologies available. Most programs use EMIT (Enzyme Multiplied Immunoassay Test) as the screening technique. Since these screening assays are not specific, a confirmatory test, usually GC-MS or HPLC-MS/MS is done when there is a positive result – that is, when drugs of abuse are present, or methadone and/or methadone metabolite is absent. Although costly, gas chromatography/mass spectrometry (GC-MS) and the newer method high pressure liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) is the standard confirmatory test because of its high specificity and enhanced sensitivity. Newer technologies, such as fluorescence polarization immunoassay (FPIA), give semi-quantitative results, which allow detection of high dose use as well as monitoring of prescribed drugs, such as benzodiazepines, to assist in assessing compliance with therapeutic regimens.

When a urine drug screen is negative for methadone or metabolite, further investigation is necessary to determine whether there is a reasonable and legitimate explanation or whether this result indicates urine tampering or methadone diversion. Confirmatory testing with GC-MS or HPLC-MS/MS will clarify whether methadone and metabolite are present, but below the threshold for reporting on the screening test. Rapid metabolizers or patients on very low doses (< 10 mg) may legitimately present with a negative screen. Patients who have missed one or more doses prior to testing may be negative for methadone after a day or two and negative for both methadone and metabolite after a more prolonged absence. In fact, pH effects of urine can alter drug reabsorption and so reduce or enhance methadone parent excretion. Methadone metabolite (EDDP) however, is not subject to pH effects. Patients who are positive for methadone but negative for metabolite need careful evaluation; this result is consistent with a tampered specimen, i.e. urine from someone not on methadone to which methadone has been added to avoid detection.

Table 8.3.1

Specimen Validity Testing

Test	Reason	Normal Range	Abnormal Range		Reason
			Low	High	
Creatinine	Dilution	Normal 20 – 200 mg/dL 6-19 mg/dL is dilute urine 5 and below = not consistent with normal human urine	0 to 10 Negative	n/a	■ a waste product of creatine (urine) ■ an amino acid contained in muscle tissue & found in urine ■ Creatinine and Specific Gravity are two ways to check for dilution and flushing ■ low Creatinine and Specific Gravity levels may indicate diluted urine
Specific Gravity	Dilution	Normal 1.003 - 1.030 Average 1.016 – 1.022	1.000	> 1.030	■ tests for sample dilution
Nitrite	Nitrites	Normal No trace	n/a	> 15 mg/dL	■ tests for commercial adulterants such as "Klear" or "Whizzies"
Glutaraldehyde	Aldehyde	Normal No trace Positive Adulterant	n/a	Positive	■ tests for the presence of an aldehyde
pH	Acidic or Basic	Normal 4.5 - 8.0	4 or below	9 or above	■ tests for the presence of acidic or alkaline adulterants in urine
Pyridinium Chlorochromate (Oxidants/PCC)	Oxidants	Normal No trace* Positive Adulterant	n/a	Positive	■ tests for the presence of oxidizing agents such as bleach and hydrogen peroxide ■ Pyridinium Chlorochromate (sold under the brand name "UrineLuck") is a commonly used adulterant
Bleach	Bleach	Normal Negative	n/a	Positive	■ tests for the presence of bleach in urine

*some traces may be found due to bacteria; nothing above 7.5 is normal

Table 8.3.2

Urine Toxicology Detection Period

DRUG	CATEGORY	CUTOFF***	DETECTION PERIOD*	PLASMA HALF LIFE
Amphetamines	stimulant	1000		
Amphetamine			2-4 days	7-34 hours
Methamphetamine			2-4 days	6-15 hours
Barbiturates	sedative-hypnotic	200		
Amobarbital			2-4 days	15-40 hours
Butalbital			2-4 days	35 hours
Pentobarbital			2-4 days	20-30 hours
Phenobarbital			up to 30 days	2-6 days
Secobarbital			2-4 days	22-29 hours
Buprenorphine	Narcotic analgesic	10	2-4 days	2-4 hours
Carisoprodol (Soma)	Muscle relaxant	500	24 hours	8 hours
Cocaine	stimulant	300		
Benzoylecgonine			12-72 hours	0.5-1.5 hours
Cannabinoids (THC/Marijuana)	euphoriant	50		
Casual use			2-7 days	20-57 hours
Chronic use			up to 30 days	20-57 hours
Ethanol (Alcohol)	sedative-hypnotic	0.025	very short**	2-14 hours
Ethyl glucuronide (EtG)	metabolite	500	up to 72 hours	2-14 hours
Fentanyl	narcotic analgesic	2	3-4 days	3-12 hours
Methadone	narcotic analgesic	300	2-4 days	15-55 hours
Methaqualone (Quaalude®)	sedative-hypnotic	300	2-4 days	20-60 hours
MDA/MDMA Ecstasy	Psychotropic	500	2-4 days	4-12 hours
Opiates	narcotic analgesic	300		
Codeine			2-4 days	1.9-3.9 hours
Hydrocodone			2-4 days	4 hours
Hydromorphone (Dilaudid®)			2-4 days	1.5-3.8 hours
Morphine			2-4 days	1.3-6.7 hours
Oxycodone (Oxycontin®)			2-4 days	4-6 hours
6-Acetylmorphine (6MAM)			6-25 minutes	6-12 hours
Phencyclidine (PCP)	hallucinogen	25		
Casual use			2-7 days	7-46 hours
Chronic use			up to 30 days	7-46 hours
Propoxyphene (Darvon®)	narcotic analgesic	300		
Casual use			2-7 days	8-24 hours
Chronic use			up to 30 days	8-24 hours

* Detection period varies; rates of metabolism and excretion are different for each drug and user. Detection periods should be viewed as estimates. Cases can always be found to contradict these approximations.
** Detection period depends on amount consumed. Alcohol is excreted at the rate of approximately 1 ounce / hour.
*** Cutoff values are taken from Opioid Treatment Facilities.

8.3.4. Windows of Detection

Table 8.3.2 outlines common windows of detection for commonly tested and reported analytes. One important caveat to this is the fact that some analytes are actually optical isomers of one another. Chiral (handedness) testing is required to distinguish between over-the-counter decongestants vs. contested results.

8.3.5. Testing Strategies

Laboratory results should be used therapeutically as clinical data to support treatment objectives, not to activate penalties or punishment. Testing should serve the clinical purpose of identifying ongoing or sporadic drug use and potential safety issues. Urine drug testing can also help honest people to keep honest. Decisions made in early recovery can often be improved by the patient knowing that they may be required to provide a UDT sample.

Drug test results should be used as a treatment tool; a positive test provides an opportunity to discuss the patient's progress in recovery, to explore barriers to abstinence, and identify strategies and resources to support future abstinence. Negative UDT results, combined with other markers of clinical stability, can serve to reinforce health changes made in a patient's recovery process and are often used to support decisions around increased take-home doses.

California regulations require that a patient's clinic attendance be increased if he or she tests positive for illicit drugs. This means the reduction and/or loss of take-home privileges unless the physician deems that the positive test is not the result of illicit drug use. The rationale for the physician's determination must be documented in the record. Some clinics will increase the frequency of urine drug testing after a positive result especially if the patient has been on a once/month UDT testing schedule, in order to clarify whether the patient has experienced a lapse or a full-blown relapse. Restriction beyond this in the form of dose reductions or discharge from treatment is usually inappropriate. In certain circumstances, it is appropriate to test beyond federal or state requirements. In these cases, the principle of "medical necessity" must be kept in mind to ensure that testing benefits the patient, rather than the clinician ordering the test.

As a general rule, there are many potentially "appropriate" actions to take in the context of an abnormal UDT result:

Table 8.3.3

Interpretation of Confirmed Opiate Results

San Diego Reference Laboratory

INTERPRETATION OF CONFIRMED OPIATE RESULTS

If the results are as follows:							Then the following condition exists:	
Morphine	Codeine	Hydro - codone	Hydro - morphone	6MAM	Oxy - codone	Oxy - morphone		
Positive	–	–	–	Positive	–	–	**Heroin use**	
Positive (M>C)	Positive	–	–	Positive	–	–	**Heroin use** plus Codeine use or Codeine impurity in the Heroin	M>C = *Morphine* Greater then Codeine
Positive (M>C)	Positive	–	–	–	–	–	**Heroin or Morphine use** plus Codeine use or Codeine impurity in the Heroin or Morphine	M>C = *Morphine* Greater then Codeine
Positive	Positive (C>M)	–	–	–	–	–	**Codeine use** (Morphine positive due to the metabolism of the Codeine in the body)	C>M = *Codeine* Greater then Morphine
Positive	–	–	–	–	–	–	**Heroin or Morphine use**	
–	Positive	–	–	–	–		**Codeine use**	
–	–	Positive	–	–	–	–	**Hydrocodone use**	(ex. Vicodin, Lortab, Norco or Panacet)
–	–	–	Positive	–	–	–	**Hydromorphone use**	(ex. Dilaudid)
–	–	Positive	Positive	–	–	–	**Hydrocodone use** Hydromorphone positive due to the metabolism of the Hydrocodone in the body OR Hydromorphone use as well	
–	–	–	–	–	Positive	–	**Oxycodone use**	
–	–	–	–	–	Positive	Positive	**Oxycodone use** (Oxymorphone is the metabolite of Oxycodone)	
–	–	–	–	–	–	Positive	**Oxymorphone use ONLY or Oxycodone Use** (ex. Opana) (Oxymorphone is the metabolite of Oxycodone and has a longer ½ life than parent drug)	

there is, however one absolutely wrong thing to do and that is to do nothing! An ignored lab result, especially one that is abnormal in some way, will almost always be viewed as a clinical deficiency.

In the context of randomized drug testing, some clinics are of the impression that randomizing sample collection around clinic or group visit days is true randomization. eg. “We only test on Tuesdays, but we don’t test EVERY Tuesday that the patient comes in.” This is a very common strategy but does not really approach the level of true sample collection randomization. Referral to the UDT Monograph is recommended for those who wish to pursue this further.

In some cases, such as end stage renal disease, a patient is unable to provide urine for drug testing. In other cases, urine may not be easily obtained for the random testing required by state and federal regulation. In these situations, it is necessary to submit an exception request to the state and to CSAT to allow another form of testing. Blood testing may be used for patients with renal failure, coordinating with the dialysis unit to send specimens for testing. Some clinics use saliva tests for patients who cannot urinate on demand, such as paraplegic or dialysis patients. These tests are useful to help monitor a patient’s progress in treatment and/or to help to clarify a patient’s status if they appear to be intoxicated. However, saliva tests are not approved for regular use under CCR Title 9. A state and CSAT exception would be required before the program could use these tests in place of urine testing for a particular patient.

In fact, the face of therapeutic drug testing in Opioid Treatment Programs is changing. More patients are seeking treatment with prescription drug use problems than street heroin. Despite this, the need for specific strategies around treatment of this diverse population is evident. In the realm of therapeutic drug testing, it is critical to maintain a close working relationship with the reference laboratory that performs the urine testing for the clinic, so that any ambiguous results can have the benefit of expert consultation. A personal relationship with knowledgeable laboratory experts can be an invaluable resource.

8.3.6. Conclusions

In treatment of drug and alcohol patients, the role of drug testing can variously be patient-centered or adversarial. It often comes down to clinic/provider policies. Urine drug test results rarely lead to a definitive diagnosis in themselves, but when combined with relevant clinical context, can assist in opening a meaningful dialogue between patient and provider. Remember, when an otherwise clinically stable patient provides an unexpected result, the patient is owed a very detailed examination of these results before a definitive adverse inference can be applied. Sometimes this can be clarified with a simple call to the lab: in other cases, a knowledgeable expert clinicians’ advice should be sought. UDT results are only one piece of the puzzle that supports or challenges clinical stability.

The topic of urine drug testing is complex; it is impossible to go into sufficient depth to answer all clinical questions the reader may have. For those interested in examining patient-centered urine drug testing in greater detail, we recommend www.udtmonograph6.com/.