Windows of detection

Topics in Drug Testing Podcast

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Understanding how drugs are metabolized and eliminated

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What is drug metabolism?

- Drug metabolism is the chemical **alteration of a drug** by the body
- Drug metabolism leads to the formation of byproducts called **metabolites**
  - Parent drug (i.e., buprenorphine) often become **large percentages** of metabolite(s)
  - Inactive metabolite: has no therapeutic effect
  - Active metabolite: has therapeutic effect
  - **We test for parent drugs and metabolites!**
- Drug metabolism predominantly takes place in the **liver**
- Drugs and metabolites are predominantly eliminated from the body by the **kidneys** via urination

What is a window of detection?

Understanding **half-life**[1]

The **half-life** of a drug is an estimate of the time it takes for an amount of drug in the body to be reduced by exactly one-half (50%). The symbol for half-life is t½

The duration of time that it takes for a drug to pass through the body and be eliminated determines the **window of detectability**

So how many times must a drug be reduced in half for it to be 99% eliminated?

1. Toutain PL, Bousquet-Mélou A. Plasma terminal half-life. *J Vet Pharmacol Ther*. 2004;27(6):427-39. doi: 10.1111/j.1365-2885.2004.00600

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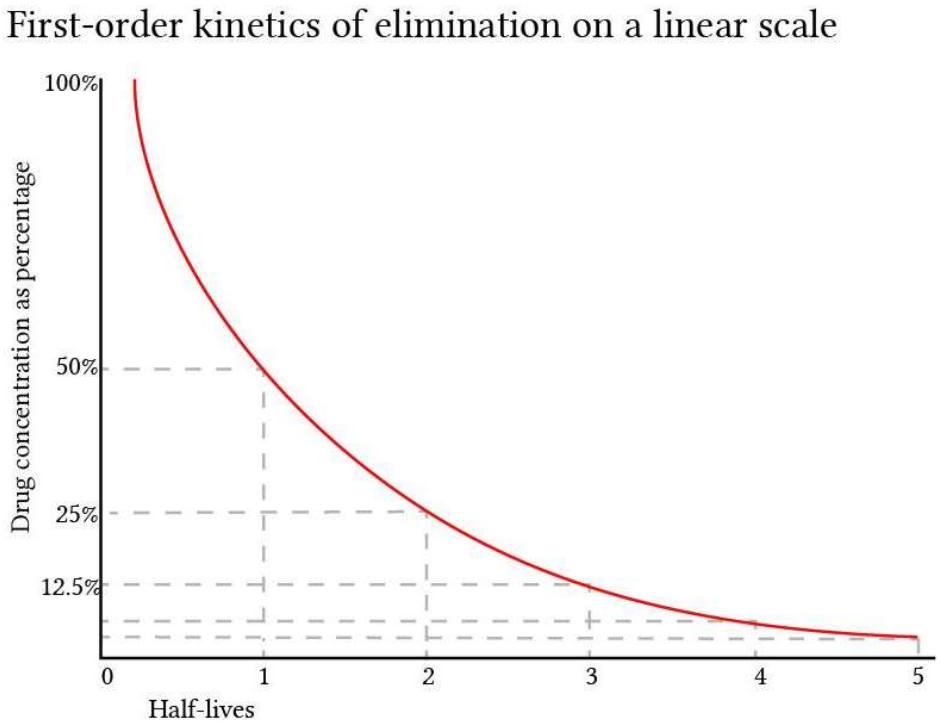
How are half-life and windows of detection related?

Drugs lose their effect around **4-5 half-lives** but that doesn't necessarily mean we can't detect them. At **~7 half-lives the drug is 99% eliminated**

- Generally, a shorter half-life translates to a more rapid elimination of the drug and a **shorter window of detection**
- Generally, a longer half-life translates to a prolonged elimination of the drug from the body and a **longer window of detection**
- 7 half-lives is achieved around 1-3 days for most opioids



Source: Toutain et al, 2004.

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Variables that impact windows of detection

A window of detection is just an **approximation**!
Here's why….

There are many variables that can impact drug levels and ultimately a window of detection!

Patient-Specific Variables	Drug-Specific Variables	Laboratory-Specific Variable

• Age
• Blood Circulation
• **Diet (ie, grapefruit juice)**
• **Hydration (ie, diuresis, dilution)**
• **Liver/Kidney Function**
• Obesity
• Preexisting Conditions (ie, pregnancy)
• **Drug-Drug Interactions**
• Smoking
• **Genetics**
	• **Drug formulation (extended release or modified release)**
	• **Drug administration (IV, IM, oral, nasal)**
	• Intrinsic drug properties
	  • **Lipophilic/Fatty deposition**
	  • Hydrophilic (water soluble) drugs –excreted without need for metabolic changes **(ie, gabapentin)**
	  • Hydrophobic drugs need to be biotransformed to make more polar
		• **Sensitivity (presumptive v definitive)**

Drugs that store in fatty tissue have expanded windows of detection!

Highly lipophilic drugs can become sequestered in adipocytes (fat cells) or other tissues and lead to protracted elimination from the body over time[1]

THC

- For a casual user (once a week), the THC metabolite is detectable for approximately **3 to 4 days**
- In a chronic user (use every day), excretion of this metabolite may take **several weeks**
- Little is known about the detection window for the newer synthetic cannabinoids. They are likely comparable to marijuana

Fentanyl[2]

- Fentanyl is highly lipophilic, allowing for rapid transport between blood plasma and the central nervous system
- Fentanyl has been detected **19 days** after last use
- Norfentanyl has been detected **26 days** following last use

1. Kale N. Urine Drug Tests: ordering and Interpreting results. *Am Fam Physician*. 2019;99(1):33-39.
2. Huhn AS, Hobelmann JG, Oyler GA, Strain EC. Protracted renal clearance of fentanyl in persons with opioid use disorder. *Drug Alcohol Depend*. 2020;214:108147. doi: 10.1016/j.drugalcdep.2020.108147.

How drug formulation and administration route can impact detection windows

Drug Formulation: Extended Release: If a drug is 'extended release' then we expect a longer half-life when compared to 'immediate release'	• **Example**: The half-life of **oxycodone**, which refers to the amount of time it takes half the drug to be effectively eliminated from your body, is about **3.2 hours**; the half-life for the time-released version (OxyContin) is about **4.5 hours**[1] • **Drug test consideration**: Oxycodone ER may have a longer window of detection when compared to Oxycodone IR
Drug Administration Route: Subcutaneous Injection: If a drug is given subcutaneously as a depot preparation, it can be stored there and release over prolonged periods of time	• **Example: Buprenorphine** when given via injection into the fatty layer of skin can lead to a urine window of detection of up to **12 months**[2] after last injection when compared to sublingual buprenorphine which has window of detection of **~7 days in urine** • **Drug test consideration:** Drugs that are given subcutaneously may have prolonged windows of detection

1. Purdue Pharma L.P. OxyContin (Oxycodone HCl Controlled-Release) Tablets [package insert].
2. https://clinicaltrials.gov/ct2/show/study/NCT03752528

Drug interactions

There are many types of drug interactions including but not limited to **drug-drug, drug-food, and drug-medical condition**

- Drug Interactions are a notable type of adverse drug event that affect millions of patients each year[1]
- A **drug-drug/food interaction** has the ability to modify the action or effect of another drug[2]
- There are many mechanisms that contribute to drug-drug/food interactions. However, some of the most common involve the ability of a drug/substance to inhibit the metabolism of another drug
- For example, CYP3A4 is responsible for the metabolism of more than **50% of medicines**. What happens if you inhibit it?

1. Ince I, Knibbe CA, Danhof M, et al. 2013. Developmental changes in the expression and function of cytochrome P450 3A isoforms: evidence from in vitro and in vivo investigations. *Clinical Pharmacokinetics* 52: 333–345.
2. Marengoni, A., & Onder, G. (2015). Guidelines, polypharmacy, and drug-drug interactions in patients with multimorbidity. *BMJ : British Medical Journal*, 350. https://doi.org/10.1136/bmj.h1059

What happens if you inhibit CYP3A4's ability to metabolize a drug?

"The Forbidden Fruit"

- **Grapefruit** (all sources) is a potent **inhibitor** of intestinal **CYP3A4** that has been proposed to interact with more than 44 medicines and result in serious adverse effects[1]
- Consuming grapefruit while using a drug that is metabolized by CYP3A4 (ie, Fentanyl, Buprenorphine (Suboxone®), Diazepam (Valium ®)) might prolong the metabolism and excretion of the drug that is metabolized by CYP3A4. This may lead to toxic side effects
  - **Drug Test Consideration:** This may also lead to an extended window of detection of a drug due to prolonged metabolism

1. Bailey DG, Dresser G, Arnold JM. 2013. Grapefruit-medication interactions: forbidden fruit or avoidable consequences? *Canadian Medical Association Journal* 185: 309–16.

Cytochrome P450 **phenotypes**

Phenotype is the ‘expression’ of a genotype

Poor (PM)	Intermediate (IM)	Normal	Ultra-Rapid (UM)
• **Prolonged metabolism and excretion** • More parent drug • **Extended window of detection**	• Moderately compromised metabolism and excretion	• Normal metabolism profile, parent to metabolite ratio	• **Rapid metabolism and excretion** • More metabolite • **Shortened window of detection**

How might genetics impact windows of detection?

- Pharmacogenomics is the study of how an individual's genetic makeup affects their **response to medications**
- Pharmacogenomics utilizes patient-specific genomic markers to assist the clinician in the **selection of medications and dosing** with the highest likelihood of success while minimizing the risk of **toxicity**

Allele

CYP2D6*5 **Non-functioning variant**

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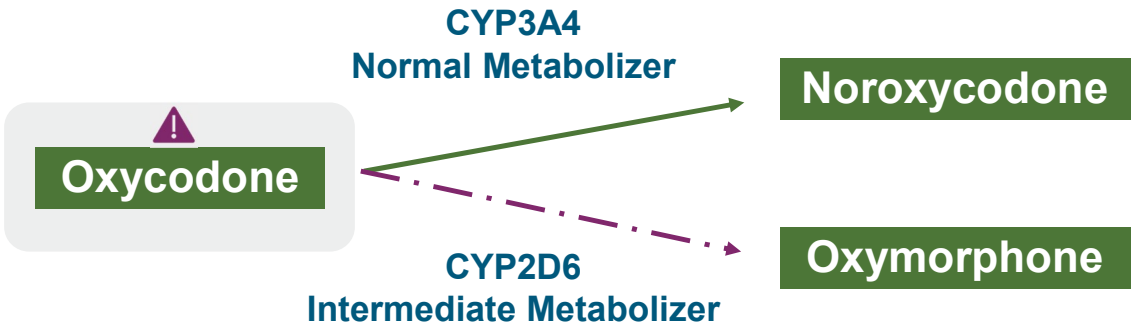
PGx Impact on opioid pain management



Previous Visit

Current Visit

Medication	Urine Drug Concentration	Medication	Urine Drug Concentration
Oxycodone	• 12450 ng/mL	Oxycodone	• 23542 ng/mL
• Oxymorphone	• 750 ng/mL	• Oxymorphone	• 981 ng/mL
• Noroxycodone	• 4526 ng/mL	• Noroxycodone	• 1025 ng/mL
• Duloxetine	• 416 ng/mL	• Duloxetine	• 320 ng/mL

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Can liver and kidney function impact windows of detection?

If a patient's liver is not working properly, will they be able to metabolize a drug efficiently?

- In **hepatic failure**, opioid clearance is reduced and drug bioavailability is increased. These changes can be secondary to reduced hepatic blood flow (limiting first-pass metabolism) or decreased CYP450 enzyme levels in these patients
  - In advanced liver failure, **oxycodone's maximum concentration increases 40%,** and **immediate-release oxycodone's half-life increases to 4.6-24.4 hours** (average 14 hours; its usual half-life is ~3.5 hours). Initial oxycodone dosing in patients with severe hepatic failure should be reduced[Purdue]
- **Uremic patients** were found to experience an **increased half-life** of oxycodone despite its 8% to 14% elimination rate as the parent compound[Dean]
- **Drug Testing considerations**: Hepatic and Kidney damage may prolong windows of detection

Purdue Pharma L.P. OxyContin (Oxycodone HCl Controlled-Release) Tablets [package insert].
Dean M. Opioids in renal failure and dialysis patients. *J Pain Symptom Manage*. 2004;28:497-504.

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Dilution

Dilution can be intentional or unintentional[1]

- A dilute specimen is a urine sample that has high water content when compared to a normal or average specimen
- Dilution can lower drug concentration within a urine specimen and generate a negative result
- Excessive consumption of water may also promote rapid urine output and eliminate a drug from the body faster than normal
- **Drug test consideration**: Intentionally or unintentionally diluting urine can shorten windows of detection

1. Sara A. Love, Jesse C. Seegmiller, Julie Kloss, Fred S. Apple, Urine Creatinine Concentrations in Drug Monitoring Participants and Hospitalized Patients, *Journal of Analytical Toxicology*, Volume 40, Issue 8, October 2016, Pages 659–662, https://doi.org/10.1093/jat/bkw092

Sensitivity – lab methods

Increasing sensitivity may lengthen windows of detection[1]

- Using high sensitivity (LC/MS/MS) confirmatory methods enable laboratories to **detect drugs at lower concentrations** when compared to less sensitive methods such as presumptive testing (i.e., immunoassay)
- **Drug testing consideration**: This permits laboratories to detect drugs at later stages of metabolism and excretion. When a drug is almost entirely eliminated from the body thereby expanding the window of detection

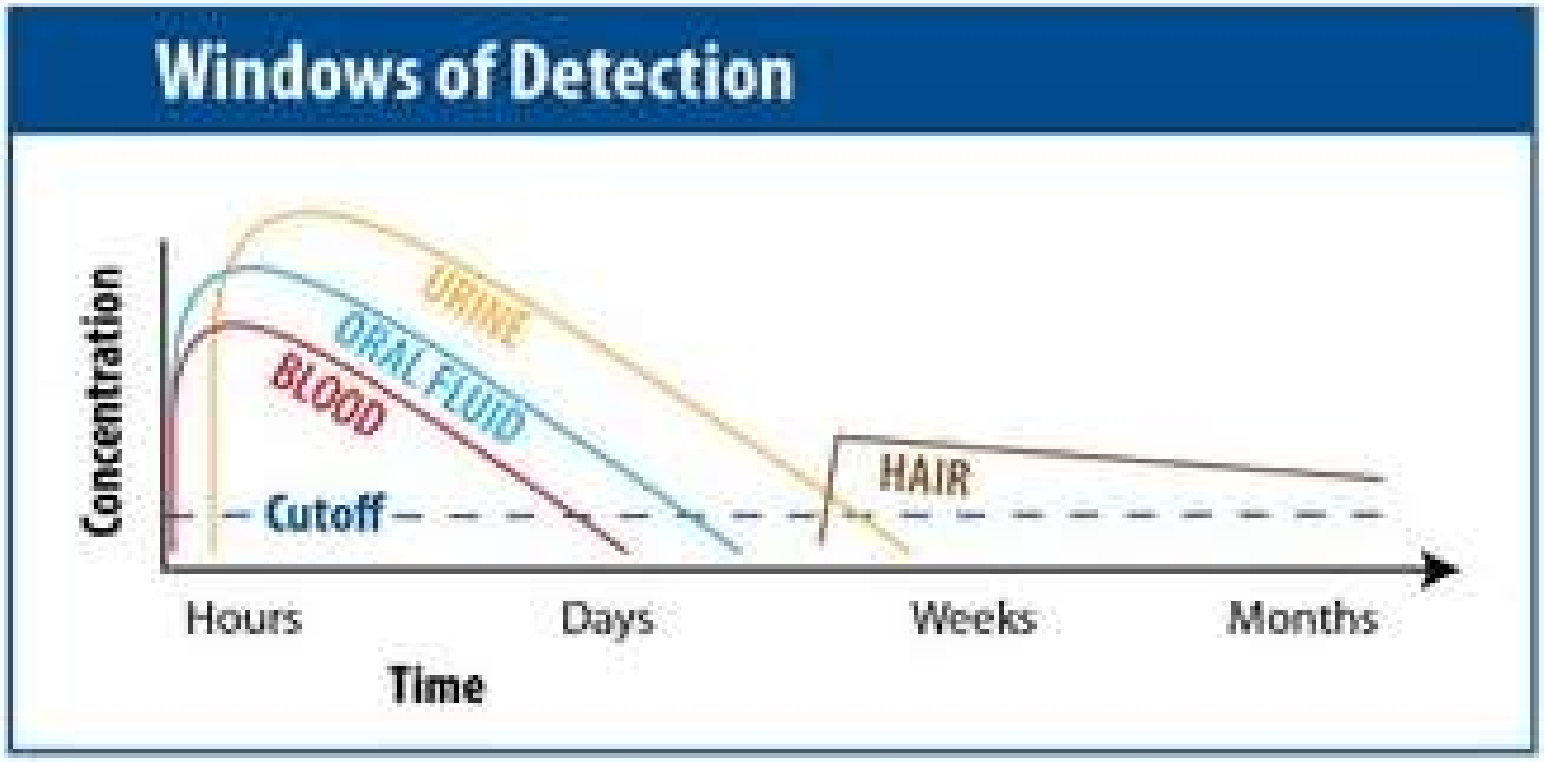
1. Krock K, Pesce A, Ritz D, Thomas R, Cua A, Rogers R, Lipnick P, Kilbourn K. Lower Cutoffs for LC-MS/MS Urine Drug Testing Indicates Better Patient Compliance. *Pain Physician*. 2017 Nov;20(7):E1107-E1113. PMID: 29149155.

Windows of detection for common specimen types and common drug classes in Clinical Drug Testing

Windows of detection in specimen types

Blood/Serum	Oral Fluid	Urine
1-2 Days	**1-2 Days**	**1-3 days**
• More parent drug because it's closer proximity to the time and site of administration • Passes through liver where it is metabolized and passed into kidneys within hours	• More parent drug because the drug passes from the blood into the oral fluid where it is "ion trapped" • A snapshot of what is in the blood at the time of collection	• More metabolite because it's distant proximity to the time and site of administration • Metabolites may have longer half life than parent drug as well

American Society of Addiction Medicine (ASAM). Drug Testing: A White Paper of the American Society of Addiction Medicine (ASAM) .Chevy Chase, MD: American Society of Addiction Medicine. 2017.



Source: SAMHSA, Drug Testing Advisory Board (DTAB) Meeting, Ron Siegel Presentation 1/26/2011

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Windows of detection for common drug classes[1]

Drug/Class	Urine Detection Window
Alcohol metabolites (ETG/ETS)	Up to 80 hours
Amphetamines	1-2/3 days
Benzodiazepines	Short acting: 1-3 days Long acting: 3 - 14 days
Cocaine metabolite	1-3 days Heavy users: >3 days
Heroin metabolite	1 day
Marijuana metabolite	Casual user: 1-3 days Heavy user: >3 days
Opioids	1-3 days Fentanyl: >3days

1. Kale N. Urine Drug Tests: Ordering and Interpreting Results. *Am Fam Physician*. 2019 Jan 1;99(1):33-39.

Windows of detection for novel psychoactive substances

- Novel psychoactive substances (NPS) have emerged worldwide in recent years, posing an ongoing threat to public health and international drug policies
- NPS are usually derivatives or analogues of *classical* recreational drugs designed to imitate their effects while circumventing regulations and/or drug testing
- Most novel psychoactive substances **do not have detection window data** published, so detection times are **estimated from similar substances**

Grafinger, K. E., Liechti, M. E., & Liakoni, E. (2020). Clinical value of analytical testing in patients presenting with new psychoactive substances intoxication. *British journal of clinical pharmacology*, *86*(3), 429–436. https://doi.org/10.1111/bcp.14115

What does a positive drug test mean?

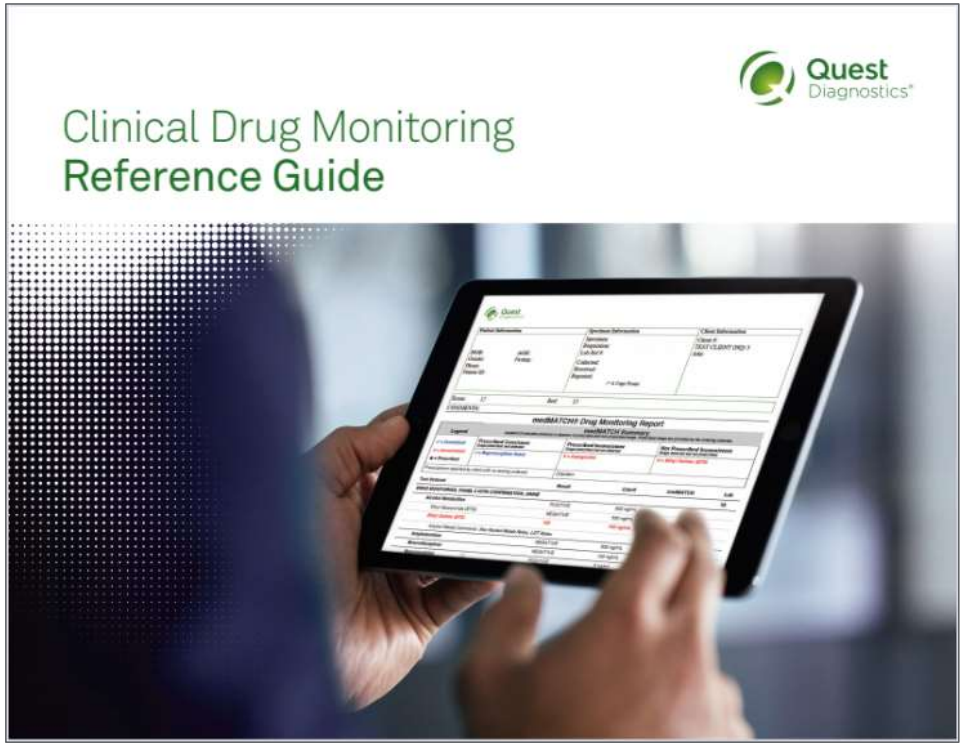
- A positive drug test simply means use/ingestion/exposure of a drug within an expected window of detection. However, even with a quantitation in urine, it is not possible to determine the amount of drug that was used or time of use (other than sometime within the detection window). It may be a first time use or chronic use
- Drug detection windows are **approximations** and it's important to understand that patients may test positive for a shorter or longer duration than anticipated
- Drug testing is just one part of the clinical picture and knowing the parameters that impact a drug test result can enable providers to interpret results in patient-centric manner

Appendix

Drug Monitoring reference guide

Clinical Drug Monitoring Reference Guide

Literature code: MI7659



- Comprehensive Clinical Drug Monitoring Test Directory in a brochure
- Multi-page resource with individual test codes, panel test codes, and a comprehensive table detailing cutoff values, reportable drug(s), and metabolite(s) associated with each drug or drug class
- For use with all clients who are looking for full details on menu and performance characteristics

QForce Link: Drug Monitoring Reference Guide

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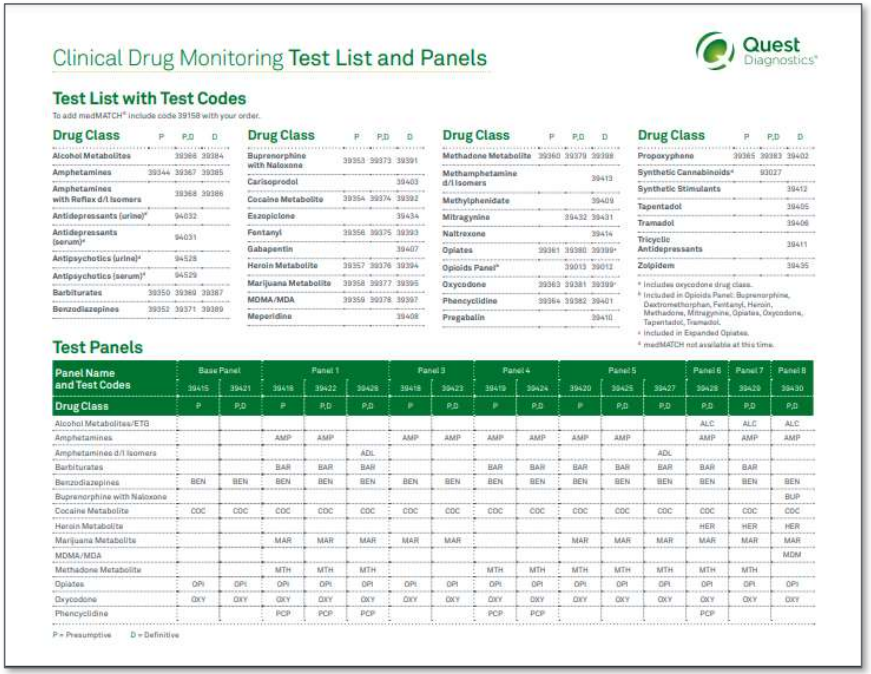
Drug Monitoring reference guide leave behind

Clinical Drug Monitoring Test List and Panels

Literature code: MI10129



Clinical Drug Monitoring **Test List and Panels**

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Test List with Test Codes

To add medMATCH® include code 39158 with your order.

Drug Class	P	P,D	D
Alcohol Metabolites		39368	39384
Amphetamines	39344	39367	39385
Amphetamines with Reflex d/l Isomers		39368	39386
Antidepressants (urine)[4]	94632		
Antidepressants (serum)[4]	94631		
Antipsychotics (urine)[4]	94528		
Antipsychotics (serum)[4]	94529		
Barbiturates	39350	39369	39387
Benzodiazepines	39352	39371	39389

Drug Class	P	P,D	D
Buprenorphine with Naloxone		39353	39373 39391
Carisoprodol			39403
Cocaine Metabolite		39354	39374 39392
Eszopiclone			39434
Fentanyl		39356	39375 39393
Gabapentin			39407
Heroin Metabolite		39357	39376 39394
Marijuana Metabolite		39358	39377 39395
MDMA/MDA		39359	39378 39397
Meperidine			39408

Drug Class	P	P,D	D
Methadone Metabolite	39360	39379	39398
Methamphetamine d/l Isomers			39413
Methylphenidate			39409
Mitragynine		39432	39431
Naltrexone			39414
Opiates		39361	39380 39399[3]
Opioids Panel[2]			39013 39012
Oxycodone		39363	39381 39399[1]
Phencyclidine		39364	39382 39401
Pregabalin			39410

Drug Class	P	P,D	D
Propoxyphene		39365	39383 39402
Synthetic Cannabinoids[4]		93027	
Synthetic Stimulants			39412
Tapentadol			39405
Tramadol			39406
Tricyclic Antidepressants			39411
Zolpidem			39435

[1] Includes oxycodone drug class.
[2] Included in Opioids Panel: Buprenorphine, Dextromethorphan, Fentanyl, Heroin, Methadone, Mitragynine, Opiates, Oxycodone, Tapentadol, Tramadol.
[3] Included in Expanded Opiates.
[4] medMATCH not available at this time.

Test Panels

Panel Name and Test Codes	Base Panel		Panel 1			Panel 3		Panel 4		Panel 5			Panel 6	Panel 7	Panel 8
	39415	39421	39418	39422	39426	39418	39423	39419	39424	39420	39425	39427	39428	39429	39430
Drug Class	P	P,D	P	P,D	P,D	P	P,D	P	P,D	P	P,D	P,D	P,D	P,D	P,D
Alcohol Metabolites/ETG													ALC	ALC	ALC
Amphetamines			AMP	AMP		AMP	AMP	AMP	AMP	AMP	AMP		AMP	AMP	AMP
Amphetamines d/l Isomers					ADL							ADL			
Barbiturates			BAR	BAR	BAR			BAR	BAR	BAR	BAR	BAR	BAR	BAR	
Benzodiazepines	BEN	BEN	BEN	BEN	BEN	BEN	BEN	BEN	BEN	BEN	BEN	BEN	BEN	BEN	BEN
Buprenorphine with Naloxone															BUP
Cocaine Metabolite	COC	COC	COC	COC	COC	COC	COC	COC	COC	COC	COC	COC	COC	COC	COC
Heroin Metabolite													HER	HER	HER
Marijuana Metabolite			MAR	MAR	MAR	MAR	MAR			MAR	MAR	MAR	MAR	MAR	MAR
MDMA/MDA															MDM
Methadone Metabolite			MTH	MTH	MTH			MTH	MTH	MTH	MTH	MTH	MTH	MTH	
Opiates	OPI	OPI	OPI	OPI	OPI	OPI	OPI	OPI	OPI	OPI	OPI	OPI	OPI	OPI	OPI
Oxycodone	OXY	OXY	OXY	OXY	OXY	OXY	OXY	OXY	OXY	OXY	OXY	OXY	OXY	OXY	OXY
Phencyclidine			PCP	PCP	PCP			PCP	PCP				PCP		

P = Presumptive D = Definitive

- This front-back brochure communicates Quest's comprehensive Drug Monitoring menu, the associated test codes, and the panel components
- This document also includes the phone number for the RX Tox Line
- This document is appropriate for use with current or new clients who need a list of the test codes
- When more details are needed, please use the Drug Monitoring reference guide

QForce Link: Drug Monitoring Reference Guide - Leave Behind

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Website: QuestDrugMonitoring.com

Platform for Drug Monitoring thought leadership content

Tools and educational resources including:

- Test directory
- Blog with the latest drug monitoring information
- Health Trends® reports and data by state
- Information for specific call points
- Patient education page (presumptive and definitive testing)
- State monitors
- **Podcast series—*Topics in Drug Testing***
- **Resource page with webinars, expert videos, and a host of other educational tools and resources**

► **For use with all customers**

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