Urine Drug Testing and its Impact on the Opioid Crisis
Clinical Pearls of Drug Testing Case Studies

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Albany College of Pharmacy & Health Sciences,
Western New England University College of Pharmacy, UCONN School of Pharmacy

www.paindr.com
## Disclosures

<table>
<thead>
<tr>
<th>Affiliation</th>
<th>Role</th>
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<tbody>
<tr>
<td>AcelRx Pharmaceuticals</td>
<td>Advisory Board</td>
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<tr>
<td>Acutis Diagnostics, Inc</td>
<td>Speaker</td>
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<td>Astra Zeneca</td>
<td>Speakers Bureau</td>
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<tr>
<td>BioDelivery Sciences International</td>
<td>Consultant</td>
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<tr>
<td>Daiichi Sankyo</td>
<td>Advisory Board, Speakers Bureau</td>
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<tr>
<td>Firstox Laboratories</td>
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<td>GlaxoSmithKline (GSK)</td>
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<td>Scilex Pharmaceuticals</td>
<td>Advisory Board</td>
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<tr>
<td>Salix Pharmaceuticals</td>
<td>Advisory Board</td>
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</table>
Learning Objectives

• Differentiate between In-Office Qualitative Testing & Laboratory Quantitative Testing
• Explain how to interpret unexpected UDT results
• Explain how to incorporate UDT results into ongoing clinical assessment and decision making
• Describe how to communicate with patients about unexpected results in a positive, therapeutic manner
PRETEST POLL: At a morphine equivalent daily dose of 20mg, which of the following will test positive by immunoassay drug screen?

A. Methadone
B. Codeine
C. Fentanyl
D. None of the above
PRETEST POLL: Which of the following can cause a false positive methadone by IA urine testing?

A. Quetiapine
B. Diphenydramine
C. Chlorpramazine
D. All of the above
The Whizzinator Kit

http://www.thewhizzinator.com/lifestyle-products/lilwhizz
Urine Drug Testing (UDT) Rationale

- Guidelines recommend UDT as standard of care when prescribing chronic opioid therapy, especially for CNCP
- Helps to ensure compliance and mitigate risk
  - Detects presence of illicit substances
  - Detects absence of prescribed medication
- Helps to justify continual prescriptions
- Supports clinician decision to discontinue controlled substance medication

Urine Drug Testing (UDT) Rationale

- Supports justification for closer monitoring
  (more frequent visits / lab monitoring)
- Supports behavior modification and referral to psychologist

Potential Pitfalls

- Patient reliability to report compliance, use and misuse is dubious and often poor
- Behavior alone is unreliable for identifying patients at risk non-compliance, abuse, misuse, and diversion
Urine Drug Monitoring Guidelines

- Federal Agencies
  - CDC\textsuperscript{1}, HHS\textsuperscript{2}, SAMHSA\textsuperscript{3}
- Consensus Guidelines
  - APS/AAPM\textsuperscript{4}, AAPM Consensus 2018\textsuperscript{5}, AACC\textsuperscript{6}, ASAM\textsuperscript{7}, others

1. CDC Guideline for Prescribing Opioids for Chronic Pain: https://www.cdc.gov/drugoverdose/prescribing/guideline.html
Implementing Guidelines if Hospitals, ED’s, and Clinics

• Why should hospitals test prior to surgery?
• Elective vs. nonelective
• Why should hospitals have ED policies for testing?
• Why should clinics routinely screen patients receiving controlled substances?
  – Opioids, amphetamines/methylphenidate, anabolic steroids, etc.
For purposes of this presentation, Clinical Chemistry (CC) Testing will be synonymous with Immunoassay (IA) Testing, as both terms are commonly used.

MOST COMMON TOXICOLOGY SCREENS
# Types of Urine Drug Testing

<table>
<thead>
<tr>
<th>Immunoassay</th>
<th>Chromatography</th>
</tr>
</thead>
<tbody>
<tr>
<td>• In office or send out</td>
<td>• Usually send-out</td>
</tr>
<tr>
<td>• Inexpensive</td>
<td>• More expensive</td>
</tr>
<tr>
<td>• Results are quick (minutes)</td>
<td>• 24 hours to 1 week (per lab)</td>
</tr>
<tr>
<td>• Helps for initial detection</td>
<td>• Final result</td>
</tr>
<tr>
<td>• Presumptive Testing</td>
<td>• Definitive testing</td>
</tr>
<tr>
<td>– False negatives/positives</td>
<td>• Justifies RX decisions</td>
</tr>
<tr>
<td>✓ KNOW YOUR PATIENT!</td>
<td>• 99.999 percent reliability</td>
</tr>
<tr>
<td>• Easier for pts to manipulate low sensitivity, esp w/ synthetics</td>
<td>high sensitivity</td>
</tr>
<tr>
<td>• Presence/absence of RX class only, no metabolites</td>
<td>• Presence/absence of RX metabolites</td>
</tr>
<tr>
<td>• No option for synthetics, designer drugs, and unique natural products</td>
<td>• Custom option for synthetics, designer drugs, and unique natural products</td>
</tr>
</tbody>
</table>
# Opioid Chemistry and Cross-sensitivity

<table>
<thead>
<tr>
<th>PHENANTHRENES</th>
<th>BENZOMORPHANS</th>
<th>PHENYLPIPERIDINES</th>
<th>DIPHENYLHEPTANES</th>
<th>PHENYLPROPYL AMINES</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Morphine" /></td>
<td><img src="image2.png" alt="Pentazocine" /></td>
<td><img src="image3.png" alt="Fentanyl" /></td>
<td><img src="image4.png" alt="Methadone" /></td>
<td><img src="image5.png" alt="Tramadol" /></td>
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</table>

<table>
<thead>
<tr>
<th>MORPHINE</th>
<th>PENTAZOCINE</th>
<th>FENTANYL</th>
<th>METHADONE</th>
<th>TRAMADOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euphronorphine*</td>
<td>Pentazocine</td>
<td>Alfentanil</td>
<td>Methadone Propoxyphene</td>
<td>Tapentadol Tramadol</td>
</tr>
<tr>
<td>Butorphanol*</td>
<td></td>
<td>Fentanyl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td></td>
<td>Remifentanil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dextromethorphan*</td>
<td></td>
<td>Sufentanil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td></td>
<td>Meperidine</td>
<td></td>
<td></td>
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<tr>
<td>Heroin (diacetyl-morphine)</td>
<td></td>
<td>Diphenoxylate*</td>
<td></td>
<td></td>
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<tr>
<td>Hydrocodone*</td>
<td></td>
<td>Loperamide*</td>
<td></td>
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<tr>
<td>Hydromorphone*</td>
<td></td>
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</tr>
<tr>
<td>Levorphanol*</td>
<td></td>
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</tr>
<tr>
<td>Methylmorphine**</td>
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<tr>
<td>Morphine (Opium, conc)</td>
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<tr>
<td>Nalbuphine*</td>
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<tr>
<td>Naltrexone*</td>
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<tr>
<td>Naloxone*</td>
<td></td>
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<tr>
<td>Naloxegol*</td>
<td></td>
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</tr>
<tr>
<td>Naltrexone**</td>
<td></td>
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</tr>
<tr>
<td>Oxycodone*</td>
<td></td>
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<tr>
<td>Oxymorphone*</td>
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</table>

## CROSS-SENSITIVITY RISK

<table>
<thead>
<tr>
<th>PROBABLE</th>
<th>POSSIBLE</th>
<th>LOW RISK</th>
<th>LOW RISK</th>
<th>LOW RISK</th>
</tr>
</thead>
</table>

*Agents lacking the 6-OH group of morphine possibly decreases cross-tolerability within the phenanthrene group

**6-position is substituted with a ketone group and tolerability is similar to hydroxylation

Jeffrey Fudin, BSPharm, PharmD, DAIPM, FCCP, FASHP, FFPSMB

[http://paindr.com/resources/quick-references](http://paindr.com/resources/quick-references) (See "Opioid Chemistry")

a. Previously incorrectly listed as "Benzomorphans"

Opioid and Benzodiazepine Metabolites
plus Validity Testing

Lab Value Resources

Table 5. SAMHSA Criteria for Validity Testing of a Urine Specimen

<table>
<thead>
<tr>
<th>Urine specimen is reported as:</th>
<th>When:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilute</td>
<td>Creatinine concentration ≥ 2 mg/dL, but &lt; 20 mg/dL, &amp; specific gravity* &gt; 1.001, but &lt; 1.003</td>
</tr>
<tr>
<td>Substituted</td>
<td>Creatinine concentration &lt; 2 mg/dL &amp; specific gravity* ≤ 1.001 or &gt; 1.020</td>
</tr>
<tr>
<td>Adulterated</td>
<td>pH &lt; 3 or ≥ 11, nitrite concentration ≥ 500 µg/mL; chromium (VI) concentration ≥ 500 µg/mL; presence of a halogen (eg, from bleach, iodine, fluoride), glutaraldehyde, pyridine, surfactant</td>
</tr>
</tbody>
</table>

*Using refractometry; using a pH meter

Opioid and Benzodiazepine Metabolites

- Alprazolam
  - alpha-hydroxylorazepam
  - oxoralprazolam
- Chlordiazepoxide
  - nordiazepam
  - oxazepam
- Chorazepate
  - nordiazepam
  - oxazepam
- Clonazepam
  - 7-aminoclonazepam
- Diazepam
  - nordiazepam
  - oxazepam
  - temazepam
  - nordiazepam
- Flunitrazepam
  - 7-amino-flunitrazepam
  - lorazepamglucuronide
- Temazepam
  - Edesmethyltemazepam
  - oxazepam

2. Clinical Drug Testing in Primary Care, Technical Assistance Publication Series TAP 32, SAMHSA

http://www.remitigate.com/resources/
Opioids and Benzodiazepine Metabolites
(continued from previous slide)

Buprenorphine
- Norbuprenorphine
Cocaine
- Morphine
- Norcodeine
- Normorphine
- Hydrocodone
- Codeine 6-glucuronide

Fentanyl (Transdermal, Transbuccal, Transmucosal, Sublingual)
- Norfentanyl
- 4-N-(N-propionylalanino) piperidine
- 4-N-(Nhydroxypropionylalanino) piperidine
- 1-(2-phenethyl)-4-N-(Nhydroxypropionylalanino) piperidine

Hydrocodone
- Hydrocodone
- Norcodeine
- 6-beta-hydrocodol
- 6-alpha-hydrocodol
- 6-beta-hydromorphol
- 6-alpha-hydromorphol
- norhydrocodeine

Heroin
- 6-acetylmorphine
- Morphine
- Morphine-3-glucuronide
- Normorphine
- 6-acetylmorphine 3-glucuronide
- Normorphine glucuronide

Hydromorphone
- Hydromorphone-3-glucuronide
- Hydromorphone-3-glucoside
- Dihydromorphone-6-glucuronide
- Dihydromorphone glucuronide

Levorphanol
- 3-glucuronide

Meperidine
- Normeperidine
- meperidine acid
- normeperidinid acid

Methadone
- EDDP (2-ethyl-1,5-dimethyl-3, 3-diphenylpyrrolinium)
- EMDP (2-ethyl-5-methyl-3,3-diphenylpyracline)

Morphine
- Morphine-3-glucuronide
- Morphine-6-glucuronide
- Normorphine
- 7,8-dihydromorphone
- codeine (minor)
- hydromorphone (minor)

Morphine/Naltrexone (Embeda)
- Morphine-3-glucuronide
- Morphine-6-glucuronide
- Normorphine
- 7,8-dihydromorphone
- codeine (minor)
- 6-beta-naltrexol
- hydromorphone (minor)

Oxycodone
- Noroxycodone
- Oxymorphone
- Oxycodyl
- Oxymoroph
- Noroxycodyl

Oxymorphone
- Oxymorphone-3-glucuronide
- 6-OH-oxymorphone

Taperadol
- Taperadol-O-glucuronide
Addressing Unexpected Results

• False or Unexpected Positive
  – Discuss findings with patient
    • Confirm false positive (as a true negative) to support and document patient’s integrity and compliance
  – Confirm unexpected positive to justify
    • ADT products, and or other RX adjustments (partial agonist, partial agonist/antagonist, etc.)
    • substance abuse counseling
    • Alternative and other behavior health intervention

• False Negative
  – Confirm false negative (as a true positive) to support and document patient’s integrity and compliance

Select Opioid Analgesic Choices

- **Extended Release Products:**
  - Buprenorphine Transdermal Patch
  - Buprenorphine Buccal Film
  - Fentanyl Transdermal Patch
  - Hydrocodone ER
  - Hydromorphone-ER
  - Morphine-ER (several products available)
  - Oxycodone-ER
  - Oxymorphone-ER

- **Synthetic Atypical:**
  - Long Biological $T_{1/2}$ & intermediate analgesic $T_{1/2}$
    - Levorphanol
    - Methadone
Case Study 1 | Face Pain

- 43 year old Caucasian male
- TMJ and trigeminal neuralgia
- Failed NSAIDs, cartilage implants, nerve blocks, iontophoresis
- Past Medical History (PMH):
  + Hep C, but otherwise inconsequential
- Current pharmacologic regimen includes:
  - Gabapentin 1200mg PO TID
  - Hydrocodone ER 20mg PO QAM
  - Oxycodone tabs 5mg, 1 PO TID PRN
# Case Study 1 | Face Pain

## What do these results mean?

<table>
<thead>
<tr>
<th>In-Office Results</th>
<th>Chromatography [send out] Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test</strong></td>
<td><strong>Result</strong></td>
</tr>
<tr>
<td>Opiate</td>
<td>Negative</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Gabapentin 1200mg PO TID
Hydrocodone ER 20mg PO QAM
Oxycodone tabs 5mg, 1 PO TID PRN
Case Study 1 | Unexpected Results

Negative for Prescribed Medications

- Lack of oxycodone PRN use
- Pharmacokinetics (when was urine collected?)
- Noncompliance
- Test is not specific for the drug tested (opiate vs. synthetic)
- Drug-drug, drug-disease, drug-food/supplement interactions
- Genetic polymorphism
Case Study 1 | Face Pain

- Speak with patient
- Give patient an opportunity to explain
- Assessment: Document justification for plan
  - Low dose hydrocodone should be negative on IA test as indicated
  - Had IA opiate screen been positive, it may have indicated use of an opiate other than what was prescribed
- Devise actionable medical plan based on lab findings
  - Change in drug therapy (Patch, ADF, no opioid)
  - Justification for f/u lab testing or not ordering chromatography
  - Justification for alternative therapies / behavioral health
Case Study 2 | Chronic Back Pain

- 50 year old Caucasian female
- History of chronic low back pain with justifiable pathology
- Back surgery x 3 (failed back)
- PMH: chronic pain, depression, hypothyroidism
- **Current pharmacologic regimen includes:**
  - Duloxetine 60mg PO QAM
  - Fentanyl 50mcg/hr changed Q72 hours
  - Hydrocodone + APAP 5/325, 1 PO Q4H PRN
**Case Study 2 | Chronic Back Pain**

What do these results mean?

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IA In-Office Results</strong></td>
<td></td>
</tr>
<tr>
<td>Opiate</td>
<td>Negative</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Positive</td>
</tr>
<tr>
<td>Benzoylecgonine (cocaine metabolite)</td>
<td>Positive</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chromatography [send out] Results</strong></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Positive</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Negative</td>
</tr>
<tr>
<td>Diazepam / oxazepam</td>
<td>Positive</td>
</tr>
<tr>
<td>Benzoylecgonine</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Duloxetine 60mg PO QAM
Fentanyl 50mcg/hr changed Q72 hours
Hydrocodone + APAP 5/325, 1 PO Q4H PRN
Case Study 2 | Is definitive testing needed?

Negative for Prescribed Medications
Positive for RX’s not prescribed and illicits

• Lack of hydrocodone PRN use
• Pharmacokinetics (when was urine collected?)
• Noncompliance (illegally obtained drugs?)
• Opiate test should be negative if PRN hydrocodone not used
  – Opiate vs. synthetic, in this case fentanyl
• Drug-drug, drug-disease, drug-food/supplement interactions
• Genetic polymorphism
Case Study 3 | Lower Chest & Abdominal Pain

Negative for Prescribed Medications
False Positive for non-prescribed and Illicits

• 33 year old American Indian male
• Lung cancer, now free of disease
• Chronic upper abdominal & chest pain following his original tumor resection and radiation
• PMH: depression
• Current pharmacologic regimen includes:
  • Morphine 90mg PO QAM
  • Venlafaxine ER 225mg PO QAM
## What do these results mean?

### In-Office Test Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opiate</td>
<td>Positive</td>
</tr>
<tr>
<td>Phencyclidine (PCP)</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Case Study 3 | Is definitive testing needed?

Morphine 90mg PO QAM
Venlafaxine ER 225mg PO QAM

### LC-MS/MS Laboratory Test Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Positive</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Positive</td>
</tr>
<tr>
<td>Phencyclidine (PCP)</td>
<td>Negative</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Positive</td>
</tr>
</tbody>
</table>
Knowledge of P-Kinetics is Essential

- Morphine Metabolism
  - Phase II Glucuronidation by UGT2B7
    - M3G (morphine-3-glucuronide)
    - M6G (morphine-6-glucuronide)
      - Less than 5% → hydromorphone
  - Positive PCP explainable by test results
Case Study 3 | Is definitive testing needed?

- Patient was compliant with
  - Morphine
  - Venlafaxine
- PCP was false positive because of venlafaxine
- Hydromorphone confirmation unexpected?
  - It is a rare metabolite of morphine
- Educate patient and clearly document in the chart
Case Study 4 | Icing on the Cake

Drugs:

- Butrans 15mg TD Patch, changed Qweek
- Quetiapine 50mg PO QHS
- Alprazolam 0.5mg PO TID
- Ibuprofen 600mg PO TID PRN
### In-Office Test Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opiate</td>
<td>Negative</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Negative</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>Negative</td>
</tr>
<tr>
<td>Cannabinoid</td>
<td>Positive</td>
</tr>
<tr>
<td>Methadone</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Butrans 15mg TD Patch, changed Q week  
Quetiapine 50mg PO QHS  
Alprazolam 0.5mg PO TID  
Ibuprofen 600mg PO TID PRN

### LC-MS/MS Laboratory Test Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine, norbuprenorphine, buprenorphine-glucuronide, and norbuprenorphine-glucuronide</td>
<td>Positive</td>
</tr>
<tr>
<td>Alpha-hydroxyalprazolam</td>
<td>Positive</td>
</tr>
<tr>
<td>Cannabinoid</td>
<td>Negative</td>
</tr>
<tr>
<td>Methadone</td>
<td>Negative</td>
</tr>
</tbody>
</table>

What do these results mean?

Case Study 4 | Unexpected Results

Butrans 15mg TD Patch, changed Q week  
Quetiapine 50mg PO QHS  
Alprazolam 0.5mg PO TID  
Ibuprofen 600mg PO TID PRN
Case Study 4 | Is definitive testing needed?

• Buprenorphine is a POTENT synthetic opioid and will not test positive for IA opiate screen at most buprenorphine TD doses
• Positive “opiate” screen would indicate that the patient was using another unprescribed drug
• Alprazolam generally will not test positive on an IA test
• Alprazolam and buprenorphine were confirmed by definitive test results
• Quetiapine may cause false positive methadone
• Ibuprofen may cause false positive cannabinoid
Patient’s RX’s include...

- Hydrocodone 20mg per day
- Alprazolam 2mg per day
- Venlafaxine 250mg per day
- Naproxen 1000mg per day
Latest Street Trends and Designer Drugs

• Synthetic Cathinones (Bath Salts)
• Synthetic Cannabinoids (K2/Spice)
• Fentanyl and other Synthetic Opioids
• Mitragynine (Kratom)
• Cannabidiol (CBD)
POST TEST POLL: At a morphine equivalent daily dose of 20mg, which of the following will test positive by immunoassay drug screen?

A. Methadone
B. Codeine
C. Fentanyl
D. None of the above
POST TEST POLL: Which of the following can cause a false positive methadone by IA urine testing?

A. Quetiapine
B. Diphenhydramine
C. Chlorpromazine
D. All of the above
Conclusions

• Urine Drug Monitoring (UDM) by immunoassay (IA) is the recognized standard of care for routine monitoring
• Every consensus guideline and federal agency that addresses safe opioid prescribing recommends routine UDM
• IA UDM is a cost-effective, efficient, and quick point-of-care test
• Clinicians must know how to interpret urine tests and should not falsely accuse patients of wrongdoing
• UDM could help detect early warning signs so that patients are referred for appropriate counseling