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

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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

- Communicate risks
- Offer tamper-resistant products
- Establish registries
- Clinical studies
- Engage KOLs

Prescriber

- Treat the patient
- Minimize doses and quantity
- PDMP

Pharmacy

- Safe dispensing
- Consultation
- Naloxone

Patient

- Follow prescriber-patient agreement
- Communicate concerns
- Don’t share; store safely

Laws and regulations

Sponsor

- Develop guidelines and consensus documents
- Publish clinical studies and case reports
- Provide education

Professional societies

- Laboratory testing
- Pill counts
- Office visits
- Adverse event reporting

Monitoring

Care providers

- Communicate risks
- Offer tamper-resistant products
- Establish registries
- Clinical studies
- Engage KOLs
Safe drug use is a team effort

- Prescriber
- Pharmacy
- Sponsor
- Professional societies
- Patient
- Laws and regulations
- Monitoring
- Care providers
- 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.


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


The AACC Academy, formerly the National Academy of Clinical Biochemistry, has developed a laboratory medicine practice guideline (LMPG) 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, institute, 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

http://jalm.aaccjnls.org/content/2/4
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...

- **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

- **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 #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 #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 #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), II (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

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?

- 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
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 #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

**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

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- **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.

*“I’ll pause for a moment so you can let this information sink in.”*
Other aspects of analytical approaches

- Cutoff concentrations, hydrolysis, and specific analytes targeted may affect detection.

- Pharmacogenetics testing may be useful in complex cases.
Post-analytical Recommendations
How to report?

- 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

- **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!!!