UPDATE

2016 Revised Edition

PtProtect®

Pain Medication Management Program Supports Patient Outcomes and Adherence

BENEFITS

- Monitors analgesic medication adherence to ensure patient safety and protect your practice
- Uses lowest detection thresholds for the most sensitive, comprehensive detection of opiates and opioids
- Offers highest testing specificity available
- Expert toxicologists available for consult
- Four comprehensive panel configurations detect up to 38 prescribed medications and illicit drugs*
- Detects non-prescribed analgesic medication use, reducing the possibility of adverse drug interactions
- Employs LC-MS/MS technology to detect opiates and opioids, avoiding false negatives from a less sensitive immunoassay screen test
- Simplifies patient management with easy-to-understand interpretations in addition to quantitative results

The PtProtect (Patient Protect) Pain Management Program offers panel test options designed to improve monitoring of prescribed controlled medications. These panels (see Pain Management Panels insert) help determine whether your patient is:

- Taking or potentially diverting pain medications currently prescribed
- Taking pain medications that are not prescribed
- Using illicit drugs

PATIENT SAFETY

The Centers for Disease Control and Prevention (CDC) has declared deaths from prescription opioid overdose an epidemic in the United States. Mortality data from CDC reports state 22,767 people in the U.S. died from pharmaceutical overdose in 2013. Of these deaths, 16,235 (71%) involved opioid prescription painkillers and, 6,973 (30%) involved benzodiazepines. The data also reveals that 1.4 million emergency room visits in 2011 involved misuse and abuse of pharmaceuticals, with 420,040 of those visits related to opioid analgesics.[1]

The possibility of adverse drug interactions makes this a significant patient and community safety issue, particularly when the patient:

- Combines prescriptions from multiple prescribers or other sources such as friends or family members
- Uses controlled substances recreationally
- Diverts prescribed medications for financial gain

COST OF PRESCRIPTION DRUG ABUSE

The overall costs associated with prescription drug abuse are estimated to be more than $70 billion per year.[2] An addicted patient who receives prescriptions from multiple doctors can cost insurers $10,000 – $15,000 a year.[3] PtProtect directly addresses the safety and financial concerns of prescription pain medication abuse by using the most sensitive and definitive assays to detect medication and illicit drugs.

Direct annual health care costs from hospitalization, outpatient visits and prescription drugs are approximately nine times higher for opioid abusers than non-opioid abusers as shown in the table below. Early monitoring of drug adherence using laboratory urine tests by mass spectrometry may provide substantial cost savings.[4,5,6]

Mean Annual Costs Per Patient (U.S. Dollars)

Medical Service	Opioid Abuser	Non-Opioid Abuser
Total direct health care	$15,884	$1,830
Hospital inpatient	$7,659	$318
Physician outpatient	$5,398	$928
Drug therapy	$2,034	$386
Other health care costs	$793	$198

WHY CHOOSE PTPROTECT FOR YOUR PAIN MANAGEMENT TESTING?

PtProtect has a U.S. patented testing algorithm* with a decade of study behind it. PtProtect provides the confidence and reliability you need to ensure successful pain medication monitoring. This complete suite of test panels and their component tests offers important features unique to PeaceHealth Laboratories:

1. Detects the lowest drug concentration available

Results that show the presence and absence of targeted opiate and opioid medications are crucial to an accurate assessment. Detection thresholds as low as 2 and 5 ng/mL increase the ability to identify recent medication use. These low-threshold sensitivities can reveal an absence of expected medications which may

indicate diversion, reduced dosages or non-adherence with the patient's prescribed medication (refer to Drug Detection insert).

2. Uses tandem mass spectrometry – the gold standard for detection

Liquid Chromatography/Tandem Mass Spectrometry (LC-MS/MS) is the most accurate and sensitive testing method to detect medications. Our anecdotal laboratory data shows that testing based on other methodologies can miss up to 30% of opiates/opioids present. LC-MS/MS is used to test opiates and opioids without relying on an initial positive screen test with less sensitivity and poor specificity. This reduces turnaround time for test reporting and provides confirmatory sensitivity and specificity for all opiates/opioids included in the panels (refer to Interpretive Report Examples and Understanding Test Results inserts).

3. Produces reports with easy-to-read interpretive comments that speed patient care

The PtProtect report provides an "Interpretive Comments" section to quickly and accurately determine whether the test results are consistent or discrepant with your patient's prescriptio

IMPORTANCE OF LOW DETECTION LIMITS

The lowest level of drug detection, known as the threshold/cutoff level, is critical to accurately monitor the presence or absence of drugs in the urine (refer to Comparison of Tests insert).

In a retrospective study of 77,881 urine specimens shown to be positive for opioids using a threshold/cutoff of 50 ng/mL, over half (59%) were below the threshold/cutoff level of 2,000 ng/mL typically used in point of care (POC) tests. These specimens would have been erroneously labeled opioid-negative with a less sensitive testing method.[7]

Moreover, 23% of the specimens fell below the 300 ng/mL cutoff level used by clinical, hospital and reference laboratories. It is recommended that laboratory urine tests using mass spectrometry should be used as a follow-up to POC tests due to the possibility of false-negative results.

HOW OFTEN TO TEST

Recommended Frequency of Urine Drug Testing	
Low risk by Opioid Risk Tool assessment	Periodic (1/year)
Moderate risk by Opioid Risk Tool assessment	Regular (2/year)
High risk by Opioid Risk Tool or opioid doses >120 mg MED/d	Frequent (3–4/year)
Aberrant behavior	At time of visit

-Washington State Agency Medical Directors' Group recommendation

METABOLIC CONSIDERATIONS

Caution must be used when interpreting opiate and opioid results since commonly prescribed opiates (such as codeine) and opioids (such as hydrocodone and oxycodone) are metabolized to active opiate and opioid drugs (codeine → morphine, hydrocodone → hydromorphone, and oxycodone → oxymorphone). These metabolites are also available as prescription medications.

In addition to the expected metabolism that occurs with standard doses of opiate and opioids, high doses of codeine or morphine administered to tolerant patients creates "minor" metabolites: codeine → hydrocodone, and morphine → hydromorphone.

QUESTIONS?

Board-certified clinical toxicologists are available to answer your questions and consult with you when interpreting test results.

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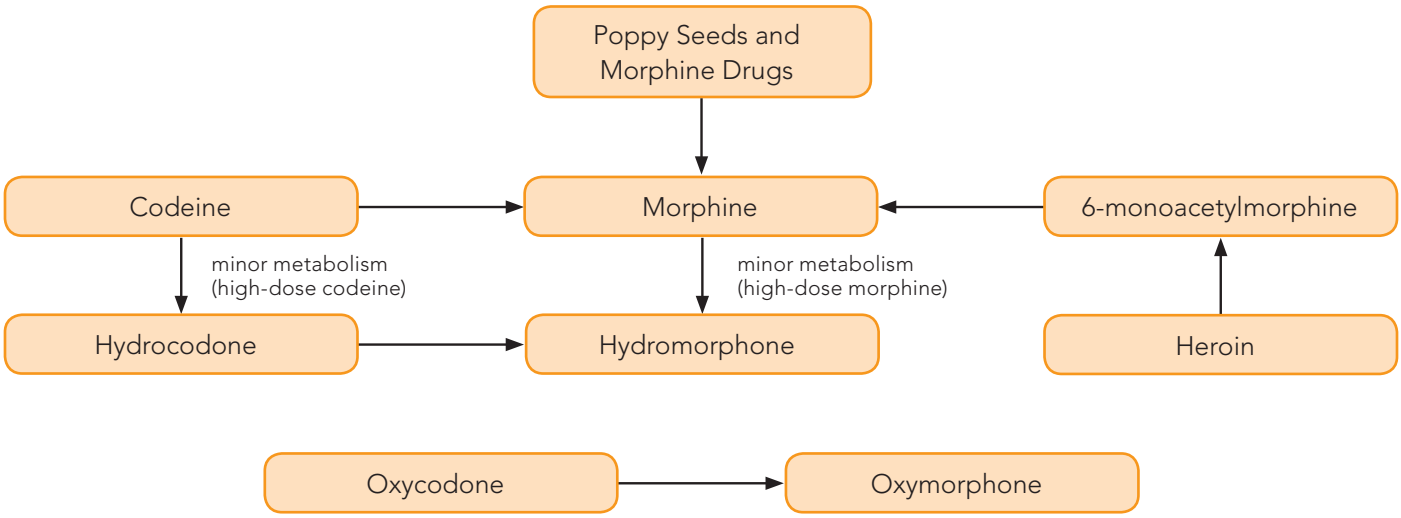
Major and Minor Metabolic Pathways for Opiates and Opioids [8,9,10]



PANEL OPTIONS, URINE					
Methodology	**Profile Components**	**LAB2770**	**LAB2772 Expanded**	**LAB2778 (No THC)**	**LAB2777 Expanded (No THC)**
Opiates/Opioids by LC-MS/MS	6-monoacetylmorphine	■	■	■	■
	Codeine	■	■	■	■
	Fentanyl	■	■	■	■
	Hydrocodone	■	■	■	■
	Hydromorphone	■	■	■	■
	Meperidine	■	■	■	■
	Morphine	■	■	■	■
	Norfentanyl	■	■	■	■
	Oxycodone	■	■	■	■
	Oxymorphone	■	■	■	■
Drug Screen by EIA and GC/MS	Amphetamines	■	■	■	■
	Barbiturates	■	■	■	■
	Benzodiazepines	■	■	■	■
	Cocaine	■	■	■	■
	Ethyl Alcohol	■	■	■	■
	Marijuana	■	■		
	Methadone	■	■	■	■
	Phencyclidine	■	■	■	■
Add-ons by LC-MS/MS	Carisoprodol and metabolite(meprobamate)	Add-on LAB2322	■	Add-on LAB2322	■
	Tramadol and metabolite	Add-on LAB448	■	Add-on LAB448	■
	Buprenorphine and metabolite	Add-on LAB2298			
	Ethyl Glucuronide (EtG) and Ethyl Sulfate (EtS)	Add-on LAB2526			
	Tapentadol	Add-on LAB6559			

SPECIMEN REQUIREMENTS	
Performed	Daily
Released	Within 72 hours
Collection	Urine in a clean plastic urine container. Avoid ethanol-containing hand cleaning lotions prior to collection.
Stability	5 days ambient. Refrigerate if transport is delayed.
Rejection Criteria	Unlabeled or labeled without two identifiers; insufficient specimen volume.

REFERENCES

1. "Deaths from Prescription Opioid Overdose" CDC Injury Prevention & Control: Prescription Drug Overdose Website, accessed 5 August 2015, http://www.cdc.gov/drugoverdose/data/overdose.html
2. "CDC Vital Signs: Overdose of Prescription Opioid Pain Relievers." Media Release. CDC Newsroom. 1 November 2011. Press Briefing Transcript, http://www.cdc.gov/media/releases/2011/t1101_prescription_pain_relievers.html
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8. Oyler, J.M., et al. Identification of hydrocodone in human urine following controlled codeine administration, J Anal Toxicol. 2000 Oct;24(7):530-5.
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10. E.J. Cone, et al. Evidence of morphine metabolism to hydromorphone in pain patients chronically treated with morphine, J Anal Toxicol. 2006 Jan-Feb;30(1):1-5.

Inserts: Drug Detection Time and Thresholds | Comparison of Tests | Interpretive Report Examples | Understanding Test Results

Drug Detection Time and Thresholds, Urine

Pt Protect®

Drug	Trade/Generic Name	Detection Time (after last dose)	Threshold
Opiates/Opioids by LC/MS/MS			
6-Monoacetylmorphine	Heroin metabolite	<8 hours	5 ng/mL
Codeine*	Tylenol-3	1–3 days	5 ng/mL
Fentanyl	Duragesic, Actiq	1–2 days	2 ng/mL
Hydrocodone*	Vicodin and others	1–3 days	5 ng/mL
Hydromorphone*	Dilaudid	2–4 days	5 ng/mL
Meperidine	Demerol	1–2 days	5 ng/mL
Morphine*	MS Contin, Roxanol	1–3 days	5 ng/mL
Norfentanyl	Fentanyl metabolite	1–4 days	2 ng/mL
Oxycodone*	Oxycontin, Tylox, Percocet	1–3 days (SR 2–4 days)	5 ng/mL
Oxymorphone*	Numorphan, Opana	1–3 days (SR 1–4 days)	5 ng/mL
Drug Screen by EIA and GC/MS Confirmation			
Alcohol	Ethanol	2–14 hours	0.02/0.02 g/dL
Amphetamine/Methamphetamine	Amphetamine MDMA, MDA Methamphetamine	1–4 days	300/150 ng/mL
Barbiturates	Amobarbital Butabarbital Butalbital Pentobarbital Phenobarbital Secobarbital	1–7 days 1–7 days 1–7 days 2–3 days 10–15 days 2–3 days	200/200 ng/mL
Benzodiazepines	Alprazolam metabolite Chlordiazepoxide metabolites Clonazepam metabolite Clorazepate metabolites Diazepam metabolites Flunitrazepam metabolite Flurazepam metabolite Lorazepam Nordiazepam Oxazepam Temazepam	2–5 days 2–5 days 2–5 days 2–10 days 7–10 days 2–5 days 1–2 days 2–5 days 2–5 days 2–5 days 2–5 days	200/50 ng/mL
Cocaine	Cocaine metabolite	1–5 days	150/100 ng/mL
Marijuana	THC metabolite	Heavy User: 4–6 weeks Moderate User: 2 weeks Light User: 0–4 days	20/15 ng/mL
Methadone	Methadone and EDDP (metabolite)	3–11 days	150/100 ng/mL
Phencyclidine	Phencyclidine	<8 days Chronic Use: up to 30 days	25/25 ng/mL

**Denotes detection of free, non-conjugated drug.*

Drug	Trade/Generic Name	Detection Time (after last dose)	Threshold
Add-On Testing			
Carisoprodol and metabolite (meprobamate)	Soma	1–4 days	0.2 µg/mL
Buprenorphine and metabolite	Buprenex, Subutex, Suboxone	1–4 days	2 ng/mL
Ethyl Glucuronide Ethyl Sulfate	Ethanol metabolites (EtG, EtS)	Up to 80 hours after moderate-excessive ethanol use	500 ng/mL 200 ng/mL
Tapentadol	Nucynta	1–2 days	25 ng/mL
Tramadol and metabolite	Ultram, Ultracet, Ryzolt	1–3 days	50 ng/mL

Note:
The Drug Detection Time and Thresholds chart indicates time estimate for drug/metabolite detection in urine following cessation of drug use. Other considerations include patient's age, fluid intake, amount and frequency of drug used, and metabolic variables influenced by genetics or interactions with other medications. This table is a general guideline.

Comparison of Tests

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Example:

Patient is taking prescription morphine (20 mg, x3/day). The last dose was taken 36 hours prior to urine specimen collection for testing. Testing is performed using an instant point-of-care (POC) test and simultaneously sent to two laboratories for testing. A comparison of the test results is listed below.

	Instant Point-of-Care Test	Immunoassay Screen national laboratory	PtProtect Test from PeaceHealth Laboratories	
Medication/Drug	**Test Result**	**Test Result**	**Test Result**	**Amount Detected with PtProtect**
Amphetamines	negative	negative	negative	
Barbiturates	negative	negative	negative	
Benzodiazepines	negative	negative	negative	
Cocaine	negative	negative	negative	
Methadone	negative	negative	negative	
Oxycodone	**NEGATIVE**	**NEGATIVE**	**POSITIVE**	**65 ng/mL**
Phencyclidine	negative	negative	negative	
Opiates	**NEGATIVE**	**NEGATIVE**	n/a*	
Propoxyphene	negative	negative	negative	
6-MAM	**not tested**	**not tested**	negative	
Alcohol	**not tested**	**not tested**	negative	
Marijuana	negative	negative	negative	
Fentanyl	**not tested**	negative	negative	
Hydrocodone	**not tested**	**not tested**	negative	
Hydromorphone	**not tested**	**not tested**	negative	
Norfentanyl	**not tested**	**not tested**	negative	
Oxymorphone	**not tested**	**NEGATIVE**	**POSITIVE**	**16 ng/mL**
Codeine	n/a*	n/a*	negative	
Morphine	**n/a***	**n/a***	**POSITIVE**	**212 ng/mL**
Meperidine	**not tested**	**not tested**	negative	

Results:

The instant test and a national laboratory produced a false negative opiates result for the prescribed morphine. The detection threshold for the POC instant test for opiates (morphine) is 2,000 ng/mL. The screening detection threshold for the national laboratory is 300 ng/mL. PtProtect is able to detect morphine at 5 ng/mL.

The patient was also taking oxycodone, an additional medication that was not prescribed. The POC instant test cup and the national laboratory would not detect oxycodone because the detection threshold for the POC instant test and the national laboratory is 100 ng/mL. PtProtect detects oxycodone down to the level of 5 ng/mL. Oxymorphone is a metabolite of oxycodone and is also detected only by PtProtect.

**The POC test and a national laboratory perform an initial screen for opiates (codeine and morphine). PtProtect directly tests for codeine and morphine plus oxycodone, oxymorphone, hydrocodone, hydromorphone, 6-monoacetylmorphine, meperidine, fentanyl and norfentanyl using LC/MS/MS on every specimen, every time.*

Interpretive Report Examples

Pt Protect®

Example 1

Hydrocodone is prescribed and both hydrocodone and hydromorphone (metabolite of hydrocodone) are detected in the urine. The ratio of hydromorphone to hydrocodone is consistent with hydrocodone use. The source of hydromorphone is the hepatic metabolism of hydrocodone. The interpretive comment would read:

Drug Class	Result	Interpretive Comment
Hydrocodone	864 ng/mL	Consistent with hydrocodone prescription
Hydromorphone	115 ng/m	Hydromorphone source from hydrocodone metabolism

Example 2

An opiate/opioid that is not prescribed is detected in the urine. For example, oxycodone (Oxycontin) where the oxymorphone to oxycodone ratio indicates that oxymorphone (Opana) is also likely being used (and not prescribed), the interpretive comment would read:

Drug Class	Result	Interpretive Comment
Oxycodone	544 ng/mL	Discrepant result; oxycodone should be negative
Oxymorphone	317 ng/mL	Oxymorphone source from oxycodone metabolism and probable oxymorphone use

Example 3

An interpretive comment will also be provided when the requisition indicates that prescription use is "unknown" or not provided to our laboratory. In the example, codeine and morphine are positive in the urine but prescription information was not provided to the laboratory. The morphine to codeine ratio indicates that morphine came from codeine metabolism. The interpretive comment would read as shown below. Recent heroin use is likely excluded as the source of morphine since the 6-monoacetyl-morphine test, a marker of heroin use, is negative. In addition, concentrations of codeine and morphine rule out poppy seed ingestion as a likely source of morphine.

Drug Class	Result	Interpretive Comment
Codeine	327 ng/mL	Consistent with codeine use
Morphine	104 ng/mL	Morphine source from codeine metabolism

Understanding Test Results

PtProtect®

Determining if a detected medication is from legitimate or illicit use can be difficult and requires clinical correlation.

1. Why would a prescribed drug not be detected?

- Non-adherence
- Diversion
- Rapid or ultra-rapid metabolizer (genetic polymorphism)
- Drug-induced metabolism (e.g., rifampin)
- Poor drug absorption (e.g., celiac disease)
- Diluted urine

2. Why would a drug that was not prescribed be detected?

- An expected opiate or opioid metabolite from a legitimate prescription
- An expected opioid metabolite found when high doses of codeine or morphine are used
  - High-dose codeine can metabolize to hydrocodone
  - High-dose morphine can metabolize to hydromorphone
- Prescription from another physician
- Medication obtained from spouse or friend
- Illicit use of drug obtained without prescription

3. What is included in a report's interpretive comments?

PtProtect reports provide interpretive comments based on prescribed medications and the analytical urine test results. The report lists medications prescribed, medications detected and the relationship between the medications and the results to facilitate the interpretation.

An interpretive comment is included even when the patient's prescription medication use is:

- Undisclosed on your requisition or order
- Unknown to you
- Not currently part of the patient's care plan

4. Can I tell whether my patient has taken more (or less) than the dose of medication I prescribed?

It is scientifically unreliable to correlate urine drug concentration to a patient's dosage. Using urine concentrations to monitor therapeutic levels is unreliable.1,2 Urine drug and drug metabolite concentrations cannot determine:

- Amount of drug used
- Exactly when the last dose was taken

5. What can I do if my patient's results are discrepant?

When a clinician receives results inconsistent with prescription history, there are several options to consider:

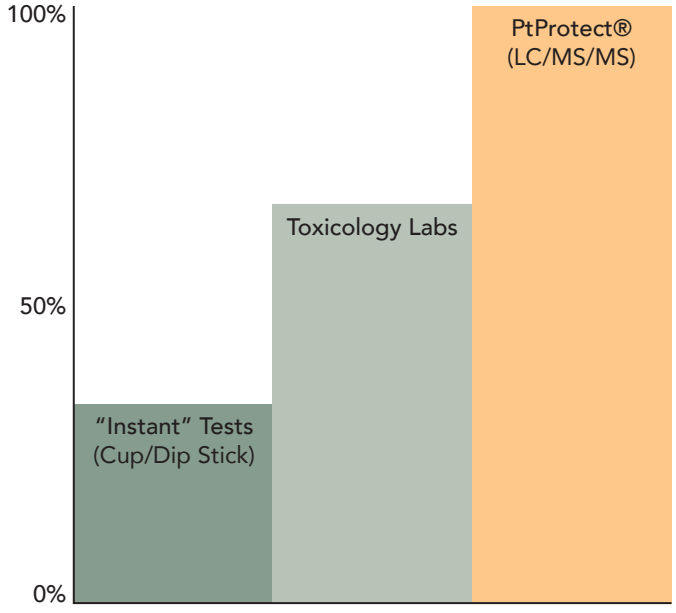
- Counsel the patient
- Modify the patient's treatment plan
- Refer the patient to a substance abuse program
- Enhance the patient's monitoring (more frequent testing, pill counts, etc.)

6. Why would an instant point-of-care (POC) test cup produce a negative result while the PeaceHealth Laboratories test is positive?

Initial screen tests are limited in their specificity and sensitivity. Screens offer a limited view of the existence of drugs that may be present. These limitations are particularly true when using instant cup drug screens, whether the indicators are on a dipstick or included as part of a cup design. Instant test cup specimens may be sent to our laboratory for more definitive testing.

For the highest accuracy and sensitivity, mass spectrometry testing is recommended to verify screen findings, whether positive or negative. See comparison of testing method detection sensitivities in the figure shown below.

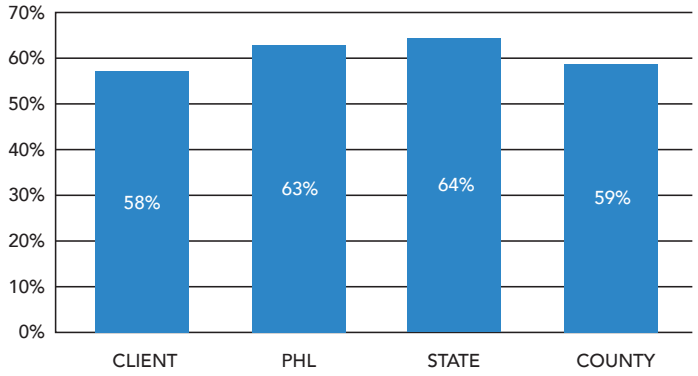
Percent of Opiate/Opioids Identified by Method



Detection Sensitivity at Low Drug Concentration Levels

7. What is a discrepancy report and how can it be useful to manage my clinic's chronic pain population?

A clinic-specific discrepancy report is a useful tool that provides an overall snapshot detailing the adherence of your patients to their prescription regimen over a specific time period. A *discrepant result* occurs when a pain medication is detected, but not prescribed; or when a pain medication is prescribed, but not detected. The discrepancy rate is the percent of the total specimens tested where one or more discrepancies are identified in your patient's test results (when prescription regimen is provided). Your clinic's discrepancy rate is compared with PeaceHealth Laboratories' average rate of patient medication compliance. This useful report can assist you to assess which specific controlled substances are highly discrepant in your pain patient population.



Total Results with Discrepant Drugs Detected

References

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