Urine Drug Testing — Common Laboratory Methodologies

Choosing the Laboratory Methodology

Clinicians can order urine drug testing with one of two main methodologies: Immunoassay or combination chromatographic/spectrometric techniques (gas chromatography/mass spectrometry [GC/MS] or liquid chromatography/tandem mass spectrometry [LC-MS/MS]).

Immunoassay (used for initial screening or presumptive testing)

PROS

- Broadly available
- Minimal initial capital expense to set up testing
- May be performed at the point of care
- Results return within minutes (point of care) to hours (in laboratory) and are typically available any time of day

CONS

- May test for a generic drug class (e.g., opiates) rather than a specific compound, so results do not indicate whether the prescribed compound was ingested (e.g., if an opiate assay is positive, this finding does not confirm the patient's adherence to a morphine prescription)
- Typically only provides results for a small number of compounds
- Does not provide results for metabolites, so does not prove that the compound was ingested (as opposed to shaved into the urine sample)
- Risk of false-negative results because cutoffs are typically set high; the test is more useful for detection of overdose than to confirm use of a medication or illicit drug
- Risk of false-positive results due to cross-reactivity with other compounds
- Unexpected results, if contested by the patient, require testing with a definitive method such as GC/MS or LC/MS-MS

Potential False-Positive Results in Immunoassays

The following agents may cause false-positive results in the immunoassays listed:

Amphetamines

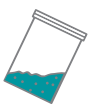
- Amantadine
- Bupropion
- Chlorpromazine
- Desipramine
- Dimethylamylamine
- Labetalol
- Metformin
- Ofloxacin
- Phentermine
- Phenylephrine
- Promethazine
- Pseudoephedrine
- Ranitidine
- Selegiline
- Trazodone

Benzodiazepines

- Oxaprozin
- Sertraline

Cocaine

- Coca leaf tea
- Salicylates (false negative)



Cannabis

- Efavirenz
- Hemp seed oil
- Nonsteroidal antiinflammatory drug (i.e., ibuprofen and naproxen)

Opioids/Heroin

- Dextromethorphan
- Diphenhydramine
- Poppy seeds
- Quinine
- Quinolone antibiotics
- Rifampin
- Verapamil

Opiate immunoassay results

What tests positive

+ Natural opiates:
  - Codeine
  - Morphine
+ Heroin metabolites
+ Oxycodone (usually only if present in urine at high concentrations such as in states of concentrated urine)

What tests negative

− Semisynthetic opioids:
  - Buprenorphine
  - Hydrocodone*
  - Hydromorphone*
  - Oxycodone (usually)
  - Oxymorphone

− Synthetic opioids:
  - Fentanyl
  - Dextroproproxyphene
  - Meperidine
  - Methadone
  - Tramadol

*cross-reactivity varies by immunoassay

GC/MS or LC-MS/MS (used for definitive or confirmation testing)

PROS

- Very sensitive and specific
- Identifies specific drugs and metabolites rather than broad drug classes
- Interpretation of drugs and metabolites present may allow determination of the parent compound ingested
- May test for broad panels of drugs
- False-negative and false-positive results unlikely
- Typically lower cutoffs — allows detection of drugs when used therapeutically, whether recent or remote

CONS

- Higher initial cost to set up (although subsequent costs are low)
- Requires substantial technical expertise in the lab for accurate results
- Not available at most sites; sample needs to be sent to a reference lab, leading to slow turnaround time
- Requires understanding of opioid metabolism for accurate interpretation of results
- Panels are not inclusive of all drugs; testing for novel or designer drugs may require sending the specimen to another laboratory

Important Concepts When Interpreting Results

General principles:

- Unexpected results may be caused by preanalytical errors (e.g., mislabeling) or by sample adulteration, including substitution of synthetic or another individual's urine.
- Results are just one medical data point, to integrate with others.
- Results cannot help clinicians differentiate prescribed substance use from addictive use and diversion.
- View the urine drug test results in conjunction with the prescribed medications (including those listed in state prescription drug monitoring programs, if available).
- Despite risk-mitigation strategies, dedicated individuals can still manipulate their samples or take prescribed medication immediately before office visits to conceal misuse or diversion.
- Use urine drug testing as an opportunity to open a discussion with the patient and to reassess the risk–benefit ratio of prescribing a high-risk medication, not to "catch" the patient doing something wrong.

Understanding cutoffs:

- The lab — depending on how the test results are to be used clinically — determines the concentration cutoff above which the test for the compound should be reported as "positive."
- Cutoffs will vary by drug and metabolite.
- Lower cutoffs allow detection of remote drug use and lead to fewer false negatives (drug present in the urine but at a concentration below the reporting cutoff).
- However, lower cutoffs may also lead to more false positives due to environmental sources.

When to suspect urine adulteration:

- Sample temperature is outside the normal range of 32°C to 38°C in the first 4 minutes after sample collection
- pH is outside the normal range of 4.5 to 8.0
- Low specific gravity (i.e., ≤1.003)
- Presence of adulterants or parent drug without metabolites
- Low creatinine concentration:
  - Creatinine <5 mg/dL is inconsistent with human urine. Specimen is not valid.
  - Creatinine 5–20 mg/dL is unusually dilute, and drugs and metabolites may be missed.

Interpretation of quantitative results:

- Quantitative results cannot be used to predict time of last dose or amount ingested due to the dynamic variables involved in parent-drug and metabolite excretion (urine pH, state of hydration, natural and prescribed diuretics).
- Very low quantities of an unexpected drug may represent a contaminant in the prescribed drug preparation.

Testing for metabolites:

- Presence of metabolites provides confirmation that the medication was actually ingested.
- Absent metabolites would suggest addition of the parent compound directly into the voided urine sample.
- Ratios of parent drugs to metabolite(s) may be useful in assessing adherence.

Opioids and Their Urinary Metabolites

Parent compound	Main metabolites
 **Heroin**	6-Monoacetylmorphine (6-MAM)
	Morphine and its metabolites
 **Morphine**	Morphine 3β-glucuronide
	Morphine 6β-glucuronide
	Hydromorphone
	Hydromorphone-3β-glucuronide
 **Codeine**	Hydrocodone
	Morphine and its metabolites
 **Oxycodone**	Oxymorphone
	Noroxycodone
 **Buprenorphine**	Buprenorphine-3β-glucuronide
	Norbuprenorphine
	Norbuprenorphine glucuronide
 **Tramadol**	*O*-Desmethyltramadol
 **Fentanyl**	Norfentanyl
 **Methadone**	EDDP (2-ethylidene-1,5-dimethyl-3, 3-di phenylpyrrolidine)

Key questions to ask when interpreting results

- Which methodology was used, and what drugs and metabolites were tested for?
- Are the results of the presumptive testing (i.e., immunoassays) consistent with the prescribed medications?
  - Is the prescribed medication present?
  - Are the metabolites consistent with ingestion of the prescribed medication?
- Are there drugs or metabolites present that were not prescribed (illicit drugs or nonprescribed medications)?
- Should I request definitive testing by GC/MS or LC-MS/MS (if the initial test was performed with an immunoassay)?

IN CASE OF DOUBT:

If clinicians are uncertain about what test to order, or how to interpret the test results (e.g., false positives or negatives, expected metabolites), they should contact their laboratory (i.e., clinical pathologist or toxicologist).

For more on this topic, see our learning resource "Urine Drug Testing — Clinical Considerations."

References:

1. Gourlay DL et al. Urine drug testing in clinical practice: the art and science of patient care, sixth edition. August 31, 2015.

2. Argoff CE et al. Rational urine drug monitoring in patients receiving opioids for chronic pain: consensus recommendations. Pain Med 2018 Jan 1; 19:97.

3. Jarvis M et al. Appropriate use of drug testing in clinical addiction medicine. J Addict Med 2017 May/Jun; 11:163.

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