Overview of the AACC Academy's LMPG: Using clinical laboratory tests to monitor drug therapy in pain management patients

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I have no financial disclosures.

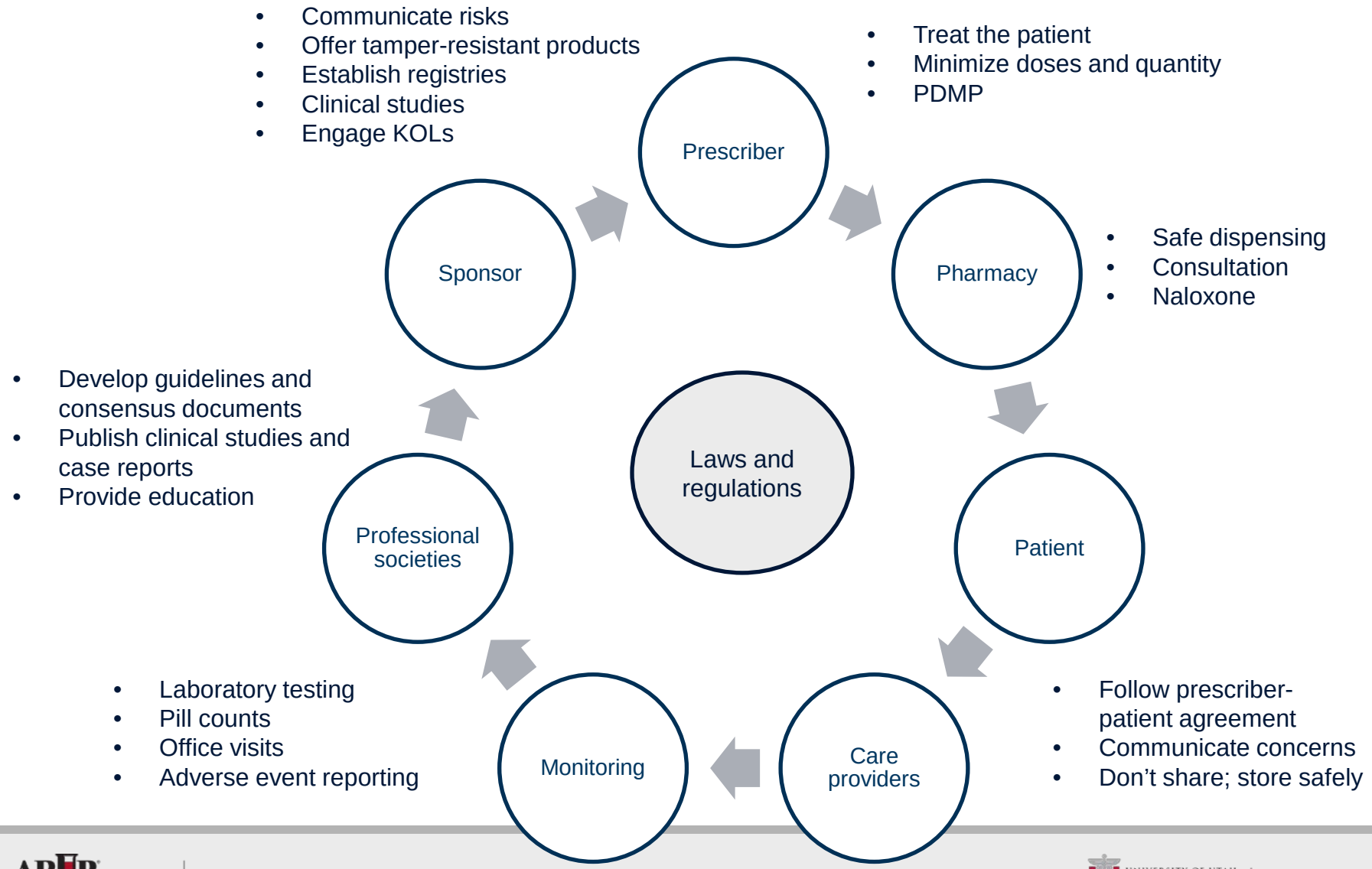
Objectives

- Describe the PICO(TS) strategy used to guide the literature search used to support authorship of the LMPG.
- Explain the scoring system used by the AACC Academy in evaluating strength of the recommendations, and quality of evidence for LMPGs.
- Explain the three tiers of drug testing described in the LMPG.
- Compare qualitative screening with qualitative definitive testing.
- List specimen validity tests and the appropriate time/location for performing such tests.

How did we get here? My observations…

- Pain was established as the “fifth vital sign.”
- Risk of addiction to opioids and related drugs was underappreciated.
- Prescribing practices were not standardized.
- Potent legal and illegal drugs became available.
- Rates of drug addiction and overdoses (including deaths) skyrocketed.
- Physicians, regulators, and payers published clinical practice guidelines, most of which recommend urine drug testing (UDT).

Safe drug use is a team effort



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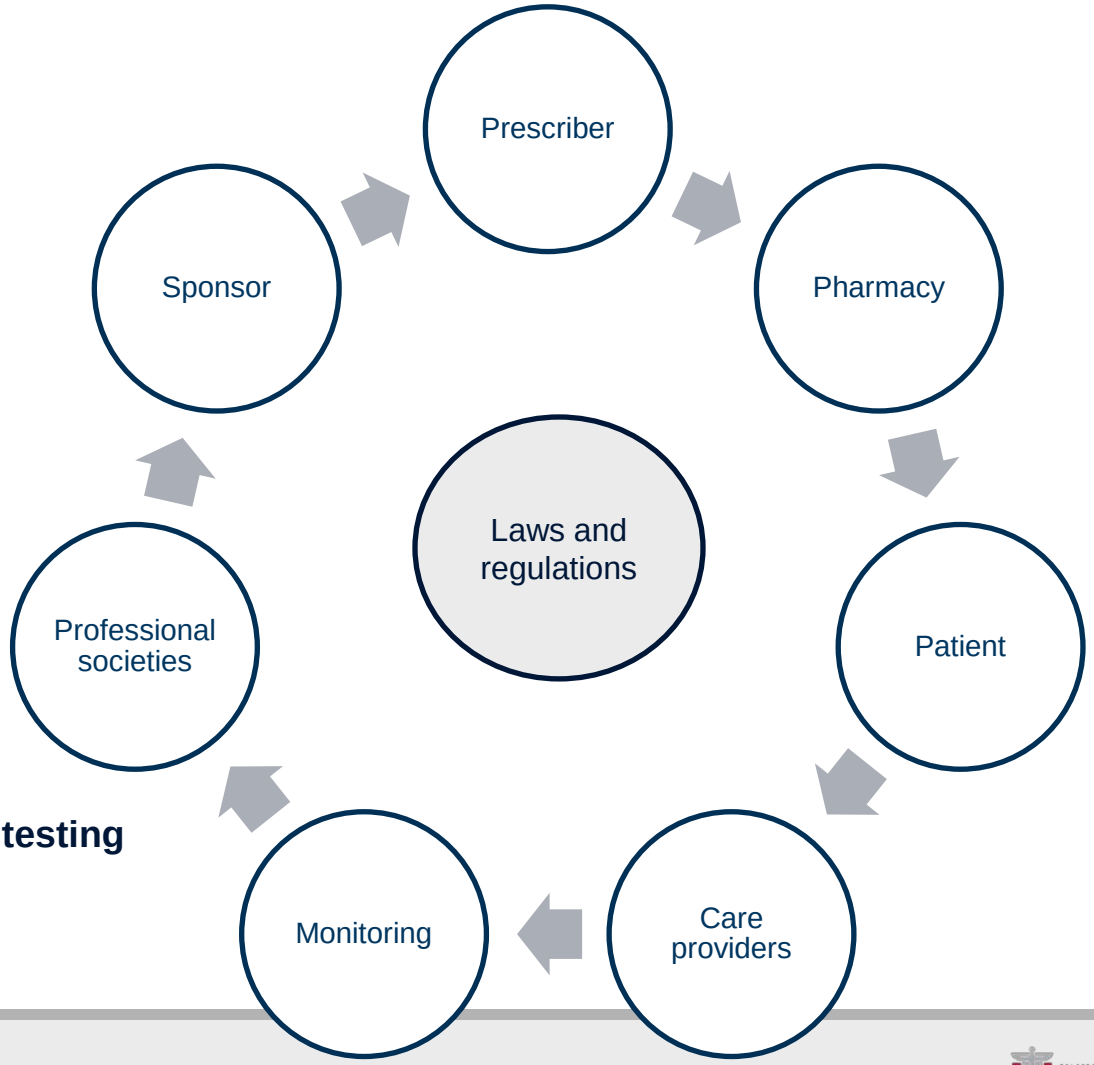
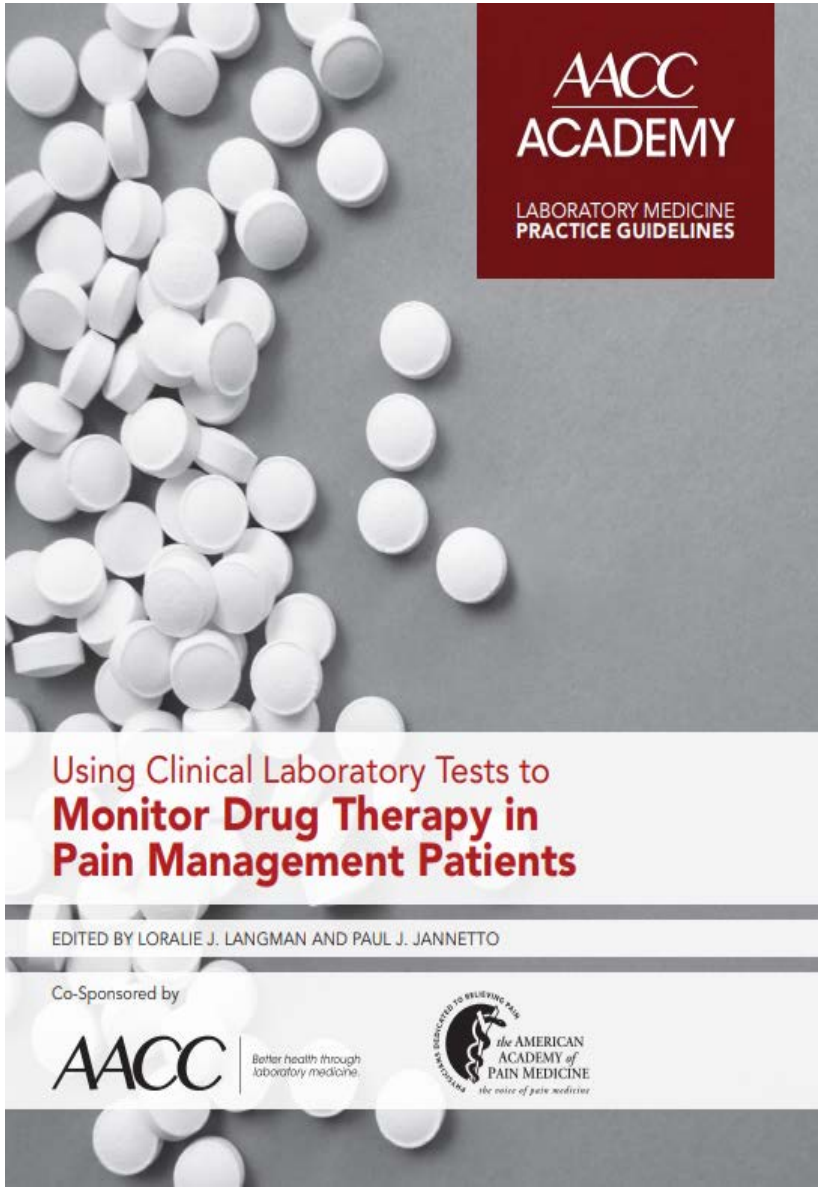


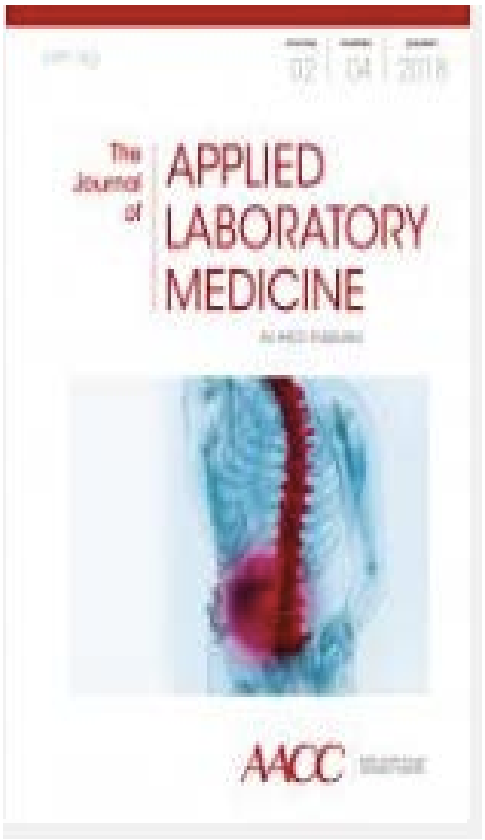
- **Laboratory testing**

Support for standardization of clinical UDT?

- College of American Pathologists (CAP) initiated proficiency testing in 2012 specifically for UDT performed to support pain management
- American Society of Addiction Medicine Consensus Statement, 2017: “Appropriate Use of Drug Testing in Clinical Addiction Medicine”
- Clinical and Laboratory Standards Institute (CLSI), guideline C63, 2018
- AACC Academy’s LMPG!!!!!



- Published on-line December, 2017 (109 pages) https://www.aacc.org
- Co-sponsored by the American Academy of Pain Medicine
- Executive summary published January, 2018 (37 pages)



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SPECIAL REPORT

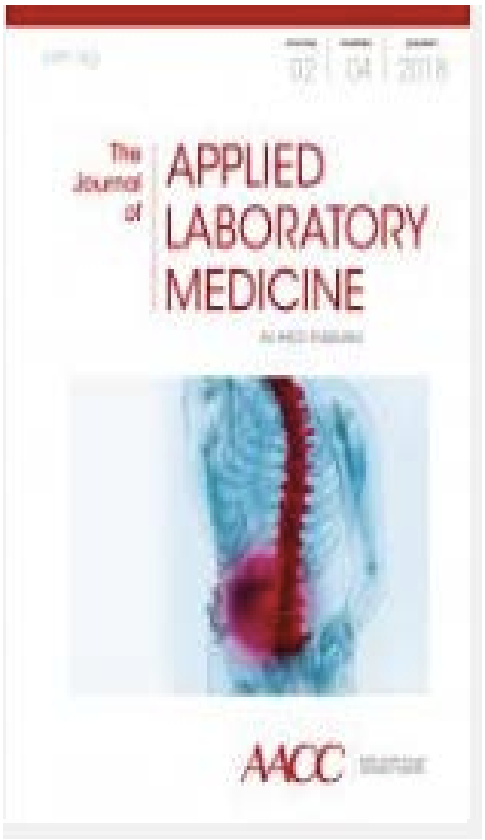
Executive Summary: American Association of Clinical Chemistry Laboratory Medicine Practice Guideline—Using Clinical Laboratory Tests to Monitor Drug Therapy in Pain Management Patients

Paul J. Jannetto,[1]* Nancy C. Bratanow,[2] William A. Clark,[3] Robin J. Hamill-Ruth,[4] Catherine A. Hammett-Stabler,[5] Marilyn A. Huestis,[6†] Cheryl A. Kassed,[7] Gwendolyn A. McMillin,[8] Stacy E. Melanson,[9] and Loralie J. Langman[1]

The AACC Academy, formerly the National Academy of Clinical Biochemistry, has developed a laboratory medicine practice guideline (LMPG)[10] for using laboratory tests to monitor drug therapy in pain management patients. The purpose of this guideline was to compile evidence-based recommendations for the use of laboratory and point-of-care (POC) urine drug tests for relevant over-the-counter medications, prescribed and nonprescribed drugs, and illicit substances in pain management patients. The exact process of preparing and publishing the LMPG is shown in Table 1.

Briefly, a multidisciplinary LMPG committee was established to include clinical laboratory professionals, which is jointly preparing an expert opinion guideline on laboratory testing for pain management (C.A. Hammett-Stabler, L.J. Langman, G.A. McMillin); College of American Pathologists (S.E. Melanson); Evidence-Based Laboratory Medicine Committee (W.A. Clark); clinical laboratories performing pain management testing (L.J. Langman, P.J. Jannetto, C.A. Hammett-Stabler, G.A. McMillin, S.E. Melanson); AACC (C.A. Kassed); American Academy of Pain Medicine (T.J. Lamer, R.J. Hamill-Ruth, N. Bratanow); active pain management clinicians (T.J. Lamer, R.J. Hamill-Ruth, N. Bratanow); and the National Institute of Drug Abuse (M.A. Huestis). Before a systematic literature search, the

Many additional articles of interest



- Cutoff concentrations
- Need for quantitative results
- Analytical methods
- Specimen validity
- Oral fluid
- Pharmacogenomics
- Economics of drug testing

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AACC Academy Guidelines

- Who? Authors were a multidisciplinary team representing key professional and regulatory organizations, but also actively involved in management of pain management patients and/or associated testing.
  - AACC Academy: L Langman, P Jannetto, W Clark
  - CLSI: C Hammett-Stabler, L Langman, G McMillin
  - CAP: G McMillin, S Melanson
  - NIDA: M Huestis
  - AAPM: T Lamer, R Hamill-Ruth, N Bratanow
- No sponsorship, honoraria or other direct funding was provided.
- AACC provided administrative support and covered expenses related to in-person meetings.

AACC Academy Guidelines

- How? Process included
  - Defining the topic, scope, target audience
  - Defining PICO(TS) to formulate questions: Patient population, Intervention, Comparator or Control group, Outcome, Time period and Setting or Study design
  - Conducting a literature search from 2000-2015, accessing 10 different databases, for relevant articles
    - 7647 abstracts were reviewed, each by at least 2 committee members, and answers to 32 questions were documented
    - 2352 manuscripts were selected for full text review
    - 562 selected for inclusion
  - Writing chapters and formulating guidelines
  - Seeking public comment
  - Publishing final version

AACC Academy Guidelines

- 26 evidence-based, 8 consensus-based recommendations, plus notes
- Recommendations were graded based on 2011 IOM approach
  - Strength of recommendation:

    A: Strong evidence that adoption improves outcomes and that benefits outweigh harm

    B: Evidence that adoption improves outcomes…

    C: No evidence that adoption improves outcomes…

    I: Insufficient evidence to make recommendations
  - Quality of evidence:

    I: Consistent, from well-designed, well-conducted studies in representative populations

    II: Sufficient to determine effects, but limited by number, quality, consistency of studies

    III: Insufficient to determine effects

Pre-analytical Recommendations

To test or not to test…

EVIDENCE-BASED RECOMMENDATION #1: Testing biological specimens for drugs/drug metabolites is recommended and effective for detecting the use of relevant over-the-counter, prescribed and non-prescribed drugs, and illicit substances in pain management patients. Laboratory testing does not specifically identify most other outcomes, but should be used in conjunction with additional information to detect other outcomes in pain management patients. **Strength of Recommendation: A; Quality of Evidence: I**

EVIDENCE-BASED RECOMMENDATION #2: More frequent laboratory testing is recommended for patients with a personal or family history of substance abuse, mental illness, evidence of aberrant behavior, or other high-risk characteristics. **Strength of Recommendation: A; Quality of Evidence: II**

EVIDENCE-BASED RECOMMENDATION #3: Laboratory testing is recommended to identify the use of relevant over-the-counter medications, prescribed and non-prescribed drugs, and illicit substances in pain management patients. However, it does not effectively identify all non-compliance with the prescribed regimen. No single monitoring approach provides adequate information about the pattern or dose of patient drug use. Safest prescribing habits should include a combination of tools and laboratory test results to correctly detect outcomes. **Strength of recommendation: A; Quality of evidence: III** (pain management population), **II** (substance abuse disorder monitoring population)

CONSENSUS-BASED EXPERT OPINION #3: Random urine testing for relevant over-the-counter medications, prescribed and non-prescribed drugs, and illicit substances is recommended to detect outcomes in pain management patients. **Strength of Recommendation: A; Quality of Evidence: III** (pain management population), **II** (substance abuse disorder monitoring population)

EVIDENCE-BASED RECOMMENDATION #4: Laboratory testing is more effective than other physician tools for the detection of relevant over-the-counter, prescribed and non-prescribed drugs, and illicit substances in pain management patients and should be used routinely to monitor compliance. **Strength of recommendation: A; Quality of evidence: II**

CONSENSUS-BASED EXPERT OPINION #1: Based on level II evidence, baseline drug testing should be performed prior to initiation of acute or chronic controlled substance therapy. In addition, random drug testing should be performed at a minimum of one to two times a year for low-risk patients (based on history of past substance abuse/addiction, aberrant behaviors, and opioid risk screening criteria), with increasing frequency for higher-risk patients prescribed controlled substances. **Strength of Recommendation: A; Quality of Evidence: II**

- **Yes**, in conjunction with clinical tools
- At baseline, and to monitor compliance
- Random
- Test frequency based on risk
  - Low: 1-2 times/yr
  - High: more often

"Drug testing should be used as a tool for supporting recovery rather than exacting punishment" *ASAM Consensus Statement, 2017*

What to test? *Tiered approach*

1. Routine monitoring:
   - Stimulants such as methamphetamine, amphetamine, MDMA, cocaine
   - Sedative-hypnotics such as barbiturates, benzodiazepines
   - Opioids such as buprenorphine, methadone, fentanyl, hydrocodone, oxycodone, tramadol, morphine, heroin metabolite
   - Cannabis metabolite

2. High-risk patients:
   - Alcohol or metabolite
   - Anticonvulsants
   - Antidepressants
   - Muscle relaxants
   - Synthetics
   - Dextromethorphan
   - Ketamine, LSD, PCP, etc.

3. As clinically indicated.

What to test?

EVIDENCE-BASED RECOMMENDATION #5: Urine testing is recommended for the detection of relevant over-the-counter medications, prescribed and non-prescribed drugs, and illicit substances in pain management patients. **Strength of recommendation: B; Quality of evidence: II**

CONSENSUS-BASED EXPERT OPINION #2: Serum or plasma is an acceptable alternate matrix for the detection of relevant over-the-counter medications, prescribed and non-prescribed drugs, and illicit substances in pain management patients with end-stage renal failure (anuria). For dialysis patients, the blood (serum/plasma) should be collected prior to dialysis. Oral fluid testing can also be used for selected drugs (e.g. amphetamine, benzodiazepines, buprenorphine, tetrahydrocannabinol, cocaine, codeine, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone). **Strength of recommendation: A; Quality of evidence: III**

There is no published evidence for or against alternate matrix testing versus urine testing relative to clinical outcomes in pain management patients. In the absence of evidence, the committee cannot make a recommendation for or against alternate matrix testing. **Strength of recommendation: I** (Insufficient); **Quality of evidence: III**

- **Urine**, for routine monitoring
- Serum/plasma for anuric patients, collected before dialysis
- Oral fluid? Hair?
- Meconium, umbilical cord tissue?

Specimen validity testing

CONSENSUS-BASED EXPERT OPINION #7: Specimen validity testing should be performed on every urine drug test for pain management patients. **Strength of recommendation: A; Quality of Evidence: II**

EVIDENCE-BASED RECOMMENDATION #15: Specimen validity testing (e.g., pH, temperature) is recommended since it is an effective tool to ensure outcomes (e.g., use of relevant over-the-counter, prescribed, and non-prescribed drugs) are correctly interpreted in pain management patients. Specimen validity testing determines the suitability of the urine specimen collected/received, which directly affects the ability to correctly identify relevant over-the-counter medications, prescribed and non-prescribed drugs, and illicit substances used by pain management patients. **Strength of Recommendation: A; Quality of Evidence: I** (workplace drug testing), **II** (pain management population)

EVIDENCE-BASED RECOMMENDATION #18: Identification of aberrant drug-taking behavior through specimen validity testing is supplemental to other tools at detecting outcomes in pain management patients. Multiple tools, including specimen validity testing, should be used as a component of urine drug testing to more reliably identify use of relevant over-the-counter medications, prescribed and non-prescribed drugs, and illicit substances in pain management patients. **Strength of recommendation: A; Quality of evidence: II**

EVIDENCE-BASED RECOMMENDATION #16: For urine specimens, the pH and temperature should be measured within 5 minutes at the point of collection and be used to determine if testing should be performed on that sample. In addition, the determination of creatinine and other adulteration tests (e.g., oxidants) should be performed on the urine specimen in the laboratory and use the federal workplace drug testing cutoffs. In the end, if any of the specimen validity tests fall outside the range of physiological urine values/acceptance criteria, the adulterated sample must not undergo further testing, and the patient should be further evaluated for aberrant drug-taking behavior. **Strength of Recommendation: A; Quality of Evidence: I** (workplace drug testing population), **III** (pain management population)

EVIDENCE-BASED RECOMMENDATION #17: Clinicians should consult the laboratory regarding proper collection, storage, and transportation of urine specimens to maintain specimen validity. **Strength of recommendation: A; Quality of evidence: III**

EVIDENCE-BASED RECOMMENDATION #19: At a minimum, it is recommended that pH, temperature, creatinine, and oxidant testing should be performed on all urine drug tests for pain management patients (timing and site of these tests as noted above). It should also be recognized that these tests will not detect all forms of adulteration. **Strength of recommendation: A; Quality of evidence: I** (workplace drug testing), **III** (pain management population)

- Important for **every** specimen
- Perform pH and temperature testing within 5 min of collection
- Laboratory should measure creatinine and make extended adulterant testing available

Analytical Recommendations

Defining analytical approaches

- Presumptive
- Screen
- Targeted
- Confirmation
- **Definitive**

- Qualitative
- Semi-Quantitative
- Quantitative

While LC-MS/MS and GC-MS techniques are often assumed to be definitive, ***assay design*** is also critical to assay performance.

AMA definition of Definitive Drug testing: qualitative or quantitative tests to identify possible use or non-use of a drug. These tests identify specific drugs and associated metabolites. Oct 26, 2011

How to test?

EVIDENCE-BASED RECOMMENDATION #6: While definitive testing is recommended and preferred, urine immunoassays performed on laboratory-based analyzers offer some clinical utility to detect the use of relevant over-the-counter medications, prescribed and non-prescribed drugs, and illicit substances in pain management patients. However, physicians using immunoassay-based tests (especially amphetamine, benzodiazepine, and opiate immunoassays) must reference the package insert if testing in the physician's office or consult with laboratory personnel to evaluate the assay's capabilities and limitations for detecting specific medications within a drug class to prevent incorrect interpretation and to determine when additional testing is necessary. **Strength of Recommendation: B; Quality of Evidence: II**

EVIDENCE-BASED RECOMMENDATION #7: Qualitative definitive tests should be used over laboratory-based immunoassays since they are more effective at identifying relevant over-the-counter medications, prescribed and non-prescribed drugs, and illicit substances in pain management patients. **Strength of Recommendation: A; Quality of Evidence: II**

EVIDENCE-BASED RECOMMENDATION #8: Qualitative definitive tests should be used when possible over immunoassays for monitoring use (compliance) to relevant over-the-counter medications, prescribed and non-prescribed drugs, and illicit substances in pain management patients due to their superior sensitivity and specificity. **Strength of Recommendation: A; Quality of Evidence: II**

EVIDENCE-BASED RECOMMENDATION #9: POC (oral/urine) qualitative presumptive immunoassays offer similar performance characteristics to laboratory-based immunoassays and can detect some over-the-counter medications, prescribed and non-prescribed drugs, and illicit substances in pain management patients. However, physicians using POC testing must reference the POC package insert and/or consult laboratory personnel to accurately determine the assay's capabilities (especially amphetamine, benzodiazepine, and opiate immunoassays) and understand the limitations for detecting specific medications within a drug class to prevent incorrect assumptions or interpretation and to determine when additional testing is necessary. **Strength of Recommendation: B; Quality of Evidence: II**

EVIDENCE-BASED RECOMMENDATION #10: Qualitative immunoassay drug testing prior to prescribing controlled substances can be used to identify some illicit drug use and decrease adverse outcomes in pain management patients. **Strength of Recommendation: B; Quality of Evidence: II**

EVIDENCE-BASED RECOMMENDATION #11: Appropriately performed and interpreted urine POC immunoassay testing can be cost-effective for detecting use or inappropriate use of some over-the-counter medications, prescribed and non-prescribed drugs, and illicit substances in pain management patients. **Strength of Recommendation: B; Quality of Evidence: II**

- First-line **definitive testing** is preferred
- If immunoassays are used, limitations of testing must be understood
- Confirm any immunoassay result that is not consistent with clinical expectations

EVIDENCE-BASED RECOMMENDATION #13: Recommend definitive testing for any immunoassay (laboratory-based or POC) result that isn't consistent with the clinical expectations in a pain management patient. **Strength of recommendation: A; Quality of evidence: III**

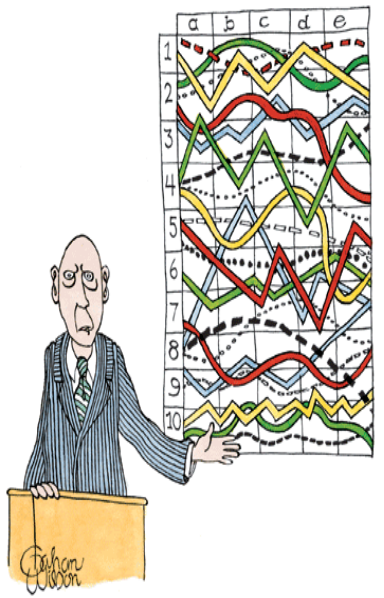
Do you need a number?

There is no evidence to suggest that qualitative/ semi-quantitative urine screening assays are more cost-effective than mass-spectrometry-based assays in detecting outcomes in pain management patients. Additional studies are needed. **Strength of Recommendation: I** (Insufficient); **Quality of Evidence: III**

EVIDENCE-BASED RECOMMENDATION #12: First-line definitive testing (qualitative or quantitative) is recommended for detecting the use of relevant over-the-counter medications, prescribed and non-prescribed drugs, and illicit substances in pain management patients. **Strength of recommendation: A; Quality of evidence: II**

EVIDENCE-BASED RECOMMENDATION #14: Quantitative definitive urine testing is not more useful at detecting outcomes in pain management patients compared to qualitative definitive urine testing. Furthermore, quantitative definitive urine testing should not be used to evaluate dosage of administered drug or adherence to prescribed dosage regimen. However, quantitative urine definitive testing is recommended to identify variant drug metabolism, detect pharmaceutical impurities, or metabolism through minor routes. Quantitative results may also be useful in complex cases to determine the use of multiple opioids, confirm spiked samples, and/or rule out other sources of exposure (e.g. morphine from poppy seeds). **Strength of recommendations: A; Quality of evidence: II**

EVIDENCE-BASED RECOMMENDATION #21: Directed quantitative drug testing (urine, serum) should be performed to verify and characterize variant pharmacokinetics and patient adherence to prescribed regimen in order to assist in the interpretation and application of genetic data. **Strength of recommendation: B; Quality of evidence: II**



"I'll pause for a moment so you can let this information sink in."

- **No.** Results do not have to be quantitative to meet the needs of testing.
- Quantitative testing should not be used to evaluate dosage.
- Quantitative testing may be useful in complex cases.

Other aspects of analytical approaches

CONSENSUS-BASED EXPERT OPINION #4: The use of lower limit-of-detection cutoff concentrations can be more effective to detect use (either partial or full compliance) or the lack of use of relevant over-the-counter medications, prescribed and non-prescribed drugs, and illicit substances in pain management patients, especially those taking lower dosages. **Strength of Recommendation: B; Quality of Evidence: II**

CONSENSUS-BASED EXPERT OPINION #5: Recommend clinicians and/or referring laboratories consult with the testing laboratory personnel about the use and efficiency of pre-analytical hydrolysis for urine drug tests, as well as the expected impact on results. **Strength of recommendation: I (Insufficient); Quality of Evidence: III**

CONSENSUS-BASED EXPERT OPINION #6: Laboratories ultimately need to measure the appropriate analytes based on the matrix (e.g. serum vs urine). In urine, the conjugated form is most prevalent and it can either be measured separately or combined with the less abundant unconjugated form after hydrolysis. **Strength of recommendation:** I (Insufficient); **Quality of Evidence: III**

EVIDENCE-BASED RECOMMENDATION #20: While the current evidence in the literature doesn't support routine genetic testing for all pain management patients, it should be considered to predict or explain variant pharmacokinetics, and/or pharmacodynamics of specific drugs as evidenced by repeated treatment failures, and/or adverse drug reactions/toxicity. **Strength of recommendation: A; Quality of evidence: II**

- Cutoff concentrations, hydrolysis, and specific analytes targeted may affect detection.
- Pharmacogenetics testing may be useful in complex cases.

Post-analytical Recommendations

How to report?

There is no evidence in the literature that the manner in which qualitative results are reported improves the accuracy of interpretation by the healthcare provider for pain management patients. Additional studies are needed. **Strength of Recommendation: I** (Insufficient); **Quality of Evidence: III**

There is no evidence in the literature that the timing of the release of screening results with respect to the completion of confirmative testing reduces or prevents negative outcomes in patient care. Additional studies are needed. **Strength of recommendation: I** (Insufficient); **Quality of evidence: III**

EVIDENCE-BASED RECOMMENDATION #22:
Quantitative or proportional patterns of some drug and drug metabolites is recommended to explain complex cases and detect: the presence of pharmaceutical impurities, simulated compliance (e.g., adding drug directly to urine), and/or the major route of metabolism in a particular patient. **Strength of Recommendation: I** (Insufficient) **for most drugs; B for some drugs; Quality of Evidence: II**

The current evidence in the literature does not support using specific patterns of conjugated and unconjugated drug and drug metabolites to define a patient's metabolic phenotype. Additional studies are needed. **Strength of Recommendation: I** (Insufficient) **for most drugs, B for other drugs** (e.g., common opioids) **Quality of Evidence: III**

EVIDENCE-BASED RECOMMENDATION #23:
Urine drug testing (quantitative or qualitative) is not recommended for approximating the time of last dose. **Strength of Recommendation: B; Quality of Evidence: II**

There is insufficient evidence to support the practice of normalizing quantitative results to creatinine or specific gravity or that doing so is an effective means of detecting compliance or misuse/diversion. Additional studies are needed. **Strength of recommendation: I** (Insufficient); **Quality of evidence: III**

There is insufficient evidence in the literature to determine if quantitative concentrations of prescribed medications, alone or in combination with a clinical algorithm, improves the use of the testing in terms of identifying compliance, efficacy, or non-compliance. Additional studies are needed. **Strength of recommendation: I** (Insufficient); **Quality of evidence: III**

- Clear and simple.
- **Provide alerts** when odd patterns are observed that could affect interpretation, but don't over-interpret (e.g. estimate time of last dose).

Customer support for interpretation

EVIDENCE-BASED RECOMMENDATION #24: Data showed that many clinical providers have insufficient knowledge and expertise to correctly interpret urine laboratory test results in pain management patients. It is recommended that clinicians should contact laboratory personnel for any test result that is inconsistent with the clinical picture and/or prescribed medications to more effectively interpret urine test results in pain management patients. **Strength of recommendation: A; Quality of evidence: I**

EVIDENCE-BASED RECOMMENDATION #25: It is recommended that laboratories provide educational tools and concise, detailed reports to guide the interpretation of urine drug tests for pain management patients by clinicians. **Strength of recommendation: A; Quality of evidence: III**

EVIDENCE-BASED RECOMMENDATION #26: It is recommended that clinical laboratories offering pain management testing must also have knowledgeable personnel who can assist clinicians to correctly interpret urine laboratory test results in pain management patients. **Strength of recommendation: A; Quality of evidence: III**

- **Know your customer** and what sort of support they need.
- Designate competent technical staff in the laboratory to consult with customers about interpretations.

Guidelines are not laws and may not be followed…

but at least we have some now!

Thank you for your attention!!!

ARUP LABORATORIES

UNIVERSITY OF UTAH
SCHOOL OF MEDICINE

Department of Pathology