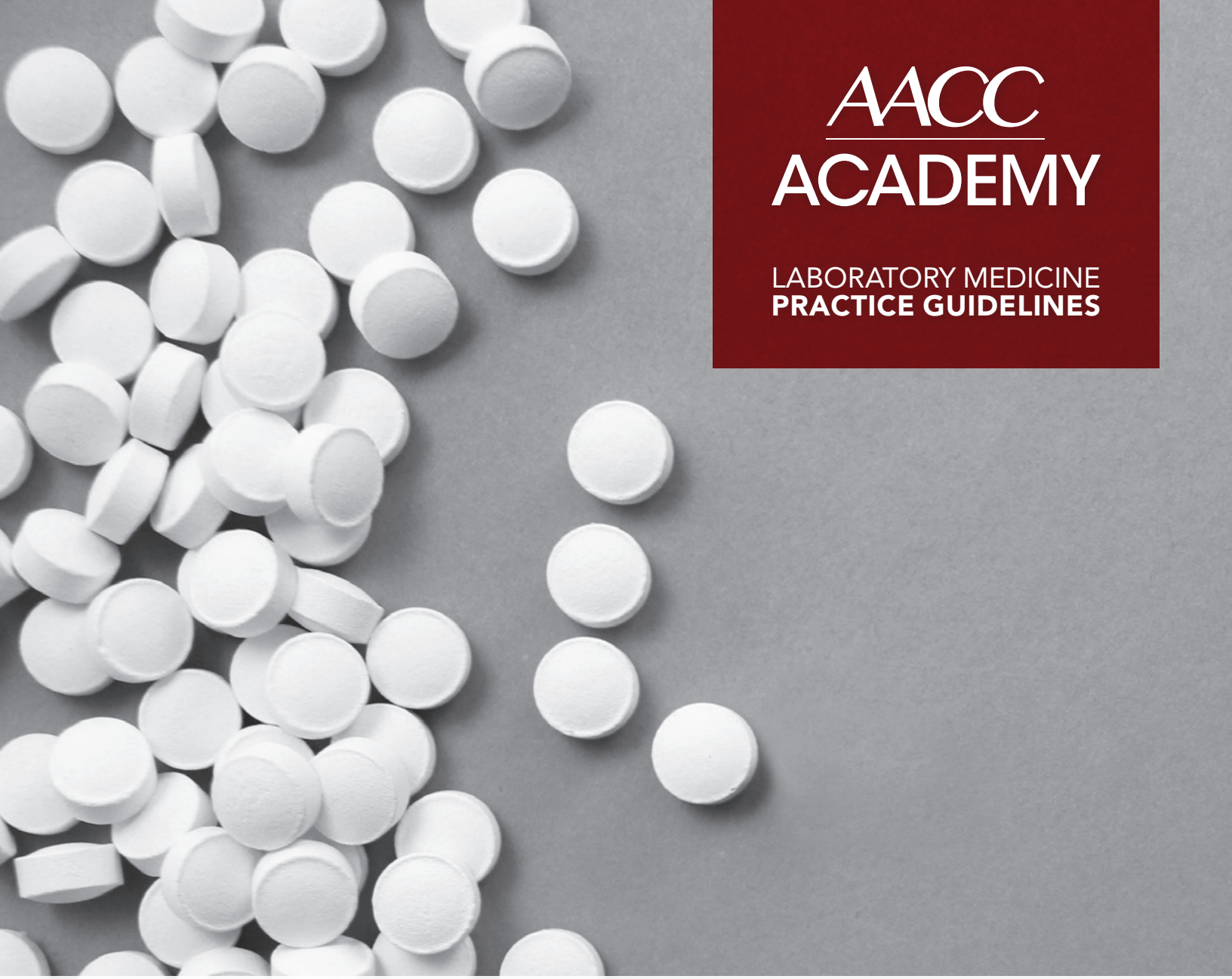

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LABORATORY MEDICINE
PRACTICE GUIDELINES

Using Clinical Laboratory Tests to **Monitor Drug Therapy in Pain Management Patients**

EDITED BY LORALIE J. LANGMAN AND PAUL J. JANNETTO

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LABORATORY MEDICINE
PRACTICE GUIDELINES

The AACC Academy
Presents
Laboratory Medicine Practice Guidelines:

Using Clinical Laboratory Tests to **Monitor Drug Therapy in Pain Management Patients**

EDITED BY LORALIE J. LANGMAN AND PAUL J. JANNETTO

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Using Clinical Laboratory Tests to **Monitor Drug Therapy in Pain Management Patients**

JANNETTO PJ, BRATANOW N, CLARK WA, HAMILL-RUTH RJ, HAMMETT-STABLER CA, HUESTIS MA, KASSED CA, MCMILLIN GA, MELANSON SE, AND LANGMAN LJ.

Introduction

The American Association for Clinical Chemistry (AACC) Academy, formerly the National Academy of Clinical Biochemistry (NACB), has developed a laboratory medicine practice guidelines (LMPG) for using laboratory tests to monitor drug therapy in pain management patients. The scope and 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 non-prescribed drugs, and illicit substances in pain management patients. The online version of this executive summary also includes the consensus-based expert opinion recommendations in areas where the evidence was limited. 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, clinicians practicing in pain management, and other relevant stakeholders, healthcare professionals, or clinical experts. The experts on the committee are listed in the guideline and represented the American Association of Clinical Chemistry Academy (L.J. Langman, P.J. Jannetto); Clinical and Laboratory Standards 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); American Association of Clinical Chemistry (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). Prior to a systematic literature search, the LMPG committee defined all the key questions that would be addressed in the guideline using the PICO(TS) strategy for construction of the questions. PICO(TS) stands for the (P)atient population, (I)ntervention, (C)omparator, (O)utcome, (T)ime period, and (S)etting. In this guideline, the patient population was acute and/or chronic pain management patients, and the interventions were the laboratory tests (screening or definitive) that were compared with other clinician tools (e.g., physician interview, medical record review, prescription monitoring programs, screener and opioid assessment for patients with pain). In general, screening tests have adequate clinical sensitivity but may not be highly spe-

cific. On the other hand, definitive or confirmatory testing (e.g. mass spectrometry- or chromatography-based) are able to identify a specific drug and/or its associated metabolites.

Outcomes included adherence, diversion, emergency department visits, and others. The time period was from January 2000-February 2015 in outpatient, inpatient, and community settings. A systematic literature search was performed using the inclusion and exclusion criteria shown in Table 2.

The following databases were searched: PubMed, the National Library of Medicine; Cochrane Database of Systematic Reviews, which includes the full text of regularly updated systematic reviews of the effects of healthcare prepared by the Cochrane Collaboration; the National Guideline Clearinghouse (an initiative of the Agency for Healthcare Research and Quality), a public resource for evidence-based clinical practice guidelines; EMBASE, which emphasizes drug-related literature and toxicology; CINAHL, which covers nursing and allied health disciplines and includes journal articles, healthcare books, nursing dissertations, selected conference proceedings and standards of professional practice; SCOPUS; Web of Science; and Psych Info. The combined literature search from 2000-2015 resulted in 7,647 articles being identified and reviewed by at least two committee members using the DistillerSR software to document the process. Of the 7,647 abstracts reviewed, 2,352 were selected for full text review. Committee members then assessed each article and documented the answers to 32 questions in the DistillerSR software, which covered everything from the author's declarations, study aims, and objectives to their conclusions. The articles were again reviewed for appropriateness, and of the 2,352 articles that had a full text review, 562 of them were ultimately used to formulate the recommendations for the guideline The strengths of each recommendation were evaluated and graded using an approach described in the 2011 IOM report. The approach was a modification of the US Preventive Services Task Force system. The strength of each recommendation was determined to be A, B, C, or I, while the grading of the quality of the evidence was either a I, II, or III (Table 3). Table 4 contains a summary of the evidence-based recommendations while Table 5 contains a summary of the consensus-based expert opinions.

Background

The use of opioids for pain management has been broadly accepted by regulatory bodies, professional organizations, and clinicians. Compliance monitoring is viewed as necessary for safe opioid prescribing, and chronic opioid prescribing includes "contracts" or treatment agreements, periodic urine drug testing, and random pill counts. The magnitude of prescription opioid abuse has grown over the last decade, leading the Centers for Disease Control (CDC) to classify prescription opioid analgesic abuse as an epidemic. This appears to be due in large part to individuals using a prescription drug non-medically, most often an opioid analgesic. Drug-induced deaths have rapidly risen and continue to be one of the leading causes of death in Americans. In 2011, the Office of National Drug Control Policy established a multifaceted approach to address prescription drug abuse, including Prescription Drug Monitoring Programs (PDMPs) that allow practitioners to determine if patients are receiving prescriptions from multiple providers and use of law enforcement to eliminate improper prescribing practices.

Over time, multiple guidelines from professional societies and organizations, and regulatory bodies have evolved to include standard practices of assessing risk and documenting responsible care in a systematic way. In general, there is agreement that urine drug testing (UDT) is recommended before the initiation of treatment with opioids and during therapy. Federal regulatory agencies have developed guidelines and policies that support compliance testing. These include the Veterans Administration/Department of Defense VA/DoD Clinical Practice Guidelines for COT: Management of Opioid Therapy for Chronic Pain, May 2010 (http://www.healthquality.va.gov/guidelines/Pain/cot/COT_312_Full-er.pdf accessed 06/29/2016). Their recommendations include obtaining a UDT before initiating opioid therapy trial and randomly at follow-up visits to confirm the appropriate use of opioids. The CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016 details the use of UDT (http://www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6501e1.pdf accessed 07-14-2017). The recommendations state that prior to starting opioids for chronic pain and periodically during opioid therapy, clinicians should use UDT to assess for prescribed opioids, as well as, other controlled substances and illicit drugs that increase risk for overdose when combined with opioids, including nonprescribed opioids, benzodiazepines, and heroin.

Forty seven states and the District of Columbia also have policies regarding Pain Management and proper prescribing. In addition, specialty boards have developed guidelines for proper opioid prescribing. The American Academy of Family Practice developed recommendations in 2012, Rational Use of Opioids for Management of Chronic Nonterminal Pain (http://www.aafp.org/afp/2012/0801/p252.html accessed 07-14-2017), with recommendations for urine drug testing pretreatment and randomly during treatment. The American Pain Society and American Academy of Pain Medicine also teamed up to develop the landmark APS/AAPM 2009 Guidelines (http://americanpainsociety.org/uploads/education/guidelines/chronic-opioid-therapy-cncp.pdf accessed 07/14/2017), which include examination of various aspects of urine drug testing and recommend pretreatment and concurrent monitoring of patients. The American Society of Addiction Medicine (ASAM) released a detailed review of urine drug testing with Drug Testing: A White Paper of the American Society of Addiction Medicine dated October 26, 2013 (http://www.asam.org/docs/default-source/public-policy-statements/drug-testing-a-white-paper-by-asam.pdf accessed 07/14/2017). They reviewed the science and practice of drug testing. It explored the wide range of applications for drug testing and its utility in a variety of medical and non-medical settings. It promoted the use of

drug testing as a primary prevention, diagnostic, and monitoring tool in the management of addiction or drug misuse in medical practice.

While urine drug testing is currently regarded as the standard for adherence monitoring of patients taking controlled substances to manage chronic pain, urine drug testing results are performed/read and interpreted by distinctly different sets of individuals. One group is clinical laboratory physicians and scientists; another group is the clinical providers, the clinicians, nurses, pharmacists, and others directly involved in the patient's care. Others may have reason to access or review such data from time to time, such as those in legal or law enforcement, policy, and insurance. Correctly interpreting test results requires that these individuals have the knowledge and experience needed for accurate interpretation, and the skill levels vary considerably within and between each group (1). In the end, the goal of this LMPG guideline for pain management was to address many of these issues and challenges described above and to provide evidence-based recommendations for clinical laboratorians and practicing pain management clinicians.

Evidence-based Recommendations/Statements

The goal of developing specific testing recommendations is to balance the completeness and accuracy of test results with the cost of the testing paradigm. It is critical that a valid specimen is obtained and enough substances evaluated to determine appropriate adherence with the treatment regimen. The testing must also be able to identify polysubstance use, abuse, addiction, and possible diversion before the patient (or recipient of diverted medications) experiences a significant adverse event. Lastly, it is also important to note that studies continue to demonstrate that the administered dosage does not necessarily correlate with the concentration of the drug in an individual's urine.

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**

Numerous studies looked at outcomes including adherence to the prescribed regimen along with detection of illicit drug use with laboratory drug testing as the tool. Although the vast majority of the reports were looking at urine, other matrices, such as plasma and oral fluid, have also been evaluated and showed some efficacy (2-5).

One other point to consider is the breadth of laboratory testing. Table 6 shows the three main tiers of drugs/drug classes that are being recommended to test in pain management patients based on risk. It should be noted that this table is not meant to be a comprehensive list of all drugs that need to be tested for in every pain management patient, but instead should be used as a guideline. Tier I represents the scope of testing that should be done as part of routine monitoring and covers the common classes of drugs of abuse, as well as the drugs commonly prescribed to pain management patients. Tier ll testing should also be added to screen for drug use/abuse in patients identified as high risk by the treating clinicians. These could include patients with a known history of abuse for medications in this category. However, it may also include drugs where the prevalence of use/abuse is endemic to local region. In addition, it applies to patients who have polypharmacy that puts them at an increased risk of adverse drug reactions, or to detect patients with multiple providers. Furthermore, it may also apply to patients who experience a lack of efficacy for one of these drugs or who may be experiencing toxicity from them. Tier III tests can also be examined when they are clinically indicated, either by history of use, medication list, or very high probability of misuse/abuse, in a specific patient rather than for every patient.

Frequency of laboratory testing

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**

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**

The evidence for specific schedules of drug testing in general is weak, mainly due to the lack of randomized clinical trials comparing the effectiveness of testing schedules or methods specifically in the chronic pain population. Existing practice guidelines make recommendations based on observational studies or expert consensus opinion (4). Existing clinical practice guidelines recommend testing at baseline and randomly, but at minimum annually for low-risk patients (American College of Occupational and Environmental Medicine, APS-AAPM, ASIPP, University of Michigan Health System, VA/DoD). However, in patients with

risk factors for misuse/abuse, more frequent monitoring is recommended, but the optimal frequency for these patients has not been determined (3).

Laboratory testing and its ability to identify non-compliance in pain management regimens

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)

Studying patient non-compliance with the therapeutic regimen is difficult unless non-prescribed medications or illicit drugs are present in the tested matrix. Generally, testing frequency is low and the windows of detection in the different matrices (urine, oral fluid, blood/plasma/serum) are usually only a few days. Thus, most of the time between biological testing, the patient is inadequately monitored. Even when the matrix has a longer window of detection, such as for hair, minimum exposure is required to give a positive result, and differences in disposition can occur based on hair color for basic drugs, or for meconium, minimum exposure frequency is needed to produce positive test results. Therefore, additional means of monitoring are highly useful to improve the detection of non-compliance, such as pill counts and interviews. Additional research studies are needed where the collection of other physician tool data (e.g., self-report, pill counts) are directly compared with biological testing data.

Laboratory testing vs. other physician tools, prescription monitoring, and self-report

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**

Most controlled administration studies of prescription and over-the-counter drugs examined urine, blood, or serum concentrations, providing a scientific database for employing these biological fluids in monitoring programs (6, 7). Urine has been the matrix of choice for monitoring pain patients, but other matrices are now being used more frequently.(5, 8, 9) In addition, urine drug testing is more effective than self-reporting at revealing recent opioid use(10).

Specimen types

Urine is typically the preferred matrix for pain management drug testing, as it has a longer window of drug detection than blood, has an adequate specimen volume for drug screening and confirmation, and drug markers (either parent drug or metabolites) are present in high concentrations. It is also less invasive and doesn't require a phlebotomist for collection. Disadvantages include a high risk of adulteration of the sample by the patient to avoid detection of non-compliance with the therapeutic regimen. Observed specimen collection is generally not performed and is disliked by patients and collectors. Specialized bathroom facilities may be needed, and specimen collectors should be of the same gender as patients. For these reasons, there is much interest in alternative matrices such as oral fluid or hair for drug testing of pain management patients.

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**

Alternative matrices such as oral fluid, blood/plasma/serum, hair, meconium, and umbilical cord show promise and offer advantages over urine for testing, but the evidence to date is insufficient to assess whether the results are equivalent to urine testing for monitoring patient compliance. Other matrices may also be appropriate in specialized circumstances, but the samples must be properly collected, stored, and transported in the appropriate collection device at the proper temperature, and tested by qualified personnel using a validated method for that matrix.

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**

As discussed above, blood/plasma/serum are good matrices for biological monitoring of patient compliance in pain management testing; however, no manuscripts were found that specifically detailed the use of these matrices during end-stage renal failure.

Alternative matrices such as oral fluid show promise and have advantages over urine or blood, but the evidence to date is insufficient to assess their benefits in predicting clinical outcomes. Heltsley et al.(11) examined the screening positivity rates for oral fluid in a chronic pain population and compared them with published positivity rates for urine drug screening in the pain population and found that the oral fluid non-negative screening rate was 83.9% compared with a previously published non-negative rate of 78% for urine screening. Within those overall positives, they found that 11.5% of the screening positives in oral fluid were for illicit drugs, compared with 10.9% of the urine screening positives from a previous urine study. The authors concluded that oral fluid screening is comparable to urine screening for detecting illicit drug use in a pain management population. In a follow-up study from the same group(12), the authors examined paired oral fluid and urine specimens from a chronic pain population (n=133). Upon screening of both specimens for each patient, they found 21.3% of specimens positive in both matrices and 63.7% negative in both matrices, for an overall agreement rate of 85%. Of the 15% that disagreed, 5.4% were positive in oral fluid and negative in urine, and 9.6% were negative in oral fluid and positive in urine. The authors concluded that the Cohen's Kappa statistical test for agreement between the two methods was 0.64, documenting substantial agreement, and that the oral fluid screening results were comparable to urine screening results.

In conclusion, while there are some studies that describe the utility of alternate specimens for drug testing in certain populations, there is no evidence that drug testing in alternate matrix specimens is more effective than urine testing for detection of drugs in pain management patients. In the absence of evidence, the committee cannot make a recommendation for or against alternate matrix testing in pain management.

Qualitative and semi-quantitative screening assays

Traditionally, urine drug testing for pain management patients has followed a forensic (legal) model and has been based on Department of Health and Human Services guidelines and protocols for drugs-of-abuse testing. As such, immunoassays are typically used as the first-line screening test. These immunoassays can either be run in a qualitative (e.g. positive/negative) or semi-quantitative mode. Laboratories often use these assays in the semi-quantitative format to assist the lab in setting dilutions on concentrated samples upfront before downstream confirmatory (e.g. mass spectrometry-based) testing is performed to minimize carryover and avoid repeat testing. While immunoassays offer several advantages, including ease of use, fast turnaround time, non-invasive collection, and lower costs, they can produce false positive and false negative results(5). In a forensic model, positive immunoassay screening tests are followed by a definitive or confirmatory test, such as mass spectrometry, to avoid false positive results. False negative results, however, remain problematic with this approach. Furthermore, the FDA-approved immunoassays originally designated by the mandatory guidelines for Federal Workplace Drug Testing Programs commonly use higher cutoffs. These cutoffs may not be clinically appropriate for adherence monitoring of pain management patients. For these reasons, modifications to the forensic model of testing where labs use orthogonal testing (e.g. immunoassay screen followed by a LC-MS/MS confirmation assay) to monitor compliance in pain management are necessary.

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**

Numerous articles have compared the accuracy of immunoassays to mass-spectrometry-based assays. However, many articles do not include pain management patients or specifically correlate results with outcomes. Overall, laboratory-based immunoassays across several populations (e.g., pain management, addiction patients) have been shown to correlate to mass-spectrometry-based testing and can be used to detect compliance/adherence to therapy and misuse/abuse of other drugs.

Qualitative Definitive Testing

Immunoassays, as described above, have known limitations. Mass-spectrometry-based assays have traditionally been considered the gold standard, despite the prevalence and ease of use of laboratory-based immunoassays. Furthermore, many qualitative immunoassays are only designed to detect a class of compounds. Therefore, a positive immunoassay result does not indicate which drug(s) in the class were present in the urine, whereas a definitive result by mass spectrometry provides this information. The specific drugs in urine can help determine compliance, as well as the potential abuse of multiple drugs within a class.

EVIDENCE-BASED RECOMMENDATION #7: Qualitative definitive tests should be used over 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**

Several articles provide evidence that qualitative definitive assays such as GC-MS and LC-MS/MS are more sensitive and specific than laboratory-based immunoassays. One may infer, therefore, that these assays are superior at detecting adherence/compliance with or diversion/misuse of various drugs/drug classes in pain management. However, none of the studies examined any patient outcomes directly. All articles demonstrate that LC-MS/MS and GC-MS are technically superior to laboratory-based immunoassays. Many of the articles state that targeted screening assays should be used for definitive or testing with legal implications. However, despite the lack of outcome data, most of the authors conclude that immunoassays are clinically acceptable and should be used to facilitate real-time clinical decisions.

Point-of-Care (POC) Testing

Urine or oral screening immunoassays are also available at the point of care. POC testing can be done in the pain clinic or physician's office using single-use dipstick or cup-based technologies and can provide immediate results for the provider and patient. Negative results are typically used to rule out drug abuse. Positive samples are usually sent for definitive laboratory-based testing to identify the drug(s) present and to determine adherence or identify abuse/diversion. POC immunoassays, similar to laboratory-based screening immunoassays, have lower sensitivity and specificity than definitive assays. In addition, quality control, quality assurance, and result documentation are challenging with POC testing. It should also be mentioned that most, but not all POC assays indicate a negative test with the presence of a line and a positive test by the absence of a line.

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**

Note: POC devices must be performed exactly according to the manufacturer's instructions. Any deviation from this can significantly alter the POC devices ability to operate correctly and may affect the interpretation of the test result. Lastly, it should also be noted that most devices require additional confirmatory testing, especially when unexpected results are observed.

Timing of Urine Drug Testing

Although guidelines recommend urine drug testing as one tool to monitor compliance in pain management, the existing guidelines do not recommend how frequently patients should be tested, if baseline testing is indicated, or whether testing should be random or scheduled. This information is critical for both providers and the laboratory to successfully manage patients and predict resource use.

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**

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)

While laboratory testing once yearly for low-risk patients and twice yearly for higher-risk patients has been recommended, the same recommendations call for POC screening every six months

for low-risk patients and every three months for higher-risk patients(13), which is far more frequent than the previously cited ASIPP recommendations(14, 15). Therefore, due to a lack of scientific evidence to suggest that random testing is superior to scheduled testing, the committee recommends random drug testing to better assess compliance and outcomes. If testing is scheduled, patients have an opportunity to adulterate their specimen before or during the visit. Furthermore, patients who know the date of testing may adhere to their prescribed medication(s) immediately prior to their visit, only to continue abuse or diversion when testing is not scheduled.

Cost-Effectiveness of Urine Drug Testing

Cost is a concern in all areas of healthcare, but particularly with laboratory testing. Providers and laboratorians are under pressure to provide the same level of patient care at a lower cost. Therefore, there is interest in whether qualitative screening immunoassays, either in the laboratory or at the POC, are more cost-effective than MS-based assays. Any cost benefits need to be weighed with the clinical benefits and sensitivity and specificity of the most cost-effective testing options.

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.

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**

There is a lack of evidence to suggest that laboratory-based qualitative/semi-quantitative urine screening assays are more cost-effective than mass-spectrometry-based assays in detecting outcomes in pain management patients. However, Manchikanti et al.(16, 17) wrote two articles that concluded that appropriate use of urine drug screening assays at POC is more cost-effective than LC-MS/MS. The authors report a cost per test of $25 for immunoassay and a cost per test of $600 for mass spectrometry and advocate for a testing algorithm to reduce costly LC-MS/MS use. According to the authors' testing algorithm, mass-spectrometry-based assays should only be performed in patients who test negative when prescribed a drug, in patents that test positive when not prescribed the drug, or in patients who test positive for an illicit drug. In the latter two scenarios, mass-spectrometry-based assays should not be confirmed if the patient admits adherent use. Instead, repeat testing should be performed by POC immunoassay at their next visit or at a random time. As stated earlier in the POC section of this chapter, it is important that providers understand the limitations of POC assays and consult the laboratory if appropriate so that the lower cost is not compromising patient care, leading to incorrect interpretations.

Definitive testing

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**

A study by Pesce et al.(18) evaluated the diagnostic accuracy of LC-MS/MS vs. immunoassay for drug testing in pain patients. In this study, the authors tested 4,200 urine specimens from pain patients for amphetamine, methamphetamine, alpha-hydroxyalprazolam, lorazepam, nordiazepam, oxazepam, temazepam, cannabinoids, cocaine, methadone, methadone metabolite, codeine, hydrocodone, hydromorphone, morphine, propoxyphene, and norpropoxyphene. The authors compared the immunoassay results to the LC-MS/MS results. Using the drug and metabolites to define a positive result by LC-MS/MS, the authors found the following false negative results in urine by immunoassay: 9.3% for amphetamines, 22% for benzodiazepines, 10.6% for cannabinoids, 50% for cocaine, 6.1% for methadone, 1.9% for opiates, and 23.4% for propoxyphene. The authors attribute the differences to variance in cross-reactivity for immunoassays, along with lower cutoffs for the LC-MS/MS methods. The authors concluded that the use of LC-MS/MS significantly reduces the risk of false negative results. Implicit in this study is that the LC-MS results are of higher quality compared to immunoassay results, as it is designated as the gold standard. There is no discussion of the impact of immunoassay or LC-MS methods of measurement on detection of outcomes.

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**

Manchikanti et al.(16) presented a comparative evaluation of a POC immunoassay kit versus LC-MS/MS for detection of UDT opioids and illicit drugs in the urine of pain management patients. In this study, the authors analyze 1,000 consecutive urine specimens submitted for analysis. The immunoassay was performed first, followed by LC-MS/MS analysis at a reference laboratory – the LC-MS/MS test was designated as the reference method. Agreement for prescribed opioids was high with the index test (80.4%).

The reference test of opioids improved the accuracy from 80.4% to 89.3%. Non-prescribed opioids were used by 5.3% of patients. The index test provided false positive results for non-opioid use in 44%, or 83 of 120 patients. For illicit drugs, the false positive rate was 0% for cocaine, 2% for marijuana, 0.9% for amphetamines, and 1.2% for methamphetamines. Overall, the authors suggest that confirmation was required in 32.9% of the samples. They state that POC immunoassay is sufficient for front-line UDT in pain management, and suggest that all samples negative for prescribed opiates, positive for non-prescribed opiates, and positive for illicit drugs should be sent for confirmatory testing. There is no discussion of the impact of this testing paradigm on clinical outcomes for pain management patients. Manchikanti et al.(17) also presented data from the same study, but focused on the detection of benzodiazepines. They drew the same conclusion for benzodiazepines that they published for opiates and illicit drugs.

Quantification vs. Qualitative Definitive Tests

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**

A number of different studies by Couto et al.(19-20) assessed the ability of an algorithms applied to urine drug levels of oxycodone or hydrocodone, in healthy adult volunteers to differentiate among low, medium, and high doses. The authors concluded that the algorithm normalized urine drug levels for pH, specific gravity, and lean body mass and could differentiate between the different daily doses of oxycodone or hydrocodone. However, there are several important limitations to both of these studies. The study patients were relatively homogenous with respect to cytochrome P450 2D6 – poor, intermediate, and ultra-rapid metabolizers were excluded from the study. In addition, they were restricted from any medications or items in their diet that could inhibit or induce the CYP2D6 enzymes. Lastly, a careful observation of the data demonstrates significant overlap between the distributions. While the medians may be statistically differentiated between the groups, a comparison of an individual result to a population distribution would not likely be able to place the patient in one particular group or another.

Detection limits

The evidence in the literature is currently insufficient to determine standardized cutoffs or limit of quantifications to determine full compliance, partial compliance, or misuse/abuse of controlled drugs by pain management patients.

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**

Crews et al.(21) demonstrated the use of LC-MS/MS to detect 6-acetylmorphine (6-AM) in the absence of morphine in pain management patients. In this study, the authors analyzed 22,361 urine specimens from chronic pain patients. From these specimens, 30 tested positive for 6-AM above a cutoff of 10 ng/mL and 23% of those had a morphine concentration less than the cutoff of 300 ng/mL. The authors suggest that using a standard screening cutoff of 300 ng/mL for morphine as a threshold for confirmation (including 6-AM) will result in a missed diagnosis of heroin use in approximately 25% of the cases. It is important to note that there is no discussion of the impact of this confirmatory testing on clinical outcomes.

A study by West et al.(22) examined the comparison of clonazepam compliance as measured by immunoassay and LC-MS/MS in a pain management population. In this study, the authors selected samples from their database prescribed clonazepam only, while eliminating any patients that were prescribed a second (or more) benzodiazepine drug. From this selection, 180 urine specimens were found that met the criteria and were analyzed using an immunoassay with a cutoff concentration of 200 ng/mL, and also analyzed with an LC-MS/MS method using cutoffs of both 200 ng/mL and 40 ng/mL that detected both clonazepam and the primary metabolite 7-aminoclonazepam. The positivity rate for the immunoassay was 21%, while the positivity rates for the LC-MS/MS method were 70% and 87% for the 200 ng/mL and 40 ng/L cutoffs, respectively. The authors attributed the differences in positivity rates to the lack of cross-reactivity of the immunoassay with the clonazepam metabolite. They suggest that a much lower cutoff (e.g., 40 ng/mL) is needed to reliably monitor clonazepam adherence. There was no discussion of the impact of using either the immunoassay or LC-MS/MS assay on clinical outcomes in pain management patients.

Pre-analytical hydrolysis (enzymatic/chemical) of urine

The evidence in the literature is inconsistent to support routine use of hydrolysis for all drug classes to more effectively detect

outcomes in pain management patients.

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**

Pre-analytical hydrolysis is commonly used to liberate glucuronide and sulfate conjugate metabolites of drug analytes in mass spectrometric methods such as GC-MS and LC-MS/MS. This practice is common for urine because many drugs are eliminated in a conjugated form. The consequence of pre-analytical hydrolysis is to increase the concentrations of drug analytes and thereby increase the sensitivity of an assay for the associated drug analytes. Hydrolysis reactions can be enzymatic or chemical. Enzymes used include β-glucuronidase from abalone, β-glucuronidase type H-3 from Helix pomatia, β-glucuronidase type L-II from Patella vulgata, and glusulase(23, 24). Recombinant β-glucuronidase is also now available (IMCSzyme from IMCS). A common approach to chemical hydrolysis includes incubation with concentrated hydrochloric acid. Hydrolysis conditions, such as substrate concentrations, temperature, pH, and time, should be evaluated and optimized by the laboratory. One study comparing three methods of hydrolysis (two enzymes, and 6 N HCl) with non-hydrolyzed recoveries on efficiency of tapentadol recovery demonstrated different yields for each method (23). The chemical hydrolysis method was preferred over the enzymatic methods due to better compatibility with the associated liquid chromatography columns. As such, chromatography quality and consistency were superior to the enzymatic hydrolysis products.

As suggested above, the efficiency of hydrolysis reactions may be incomplete, despite optimization of conditions. For example, a study using β-glucuronidase demonstrated that between 17%-27% of morphine-3-glucuronide was not cleaved. Similarly, between 32%-45% of morphine-6-glucuronide was not cleaved (25). When comparing hydrolyzed and unhydrolyzed urine samples collected from pain management patients prescribed tramadol, no qualitative differences in detection were observed. This study suggests that qualitative drug testing can be performed with unhydrolyzed urine, and that doing so considerably reduces matrix interferences in mass spectrometric methods(26). Unconjugated tapentadol (cutoff 50 ng/mL) and the n-desmethyltapentadol metabolite (cutoff 100 ng/mL) were detected when urine was unhydrolyzed. Only one of eight patient samples evaluated required hydrolysis for detection. However, concentrations of tapentadol and metabolite were significantly increased after hydrolysis. It was estimated that the average amount of tapentadol conjugated is 65%, and the metabolite is approximately 20% conjugated(23). However, the inclusion of a known concentration of conjugated metabolites should be included as quality control material to assure stability and consistency of hydrolysis efficiency.

Use of conjugated and unconjugated drug metabolites

The evidence in the literature is currently insufficient to make any recommendations at this time regarding the use or superiority of conjugated vs. unconjugated drug metabolites in definitive tests for pain management patients.

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**

Direct measurement of glucuronide or other conjugated metabolites will improve detection of drug use with or without use of pre-analytical hydrolysis. This approach also overcomes the variation in efficiency of hydrolysis reactions. One study demonstrated that detection of morphine-3-glucuronide, morphine-6-glucuronide, oxymorphone glucuronide, hydromorphone glucuronide, and norbuprenorphine glucuronide significantly increased detection of the associated drugs when evaluating medication adherence in pain management patients. Between 10%-100% of samples would have been misclassified if glucuronide metabolites were not included (27). The interpretive value of quantitative analysis of conjugated and unconjugated drug metabolites depends on the efficiency of hydrolysis and the cutoff concentration used for detection. Ratios of conjugated metabolites may provide phenotype information, although this finding is controversial (28).

Adulterant/Specimen Validity testing

For drug testing results to be used appropriately in clinical decision making, the results must be valid. The goal of drug testing in the pain management population is to confirm compliance with appropriate use of prescribed medications, but also to identify aberrant behaviors and the risk of adverse outcomes. Non-compliance can include binging, use of non-prescribed and/or non-reported medications and illicit substances, as well as diversion. Press and political attention often focus on overdose deaths, but diversion is also another significant public health issue that also contributes indirectly to the overdose statistics.

The ease of urine sample adulteration makes it critical to address the method of collection. In an ideal world, all urine sample collections would be observed, although attempts have been made to foil this approach as well (http://realwhizzinatorxxx.com/, accessed 07/14/2017). Data regarding these more stringent standards for specimen collection can be found in the ad-

diction and occupational screening literature, but no references were found for the pain management population. This method is time-consuming, expensive due to staffing requirements, and often not possible in a busy practice. Alternatives include specialized collection facilities in which the water can be turned off and the toilet water is colored. The risk of an invalid specimen increases as the level of supervision diminishes. In addition, announced urine drug testing or testing performed at an off-site lab provides the opportunity not only for planned adulteration or urine specimen substitution, but also for the patient to take enough of their medication to have an appropriate test result. This fails to identify potential binging or diversion. Finally, time from request for a urine specimen to time of actual void can affect results. While review articles may make recommendations for specimen collection methods for pain patients, these guidelines are extrapolated from the addiction literature. Diuretics and excessive fluid intake provide a delayed effect on urine content, which can take an hour or more to be seen, so some guidelines go so far as to suggest a 20-minute window during which the specimen should be provided. Due to these issues, alternative matrices like oral fluid are proposed as another alternative to get a valid "witnessed" sample.

Specimen Validity Testing

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 using 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**

In an evidence-based analysis looking at methadone compliance testing by the Ontario Medical Advisory Secretariat (29), urine temperature of 32.5 C to 37.7 C was shown to be a good indicator that a specimen was just provided by the identified donor. However, it was noted that this specimen validity method could potentially be circumvented by warming substituted urine specimens. As a result, volume collection could be used to increase the validity of temperature readings and ensure specimen validity from the donor. In addition, laboratory analysis of the urine's pH and creatinine could offer enhanced reliability of test result. The absence of drug detected in a concentrated urine specimen was found to be more reliable in terms of non-use than a negative test result in a diluted sample. pH, in a similar fashion, could affect the amount of drug (e.g., parent methadone) in the urine and be used to better interpret inappropriate negative results in a patient who was actually taking methadone as prescribed. In the end, it was recommended that pH and creatinine should be determined on all urine specimens (personal communication, clinical expert, December 4, 2006). Another expert opinion suggested that urinary creatinine, pH, and temperature should be used to assist with result interpretation and increase specimen reliability for pain management patients(30). Further evidence in pain patients, heroin users, and marijuana/cocaine users showed that normalization of drug concentrations to specific gravity and creatinine were effective ways to cope with diluted urine specimens(31). In this study, 10,899 urine specimens were used from pain patients being chronically treated with opioids from 31 pain clinics in six states where they had concurrent specific gravity and creatinine measurements. Drug/metabolite concentrations were performed by GC-MS. Correlations of corrected drug concentrations and specific gravity/creatinine relationships were high for all 28 drug/metabolite groups. The overall average positivity rates increased (9.8% by specific gravity correction; 4.2% by creatinine correction) and took into account a large portion of variation caused by different patterns of fluid intake.

Specimen validity testing vs. other physician tools

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**

There were no papers identified that specifically compared efficacy of adulteration testing to other physician tools. Moore and colleagues(32) compared structured interview with the Screener and Opioid Assessment for Patients with Pain (SOAPP), the Diagnosis, Intractability Risk, and Efficacy inventory (DIRE), and/or the Opioid Risk Tool (ORT). They evaluated a cohort of 48 chronic pain patients who were subsequently discontinued from their opioids for significant aberrant drug-related behaviors. Because the authors did not include drug testing data in their paper, no conclusions can be made that are pertinent to this paper. However, psychologist interview was most sensitive (0.77), and the SOAPP was the most sensitive of the questionnaires (0.72) for identifying likelihood of aberrant behavior. Combination of the two gave a sensitivity of predicting aberrant behavior of 0.90. Hamill-Ruth(33) compared patient report to the medical record, prescription monitoring report, and POC urine drug screening in an anonymous and voluntary quality improvement project evaluating utility of POC UDT in chronic pain patients using), a 10-class test cup with temperature and internal adulteration testing. In addition, adulteration test strips were used. 4.2% of specimens had a temperature below the cutoff limit. Less than 1% showed overt adulteration, but confirmatory testing was not allowed due to the anonymity requirements of the Quality Improvement project. Consequently, the rigor of the adulteration screening was also limited. The authors did find that patient report was frequently inconsistent with the urine screen, the medical record, and/or the Prescription Monitoring Program (PMP). The addition of the UDS and PMP identified nine times as many inconsistencies than the combination of the medical record and patient report alone.

Timing of 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**

Multiple guidelines recommend UDT prior to initiation of therapy, and then randomly (34), and two to four times/year for lower-risk patients, although high-risk patients may need more frequent monitoring (35, 36). Guidelines strongly support random drug testing, but none of these addresses the frequency of specimen validity testing. Random specimen validity testing, on the other hand, can be predicted to decrease the number of specimens that would be confidently considered valid. Accurate interpretation of urine drug testing is critical to clinical decisions for continued prescribing. Hence, efforts to maximize the identification of a valid specimen are paramount. Failure to perform validity testing on all specimens could lead to inappropriate and inaccurate interpretation of drug test results.

Broad vs. targeted specimen validity testing

There is no evidence in the literature to support the statement that targeted specimen validity testing is less effective than broad panel specimen validity testing at detecting outcomes in pain management patients.

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)

There is no published evidence for or against targeted specimen validity testing versus broad panel specimen validity testing relative to clinical outcomes. In the absence of evidence, the committee cannot make a recommendation for or against targeted specimen validity testing. The recommendation is that routine specimen validity testing be performed as part of a UDT program to improve the likelihood of accurate interpretation of results. 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, recognizing that these tests will not detect all forms of adulteration. As noted above, temperature and pH should be checked preferably within 5 minutes of specimen collection; creatinine and oxidants (which detects pyridinium chlorochromate, nitrite, and glutaraldehyde) should be tested at the laboratory. At a minimum, POC testing should include on-site specimen validity testing, including temperature, pH, creatinine, and oxidant testing, either incorporated in the testing device or with validated adulterant test strips, if they are to be used for clinical decision making without definitive testing results available. POC UDT results should be interpreted with caution due to incomplete adulterant testing and limitations of this technology.

Pharmacogenomic considerations

Understanding the details of the human genome supports research designed to identify heritable causes of disease and response to medications. As such, genetic and genomic testing are rapidly evolving tools for achieving personalized, precision medicine. In pain and addiction medicine, genomic variation has been studied to identify associations between gene variants and the pathophysiology of pain sensation, rare pain disorders, pain threshold, as well as patterns of response to pain medications and likelihood for drug addiction. Evidence-based outcome studies are currently lacking for routine clinical application of genomic or genetic testing to guide diagnosis, characterization and management of chronic pain and drug addiction. However, genetic information is sometimes used to guide drug and dose selection; this application of genetic testing is referred to as pharmacogenetics.

Use of pharmacogenetics to guide drug and dose selection

Drug response requires a coordinated effort between the two major processes of pharmacology: pharmacokinetics and pharmacodynamics. Pharmacokinetics describes the absorption, distribution, metabolism, and elimination of a drug, while pharmacodynamics describes the mechanisms of both desirable and undesirable drug effects.

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**

The vast majority of evidence for pharmacogenetics associations comes from retrospective or observational studies as opposed to randomized prospective clinical trials. One retrospective study evaluated rates of abnormal pharmacogenetics findings in a pain practice for 104 adult patients, with a focus on four genes that code for drug metabolizing enzymes(37). Overall, 42.3% of test results were normal, 25.5% suggested intermediate metabolizer phenotypes, 7% were poor metabolizers, and 7.2% were ultra-rapid metabolizers. Only three patients had normal metabolizer phenotypes for all four genes. The authors acknowledge a need for large prospective studies conducted with diverse populations to evaluate the generalizability of these results. Another study evaluating the effect of pharmacogenetics on opioid therapy outcomes in an outpatient pain clinic found that the frequency of genetic variants was equivalent to average population frequencies, and only modest associations with opioid dose requirements were observed (38). Nonetheless, gene-based dosing guidelines have been published for select gene-drug pairs, many of which are relevant to chronic pain management. A commonly cited source of gene-based dosing guidelines is the Clinical Pharmacogenomics Implementation Consortium (CPIC). The CPIC assigns a level of evidence to each gene-drug pair ranging from "A" (highest level of evidence in favor of changing prescribing of an affected drug) to "D," wherein evidence is limited and may be conflicting. However, the CPIC does not advocate or recommend testing. The guidelines provide expert review of associated literature and guidance for translation of results into actions, when testing is performed. All gene-drug pairs represented by a published guideline have achieved the "A" level of evidence. CPIC guidelines are available publicly through its website: https://cpicpgx.org/ (accessed 07/14/2017). The Pharmacogenomics Knowledgebase (https://www.pharmgkb.org/, accessed 07/14/2017) provides summaries of many such associations, along with clinical annotations that are categorized based on the level of evidence surrounding the association. Examples of genes that were identified in 10 or more studies to have associations with opioid response and/or dose are summarized in Table 7.

Supportive testing of pharmacogenetics

Results of pharmacogenetic testing could impact optimal dose and dosing of a specific drug for an individual patient. The impact of the variant metabolic phenotype may be characterized and/or illustrated by metabolic ratios determined with quantitative urine or serum drug testing. Recognizing metabolic patterns and how they may be affected by pharmacogenetic variability is important for interpretation of drug testing results, and for detecting drug-drug interactions. For example, a poor metabolizer may not generate a metabolite that is common to normal metabolizers and could be viewed as non-compliant due to the lack of metabolite in the urine. Likewise, a rapid metabolizer may not realize the benefit of a drug, and may request higher doses because of accelerated elimination; such a patient could be inappropriately viewed as a drug seeker. Drug-drug interactions can produce or change a variant CYP metabolic phenotype, such as by inhibition of CYP enzyme function. As such, directed quantitative urine or serum drug testing, and evaluations of metabolic ratios may help evaluate and monitor the effects of abnormal drug metabolism on drug testing results.

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**

Gene-dose guidelines often recommend therapeutic drug

monitoring to optimize dose when impaired metabolic phenotypes are predicted(39, 40). For example, therapeutic drug monitoring was used in combination with CYP2D6 genotyping to more quickly attain therapeutic plasma concentrations and metabolic ratios of imipramine/desipramine(41). The plasma concentrations ratios of several antidepressants were shown to be higher in CYP2D6 poor metabolizers, and often exceeded the therapeutic ranges in a retrospective study of 62 hospitalized psychiatric patients(42). The ultra-rapid metabolizer phenotype for CYP2D6 has been associated with steady-state concentrations of methadone, normalized for dose and patient weight, that were 54% of the concentrations observed in poor metabolizers, suggesting that individualization of methadone dose could be based on plasma concentrations (43). Therapeutic drug monitoring with plasma has also been proposed as a complementary tool for optimizing dose of many other drugs when variant metabolic phenotypes are recognized through pharmacogenetics testing (44-47).

Urine testing results may reflect variation in CYP phenotypes as well. For example, hydromorphone is an expected metabolite of hydrocodone. The ratio of hydromorphone:hydrocodone may represent a patient phenotype that could be explained by variation in CYP2D6 activity(48). In a retrospective evaluation of 25,200 urine samples that contained both hydrocodone and hydromorphone, the median metabolic ratio calculated with creatinine-corrected concentrations (mg/g creatinine) was 0.162, and the central 50% range (25th and 75th percentile) was 0.074 – 0.351. The authors suggest that low metabolic ratios could reflect CYP2D6 metabolic phenotype, although this was not specifically tested. Theoretically, CYP2D6 poor metabolizers would not produce hydromorphone, whereas ultra-rapid CYP2D6 metabolizers would produce higher-than-expected amounts of hydromorphone. Monitoring metabolic ratios could identify CYP2D6 metabolic phenotype and could also detect drug-drug interactions that affect the phenotype for an individual patient. Studies have demonstrated that CYP metabolic status is reflected in the urine metabolic ratios for several other opioids such as meperidine, oxycodone, buprenorphine, fentanyl, methadone, and propoxyphene and the benzodiazepine drug diazepam(49-52).

Reporting, interpretation, and communication of laboratory results with physicians

Standards specified by various regulatory agencies, such as the Centers for Medicare and Medicaid Services (CMS) through the Clinical Laboratory Improvement Act (CLIA), the College of American Pathologists (CAP), and the Joint Commission (TJC) define critical elements that are common to all testing reports. (http://www.ecfr.gov/cgi-bin/text-idx?SID=1248e3189da5e-5f936e55315402bc38b&node=pt42.5.493&rgn=div5, accessed 07/14/2017, Laboratory General Checklist, College of American Pathologists, 07-28-2015 Edition) Outside of these required elements, there is not a standard, uniform format agreed upon or in use specifically related to the reporting of UDT results for clinical purposes. A review of reports from a variety of laboratories conducting this testing shows a range of formats in use, not dissimilar to the variations observed for any other test report. Reporting formats range from the very simple to the inclusion of colorful graphics and interpretative "aids." These variations represent differences in information services support and marketing, and do not represent the quality of the laboratory testing.

Despite the variety in reporting, there are some unique features to consider when configuring a format for reporting UDT results:

- The test name should clearly identify the test performed by the drug or drug class as well as purpose or methodology to avoid confusion. For example, naming testing for opiates as "opiate class, screening (immunoassay)" or "opiates, confirmation (LC-MS/MS)" reduces confusion as to what the end user should expect. Today's EMR and LIS should not be encumbered by overly restrictive character limitations.
- Reference intervals in the traditional sense are not applicable, and clinical laboratories, in order to comply with the requirement to provide a reference, or "normal," range, use a variety of comments in this field, from "not detected" to "not applicable." It is important to note that the term "not detected" or "negative" may be appropriate for some drugs, e.g., cocaine, and in some situations, but not universally. Certainly, one expects to detect the prescribed medications discussed in this guideline in the urine specimens of compliant patients.
- The cutoff(s) employed should be defined. For screening methods, these are typically established by the assay manufacturer, and many manufacturers make several cutoff options available to accommodate the various settings in which these assays are used, e.g., many opiate screening immunoassays have the option of using a cutoff of either 2,000 ng/mL or 300 ng/mL. Where the testing method is developed by the laboratory, as is typically the case when LCMSMS or GCMS methods are used, the cutoff is based upon validation data, such as the limits of detection (LOD) and quantification (LOQ). As will be discussed below, there is no evidence that reporting the cutoff improves the accuracy of the interpretation, but the committee believes it is important. Cutoff values may be set high to avoid false positive results, and providers should take that into account when interpreting a result below the cutoff.
- If test(s) are not FDA-approved, that should be noted with the result. Furthermore, CAP-accredited laboratories should clearly state if the method was internally developed and validated by the laboratory.

Additional information regarding the method and testing may be helpful to the interpretation, but impractical to provide or maintain as part of the report. This information should be maintained as part of the laboratory formulary, handbook, testing menu, or other similar resource.

While there is not a standard format in which UDT results for

pain management are reported, the committee agrees that the laboratory should use a format that conveys the results in a clear, concise, and understandable manner, and that this is especially important both when done through an EMR system. Additional details regarding reporting are found in CLSI C63, Laboratory Support of Pain Management.

Reporting of Qualitative or Screening Results

The manner in which results are reported should be considered carefully. The use of the terms positive and negative in the reporting of qualitative results may mislead the reader who sees these terms as definitive, that is, drug is present and drug is absent from the sample. As an alternative, some laboratories have adopted the use of the assay cutoff (< 300 ng/mL or ≥ 300 ng/mL) in hopes that such would convey to the reader that a less than result could range from not detected to just below the reported number (e.g. 0-299 ng/mL) and thus facilitate interpretation. Unfortunately, the literature searches revealed that while this is an often-discussed issue, there have been no studies conducted to demonstrate if either manner of reporting, or an alternative, is effective.

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.

Turnaround Time of Reporting Screening Results

There has also been considerable debate as to how quickly screening results are needed and if such results should be held until confirmatory testing is completed. At the center of this debate is the concern that the release of unconfirmed results could lead to a negative patient care outcome, such as inappropriate dismissal from a facility based on a false positive screening result.

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.

There may be circumstances where reporting presumptive immunoassay results may be clinically useful. Other providers may prefer all testing be complete prior to reporting. The committee recommends that laboratories and healthcare providers communicate and determine which pattern of reporting is important to their specific clinical setting. When screening results are reported without confirmation or definitive testing, a reminder should be appended that additional, i.e., confirmatory or definitive, testing is available upon request when unexpected results are obtained (unexpected results may include both negative and positive screening results).

Reporting of Quantitative Results

The application of mass spectrometry-based methods to UDT permits both the identification of the compounds present in the sample and the quantification of the result. What to report and how to use the data for patient care warrants discussion.

Reporting patterns of drug and drug metabolites to infer compliance and non-compliance

The literature readily supports that identification of an excreted drug and/or drug metabolite is useful in detecting recent exposure to a drug. Not all drugs are metabolized, but when metabolites are known, detection of common metabolites assures that the drug has been processed by the body, which would infer drug ingestion and possibly compliance.

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.

Dickerson et al. found that direct measurement of glucuronide metabolites in urine improved detection of opioids including codeine, morphine, hydromorphone, oxymorphone, and buprenorphine(27). Of significance, no patients were positive for buprenorphine parent only, suggesting that either hydrolysis or direct measurement of glucuronides was required to evaluate adherence to buprenorphine in this population. Another retrospective study, 216 urine samples from 70 patients prescribed buprenorphine were evaluated (24). Buprenorphine was found in only 33 samples, whereas norbuprenorphine was found in all samples. There was strong evidence that nine samples were adulterated. Of the adulterated samples that could be further evaluated (n=6), the norbuprenorphine/buprenorphine ratio was less than 0.02 as compared to ratios of >0.99 for typical samples. Four of the samples had buprenorphine concentration in the 10,000 – 50,000 ng/mL range and naloxone concentrations between 4,000 – 15,000 ng/mL. Because the expected ratio of the pharmaceutical product Suboxone is 4:1, these data suggest that the patients

who provided these urine samples had added drug directly to the urine after voiding to mimic compliance.

In a retrospective case-controlled study, the prevalence of hydromorphone as a metabolite of morphine was evaluated relative to morphine dose and gender (53). Patients were included if the urine drug screen and chart review indicated that the patient was only taking morphine. Of the 32 patients meeting the inclusion criteria, 11 patients did not show evidence of hydromorphone and were designated as the controls. The remaining 21 patients showed evidence of both morphine and hydromorphone (prevalence 66%). The assay reporting limit was 50 ng/mL. Hydromorphone was observed in 87% of positive urine samples collected from women and 47% of positive samples collected from men, but the ratio of hydromorphone to morphine in urine was not significantly different between genders. In general, the concentration of hydromorphone was approximately 2% of the total morphine concentration, suggesting that hydromorphone occurs as a minor metabolite of morphine. Detection of hydromorphone is likely to be associated with the detection limit of the assay employed. A similar relationship has been described for hydrocodone as a minor metabolite of codeine in both controlled administration and postoperative patient studies(54). The concentration of hydrocodone could appear in urine at up to 11% of the parent (codeine) concentration.

In another retrospective study of urine drug test results wherein pharmacy history was known, a small amount of codeine was observed in the urine collected from patients prescribed only morphine. (55)Fifteen samples of 535 samples evaluated were described to contain total morphine concentrations in the range of 10,000 – 150,000 ng/mL, and total codeine concentrations between 20-50 ng/mL. Using average concentrations of morphine (94,000 ng/mL) and codeine (40 ng/mL), it was estimated that the fraction of codeine nearly approximates the estimated impurity observed in pharmaceutical morphine (0.04%). The authors conclude that their data suggest evidence of pharmaceutical impurity rather than a minor route of metabolism.

Approximation of the time of last dose:

Some laboratories have applied therapeutic drug monitoring principles appropriate to serum, plasma, or blood concentrations to the quantified urine results with claims of such permitting a more effective assessment of the approximate time of the patient's last dose.

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

In a retrospective study of 161 patients prescribed transdermal fentanyl, the medial metabolic ratio of norfentanyl:fentanyl in urine was 6 with the central 50% range (25th and 75th percentile) 3-12(56). However, the study also acknowledged that the metabolic ratio could vary in a single subject by 10-fold, and between subjects by 37-fold. No pattern was demonstrated between the total amount of drug excreted and the metabolic ratio, suggesting that metabolic ratio does not correlate with dose. Studies with oxycodone and hydrocodone in urine have suggested that use of a proprietary algorithm can predict dose compliance (19, 20), but these data were challenged based on substantially overlapping distributions of urine concentrations by dose. Misclassification of dose estimates occurred in more than 25% of patients (57, 58).

Normalization of Quantitative Results to Creatinine or Specific Gravity

The reporting of quantitative urine drug testing results normalized to creatinine (ng drug/mg creatinine) or to specific gravity stems from the use of the practice in the testing of other urinary analytes, especially hormones, where it serves as a means of assessing the completeness of a 24-hour collection and accounting for variations between random sample collections.

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.

Two papers were identified related to the normalization of results. In the first, Pesce et al.(59) used mathematical modeling to assess the upper limits of drug excretion observed for 8,971 patients and to define reference intervals for the measured opiates. The distribution pattern obtained was minimally affected when the excreted drug concentrations were normalized to creatinine. Insufficient data were provided to fully assess the impact of this transformation. Barakat et al.(48) investigated the utility of the excretion of urinary hydrocodone concentrations and urinary hydromorphone concentrations to assess the variability of hydrocodone metabolism. Concentrations were normalized to creatinine before modeling, but non-normalized data were not provided.

Interpretation of Results

Much has been written and discussed about the ability of physicians and other healthcare providers to consistently and correctly interpret urine drug testing results. Urine results for any analyte are among the most complicated to interpret, and those for drug analysis are no exception. One must begin with sound knowledge of the pharmacology of the drugs (including the expected metabolic profiles), appreciate the variation in renal function over the course of the day and between individuals, recognize the inherent limitations of a randomly collected urine sample, and tie all

of these together in light of the limitations and strengths of the analytical methods used to generate the result. Unfortunately, the data show that many clinical providers have insufficient knowledge and expertise to correctly interpret urine laboratory test results for pain management patients.

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**

To assess physician knowledge on UDT interpretation, Reisfield et al. developed a questionnaire consisting of seven multiple-choice questions(60, 61). The questions included assessment of knowledge regarding the metabolism and excretion patterns expected for codeine, morphine, and heroin, the interpretation of unexpected negative screening results, the effects of poppy seed ingestion, and implications of second-hand exposure to marijuana smoke. The authors administered the assessment to 170 physicians attending two conferences: one an opiate education conference(60), the second a family medicine conference(61). Of the 114 physicians attending the opioid education conference who completed the questionnaire, 77 reported using UDT as part of their management, while 37 did not. None of the physicians achieved a score of 100%, and only 30% answered more than 50% correctly. The performance of the physicians who performed UDT was the same as those who did not. Of the 60 family medicine physicians who participated in the second assessment, 44 reported using UDT and 16 did not. Again, none achieved a score of 100%, and only 20% answered more than half the questions correctly. For this group, the highest score was five out of seven questions correct, or 71%, and those who self-identified as routinely ordering UDT performed better on only four of the seven questions compared to those physicians who indicated they did not routinely order the testing. A new question was added surveying who would consult the laboratory director when abnormal or unexpected findings were reported and found only 23% of physicians indicated they would contact the laboratory director. For each group, the authors concluded that physician knowledge of UDT interpretation is inadequate, that physicians are making important clinical decisions without understanding how to interpret the results, which could have severe consequences for both the patient and physician when tests are misinterpreted, and that efforts should be made to increase physician knowledge and encourage laboratory consultation.

Although there are a few papers that demonstrate that physicians are not proficient in interpreting UDT, there is no evidence that clinical pathology/laboratory medicine consultations are more effective for correct interpretation of urine test results for any drug given in pain management patients. This is most likely because providers are unaware of their knowledge gap and do not currently contact the laboratory director. Therefore, the studies cannot be performed. Despite the lack of evidence of the efficacy of laboratory medicine consultations, we strongly recommend that laboratories offering pain management testing have knowledgeable personnel to assist clinicians. Laboratories, in all aspects of testing, are responsible for providing accurate results, and assisting with interpretation and pain management testing should be no exception. At a minimum, laboratories should provide educational resources and detailed reports, including whom to contact with questions regarding interpretation.

Utility of Clinical Algorithms

Quantitative UDT results have been used alone or in combination with clinical data (e.g., drug dose, clinical presentation) to predict drug efficacy and side effects, guide drug dosing, and/or assess compliance. However, the utility and accuracy of these clinical-based algorithms is unclear.

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.

There are a few articles that describe the use of quantitative testing and clinical algorithms, but none demonstrate how their use improved outcomes. Therefore, there is no evidence that the reporting of quantitative drug concentrations is more effective in facilitating the assessment of any outcomes for pain management patients(25, 50, 56, 59, 62-64).

Conclusion

In the end, 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 non-prescribed drugs, and illicit substances in pain management patients. While these guidelines did find evidence to address several important areas/questions, it also uncovered significant gaps in the literature where additional research studies are needed to provide evidence for future recommendations.

Table 1. Process of Preparing and Publishing a Laboratory Medicine Practice Guideline

Step	Process
1	Define topic, scope, and target audience
2	Select multidisciplinary LMPG committee and establish clinical collaborations
3	Define key PICO(TS) questions
4	Conduct a systematic review of the evidence
5	Formulate and evaluate the quality and strength of each recommendation
6	Public presentation of key LMPG information
7	Public posting of LMPG
8	Incorporation of comments and preparation of second draft
9	Internal/external review and approval of final draft
10	Publication/distribution of final LMPG and executive summary

Table 2. Systematic Literature Search Inclusion/Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
Publication dates	2000-2013 originally, then expanded to February 2015	Prior to 2000
Language	English	Non-English
Species	Human	Non-Human
Age group	All	None
Sex	All	None
Journal subset	All	None
Article types	Clinical Trial (phase I-IV), Case Reports, Clinical Conference, Comparative Study, Consensus Development Conference, Evidence-based Practice, Guideline, Journal Article, Legal Cases, Legislation, Meta-Analysis, Multicenter Study, Patient Education Handout, Practice Guidelines, Randomized Controlled Trial, Research Support, Review, Systematic Reviews	Others not listed under inclusion

Table 3. Strength and Grading of the Recommendations

Strength of Recommendation	A. The NACB strongly recommends adoption; there is good evidence that it improves important health outcomes, and it concludes that benefits substantially outweigh harms.
	B. The NACB recommends adoption; there is at least fair evidence that it improves important health outcomes, and it concludes that benefits outweigh harms.
	C. The NACB recommends against adoption; there is evidence that it is ineffective or that harms outweigh benefits.
	I. The NACB concludes that the evidence is insufficient to make recommendations; evidence that it is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms can't be determined.
Grading of the Quality of the Evidence	I. Evidence includes consistent results from well-designed, well-conducted studies in representative populations.
	II. Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.
	III. Evidence is insufficient to assess the effects on health outcomes because of the limited number of power studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Table 4. Summary of Evidence-based LMPG Recommendations

#	Recommendation	Grading: Strength of recommendation, Quality of evidence	Target Group		
			Lab	Clinician	Policy¥
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.	A, I	X	X	X
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.	A, II		X	X
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.	A, III (pain management) II (substance abuse disorder monitoring population)		X	X
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.	A, II		X	X
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.	B, II		X	X
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.	B, II		X	X
7	Qualitative definitive tests should be used over 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.	A, II	X	X	X
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.	A, II	X	X	X

Table 4 *continued*

#	Recommendation	Grading: Strength of recommendation, Quality of evidence	Target Group		
			Lab	Clinician	Policy¥
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.	B, II		X	X
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.	B, II		X	X
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.	B, II		X	X
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.	A, II	X	X	X
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.	A, III		X	X
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).	A, II	X	X	X
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.	A, I (workplace drug testing) II (pain management)	X	X	X
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 using 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.	A, I (workplace drug testing) III (pain management)	X	X	X

Table 4 *continued*

#	Recommendation	Grading: Strength of recommendation, Quality of evidence	Target Group		
			Lab	Clinician	Policy[¥]
17	Clinicians should consult the laboratory regarding proper collection, storage, and transportation of urine specimens to maintain specimen validity.	A, III		X	
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.	A, II		X	
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.	A, I (workplace drug testing) III (pain management)	X	X	X
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.	A, II		X	X
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.	B, II	X	X	X
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.	I, II	X	X	X
23	Urine drug testing (quantitative or qualitative) is not recommended for approximating the time of last dose.	B, II		X	
24	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.	A, I		X	
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.	A, III	X		
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.	A, III	X		

[¥]Policy: Includes policy makers, regulatory bodies, and health insurance companies.

Table 5. Summary of consensus-based expert opinions

#	Expert Opinion	Grading: Strength of recommendation/ Quality of evidence	Target Group		
			Lab	Clinician	Policy
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.	A, II		X	X
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).	A, III	X	X	X
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.	A, III (pain management), II (substance abuse disorder monitoring population)		X	X
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.	B, II	X	X	
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.	I, III		X	
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.	I, III	X		
7	Specimen validity testing should be performed on every urine drug test for pain management patients.	A, II	X	X	X

¥Policy: Includes policy makers, regulatory bodies, and health insurance companies.

Table 6. Tiers of drug testing

Tier	When to Order	Drug Class	Examples of Drugs or Drug Metabolites within the Drug Class*
I	Routine Monitoring	Amphetamines	Amphetamine
			Methamphetamine
			Methylenedioxymethamphetamine (MDMA)
			Methylenedioxyamphetamine (MDA)
			Methylenedioxyethylamphetamine (MDEA)
		Barbiturates	Amobarbital
			Butalbital
			Phenobarbital
			Pentobarbital
			Secobarbital
		Benzodiazepines	Alprazolam
			Chlordiazepoxide
			Clonazepam
			Clorazepate
			Diazepam
			Estazolam
			Flurazepam
			Halazepam
			Lorazepam
			Medazepam
			Midazolam
			Oxazepam
			Prazepam
			Temazepam
			Triazolam
		Cannabinoids	Δ9-tetrahydrocannabinol (THC) 11-nor-9-carboxy-THC (THCCOOH)
		Cocaine	Cocaine
			Benzoylecgonine
		Opiates/Opioids	6-acetylmorphine (6-AM)
			Buprenorphine
			Codeine
			Dihydrocodeine
			Fentanyl
			Hydrocodone
			Hydromorphone
			Methadone
			Morphine
			Oxycodone
			Oxymorphone
			Tapentadol
			Tramadol

Table 6 *continued*

Tier	When to Order	Drug Class	Examples of Drugs or Drug Metabolites within the Drug Class*
II	High-risk patients with known history of abuse for this medication or prevalence of drug use is endemic to local region, risky polypharmacy, multiple providers, or if prescribed and patient shows lack of efficacy or toxicity	Alcohol	Ethanol or metabolite
		Anticonvulsants	Carbamazepine
			Felbamate
			Gabapentin
			Lacosamide
			Lamotrigine
			Levetiracetam
			Oxcarbazepine
			Phenytoin
			Pregabalin
			Rufinamide
			Tiagabine
			Topiramate
			Valproic acid
		Antidepressants	Amitriptyline
			Citalopram
			Clomipramine
			Desipramine
			Doxepin
			Duloxetine
			Fluoxetine
			Imipramine
			Nortriptyline
			Paroxetine
			Sertraline
			Venlafaxine
		Synthetic cathinones	Compounds ever-changing, representative examples include: methylone, mephedrone, and alpha-PVP
		Antitussive	Dextromethrophan
		Dissociative anesthetic	Ketamine
		Hallucinogens	Lysergic acid diethylamide (LSD)
			Phencyclidine
		Muscle relaxants	Carisoprodol
			Meprobamate
			Methocarbamol
		Narcotic pain-reliever	Propoxyphene

Table 6 *continued*

Tier	When to Order	Drug Class	Examples of Drugs or Drug Metabolites within the Drug Class*
III	As Clinically Indicated	OTC analgesic	Acetaminophen
			Salicylate
		Antihistamine	Certirizine
			Chlorpheniramine
			Diphenhydramine
			Loratidine
		Antipsychotics	Amisulpride
			Amoxapine
			Chlormethiazole
			Clopenthixole
			Chlorpiprazine
			Chlorprothixene
			Cloxazepine
			Clozapine
			Distraneurine
			Dixyrazine
			Chlorpromazine
			Fluentixol decanoate
			Fluphenazine
			Haloperidole
			Loxapine
			Melperone hydrochloride
			Methotrimeprazine
			Olanzapine
			Oxilapine
			Perphenazine
			Phenothiazine
			Pimozide
			Quetiapine
			Risperidone
			Sulpiride
			Thioridazine
			Tiapride
			Trifluoroperazine
			Ziprasidone
			Zotepine
		Synthetic cannabinoids	Compounds ever-changing, representative examples include: JWH-018, ADB-FUBINACA, 5F-ADB, FUB-AMB, and ADB-PINACA.

*Note: This table is not meant to be a comprehensive list of all drugs that must be tested for in every pain management patient. The list only represents examples of drugs from each particular drug class. The provider should take into account the medications prescribed to the patient, the patient's past substance abuse history, along with other accessible or locally abused drugs, and the patient's clinical presentation when selecting which tests to order. Furthermore, it may be more appropriate to look for and identify a drug's metabolite based on what is found in the matrix (e.g., urine). As a result, laboratory tests must include the appropriate parent drug and/or metabolites based on each matrix.

Table 7. Genes associated with opioid responses and/or dosages

Gene symbol (full name)	Description of protein function and potential role in pain management	Examples of associated drug(s)	References
ABCB1 (ATP-binding cassette, subfamily B, member 1, also known as multi-drug resistance, MDR 1)	Codes for p-glycoprotein (P-gp), which transports drugs from intracellular to extracellular domains, in various tissues. Variants may affect dose requirements, response, and risk of adverse effects for P-gp substrates due to changes in the amount of drug absorbed, eliminated, and/or transported into the compartments such as the central nervous system.	Morphine Methadone Fentanyl	(65, 66) (67-76)
COMT (catechol-O-methyltransferase)	COMT mediates the transfer of a methyl group from S-adenosylmethionine to catecholamines such as neurotransmitters, and catechol drugs. Variants may be associated with pain sensitivity, dose requirements, risk of adverse effects such as nausea and vomiting or sedation, as well as risk of heroin addiction.	Morphine Triptans	(67, 72, 73, 77-84)
CYP2D6 (Cytochrome P450 2D6)	CYP2D6 is a member of the cytochrome P450 mixed-function oxidase system involved in the metabolism and elimination of ~25% of clinically used drugs by hydroxylation, demethylation or dealkylation.	Codeine Tramadol Oxycodone Nortriptyline Desipramine	(85)(86)(39)
OPRM1 (μ-opioid receptor, exon 1)	The μ-opioid receptor is a principal target for opioid analgesics. Variants are thought to play a role in dose requirements, response, and risk of adverse effects, such as nausea and vomiting or sedation from opioids. In addition, addiction to opioids, alcohol, nicotine, and other drugs, as well as response to addiction treatment, has also been associated with OPRM1 variants.	Morphine Hydrocodone Fentanyl Oxycodone	(65, 67-69, 72, 73, 75, 78, 79, 83, 87-100)

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Preamble

The American Association for Clinical Chemistry (AACC) Academy, formerly the National Academy of Clinical Biochemistry (NACB), has developed numerous laboratory medicine practice guidelines (LMPGs). The AACC LMPGs are documented practice recommendations created using evidence-based approaches to address specific questions regarding the appropriate use of diagnostic laboratory testing in a defined scientific and/or clinical discipline. LMPGs include recommendations intended to improve the use of diagnostic laboratory tests in a manner that optimizes patient care based on practice recommendations informed by a systematic review of evidence. These guidelines were developed to address, incorporate, and/or conform to the standards stated in the 2011 Institute of Medicine (IOM) reports (Clinical Practice Guidelines We Can Trust(1) and Finding What Works in Health Care(2)) and followed the standard operating procedure for preparing, publishing, and revising NACB/AACC Academy LMPGs. (https://www.aacc.org/~/media/files/nacb/nacb_lmpg_sopc_jan_2014.pdf?la=en, last accessed 4-6-16) The creation of the guideline was designed to fulfill the methodological quality criteria of the Appraisal of Guidelines for Research and Evaluation (AGREE) II Instrument. (Appraisal of Guidelines for Research & Evaluation II. AGREE II instrument. The AGREE Next Steps Consortium, May 2009, 56 p. http://www.agreetrust.org/resource-centre/agree-ii, last accessed 5-15-16)

The process of preparing and publishing this laboratory medicine practice guideline (Table 1):

Table 1. Process of Preparing and Publishing a Laboratory Medicine Practice Guideline

Step	Process
1	Define topic, scope, and target audience
2	Select multidisciplinary LMPG committee and establish clinical collaborations
3	Define key PICO(TS) questions
4	Conduct a systematic review of the evidence
5	Formulate and evaluate the quality and strength of each recommendation
6	Public presentation of key LMPG information
7	Public posting of LMPG
8	Incorporation of comments and preparation of second draft
9	Internal/external review and approval of final draft
10	Publication/distribution of final LMPG and executive summary

STEP 1: Define the topic, scope, and target audience

The scope and 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 non-prescribed drugs, and illicit substances in pain management patients. Current published recommendations from the World Health Organization (WHO) and other medical societies recommend pharmacotherapy using opioids as the mainstay therapy for moderate and severe pain. Unfortunately, these medications pose the risk of addiction and abuse, so monitoring of patients for compliance, or lack thereof, is commonplace. In addition, clinicians in the United States are mindful of the Drug Enforcement Administration's (DEA's) efforts to crack down on the growing abuse and deaths related to pain management medications. Therefore, numerous professional organizations, including the Centers for Disease Control and Prevention (CDC), have published recommendations that include the use of urine drug tests to document compliance or assess possible diversion of pain medications. This guideline specifically reviewed the literature to assess and define recommendations regarding the clinical utility and use of urine and alternative spec-

imen types, assorted assay formats (laboratory-based vs. POC), different assay types (screening vs. definitive), inclusion of specimen validity testing and pharmacogenomics testing, as well as the reporting, communication, and interpretation of test results back to clinicians. The intention of this guideline was to provide evidence-based recommendations on how urine drug testing for pain management patients should be performed. Alternatively, in the absence of evidence or only weak evidence, recommendations were based on consensus expert opinion. In the end, the target audience for this guideline was both the laboratories and laboratorians who perform pain management testing and the clinicians who order, use, and interpret these tests.

STEP 2: Select a multidisciplinary LMPG committee and establish clinical collaborations

The guideline committee included representatives of key stakeholders to whom the recommendations were meant to apply. As a result, the committee was made up of clinical laboratory professionals, clinicians practicing in pain management, and other relevant stakeholders, healthcare professionals, or clinical experts. The experts on the committee are listed in the guideline and represented the AACC Academy (L.J. Langman, P.J. Jannetto); Clinical and Laboratory Standards Institute, which was 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); American Association of Clinical Chemistry (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). While all the members of the guideline committee were from the United States, where laboratory testing for pain management has become a major public health focus, the perspectives and views of other international organizations representing broader laboratory and clinical professionals, as well as other potential stakeholders (e.g., patients, policy makers, regulatory bodies, and health insurance companies) will be taken into account during the public-consultation process (steps 7 and 8; Figure 1).

The guideline committee received no sponsorship, honoraria, or other direct funding related to the development of this guideline. AACC supported the development of the guideline process by providing funds to cover the expenses of meetings and provided administrative support. All authors who contributed to the development of this guideline have also declared any financial, personal, or professional relationships that might constitute conflicts of interest with this guideline and will be published on the AACC website.

STEP 3: Define key PICO(TS) questions

Prior to a systematic literature search, the LMPG committee defined all the key questions that would be addressed in the guideline using the PICO(TS) strategy for construction of the questions. PICO(TS) stands for the (P)atient population, (I)ntervention, (C)omparator, (O)utcome, (T)ime period, and (S)etting. In this guideline, the patient population was acute and/or chronic pain management patients, and the interventions were the laboratory tests (screening or definitive) that were compared with other clinician tools (e.g., physician interview, medical record review, prescription monitoring programs, screener and opioid assessment for patients with pain). Outcomes included adherence, diversion, emergency department visits, and others. Appendix 1 lists all terms used for the PICO(TS) style questions and systematic literature search. The time period was from January 2000-February 2015 in outpatient, inpatient, and community settings. The PICO(TS) questions were defined at a face-to-face meeting and finalized after numerous conference calls.

STEP 4: Systematic literature search for relevant key publications that address the PICO(TS) questions

A Mayo Clinic librarian (P. Erwin) performed the systematic literature search using the inclusion and exclusion criteria defined by the LMPG committee. The inclusion and exclusion criteria are shown in Tables 2 and 3. It should be noted that the original literature search only included publications up to December 2013 (when the committee finalized the PICO(TS) questions), but the literature search was updated again in February 2015 to capture any additional publications (January 2014-February 2015) to keep the document current during the lengthy and time-consuming guideline process and followed the same process outlined above.

Table 2. Systematic Literature Search Inclusion Criteria

Publication dates	2000-2013 originally, then expanded to February 2015
Language	English
Species	Human
Age group	All
Sex	All
Journal subset	All
Article types	Clinical Trial (phase I-IV), Case Reports, Clinical Conference, Comparative Study, Consensus Development Conference, Evidence-based Practice, Guideline, Journal Article, Legal Cases, Legislation, Meta-Analysis, Multicenter Study, Patient Education Handout, Practice Guidelines, Randomized Controlled Trial, Research Support, Review, Systematic Reviews

Table 3. Systematic Literature Search Exclusion Criteria

Publication dates	Prior to 2000
Language	Non-English
Species	Non-Human
Age group	None
Sex	None
Journal subset	None
Article type	Others not listed in table 1

The following databases were searched: PubMed, the National Library of Medicine; Cochrane Database of Systematic Reviews, which includes the full text of regularly updated systematic reviews of the effects of healthcare prepared by the Cochrane Collaboration; the National Guideline Clearinghouse (an initiative of the Agency for Healthcare Research and Quality), a public resource for evidence-based clinical practice guidelines; EMBASE, which emphasizes drug-related literature and toxicology; CINAHL, which covers nursing and allied health disciplines and includes journal articles, healthcare books, nursing dissertations, selected conference proceedings and standards of professional practice; SCOPUS; Web of Science; and Psych Info. Appendix B lists the complete search strategy used for the MEDLINE database; a similar strategy was employed for the other data bases.

The combined literature search from 2000-2015 resulted in 7,647 articles being identified. Each abstract was assigned to two committee members for review. Using the DistillerSR software to document the entire review process, each abstract was then independently reviewed to determine if it was relevant to the PICO(TS) key questions and could proceed to the next phase of review (full text review). However, if either reviewer determined that the article should not undergo a full text review, they had to document the reason (e.g., publication out of scope) in the software. Both reviewers had to agree to move a publication from the abstract review phase to the full text review phase. Any discordance between the two reviewers was then resolved by either the chair or co-chair, who cast the third and tie-breaking vote. Of the 7,647 abstracts reviewed, 2,352 were selected for the full text review phase. An electronic version of all the remaining articles was then retrieved and divided up among the entire committee for review. Committee members then assessed each article and documented the answers to 32 questions in the DistillerSR software, which covered everything from the author's declarations, study aims, and objectives to their conclusions. The articles were again reviewed for appropriateness, and, of the 2,352 articles that had a full text review, 562 of them were ultimately used to formulate the recommendations for the guideline.

STEP 5: Formulate and evaluate the strength of each recommendation

Committee members worked in teams, with each member taking the lead on a different section of the guideline to formulate recommendations for their assigned PICO(TS) questions. The strengths of each recommendation were evaluated and graded using an approach described in the 2011 IOM report. The approach was a modification of the US Preventive Services Task Force system. The strength of each recommendation was determined to be A, B, C, or I, while the grading of the quality of the evidence was either a I, II, or III (Table 4).

Table 4. Strength and Grading of the Recommendations

Strength of Recommendation	A. The NACB strongly recommends adoption; there is good evidence that it improves important health outcomes, and it concludes that benefits substantially outweigh harms.
	B. The NACB recommends adoption; there is at least fair evidence that it improves important health outcomes, and it concludes that benefits outweigh harms.
	C. The NACB recommends against adoption; there is evidence that it is ineffective or that harms outweigh benefits.
	I. The NACB concludes that the evidence is insufficient to make recommendations; evidence that it is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms can't be determined.
Grading of the Quality of the Evidence	I. Evidence includes consistent results from well-designed, well-conducted studies in representative populations.
	II. Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.
	III. Evidence is insufficient to assess the effects on health outcomes because of the limited number of power studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

STEP 6: Public presentation of LMPG recommendations

The recommendations in this LMPG were first presented in February 2016 at the American Academy of Pain Medicine (AAPM) annual meeting to pain management clinicians for public review and feedback. Emailed suggestions were taken into account and the modified guideline was then presented again at the August 2016 AACC annual meeting for additional review and feedback. Comments submitted by the AACC website or email were reviewed and discussed by the committee. Additionally, the document was directly circulated to a number of experts in the field for additional comments.

STEP 7: Public posting of the first draft of the LMPG document

The draft guideline was also posted on the AACC website for a minimum of 30 days for public comment. Comments made during the online documentation process were reviewed and addressed by the LMPG committee. This process documented the comment receipt and final resolution.

STEP 8: Incorporation of comments and preparation of second draft

After all public presentations and postings, the LMPG reviewed and addressed all the comments. Any necessary updates were then incorporated into the second draft of the guideline.

STEP 9: Internal/external review and endorsement of final draft

The final LMPG was then submitted to evidence-based laboratory medicine committee (EBLMC) for review and approval before being presented to the AACC Academy Council and AACC Board of Directors for final approval. The submission contained the LMPG committee response, clarification, and explanation of their reply to each and every comment provided by the other reviewers of the draft guideline. Other external organizations (CAP, AAPM, etc.) will also get time to review and endorse the final guidelines.

STEP 10: Publication of final LMPG

The final, approved guideline will then be published online on the AACC website where external clinical organizations that endorsed it can directly link to it from their websites. In addition, an executive summary will also be prepared and published in Clinical Chemistry or another relevant clinical specialty journal for the topic. Per the AACC Academy standard operating procedure for preparing, publishing, and revising LMPGs, this guideline will be reviewed and updated (if necessary) again in a five to ten year time frame.

Introduction

Background

Pain: An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN, 1979

Once thought to be a necessary part of human existence due to a lack of scientific understanding and deep roots in philosophical and religious traditions, pain is now recognized as a complex clinical problem. The great, often challenging, variation in response across individuals to a painful stimulus arises from a combination of biological, psychological, environmental, and societal factors. Equally challenging is the range of responses in treating pain. Many of the early attempts to control pain—for example, through the use of trephination or bleeding—may seem quite barbaric and cruel, but for many years pain was seen as a necessary part of the human condition, and to violate this was considered unethical. Each person experienced pain in order to experience life and to instill various concepts of order and behavior. Debates along these lines continued well into modern times.

For much of history, the ill and injured, as well as their caretakers, relied upon plant-derived products to ease pain. In fact, the use of opium as a tincture or soak (on sponges) is documented in the medical and lay literature of ancient Egypt, Greece, and China(3). Nitrous oxide was discovered by the English chemist Joseph Priestley in 1772; his work attracted early interest, but soon the use of ether, chloroform, and other compounds become more prevalent(4). In 1806, the compound responsible for opium's sedative and anesthetic properties was isolated by Friedrich Sertürner. He named this compound morphine, after Morpheus, the god of dreams(3).

Another milestone of the 1800s was the mass production of various pharmaceutical agents. Pain relief could now more easily be purchased from the local pharmacist. The end of the century saw the introduction of diacetyl morphine (heroin) as a cough remedy and acetylated salicylic acid (aspirin) for both analgesia and antipyresis. The pharmaceutical regulations under which we currently operate did not exist at this time—patients and non-patients self-medicated. Physicians and citizens expressed concerns about the growing "morphine habit," leading Congress to enact laws governing the sale and use of narcotics (the 1914 Harrison Narcotic Tax Act(5) and 1956 Narcotic Control Act(6)). It would be another 20 years before additional issues related to safe manufacturing practices for drugs and cosmetics, particularly in response to the deaths attributed to the presence of diethylene glycol in elixir sulfanilamide, led to the enactment of the Food, Drug, and Cosmetic Act of 1938(7), which set into motion the creation of the Food and Drug Administration of today.

The 1970s saw the creation of the first programs in the US to specifically treat patients with chronic pain. And although cancer pain has been treated through the years with opioid medications, it was in the 1990s that opioids began to be used more frequently in non-cancer pain. It was thus somewhat of a surprise when surveys conducted in the 1990s suggested that many patients reported unresolved pain during hospitalizations(8). In response to these reports and pressure from numerous advocacy groups, the Department of Veterans Affairs and the Joint Commission on Accreditation of Healthcare Organizations adopted pain as the "5th vital sign." The mandate was designed not only to recognize a patient's pain sooner, but also to initiate treatment. In 2000, Congress declared 2000-2010 to be the "Decade of Pain Control and Research." Pain management became a major public health focus with resources targeting research, interventions, and education(9).

The consequences of this action and the events of the ensuing years are mixed. Much has been learned of the mechanisms of pain—its genetics, evolution, and complexity. Advancements have been made in treatment, though not as greatly as one would have hoped. Opiates remain the mainstay of drug therapy. A 2014 National Institutes of Health workshop reported about one-third of the US population experiences chronic pain, with a quarter of these individuals limited in daily activities as a result. The report also estimates the economic impact of chronic pain at $560 billion to $630 billion per year. (https://prevention.nih.gov/docs/programs/p2p/ODPPainPanelStatementFinal_10-02-14.pdf, accessed 12-24-2015) The CDC released data from a 2012 National Health and Nutrition Examination Survey showing that although there was not an increase in the percentage of adults (6.9%) who reported using an opioid analgesic from 2003 to 2012, those using an opioid stronger than morphine increased from 17% to 37%. (http://www.cdc.gov/drugoverdose/, accessed 12-24-2015)(10)

Misuse and abuse of pain management medications

While pain remains an issue, data show a significant rise in abuse and misuse. Sadly, the concerns raised a hundred years earlier related to opiate addiction have been magnified(11-14). (https://prevention.nih.gov/docs/programs/p2p/ODPPainPanelStatementFinal_10-02-14.pdf, accessed 12-24-2015; http://www.asam.org/docs/default-source/advocacy/opioid-addiction-disease-facts-figures.pdf, accessed 12-24-2015) In a study assessing the amount of opioids dispensed from 1999 to 2008, Brady et al.(12) found the amount of opiates dispensed (as morphine milligram equivalents) increased progressively until 2007, at which time the volume stabilized and even trended slightly downward, possibly in response to broader use of prescription drug monitoring programs. Over the same timeframe, it was found that non-medical use of opioids resulted in a 111% increase in emergency department visits [DAWN reports] and the number of overdose deaths tripled(12).

The medical world has responded to the precipitous rise in overdose deaths by emphasizing more rigorous adherence to best practices for safe opioid prescribing. There are many ways this is manifested—in day-to-day clinical care and also the development of guidelines. There are not as many formal research laboratory studies in terms of compliance (evidence-based medicine), but there are common features to almost every guideline that has been developed that include the understanding of the risk of misuse, abuse, and diversion of prescribed medication. Certain patients are at risk, perhaps genetically, of developing addiction. Periodic urine drug testing for monitoring of compliance and for screening for abuse of drugs is recognized to be an objective way to try to assess this. The frequency of testing is not firmly established, and varies—in state and federal policies, with the global recognition of the need for compliance testing with urine drug screening, and from state to state in their statutes.

There is a serious problem of diversion and abuse of opioid drugs, as well as questions about their long-term usefulness. However, when opioids are used as prescribed and appropriately monitored, they can be safe and effective, especially for acute, postoperative, and procedural pain, as well as for patients near the end of life who desire more pain relief. Data supporting efficacy of long-term opioids for chronic benign pain, on the other hand, are scarce. In light of the sparse data, recommendations typically focus on improved function as a critical measure of effectiveness.

A large national diagnostic laboratory recently published a report (not peer-reviewed) of data derived from 227,402 urine samples, indicating that 60% of patients prescribed commonly abused medications such as opioids, central nervous system depressants, and stimulants had findings suggestive of misuse(14). Of these, 42% had urine samples with the prescribed drug absent, 33% had non-prescribed drugs present in addition to the prescribed drug, and 25% had non-prescribed drugs present and the prescribed drug absent(15). In a retrospective analysis of data from 470 patients with chronic pain who were prescribed opioids in a pain management program, 45% had an abnormal urine toxicology screening(16). The presence of illicit substances was found in the majority of the abnormal urine toxicology screens.

Drug testing is a common component of effective adherence monitoring and of appropriate prescribing. Urine has predominated, as it is a relatively inexpensive, readily accessible, non-invasive tool that provides information about drug use over a clinically relevant time frame, and can include data regarding primary drugs as well as metabolites. However, other specimens such as hair, saliva, and serum can be used as well.

As time and science have evolved, other helpful ways to glean information have become apparent, including pharmacogenomics testing to try to understand the patient's drug metabolism, risk of addiction or adverse events, and chance of medication interactions, thereby minimizing adverse effects while maximizing proper dosing, efficacy and safety. This can allow the individualization of treatment for the patient, an important component of personalized medicine.

Definition of terms

Terms used throughout this document are defined as in the following citations.

	Definition	Citation
Pain	An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage	(17)
Chronic pain	Pain that persists beyond the usual course of an acute disease or a reasonable time for any injury to heal that is associated with chronic pathologic processes that cause continuous pain or pain at intervals for months or years. Pain that is not amenable to routine pain control methods. Pain where healing may never occur. Chronic pain has been defined as that which persists beyond three months—assumed to be "normal" tissue healing time	(18, 19); 10:113-30; (20)
Chronic	A disease or treatment course that lasts three months or more	http://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm (accessed 06-09-2016)

Definition of terms *continued*

	Definition	Citation
Adverse drug reactions (ADRs)	Inappropriate or unintentional responses from one or more pharmaceutical preparations	
Addiction	A primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm and craving. Controlled Substance Act: The habitual use of a narcotic drug so as to endanger the public morals, health, safety, welfare, or the loss of self-control with reference to narcotic drugs	(18, 21, 22)
Pseudoaddiction	An iatrogenic syndrome of behaviors developing as a direct consequence of inadequate pain management	(21, 23, 24)
Diversion	The intentional removal of a medication from legitimate distribution and dispensing channels	(21)
Adherence/ Compliance	The use of a prescription medication as prescribed or indicated	
Dependence	A state of adaptation that is manifested by a drug-class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist	(21, 22)
Abuse	Any use of an illegal drug. The intentional self-administration of a medication for a non-medical purpose, such as altering one's state of consciousness	(21)
Misuse	Use of a medication (for a medical purpose) other than as directed or as indicated, whether willful or intentional, and whether harm results or not	(21)
Pain catastrophizing	A maladaptive cognitive style, in which the patient has the tendency to amplify the potential threat of a painful experience and to have limited confidence in their ability to tolerate it	(25)
Tolerance	A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time	(21, 22)
Nociceptive pain	Pain caused by invasion and destruction of, or pressure on, superficial somatic structures like skin, deeper skeletal structures such as bone and muscle, and visceral structures and organs. Types: superficial, deep, visceral. Superficial and deep nociceptive pain is usually localized and non-radiating. Visceral pain is more diffuse over the viscera involved.	
Neuropathic pain	Pain caused by pressure on or destruction of peripheral, autonomic, or central nervous system structures and often radiating along dermatomal or peripheral nerve distributions. Often described as burning and/or deep aching. May be associated with dysesthesia, hypoesthesia, hyperesthesia, and allodynia. May also be accompanied by lightning-like jabs of brief, sharp pain (lancinating pain).	
Presumptive drug testing	Drug testing that may be qualitative, semi-quantitative, or quantitative to identify use or non-use of a drug or drug class, but where the methods can't distinguish between structural isomers and are considered presumptive	
Definitive drug testing	Definitive methods (e.g. mass spectrometry or chromatography-based) are able to identify use or non-use of a specific drug and/or its associated metabolites. It can be quantitative or qualitative.	
Qualitative drug testing	Testing that is not quantitative and reported as present vs. absent, or positive vs. negative.	
Controlled substance	A drug declared by federal or state law to be illegal for sale or use, but may be dispensed under a physician's prescription. The basis for control and regulation is the danger of addiction, abuse, physical and mental harm (including death), the trafficking by illegal means, and the dangers from actions of those who have used the substances.	
Forensic Toxicology testing	Qualitative and quantitative analysis of drugs or poisons in biological specimens to aid in the medical or legal investigation of death, poisoning, and drug use.	

Review of Common Medications Used in the Management of Acute/Chronic Pain

The ideal treatment for any pain is to remove the cause; however, treatment can be initiated immediately while trying to establish the underlying etiology. Sometimes, treating the underlying condition does not immediately relieve pain, and some conditions are so painful that rapid and effective analgesia is essential (e.g., the postoperative state, burns, trauma, cancer, or sickle cell crisis). The strategies and classes of drugs chosen depend not only on the cause of pain, but also its anticipated duration.

Medications for Acute Pain

Aspirin, Acetaminophen, and Non-Steroidal Anti-Inflammatory Agents (NSAIDs)

These drugs can be reviewed together (Table 5) because they are used for similar problems and may have a similar mechanism of action. In general, these compounds inhibit cyclooxygenase (COX), and, except for acetaminophen, all have anti-inflammatory actions, especially at higher dosages(26). They are absorbed well from the gastrointestinal tract and have minimal side effects. With chronic use, gastric irritation is a common side effect of aspirin and NSAIDs and is the problem that most frequently limits the dose that can be given. They are particularly effective for mild to moderate headache and for pain of musculoskeletal origin.

The introduction of parenteral forms of NSAIDs, ketorolac and diclofenac, extends the usefulness of this class of compounds in the management of acute severe pain. Both agents are sufficiently potent and rapid in onset to supplant opioids for many patients with acute severe headache and musculoskeletal pain(26).

Table 5. Common Non-narcotic Analgesics

Generic Name
Acetylsalicylic acid
Acetaminophen
Ibuprofen
Naproxen
Fenoprofen
Indomethacin
Ketorolac
Celecoxib
Valdecoxib

Opioids are the most potent pain-relieving drugs currently available (Table 6). They have the broadest range of efficacy and provide the most reliable and effective method for rapid pain relief(26). Although side effects are common, most are reversible: nausea, vomiting, pruritus, and constipation are the most frequent and bothersome side effects. Respiratory depression is uncommon at standard analgesic doses, but can be life-threatening. Opioid-related side effects can be reversed rapidly with the narcotic antagonist naloxone(26).

Table 6. Common Narcotic Analgesics

Narcotic Analgesic Generic Name
Codeine
Oxycodone
Morphine
Hydrocodone
Hydromorphone
Methadone
Meperidine
Butorphanol
Fentanyl
Buprenorphine
Tramadol

Opioids produce analgesia by actions in the CNS. They activate pain-inhibitory neurons and directly inhibit pain-transmission neurons. Most of the commercially available opioid analgesics act at the same opioid receptor (μ-receptor), differing mainly in potency, speed of onset, duration of action, and optimal route of administration(26). Some side effects are due to accumulation of non-opioid metabolites that are unique to individual drugs.

Opioid and COX Inhibitor Combinations

When used in combination, opioids and COX inhibitors have additive effects. Because a lower dose of each can be used to achieve the same degree of pain relief and their side effects are non-additive(26), these combinations can be used to lower the severity of dose-related side effects. However, fixed-ratio combinations of an opioid with acetaminophen carry an important risk. Dose escalation as a result of increased severity of pain or decreased opioid effect as a result of tolerance may lead to ingestion of levels of acetaminophen that are toxic to the liver(26). Although acetaminophen-related hepatotoxicity is uncommon, it remains a significant cause for liver failure. Thus, many practitioners have moved away from the use of opioid-acetaminophen combination analgesics to avoid the risk of excessive acetaminophen exposure as the dose of the analgesic is escalated.

Medications for Chronic Pain

Antidepressant Medications

The tricyclic antidepressants (TCAs), particularly nortriptyline and amitriptyline (Table 7), are useful for the management of chronic pain. Although developed to treat depression, the TCAs have a spectrum of dose-related biologic activities that include analgesia in a variety of chronic clinical conditions. Although the mechanism is unknown, the analgesic effect of TCAs has a more

rapid onset and occurs at a lower dose than is typically required for the treatment of depression(26).

There is evidence that TCAs potentiate opioid analgesia, so they may be useful adjuncts for the treatment of severe, persistent pain such as that which occurs with malignant tumors. TCAs are of particular value in the management of neuropathic pain, such as that which occurs in diabetic neuropathy and postherpetic neuralgia, for which there are few other therapeutic options.

Table 7. Common Antidepressants and Anticonvulsants Used to Treat Pain

Antidepressants (Generic Name)	Anticonvulsants (Generic Name)
Doxepin	Phenytoin
Amitriptyline	Carbamazepine
Imipramine	Oxcarbazepine
Nortriptyline	Clonazepam
Desipramine	Gabapentin
Venlafaxine	Pregabalin
Duloxetine	

TCAs have significant side effects, including orthostatic hypotension, drowsiness, cardiac conduction delay, memory impairment, constipation, and urinary retention. These are particularly problematic in elderly patients, and several are additive to the side effects of opioid analgesics. The selective serotonin reuptake inhibitors such as fluoxetine (Prozac) have fewer and less serious side effects than TCAs, but they are much less effective for relieving pain. It is of interest that venlafaxine and duloxetine block both serotonin and norepinephrine reuptake, appear to retain most of the pain-relieving effect of TCAs but have a side effect profile more like that of the selective serotonin reuptake inhibitors, and may be useful in patients who cannot tolerate the side effects of TCAs.

Anticonvulsants

These drugs are useful primarily for patients with neuropathic pain. Phenytoin (Dilantin) and carbamazepine (Tegretol) were first shown to relieve the pain of trigeminal neuralgia. In fact, anticonvulsants seem to be particularly helpful for pains that have such a ¬lancinating quality. Newer anticonvulsants, gabapentin (Neurontin) and pregabalin (Lyrica), are effective for a broad range of neuropathic pains. Furthermore, because of their favorable side effect profile, these newer anticonvulsants are often used as first-line agents.

Neuroleptics

Neuroleptic medications may occasionally be useful for patients with refractory neuropathic pain, and may be most helpful in patients with marked agitation or psychotic symptoms. The most commonly used agents are fluphenazine, haloperidol, chlorpromazine, and perphenazine(27). Long-term side effects include akathisia (extreme restlessness) and tardive dyskinesia (involuntary choreoathetoid movements of the tongue, lip smacking, and truncal instability)(27).

Antispasmodics and Muscle Relaxants

Antispasmodics (e.g., cyclobenzaprine, and baclofen) may be helpful for patients with musculoskeletal sprain and pain associated with spasm or contractures. Cyclobenzaprine also may be effective for muscle spasm in conditions such as multiple sclerosis, low back pain, and spastic diplegia, but its precise mechanism of action is unknown. Carisoprodol blocks interneuronal activity in descending reticular formation and spinal cord, resulting in blocking of pain sensations. It can be highly addictive and metabolizes to meprobamate. Baclofen is particularly effective in the treatment of muscle spasm associated with multiple sclerosis or spinal cord injury when administered by continuous intrathecal drug infusion(27).

Chronic Opioid Medication

The long-term use of opioids is accepted for patients with pain due to malignant disease, and encompasses the same drugs used for acute pain (Table 6). Although opioid use for chronic pain of non-malignant origin is controversial, it is clear that for many patients, opioids are the only option that produces meaningful pain relief.

Some degree of tolerance and physical dependence is likely with long-term use. Furthermore, animal studies suggest that long-term opioid therapy may worsen pain in some individuals, and one must not overlook the small but not insignificant possibility of opioid dependence developing. Therefore, before embarking on opioid therapy, other options should be explored, and the limitations and risks of opioids should be explained to the patient. It is also important to point out that some opioid analgesic medications have mixed agonist-antagonist properties (e.g., butorphanol and buprenorphine). From a practical standpoint, this means that they may worsen pain by inducing an abstinence syndrome in patients who are physically dependent on other opioid analgesics.

With chronic outpatient use of orally administered opioids, it is desirable to use long-acting compounds such as methadone, sustained-release morphine, or transdermal fentanyl. The pharmacokinetic profiles of these drug preparations enable the maintenance of sustained analgesic blood levels, potentially minimizing side effects such as sedation that are associated with high peak plasma levels, and reducing the likelihood of rebound pain associated with a rapid fall in plasma opioid concentration. Although long-acting opioid preparations may provide superior pain relief in patients with a continuous pattern of ongoing pain, others suffer from intermittent severe episodic pain and experience superior pain control and fewer side effects with the periodic use of short-acting opioid analgesics. Constipation is a

virtually universal side effect of opioid use and should be treated expectantly.

It is worth emphasizing that many patients, especially those with chronic pain, seek medical attention primarily because they are suffering and because only clinicians can provide the medications required for pain relief. A primary responsibility of all clinicians is to minimize the physical and emotional discomfort of their patients. Familiarity with pain mechanisms and analgesic medications is an important step toward accomplishing this aim.

Regulatory Challenges and Existing Clinical Practice Guidelines for Laboratory Testing

The use of opioids for pain management has been broadly accepted by regulatory bodies, professional organizations, and clinicians. Compliance monitoring has been viewed as necessary for safe opioid prescribing, and chronic opioid prescribing has included "contracts" or treatment agreements, periodic urine drug testing, and random pill counts. The magnitude of prescription opioid abuse has grown over the last decade, leading the CDC to classify prescription opioid analgesic abuse as an epidemic. This appears to be due in large part to individuals using a prescription drug non-medically, most often an opioid analgesic. Drug-induced deaths have rapidly risen and continue to be one of the leading causes of death in Americans. In 2011, the Office of National Drug Control Policy established a multifaceted approach to address prescription drug abuse, including Prescription Drug Monitoring Programs (PDMPs) that allow practitioners to determine if patients are receiving prescriptions from multiple providers and use of law enforcement to eliminate improper prescribing practices. As more states developed PDMPs, this became part of the typical routine of monitoring patients. Some clinics even refer to their state court system's circuit court records for evidence of previous criminality (and convictions for driving under the influence).

Data are plentiful regarding the inaccuracy of patient reports of medication and illicit drug use, particularly in those with substance abuse disorders(28-30). The overdose data identify polypharmacy as a major risk factor(31-33). Hence, objective data are necessary for safe prescribing of many medications, including controlled substances. While the PDMP provides evidence of prescriptions that have been filled, there may be delays in recording by pharmacies, and there are limited links to other state programs. The PDMP also often fails to include drug treatment maintenance medications, medications prescribed for behavioral health, and medications provided through the Veterans Health Administration. It is also difficult to track prescriptions that are shipped across state lines through the PDMP. In order to know what a patient has actually taken, drug testing is required.

In another retrospective chart review of primary care physicians in 12 university clinics, Adams(34) found that only 42% of providers used written agreements (almost half of which were over a year old), and 8% ordered urine drug testing (UDT) to monitor chronic opioid patient compliance, but this accounted for only 2% of the 209 patients. Interestingly, 26% of the patients were receiving chronic opioid therapy (COT) for fibromyalgia and 23% for headache. In this population, high doses of long-acting opioids were common: 20% received morphine ER (mean dose 231 mg/day), 11% oxycodone ER (107 mg/day), and 8% methadone (52 mg/day).

Physicians think of guidelines as something helpful, a higher perspective in addition to our own professional experience, yet the legal and regulatory worlds view guidelines as the enunciation of the standard of care. It is also true in most areas of medicine that there are insufficient studies to determine the exact evidence-based path, while the need for proper clinical care is pressing, with an accepted clinical standard of care developed to include routine and random drug adherence testing. Increasing regulatory oversight fuels fear and caution, yet the legislative actions are driven in part by an inadequate response of the medical community to the rapid rise in prescription drug abuse and associated morbidity and mortality(35).

The practice of safe opioid prescribing has evolved over time to include standard practices of assessing risk and documenting responsible care in a systematic way. It has long been understood that it is necessary to consider all patients potentially at risk. One of the earliest clear statements of careful practice was the policy of Universal Precautions (https://www.gpo.gov/fdsys/pkg/CFR-2010-title29-vol6/pdf/CFR-2010-title29-vol6-sec1910-1030.pdf accessed 06/29/2016) for blood borne pathogens, which emphasizes that all patients should be considered at risk. It has since become a standard of practice to routinely assess the risk of opioid addiction and abuse. Various tools are employed by prescribers in screening patients initially and subsequently to assess their likelihood of difficulties with opioids. These include the CAGE Questionnaire, Opioid Risk Tool, SOAPP*R, COMM, CRAFFT Screening Interview, DIRE, and the NIDA Drug-Use Screening Tool.

Over time, multiple guidelines from professional societies and organizations, and regulatory bodies have echoed this philosophy. Acknowledgment of societal responsibility of prescribing, necessitating documentation and diligent monitoring of compliance in patients, has evolved with multiple guidelines from all sectors stressing these practices. There is general agreement that testing is recommended before the initiation of opioids and during therapy. Federal regulatory agencies have developed guidelines and policies that support compliance testing. These include the Veterans Administration/Department of Defense VA/DoD Clinical Practice Guidelines for COT: Management of Opioid Therapy for Chronic Pain, May 2010 (http://www.healthquality.va.gov/guidelines/Pain/cot/COT_312_Full-er.pdf accessed 06/29/2016). Their recommendations include obtaining a UDT before initiating opioid therapy trial and randomly at follow-up visits to confirm the appropriate use of opioids.

The Federation of State Medical Boards has had a series of Model Policies on the Use of Controlled Substances over the years

regarding proper prescribing, beginning in May 1998, then May 2004, and the July 2013 Model Policy on the Use of Opioid Analgesics in the Treatment of Chronic Pain, with this policy superseding the previous ones (http://www.painpolicy.wisc.edu/sites/www.painpolicy.wisc.edu/files/FSMB_pain_policy_july2013.pdf accessed 06/29/2016). The Policy includes the patient's agreement to periodic drug testing (i.e. urine, blood, hair, or saliva), and that patients being treated for addiction should be tested as frequently as necessary to ensure therapeutic adherence, but for patients being treated for pain, clinical judgment trumps recommendations for frequency of testing.

The Centers for Disease Control Guideline for Prescribing Opioids for Chronic Pain—United States, 2016 details the use of urine drug testing (http://www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6501e1.pdf accessed 06/29/2016). The recommendations include that when prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications, as well as other controlled prescription drugs and illicit drugs. Prior to starting opioids for chronic pain and periodically during opioid therapy, clinicians should use urine drug testing to assess for prescribed opioids as well as other controlled substances and illicit drugs that increase risk for overdose when combined with opioids, including nonprescribed opioids, benzodiazepines, and heroin. They include that in most situations, initial urine drug testing can be performed with a relatively inexpensive immunoassay panel for commonly prescribed opioids and illicit drugs. Patients prescribed less commonly used opioids might require specific testing for those agents. Their position is that the use of confirmatory testing adds substantial costs and should be based on the need to detect specific opioids that cannot be identified on standard immunoassays or on the presence of unexpected urine drug test results. In addition, clinicians should not test for substances for which results would not affect patient management or for which implications for patient management are unclear. They recommend clinician familiarity with results, explaining the tests to patients, and discussing unexpected results with the laboratory and the patient. If unexpected results are not explained, a confirmatory test using a method selective enough to differentiate specific opioids and metabolites (eg, gas or liquid chromatography/mass spectrometry) might be warranted. They include actions to be taken for unexpected results.

Forty seven states and the District of Columbia have policies regarding Pain Management and proper prescribing. Many of them include the Federation of State Medical Boards Guidelines. State agencies have also formulated guidelines, including the Washington State Agency Medical Directors' Group (AMDG) (http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf accessed 06/29/2016), which gives detailed specific information and recommendations. Wisconsin has recently issued the Chronic Opioid Clinical Management Guidelines for Wisconsin Worker's Compensation Patient Care (https://dwd.wisconsin.gov/wc/medical/pdf/CHRONIC%20OPIOID%20CLINICAL%20MANAGEMENT%20GUIDELINES%20.pdf accessed 06/29/2016).

Specialty Boards have developed guidelines for proper opioid prescribing. The American Academy of Family Practice developed recommendations in 2012, Rational Use of Opioids for Management of Chronic Nonterminal Pain (http://www.aafp.org/afp/2012/0801/p252.html accessed 06/29/2016), with recommendations for urine drug testing pretreatment and randomly during treatment. Differences in types of testing are discussed. Professional societies and organizations have also developed guidelines and policies. The American Pain Society and American Academy of Pain Medicine teamed up to develop the landmark APS/AAPM 2009 Guidelines (http://americanpainsociety.org/uploads/education/guidelines/chronic-opioid-therapy-cncp.pdf accessed 06/29/2016), which include examination of various aspects of urine drug testing and recommend pretreatment and concurrent monitoring of patients.

The American Society of Addiction Medicine (ASAM) released a detailed review of urine drug testing with Drug Testing: A White Paper of the American Society of Addiction Medicine dated October 26, 2013 (http://www.asam.org/docs/default-source/public-policy-statements/drug-testing-a-white-paper-by-asam.pdf accessed 06/29/2016). The reviewed the science and practice of drug testing. It explored the wide range of applications for drug testing and its utility in a variety of medical and non-medical settings. It promoted the use of drug testing as a primary prevention, diagnostic, and monitoring tool in the management of addiction or drug misuse in medical practice.

The American Society of Interventional Pain Physicians (ASIPP) has published an updated two-part Guideline for Responsible Opioid Prescribing in Chronic Non-Cancer Pain. The guidelines include an updated literature review and eliminated some of the inaccuracies found in the previous version(36). Part I(37) is an assessment of the evidence surrounding use of COT. They found that there is good evidence that non-medical use of opioids is "extensive." Approximately 30% of chronic pain patients "may not" use their controlled substances as prescribed, and this group is at higher risk of illicit drug use. Limited evidence was found for reliability and accuracy of drug screening tests. The guidelines cite fair evidence to support use of UDT and PDMP reports to identify patients who are non-compliant, have the potential for abuse, or who are using illicit substances. In Part II(38) the authors recommend that UDT must be done at initiation of therapy, and then to monitor adherence and identify potential abuse.

The Pain Association of Singapore Task Force published evidence-based guidelines for use of opioids for chronic non-cancer pain in 2013(39). The adherence monitoring steps recommended in the text include urine drug screening, pill counts, and regular office visits. They also suggest that review of the patient's medication history should be done regularly. Monitoring of functional goals is also recommended to be included. There is no detail offered regarding type of drug testing, frequency of tests, or how results should be managed.

"Urine Drug Testing: Current Recommendations and Best Practices," guidelines from The Texas Pain Society published in 2012(40), recommend obtaining a patient report of medications taken and timing of last doses prior to requesting a test. Timing of UDTs should be random to avoid substitution or other methods of falsification of the specimen, yet these guidelines recommend referring the patient to an independent laboratory for urine collection and testing. This collection technique offers ample opportunity for falsification. They also suggest that if collection is performed in the physician's office, the patient should change into a gown first, and then provide the specimen in a bathroom with exterior water shut off and with colored toilet water. Neither of these options exists in most physicians' offices, and plumbing alterations are expensive. The authors note that strict chain-of-custody protocols similar to the Department of Transportation and Mental Health Services Administration have not been applied consistently to physicians treating chronic pain. They suggest that a blood sample can be obtained if the patient is unable to provide a urine specimen.

Recommendations include basing frequency of testing on risk assessment. High-risk patients should be screened at least four times per year, up to every month or every office visit(40), although these approaches eliminate the "random" component. For low-risk patients, random screening once or twice per year was suggested to be adequate. Patients who exhibit abnormal UDT results or aberrant behaviors should be considered higher risk. Urine drug testing should include adulteration testing (specific gravity, temperature at the time of collection, creatinine, and pH). Immunoassay testing offers rapid feedback, but is subject to false positive and false negative results. Also, they note that point-of-care testing (POCT) devices that were developed for workplace screening use high cutoff thresholds, and hence offer low sensitivity. They recommend that POCT testing be considered preliminary and go so far as to say that "failure to send urine for confirmatory testing is a poor practice" (ES124). Confirmatory testing should be done by either LC-MS/MS, GC-MS, or GC-MS/MS, as these techniques offer high sensitivity and specificity for specific drugs and metabolites. Finally, the authors state that quantitative testing cannot be used to verify compliance with a particular dosing regimen because of variations in muscle density, volume of distribution, and other variations in drug metabolism.

The use of drug testing for compliance monitoring has clearly become an accepted and required part of the care of pain management patients. As in much of medicine, the scientific evidence is being developed over time. Information and the methods of addiction medicine are being used to help define the domain. Studies have helped the development of medications less appealing for diversion or abuse. The requirement for the use of laboratory testing for compliance when prescribing opioids is firm, as it is the only concrete tool to approximate actual medication and drug use. When cases are reviewed by regulatory and legal authorities or, increasingly, some payers, prescribers and their practices are judged to be inadequate if there is not routine compliance lab testing. Prescribers can be sanctioned for too little testing, as well as too much testing, with overuse of resources. The exact definition of these terms is not available, and is judged by what is considered proper care for the patient and those around him.

Challenges with the Interpretation of Laboratory Test Results

While urine toxicology testing is currently regarded as the standard for adherence monitoring of patients taking controlled substances to manage chronic pain, urine drug testing results are performed/read and interpreted by distinctly different sets of individuals. One group is clinical laboratory physicians and scientists; another group is the clinical providers, the clinicians, nurses, pharmacists, and others directly involved in the patient's care. Others may have reason to access or review such data from time to time, such as those in legal or law enforcement, policy, and insurance. Correctly interpreting test results requires that these individuals have the knowledge and experience needed for accurate interpretation, and the skill levels vary considerably within and between each group. The earliest reference to this failing was in 1998, when Durback(41) surveyed 227 West Virginia emergency department physicians and found that few understood what such testing included. Of note, the investigators surveyed the corresponding laboratories beforehand and had a comprehensive listing of the tests performed and available. Generally, there was confusion as to which benzodiazepines and amphetamines could be detected through urine drug testing. Of the 81 responding physicians, only four correctly identified the exact drugs identified by their laboratories. The point of this survey was to demonstrate the potential for misinterpretation of test results if those who read the results are not aware of the testing limitations(41).

Reisfield and colleagues(42, 43) conducted similar studies assessing the urine toxicology knowledge base of physicians attending educational meetings. One set of meetings focused on pain management (three conferences across three months)(43), while the other was a review course for family medicine physicians(43). All participating physicians were asked to complete a questionnaire, and those attending the family medicine meeting were surveyed about their interactions with their clinical laboratory. The quiz covered drug metabolism (five questions), use of confirmatory or definitive testing (one question), passive inhalation of marijuana (one question), and presence of morphine and codeine in poppy seeds (one question). Of the 174 physicians who completed the materials, 123 self-identified as being involved in pain management. It was disappointing that none of the participants achieved a perfect score and that less than 25% were able to correctly answer more than half of the questions. The questions with the fewest correct responses were those relating to basic pharmacology, e.g., drug metabolism and excretion, not testing issues or limitations. A comparison of the responses between those attending the pain management meetings to those

attending the family medicine meeting found involvement in pain management did not translate into a higher skill set.

Starrels et al.(44) used the same set of questions to assess the knowledge of internal medicine residents in a university health system and simultaneously assessed the trainees' confidence in interpreting drug testing results. Of the 99 residents included in the data analysis, 16.2% routinely ordered UDT when caring for chronic pain patients receiving opioids and 29.3% occasionally ordered testing for most or all patients, while 23.2% only ordered UDT when there were concerns or when a preceptor requested it, and 27.3% never ordered the testing. The number of correct responses on the knowledge assessment ranged from zero to six, with 27.3% correctly answering four or more test items. In this cohort, the true-false question dealing with second-hand marijuana smoke exposure received the greatest number of correct responses. Items with the least number of correct responses were those related to metabolic pathways, similar to what was observed previously. The survey also included questions related to the trainee's confidence in interpreting UDT results, and, interestingly, found that 55.6% were confident in their ability to interpret the results. The investigators classified those who expressed confidence but answered less than half of the questions correctly as "overconfident." Using these criteria, 40.4% were overconfident.

In a survey of Canadian family physicians, Allen and colleagues(45) found that 68% performed UDT "never or less than 25% of the time" prior to starting opioids. For monitoring of compliance after starting chronic opioids, 58% had the same response. Of the surveyed physicians, 72% felt that their knowledge of the practical aspects of UDT was important to optimize opioid prescribing, but their specific knowledge of UDT interpretation was not evaluated.

In a retrospective chart review of 333 patients treated with opioids for at least three months, Colburn and colleagues(46) compared cohorts of attending physicians' patients to those of residents. Residents had significantly more opioid patients (13.9% vs. 5.9%, $p<0.001$). Patients followed by residents were significantly more likely to have aberrant behaviors, such as reporting lost or stolen medications (25.7% vs. 12.2%, $p<0.003$), receiving opioids from other providers (17.8% vs. 7.6%, $p<0.008$), having a positive UDT for non-prescribed opioids, stimulants, or sedative medications (13.4% vs. 3.8%, $p<0.004$), and were more likely to have had a report of overdose or intoxication (4.5% vs. 0.0%, $p = 0.014$).

Allen et al.(45) conducted a survey focused on the knowledge and experiences of family physicians practicing within Canada. Of 649 respondents, 72% considered knowledge of the practical aspects of urine drug screening an important or useful factor allowing them to optimize the use of opioids in the treatment of their chronic non-cancer pain patients. Similarly, studies by McCarberg and others(47-49) each concluded that there is a need for physician education about descriptions of testing methods employed, proper test utilization, and limitations of drug testing. Such knowledge is helpful, but as with any subject matter, attainment of a sufficient level of competency or expertise comes with constant education and practice.

In the end, the goal of this LMPG guideline for pain management is to address many of these issues and challenges described above and to provide evidence-based recommendations for clinical laboratorians, practicing pain management clinicians, and policy-makers (e.g. regulatory bodies and health insurance companies). Table G and H (Appendix B) show a summary of the evidence-based LMPG recommendations and consensus-based expert opinions, respectively.

CHAPTER 1

Testing for common classes of relevant over-the-counter, prescribed, and non-prescribed drugs and illicit substances abused by pain management patients

Healthcare providers who treat pain patients may order drug testing to understand if the selected pharmacotherapy is effective for symptom relief or functional improvement without unacceptable adverse effects; to optimize treatment or make medication adjustments; to ensure compliance with the treatment regimen; or to understand if there is a potential for medication misuse. Many of these providers will order clinical laboratory drug testing but may be unsure of the effectiveness of these tests. The literature reviewed in this chapter addressed the evidence for effectiveness and minimum frequency of drug testing in pain management patients. This section will address the various medications used in pain management and determine which ones laboratories need to be able to detect in pain patients.

Laboratory drug testing and clinical outcomes in pain management testing

The goal of developing specific testing recommendations is to balance the completeness and accuracy of test results with the cost of the testing paradigm. It is critical that a valid specimen is obtained and enough substances are evaluated to determine appropriate adherence with the treatment regimen. The testing must also be able to identify polysubstance use, abuse, addiction, and possible diversion before the patient (or recipient of diverted medications) experiences a significant adverse event. Lastly, it is also important to note that studies continue to demonstrate that the administered dosage does not necessarily correlate with the concentration of the drug in an individual's urine.

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**

Numerous studies looked at outcomes including adherence to the prescribed regimen along with detection of illicit drug use with laboratory drug testing as the tool. Although the vast majority of the reports were looking at urine, other matrices, such as plasma and oral fluid, have also been evaluated and showed some efficacy(50, 51).

One other point to consider is the breadth of laboratory testing. Table 8 shows the three main tiers of drugs/drug classes that are being recommended to test in pain management patients based on risk. It should be noted that this table is not meant to be a comprehensive list of all drugs that need to be tested for in every pain management patient, but instead should be used as a guideline. Tier I represents the scope of testing that should be done as part of routine monitoring and covers the common classes of drugs of abuse, as well as the drugs commonly prescribed to pain management patients. Tier ll testing should also be added to screen for drug use/abuse in patients identified as high risk by the treating clinicians. These could include patients with a known history of abuse for medications in this category. However, it may also include drugs where the prevalence of use/abuse is endemic to local region. In addition, it applies to patients who have polypharmacy that puts them at an increased risk of adverse drug reactions, or to detect patients with multiple providers. Furthermore, it may also apply to patients who experience a lack of efficacy for one of these drugs or who may be experiencing toxicity from them. Tier III testscan also be examined when they are clinically indicated, either by history of use, medication list, or very high probability of misuse/abuse, in a specific patient rather than for every patient.

Table 8. Tiers of drug testing

Tier	When to Order	Drug Class	Example Drugs or Drug Metabolites*
I	Routine Monitoring	Amphetamines	Amphetamine
			Methamphetamine (MDMA)
			Methylenedioxymethamphetamine (MDA)
			Methylenedioxyethylamphetamine (MDEA)
		Barbiturates	Amobarbital
			Butalbital
			Phenobarbital
			Pentobarbital
			Secobarbital
		Benzodiazepines	Alprazolam
			Chlordiazepoxide
			Clonazepam
			Clorazepate
			Diazepam
			Estazolam
			Flurazepam
			Halazepam
			Lorazepam
			Medazepam
			Midazolam
			Oxazepam
			Prazepam
			Temazepam
			Triazolam
		Cannabinoids	Δ9-tetrahydrocannabinol (THC) 11-nor-9-carboxy-THC (THCCOOH)
		Cocaine	Cocaine
			Benzoylecgonine
		Opiates/Opioids	6-acetylmorphine (6-AM)
			Buprenorphine
			Codeine
			Dihydrocodeine
			Fentanyl
			Hydrocodone
			Hydromorphone
			Methadone
			Morphine
			Oxycodone
			Oxymorphone
			Tapentadol
			Tramadol

Table 8 *continued*

Tier	When to Order	Drug Class	Example Drugs or Drug Metabolites*
II	High-risk patients with known history of abuse for this medication or prevalence of drug use is endemic to local region, risky polypharmacy, multiple providers, or if prescribed and patient shows lack of efficacy or toxicity	Alcohol	Ethanol or metabolites (metabolites offers more useful window of detection for chronic pain patients)
		Anticonvulsants	Carbamazepine
			Felbamate
			Gabapentin
			Lacosamide
			Lamotrigine
			Levetiracetam
			Oxcarbazepine
			Phenytoin
			Pregabalin
			Rufinamide
			Tiagabine
			Topiramate
			Valproic acid
		Antidepressants	Amitriptyline
			Citalopram
			Clomipramine
			Desipramine
			Doxepin
			Duloxetine
			Fluoxetine
			Imipramine
			Nortriptyline
			Paroxetine
			Sertraline
			Venlafaxine
		Synthetic cathinones	Compounds ever-changing, representative examples include: methylone, mephedrone, and alpha-PVP
		Antitussive	Dextromethrophan
		Dissociative anesthetic	Ketamine
		Hallucinogens	Lysergic acid diethylamide (LSD)
			Phencyclidine
		Muscle relaxants	Carisoprodol
			Meprobamate
			Methocarbamol
		Narcotic pain-reliever	Propoxyphene

Table 8 *continued*

Tier	When to Order	Drug Class	Example Drugs or Drug Metabolites*
III	As Clinically Indicated	OTC analgesic	Acetaminophen
			Salicylate
		Antihistamine	Certirizine
			Chlorpheniramine
			Diphenhydramine
			Loratidine
		Antipsychotics	Amisulpride
			Amoxapine
			Chlormethiazole
			Clopenthixole
			Chlorpiprazine
			Chlorprothixene
			Cloxazepine
			Clozapine
			Distraneurine
			Dixyrazine
			Chlorpromazine
			Fluentixol decanoate
			Fluphenazine
			Haloperidole
			Loxapine
			Melperone hydrochloride
			Methotrimeprazine
			Olanzapine
			Oxilapine
			Perphenazine
			Phenothiazine
			Pimozide
			Quetiapine
			Risperidone
			Sulpiride
			Thioridazine
			Tiapride
			Trifluoroperazine
			Ziprasidone
			Zotepine
		Synthetic cannabinoids	Compounds ever-changing, representative examples include: JWH-018, ADB-FUBINACA, 5F-ADB, FUB-AMB, and ADB-PINACA.

Note: This table is not meant to be a comprehensive list of all drugs that must be tested for in every pain management patient. The list only represents examples of drugs from each particular drug class. The provider should take into account the medications prescribed to the patient, the patient's past substance abuse history, along with other accessible or locally abused drugs, and the patient's clinical presentation when selecting which tests to order. Furthermore, it may be more appropriate to look for and identify a drug's metabolite based on what is found in the matrix (e.g., urine). As a result, laboratory tests must include the appropriate parent drug and/or metabolites based on each matrix.

Frequency of laboratory testing

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**

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**

The evidence for specific schedules of drug testing in general is weak, mainly due to the lack of randomized clinical trials comparing the effectiveness of testing schedules or methods specifically in the chronic pain population. Existing practice guidelines make recommendations based on observational studies or expert consensus opinion. Existing clinical practice guidelines recommend testing at baseline and randomly, but at minimum annually for low-risk patients (American College of Occupational and Environmental Medicine, APS-AAPM, ASIPP, University of Michigan Health System, VA/DoD). However, in patients with risk factors for misuse/abuse, more frequent monitoring is recommended, but the optimal frequency for these patients has not been determined(51).

Laboratory testing and its ability to identify non-compliance in pain management regimens

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)

Studying patient non-compliance with the therapeutic regimen is difficult unless non-prescribed medications or illicit drugs are present in the tested matrix. Generally, testing frequency is low and the windows of detection in the different matrices (urine, oral fluid, blood/plasma/serum) are usually only a few days. Thus, most of the time between biological testing, the patient is inadequately monitored. Even when the matrix has a longer window of detection, such as for hair, minimum exposure is required to give a positive result, and differences in disposition can occur based on hair color for basic drugs, or for meconium, minimum exposure frequency is needed to produce positive test results. Therefore, additional means of monitoring are highly useful to improve the detection of non-compliance, such as pill counts and interviews. Additional research studies are needed where the collection of other physician tool data (e.g., self-report, pill counts) are directly compared with biological testing data.

A few manuscripts compare the success of different tools for identifying patient non-compliance. Cone et al.(14) evaluated the critical components of an opioid risk management program, based on North American evidence-based guidelines, and Heit et al.(53) presented reasons urine is the specimen of choice for monitoring pain management patients. Evidence in the latter manuscript was based on prior literature and experience. The report contained no original data.

CHAPTER 2

Specimen types and detection times

This section discusses alternative biological specimens for the detection of over-the-counter medications, prescribed and non-prescribed drugs, and illicit substances in pain management patients undergoing compliance monitoring. Each biological specimen provides a unique perspective on an individual's drug exposure and may reveal data on route of administration, and the amount, frequency, and duration of drug use. Drugs are deposited into biological fluids and tissues based on absorption, distribution, biotransformation, and excretion processes. A drug's chemical and physical properties, route of drug administration, extent of protein binding, tissue blood flow, and amount, duration, and frequency of drug exposure affect drug disposition. Drug molecular weight, pKa, protein binding and lipophilicity and tissue pH will determine drug disposition in the matrix. Drug testing provides an objective measure of whether an individual was previously exposed to drugs, and is superior to self-reported drug use history, especially when compliance with a therapeutic scheme is assessed. The clinical utility, detection windows, and advantages and limitations of each biological matrix for commonly prescribed and abused medications in pain management patients are described.

Urine is typically the preferred matrix for pain management drug testing, as it has a longer window of drug detection than blood, has an adequate specimen volume for drug screening and confirmation, and drug markers (either parent drug or metabolites) are present in high concentrations. It is also less invasive and doesn't require a phlebotomist for collection. Disadvantages include a high risk of adulteration of the sample by the patient to avoid detection of non-compliance with the therapeutic regimen. Observed specimen collection is generally not performed and is disliked by patients and collectors. Specialized bathroom facilities may be needed, and specimen collectors should be of the same gender as patients. For these reasons, there is much interest in alternative matrices such as oral fluid or hair for drug testing of pain management patients.

Oral fluid offers an observed, non-invasive, and gender-neutral specimen collection and presence of the parent drug generally, as well as metabolites. Disadvantages include limited sample volume and shorter window of drug detection, similar to that of blood. Passive diffusion, ultrafiltration and/or active secretion from blood are means for incorporation of drugs into the alternative matrices. Diffusion across cell membranes is limited for drugs with molecular weights greater than 500 daltons, and for ionized and protein-bound drugs. Plasma and saliva pH and a drug's pKa and degree of protein binding control passage across plasma membranes and incorporation into oral fluid. If drug is administered by the oral, smoked, or intranasal route, contamination of oral fluid may occur, resulting in elevated drug concentrations for several hours, prior to equilibration with the free fraction of drug in blood.

Monitoring drugs in sweat generally offers a comparable window of detection to urine and also a non-invasive collection. Another advantage is a long detection window of seven days, the period the sweat patch is generally worn. However, there is significant variability in sweat production, and the amount of sweat excreted is highly variable depending upon the environmental temperature, amount of physical exercise, and stress. A non-occlusive sweat collection device can be worn for an extended time period and concentrates solutes on a collection pad while allowing water to evaporate from the patch. Sweat testing is relatively non-invasive, and identification of drug in sweat may serve as a means of monitoring drug use. Passive diffusion and transdermal migration of drugs into sweat are the primary mechanisms of drug incorporation onto the sweat patch. Highly lipid-soluble drugs will preferentially accumulate into sweat. Single and multiple drug use over seven days is continuously monitored.

Hair offers the largest window of drug detection, but does not detect recent drug exposure. Hair also offers a non-invasive and observed specimen collection, but drug incorporation and detection can be altered with bleach, color or straightening agents. Hair may also be externally contaminated. Basic drugs preferentially bind to melanin in dark-colored hair, creating a color bias, whereby brunettes will have more drug in their hair than blondes when exposed to the same drug dose. Another disadvantage is the potential for external contamination from drug-laden smoke in the environment. Hair growth rates vary according to body location, sex, and age, but average 1.3 cm/month. There are multiple mechanisms for drug incorporation into hair, including passive diffusion from blood into the hair follicle; excretion onto the surface of hair from sweat and sebum; and external contamination. Parent drugs rather than metabolites are the primary analytes found in hair. Analysis of hair segments may provide historical drug use over months to years.

Prenatal drug exposure is a major public health and safety issue. Accurate identification of drug-exposed infants is necessary to determine the type and magnitude of adverse drug effects. Ma-

ternal self-report of drug intake is unreliable due to the fear of legal and child custody consequences. Urine drug monitoring of newborns is difficult, and the window of detection of maternal drug use is restricted to a few days prior to birth. Meconium collected usually during the first three days after delivery provides a much wider window of detection of drug exposure, possibly extending back to the 12th gestational week. Meconium is easily and non-invasively collected from the diaper. An important issue is to determine the best markers of in utero drug exposure in meconium, and if lower limits of detection need to be achieved. It cannot be assumed that markers in meconium will be the same drug markers used in adult urine samples. It is also difficult to determine if a drug or metabolite comes from the mother via passive diffusion across the placenta or fetal swallowing of amniotic fluid, as drug-metabolizing enzymes are present in in both. There also is substantial variation in the maturity of the fetal liver and therefore the ability to metabolize drugs is equally variable. .

An alternative to meconium testing for in utero drug exposure is the umbilical cord. Umbilical cord testing is rapidly growing due to the immediate availability and ease of collection of this specimen at the time of delivery, adequate specimen amount. However, the exact mechanism of drug deposition in the umbilical cord is not fully understood.

Another potential alternative matrix is breast milk. Breastfed infants may be exposed to drugs of abuse present in breast milk. Exposure to drug in breast milk is generally much lower than exposure of the fetus in utero. Many factors determine the concentration of drug in breast milk, including the mother's free plasma drug concentration, maternal metabolic processes, high plasma protein binding, and the amount of blood flow to the mammary glands. Inactive glucuronide drug metabolites may be deconjugated in the infant's gastrointestinal tract to produce the active compound for absorption. Drugs passively diffuse across the mammary epithelium and filter into breast milk. Ion trapping of weakly basic drugs in the milk occurs because the pH of breast milk is slightly acidic relative to plasma. However, limited data exists around this matrix and direct testing of the infant is still preferred.

In the end, efficient and reliable laboratory analytical methods have been developed to monitor drugs in multiple matrices. Many methods were developed for drugs in urine, as this is the historical matrix of choice, and most methods focused on analgesic identification and quantification. Investigators extended testing to include ethanol use monitoring by examining ethyl glucuronide and ethyl sulfate in urine following various ethanol drinking sessions.(54, 55) Another group validated a LC-MS/MS method for simultaneously quantifying hydrocodone, hydromorphone, norhydrocodone, dihydrocodeine, oxycodone, oxymorphone, morphine, and codeine in serum from 154 obstetric patients undergoing Cesarean section(56). Kokki et al.(57) determined oxycodone serum pharmacokinetics after controlled administration to pregnant women and their neonates, improving interpretation of expected concentrations and facilitating oxycodone monitoring. Jeleazcov et al.(58) determined hydromorphone concentrations in blood in postoperative pain patients and determined pharmacokinetic parameters. They reported individual differences between patients and useful clinical data for understanding the range of expected laboratory results. Bista et al.(59) monitored fentanyl and norfentanyl concentrations in 11 paired, simultaneously collected oral fluid and plasma samples following controlled 25 to 100 ug/h transdermal fentanyl administration. They also noted that fentanyl adsorbed to the Salivette® oral fluid collection device, reducing concentrations. Dried blood spots (DBS) are collected less invasively, and drugs are more stable in this matrix, offering advantages for monitoring drug use in pain management settings(60, 61).

Laboratory testing vs. other physician tools, prescription monitoring, and self-report

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**

Most controlled administration studies of prescription and over-the-counter drugs examined urine, blood, or serum concentrations, providing a scientific database for employing these biological fluids in monitoring programs (62, 63). Urine has been the matrix of choice for monitoring pain patients, but other matrices are now being used more frequently.(64-66) In addition, urine drug testing is more effective than self-reporitng at revealing recent opioid use(67).

Poklis et al.(68) studied urine concentrations of fentanyl and norfentanyl during application of Duragesic transdermal patches to patients with chronic pain. Patients (n=546) received either 25, 50, 75, or 100 μg/h continuous-release fentanyl patches and provided urine specimens hours and days after application.. These data are helpful for interpreting urine fentanyl results and for identifying the importance of monitoring norfentanyl as a marker of fentanyl intake due to much higher concentrations than the parent drug itself. Heltsley et al.(69), in a similar report, described expected oral fluid drug concentrations. Cao et al.(70) reported opioid concentrations in simultaneously collected urine and oral fluid samples, improving our understanding of drug disposition in the two matrices.

Analytical methods for opioids in hair (71-76) are well established and applicable for selected clinical situations. Hair is an excellent matrix to extend detection times, a useful matrix when biological monitoring occurs only sporadically. These studies also address some of the limitations of hair analysis, including the potential for external contamination from the environment and col-

or bias (the potential for greater basic drug accumulation in hair with high melanin content [dark hair]).

Meconium and/or umbilical cord analysis offers a means to identify if a fetus was exposed in utero to drug use by the mother(77-79). Meconium begins forming during about the 12th week of gestation, providing a much wider window of drug detection during pregnancy; however, indications are that meconium better reflects the last trimester of pregnancy due to the large accumulation of meconium during this period. Meconium is well established for evaluation of drug use during gestation. Umbilical cord testing is the newest means of evaluating maternal drug use and offers the advantage of immediate collection at birth and availability from all neonates.

Postmortem testing is relevant for determining cause and manner of death, but also to evaluate adverse clinical outcomes. Davis et al.(80) reported the position of the National Association of Medical Examiners (NAME) on proper collection of postmortem blood, vitreous, and urine. They stated that proper interpretation of opioid concentrations must include consideration of medical history. The report was a position paper and contained no original data. Fernandez et al.(81) examined vitreous fluid for evidence of cannabinoids, cocaine, amphetamines, and opiates using a Cozart DDS system with confirmation by GC-MS or LC-MS/MS. They found agreement of the Cozart screening method with the chromatographic confirmations for identifying cocaine, but mixed results with other drugs. Al-Asmari et al.(82) reported a LC-MS/MS method for multiple drugs in postmortem blood. This procedure may be useful for assessing unsuccessful clinical outcomes resulting in overdose and/or death.

While the studies described below were given a quality rating of only III (evidence is insufficient to assess the effect on health outcomes because of the limited number of patients or power of the study, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information), the information contributes to the body of science supporting laboratory testing in pain management and other monitoring programs. Backer et al.(83) compared a Microgenics DRI oxycodone immunoassay for screening urine with a GC-MS confirmation method. With a 100 ug/L immunoassay and GC/MS confirmation, 433 of 435 urine specimens from a pain management program were confirmed. The investigation did not determine false negative tests. Heit et al.(53) presented reasons why urine is the specimen of choice for monitoring pain management patients. Evidence was based on prior literature and experience. The report offered no original data. Shaw et al.(84) developed a simple assay for 5-aminosalicylates and outpatients' concentrations, comparing this new method to the standard urine salicylate method. Although a strong correlation (R range=0.91-0.98) was noted, comparison of paired samples was not included. Shen et al.(85) determined 6-acetylmorphine (6-AM, 6-MAM), morphine, and codeine concentrations in hair of heroin users in a treatment program who abstained from drug use. They determined that after six months, the proximal 3 cm of hair tested negative for 6-AM. Pujol et al.(86) validated an IDS One-Step ELISA for cannabinoids, cocaine, opiates, and amphetamines in hair using GC-MS for confirmation. The study reported cutoff concentrations that optimized sensitivity and specificity.

Applications for alternative matrices

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**

Alternative matrices such as oral fluid, blood/plasma/serum, hair, meconium, and umbilical cord show promise and offer advantages over urine for testing, but the evidence to date is insufficient to assess whether the results are equivalent to urine testing for monitoring patient compliance. Other matrices may also be appropriate in specialized circumstances, but the samples must be properly collected, stored, and transported in the appropriate collection device at the proper temperature, and tested by qualified personnel using a validated method for that matrix. Additional studies are still needed.

Martins et al.(87) performed a quantification of (R)-methadone and its (L)-EDDP metabolite enantiomers in oral fluid, finding that these enantiomers reflected the free fraction of the drug in blood. Ontario Health Quality(88) performed an evidence-based evaluation of oral fluid drug testing for methadone compliance by directly comparing simultaneous urine and oral fluid samples. Their review of only four relevant manuscripts resulted in the following conclusions: The window of drug detection in oral fluid is shorter than in urine, suggesting its usefulness when recent drug use is suspected; and oral fluid offers an alternative when urine collection is not possible or when adulteration of urine is suspected. Disadvantages of oral fluid testing include point-of-collection devices for oral fluid, small sample volume, and potentially elevated oral fluid concentrations following oral methadone administration. Janowska et al.(89) evaluated oral fluid testing for opiates during addict detoxification by comparing serum and oral fluid concentrations of morphine and codeine after heroin intake. Although morphine concentrations were moderately correlated in serum and oral fluid, codeine concentrations were not, and serum morphine concentrations exceeded serum oral fluid concentrations. Oral fluid morphine concentrations were useful for monitoring decreases following heroin administration. Peters et al.(90) used 50 µL oral fluid as a matrix for determining enantiomeric amphetamine concentrations with negative chemical ionization gas chromatography-mass spectrometry assay in a controlled racemic MDMA administration study. Peak MDMA oral fluid concentrations occurred one to four hours after MDMA administration, with R- enantiomers significantly exceeding S-en-

antiomers, and R/S ratios increasing over time.

For example, Rittau and McLachlan(91) evaluated paracetamol and metabolite pharmacokinetics in venous and capillary blood, and oral fluid in 20 healthy normal participants after two 500 mg doses at steady state. Paracetamol, paracetamol sulfate, and paracetamol glucuronide were quantified in venous and capillary blood, but metabolites were not identified in oral fluid. Pharmacokinetics were similar in all three matrices for paracetamol, but the Cmax was significantly higher in venous blood than the other two less invasive sampling methods. Pharmacokinetics were similar across matrices, with the correlation strongest during absorption in the first hour following administration. Saracino et al.(92) found that when methadone concentrations in dried blood spots were compared with plasma concentrations, the mean of duplicate dried blood spot samples correlated well with plasma concentrations after adjusting for hematocrit and sample volume. The higher variability in DBS concentrations required duplicate analyses for this matrix as a potential new matrix for pain management monitoring. Clavijo et al.(93) demonstrated the usefulness of a method for quantifying concentrations of morphine and 3- and 6-morphine glucuronide in 20 µL dried blood spots in a single pediatric patient receiving morphine for pain, and demonstrated a good correlation with plasma concentrations.

Stramesi et al.(94) compared performance of nine hair testing laboratories in Italy and Spain for qualitative and quantitative analysis of opiates, cocaine, cannabinoids, and methadone. Although qualitative results were similar, quantitative results varied considerably, and the analyte of interest for cannabinoids was the parent THC rather than the consensus target of 11-nor-9-carboxy-THC. Lendoiro et al.(73) were able to analyze 35 therapeutic and illicit drugs important for pain management testing in hair by LC-MS/MS.

Concheiro et al.(50) demonstrated that it is possible to simultaneously quantify by LC-MS/MS 14 markers for buprenorphine, methadone, cocaine, opiates, and nicotine metabolites in sweat. Proof of concept for the applicability of this method was shown by monitoring a single buprenorphine-maintained opiate-dependent pregnant woman's drug use over 16 weeks.

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**

As discussed above, blood/plasma/serum are good matrices for biological monitoring of patient compliance in pain management testing; however, no manuscripts were found that specifically detailed the use of these matrices during end-stage renal failure.

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**

Alternative matrices such as oral fluid, hair, meconium, and umbilical cord show promise and have advantages over urine or blood, but the evidence to date is insufficient to assess their benefits in predicting clinical outcomes. Heltsley et al.(69) examined the screening positivity rates for oral fluid in a chronic pain population and compared them with published positivity rates for urine drug screening in the pain population and found that the oral fluid non-negative screening rate was 83.9% compared with a previously published non-negative rate of 78% for urine screening. Within those overall positives, they found that 11.5% of the screening positives in oral fluid were for illicit drugs, compared with 10.9% of the urine screening positives from a previous urine study. The authors concluded that oral fluid screening is comparable to urine screening for detecting illicit drug use in a pain management population. In a follow-up study from the same group(95), the authors examined paired oral fluid and urine specimens from a chronic pain population (n=133). Upon screening of both specimens for each patient, they found 21.3% of specimens positive in both matrices and 63.7% negative in both matrices, for an overall agreement rate of 85%. Of the 15% that disagreed, 5.4% were positive in oral fluid and negative in urine, and 9.6% were negative in oral fluid and positive in urine. The authors concluded that the Cohen's Kappa statistical test for agreement between the two methods was 0.64, documenting substantial agreement, and that the oral fluid screening results were comparable to urine screening results.

Shen et al.(85) demonstrated the utility of hair for monitoring opiate abuse, specifically showing that it takes approximately six months for the hair to be free of analytes after cessation of drug use. However, there was no direct comparison of paired hair and urine tests.

Concheiro et al.(78) examined umbilical cord buprenorphine concentrations and correlated them with maternal dose; however, the sample size was small and the finding has not yet been replicated.

Fucci et al.(96) investigated the utility of sweat testing in methadone patients by applying a sweat collection patch for one week to the bodies of 10 known heroin abusers and three non-drug-using volunteers. After one week, the patches were an-

alyzed, and methadone was detected in all the users and there were no false positives in the volunteers. In addition, cocaine was detected in two of the patients treated with methadone. Based on these results, the authors suggested that sweat is a viable alternative to urine screening for detecting illicit drug intake in pain management testing and provided a wider window of drug detection. Huestis et al.(63) directly compared 355 paired sweat and urine samples from 44 opioid-dependent patients in methadone-assisted treatment (n= matched urine and sweat patch specimens) for positive opiate results. Identifying the urine immunoassay test as the reference method, the authors found a diagnostic sensitivity and specificity of 68.6% and 86.1%, respectively. There were 13.5% false negative results and 7.9% false positive results for sweat tests compared to urine testing. The authors suggested that the sweat patches may provide a viable alternative to urine testing with a longer window of detection, but that the relatively high false negative rate may mean that weekly sweat testing would be less sensitive than more frequent urine testing.

In conclusion, while there are some studies that describe the utility of alternate specimens for drug testing in certain populations, there is no evidence that drug testing in alternate matrix specimens is more effective than urine testing for detection of drugs in pain management patients. In the absence of evidence, the committee cannot make a recommendation for or against alternate matrix testing in pain management.

CHAPTER 3

Qualitative/semi-quantitative screening assays

Traditionally, urine drug testing for pain management patients followed a forensic (legal) model and was based on Department of Health and Human Services guidelines and protocols for drugs-of-abuse testing. As such, immunoassays are typically used as the first-line screening test. These immunoassays can either be run in a qualitative (e.g. positive/negative) or semi-quantitative mode. Laboratories often use these assays in the semi-quantitative format to assist the lab in setting dilutions on concentrated samples upfront before downstream confirmatory (e.g. mass spectrometry-based) testing is performed to minimize carryover and avoid repeat testing. While immunoassays offer several advantages, including ease of use, fast turnaround time, non-invasive collection, and lower costs, they can produce false positive and false negative results(64). In a forensic model, positive immunoassay screening tests are followed by a definitive or confirmatory test, such as mass spectrometry, to avoid false positive results. False negative results, however, remain problematic with this approach. Furthermore, the FDA-approved immunoassays originally designated by the mandatory guidelines for Federal Workplace Drug Testing Programs commonly use higher cutoffs. These cutoffs may not be clinically appropriate for adherence monitoring of pain management patients. For these reasons, modifications to the forensic model of testing where labs use orthogonal testing (e.g. immunoassay screen followed by a LC-MS/MS confirmation assay) to monitor compliance in pain management are necessary.

While numerous clinical guidelines recommend urine drug testing for pain management patients as one tool to monitor compliance(36-38, 49, 97), the existing guidelines lack specific recommendations on which testing algorithm to use, including appropriate test platform(s) and testing frequency. This chapter will discuss the effectiveness of qualitative screening assays (laboratory-based and/or point of care (POC) immunoassays) at detecting relevant over-the-counter medications, prescribed and non-prescribed drugs, and illicit substances in pain management patients. It will also discuss whether laboratory-based immunoassays are better at detecting various outcomes compared to POC screening tests or quantitative mass spectrometry-based definitive tests. This chapter will emphasize that healthcare practitioners need to understand the analytical limitations (e.g., cross-reactivity, sensitivity, false positives, and false negatives) of the screening assays (laboratory-based and POC immunoassays) used to monitor their pain management patients. Furthermore, the evidence related to the appropriate timing (random vs. scheduled) of urine qualitative urine testing will be reviewed.

Clinical Utility of Laboratory-Based Screening Immunoassays

Laboratory-based immunoassays are frequently used for urine drug testing in pain management due to their rapid turnaround time, lower cost, and ease of use. However, immunoassays have limitations, including lower sensitivity and specificity. False positive and false negative results can negatively impact patient care and society. For example, patients may be falsely accused of misuse or non-adherence and therefore not receive the appropriate treatment for their chronic pain. Additionally, patients diverting medication may be missed, contributing to the societal drug abuse epidemic.

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**

Numerous articles have compared the accuracy of immunoassays to mass-spectrometry-based assays. However, many articles do not include pain management patients or specifically correlate results with outcomes. Overall, laboratory-based immunoassays across several populations (e.g., pain management, addiction patients) have been shown to correlate to mass-spectrometry-based testing and can be used to detect compliance/adherence to therapy and misuse/abuse of other drugs.

A study(65) of 20,089 urine specimens from chronic pain patients provided a unique opportunity to evaluate the prevalence of prescription opiates and metabolites, and compare opiate and

oxycodone screening results to LC–MS/MS results. All specimens were tested simultaneously with two tandem screening assays (opiates and oxycodone) and LC–MS/MS. Evaluations were performed of an opiate screening assay and two oxycodone screening assays (oxycodone ELISA and oxycodone EIA). Comparison of the opiate ELISA and oxycodone ELISA results with LC–MS/MS revealed high agreement (82.6%), whereas testing with opiate ELISA and oxycodone EIA produced moderate (55.5%) agreement with LC–MS/MS. Greater selectivity with the oxycodone EIA (less cross-reactivity with other opiate analytes) appeared to be the cause of the lower overall agreement with the opiate ELISA. However, use of the opiate ELISA in tandem testing with either oxycodone screening assays resulted in low false negative results compared with LC–MS/MS.

In general, opiate immunoassays perform very well compared to targeted screening when evaluating morphine, but at the other extreme is oxycodone/oxymorphone, where the cross-reactivity varies among manufacturers. That being said, there are immunoassays designed specifically for detection of oxycodone, and they can perform well compared to mass-spectrometry-based assays. These immunoassays specifically look for oxycodone and its metabolite with sensitivities and specificities ~99% (98). A different study (83) looked at 1,523 urine samples from pain management patients using an immunoassay for oxycodone compared to GC-MS. The immunoassay was shown to be highly reliable for the detection of oxycodone and oxymorphone in urine.

For the classic drugs of abuse (cocaine, amphetamine type stimulants, PCP, THC) immunoassay-based screening tests compare well with definitive tests, with sensitivities and specificities >95%, and are suitable for screening for these drugs(99, 100). For other drugs commonly prescribed for pain management patients, the effectiveness is less certain and is very dependent on methodology and manufacturer. Since most opioids will not be detected by a urine opiates immunoassay, they require specific immunoassays to detect them. Immunoassays specific to fentanyl, methadone/EDDP, and buprenorphine all compared well, with sensitivities and specificities ~95%, and studies showed they were suitable for screening for these drugs (101, 102). Another study evaluated a fentanyl homogeneous enzyme immunoassay (HEIA; Immunalysis Corporation) for its ability to accurately detect fentanyl in 307 urine samples from patients prescribed chronic opioid therapy. Samples were screened by HEIA and confirmed by LC–MS/MS and ELISA for diagnostic comparison. The HEIA urine fentanyl was shown to provide rapid and accurate fentanyl detection, illustrating its utility in monitoring fentanyl compliance and abuse(103). However, any screening immunoassay still has the potential for false positive and false negative results.

There is a similar phenomenon with benzodiazepines, where an immunoassay for benzodiazepines could fail to provide accurate information regarding patient-specific medication use. The false positive and false negative rates of benzodiazepine immunoassays can be particularly high for clonazepam and lorazepam(104). Another study looked at 299 urine specimens from patients treated for chronic pain using the HS-CEDIA, CEDIA, and KIMS benzodiazepine assays(105). The sensitivity and specificity of the screening assays were determined using the LC-MS/MS results as the reference method. Of the 299 urine specimens tested, 141 (47%) confirmed positive for one or more of the benzodiazepines/metabolites by LC-MS/MS. All three screens were 100% specific with no false positive results. The CEDIA and KIMS sensitivities were 55% (78/141) and 47% (66/141), respectively. Despite the relatively higher sensitivity of the HS-CEDIA screening assay (78%; 110/141), primarily due to increased detection of lorazepam, it still missed 22% (31/141) of benzodiazepine-positive urine specimens. The KIMS, CEDIA, and HS-CEDIA assays yielded accuracies of 75%, 79%, and 90%, respectively, in comparison with LC-MS/MS. While the HS-CEDIA provides higher sensitivity than the KIMS and CEDIA assays, it still missed an unacceptably high percentage of benzodiazepine-positive samples from patients treated for chronic pain. Definitive testing still offers superior sensitivity and specificity for monitoring benzodiazepines in patients treated for chronic pain(105).

A POC immunoassay format for urine drug testing in a clinician's office setting may also be appropriate, convenient, and cost-effective. Compared with laboratory testing for opioids and illicit drugs, POC immunoassays in office testing were shown to have high specificity and agreement in one study(106), demonstrating the value of this drug testing. However, clinicians need to be aware of the variable sensitivity and should take a cautious approach when interpreting the results. Definitive or confirmatory testing would ultimately still be needed to identify which drug was used in the case of a positive opiate immunoassay. Nevertheless, clinicians should feel comfortable conducting in-office UDT immunoassay testing, as long as they acknowledge the limitations of all immunoassays (e.g., they detect a drug class [benzodiazepines] and don't tell you which drug was present or cross-react with all the drugs within that drug class). The present study did show that it can be reliable, expedient, and fiscally sound for all involved. In another study, POC immunoassay testing compared favorably with laboratory testing for benzodiazepines, offering both high specificity and agreement (107). However, clinicians again should be vigilant and wary when interpreting results, weighing all factors involved in their decision.

Qualitative Definitive Testing

Immunoassays, as described above, have known limitations. False positive and false negative results can negatively affect patient care, emphasizing the importance of accurate results for prescribed, non-prescribed, and illicit drugs. Mass-spectrometry-based assays have traditionally been considered the gold standard, despite the prevalence and ease of use of laboratory-based immunoassays. Furthermore, many qualitative immunoassays are designed to detect a class of compounds. Therefore, a positive immunoassay result does not indicate which drug(s) in the class was present in the urine, whereas a definitive result by

mass spectrometry provides this information. The specific drugs in urine can help determine compliance, as well as the potential abuse of multiple drugs within a class.

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**

Several articles provide evidence that qualitative definitive assays such as GC-MS and LC-MS/MS are more sensitive and specific than laboratory-based immunoassays. One may infer, therefore, that these assays are superior at detecting adherence/compliance with or diversion/misuse of various drugs/drug classes in pain management. However, none of the studies examined any patient outcomes directly. All articles demonstrate that LC-MS/MS and GC-MS are technically superior to laboratory-based immunoassays. Many of the articles state that targeted screening assays should be used for definitive or testing with legal implications. However, despite the lack of outcome data, most of the authors conclude that immunoassays are clinically acceptable and should be used to facilitate real-time clinical decisions. The discussion has been divided by drug/drug class, and the published studies that determine the rate of false positive or false negative results as well as the sensitivity, specificity, and accuracy of laboratory-based immunoassays are summarized.

AMPHETAMINES: The positive predictive value (PPV) of amphetamine immunoassays for detecting amphetamine abuse was low in a military population(108). The performance of the Roche Abuscreen Online Amphetamine immunoassay and the Microgenics DRI Ecstasy immunoassay were compared to GC-MS, all using a cutoff of 500 ng/mL. The confirmation rates were 73% and 63%, respectively. The specificity of the immunoassays was not assessed, as negative screens were not confirmed, but the study did show a high rate of false positives with both assays. However, some of the false positive results contained amphetamines <500 ng/mL. Another study showed that the use of a dose-response relationship in serially diluted urine specimens can improve the PPV of amphetamine immunoassay, but that targeted screening methods are required to detect low amphetamine concentrations in a hospital setting(109). False negative results for amphetamine may also be obtained. One study compared the performance of the DRI amphetamine immunoassay to LC-MS/MS and showed that 9.3% (n=14) were falsely negative. However, the cutoff for the DRI assay was 1000 ng/mL, as opposed to 100 ng/mL for LC-MS/MS(110) Mikel et al. showed similar results, with false negative rates around 25%(111).

The oral fluid amphetamine immunoassays have also been shown to have a high rate of false positive results when compared to LC-MS/MS. Positive screening results were confirmed in only 43.8% of patients, yielding a false positive rate of 56.2%. Methamphetamine was similar, with a false positive rate of 36.4%(69).

BARBITURATES: Barbiturate immunoassays using oral fluid have been shown to have a high rate of false positive results compared to LC-MS/MS. In one study, positive screening results were confirmed in only 71.9% of patients, yielding a false positive rate of 28.1%(69).

BENZODIAZEPINES: Benzodiazepine immunoassays can also produce false negative results. As mentioned previously, false negative results are commonly seen in a pain management population in patients prescribed lorazepam and clonazepam(112). Darragh et al.(105) compared the KIMS, CEDIA, and High Sensitivity CEDIA (HS-CEDIA) benzodiazepine assays to LC-MS/MS in a pain management population. The authors concluded that immunoassays are inadequately sensitive for detection of all benzodiazepines in urine from patients treated for chronic pain. Alternatively, West et al.(113) studied the performance of the Microgenics DRI benzodiazepine assay (cutoff 200 ng/mL) in patients in the pain management population prescribed clonazepam and no other benzodiazepines. If a cutoff of 200 ng/mL was used for both immunoassay and LC-MS/MS, the positivity rates were 21% and 70%, respectively. The positivity rate for LC-MS/MS increased to 87% if a limit of detection of 40 ng/mL was employed. The authors conclude that a cutoff of 200 ng/mL is not sufficient to monitor clonazepam compliance and that LC-MS/MS, due to its ability to have lower limits of detection, is superior. Another study compared the performance of the DRI benzodiazepine immunoassay (not restricted to clonazepam alone) to LC-MS/MS and showed that 22% (n=280) were falsely negative. However, the cutoff for the DRI assay was 200 ng/mL and 20 ng/mL for LC-MS/MS (110). Mikel et al. showed similar results, with false negative rates of approximately 35%(111).

One study demonstrated that in oral fluid, benzodiazepine immunoassays had a low rate of false positive results compared to LC-MS/MS. Positive screening results were confirmed in 98.9% of patients, yielding a false positive rate of 1.1%(69).

BUPRENORPHINE: Several immunoassays are available to detect buprenorphine in urine, including CEDIA (Microgenics), HEIA (Immunalysis), and EIA (Lin Zhi). Leino et al.(114) compared one laboratory-based buprenorphine assay (CEDIA) to LC-elec-

trospray(ES)/MS and illustrated that CEDIA had a specificity of 95% and sensitivity of 100%, including one false positive result. However, this study included only 49 urine specimens, 29 of which were positive by MS, limiting the power of the study. Another study found similar sensitivity (100%) and specificity (87.5%) for the CEDIA assay compared to LC-MS/MS, noting two false positive screening results. Furthermore, the 5 ng/mL cutoff agreed analytically with LC-MS/MS in 97.9% of the samples(115). Both of these studies were performed in the pain management population.

The EIA buprenorphine immunoassay (LinZhi) had higher sensitivity and specificity than the CEDIA immunoassay compared to LC-MS/MS, as shown in one study. At a cutoff of 5 ng/mL, the EIA had a sensitivity of 81% and a specificity of 100%, while the CEDIA had a sensitivity of 88% and specificity of 75%. The overall agreement with LC-MS/MS was higher with the EIA assay (95% vs. 79%). Opiates, methadone, tramadol, hydroxychloroquine, and chloroquine have all been shown to cross-react with the CEDIA and can produce false positive results. The authors concluded that the EIA assay was preferable to the CEDIA to screen for buprenorphine compliance and abuse in the pain management setting, although neither is as sensitive or specific as LC-MS/MS(116).

Pretreatment of EIA, CEDIA, and HEIA with β-glucuronidase improved the sensitivity of each immunoassay to 97% when compared to LC-MS/MS, but the specificity of the CEDIA assay decreased to 67% in a pain management population(117). As described by the authors, pretreatment of the urine hydrolyzes the glucuronide metabolites to produce the detectable free drug. The free drugs cross-react better with the antibody than the glucuronidated metabolites, leading to improved sensitivity. In the end, EIA and HEIA had 99% agreement with LC-MS/MS after pre-treatment, while CEDIA was 75%. For laboratories that cannot perform confirmatory testing, the authors recommend pre-treating urine samples with β-glucuronidase prior to performing immunoassay testing.

The oral fluid buprenorphine immunoassays have also been shown to produce false positive results compared to LC-MS/MS. Positive screening results were confirmed in 95.9% of patients, yielding a false positive rate of 4.1%(69).

CANNABINOIDS: One study compared the performance of the DRI cannabinoids immunoassay to LC-MS/MS and showed that 10.6% (n=14) were falsely negative. However, the cutoff for the DRI assay was 50 ng/mL, while it was 10 ng/mL for LC-MS/MS(110). Mikel et al. showed similar results, with false negative rates of approximately 40% (111).

On the other hand, oral fluid cannabinoids immunoassays have been shown to have a high rate of false positive results compared to LC-MS/MS. Positive screening results were confirmed in only 84.8% of patients, yielding a false positive rate of 15.2%(69).

CARISOPRODOL: False negative carisoprodol screens can be obtained. Mikel et al. showed that the rate of false negative carisoprodol screens was approximately 5% compared to LC-MS/MS in patients being treated for chronic pain(111).

In contrast, the oral fluid carisoprodol immunoassays have also been shown to have a low rate of false positive results when compared to LC-MS/MS. Positive screening results were confirmed in 97.8% of patients, yielding a false positive of 2.2%(69).

COCAINE: Carney et al.(118) compared the performance of two enzyme immunoassays (DRI and LinZhi) for detection of the cocaine metabolite benzoylecgonine (cutoff 300 ng/mL) to GC-MS (cutoff 150 ng/mL). Using 1,398 urine specimens from criminal justice and pain management populations, the overall agreement of both immunoassays with GC-MS was 98%. There was one false positive in both immunoassays, 21 false negatives with DRI, and 29 false negatives with LinZhi. However, only urine specimens that were positive by immunoassay or had negative results significantly above the negative control were run by GC-MS. The authors concluded that both DRI and LinZhi are precise and reliable, despite the technical superiority of GC-MS. Pesce et al.(110) also showed a high number (128, or 50%) of false negative cocaine results with the DRI immunoassay. However, the cutoff for the DRI assay was 300 ng/mL, while it was 25 ng/mL with LC-MS/MS. Similarly, Mikel et al. showed false negative rates of approximately 40%(111).

In a forensic setting, the CEDIA serum cocaine assay was very sensitive and specific when compared to GC-MS, especially when cocaine and its metabolite were present at low levels. However, the authors stated that confirmation with conclusive methods such as GC-MS or LC-MS/MS is still required for valid identification, metabolite determination, and quantitative values(119).

The oral fluid cocaine immunoassays can also produce false positive results when compared to LC-MS/MS. In one study, positive screening results were confirmed in 98.6% of patients, yielding a false positive rate of 1.4%(69).

ETHANOL: False positive ethanol results have been described when automated assay screening was performed. Furthermore, the ethanol assay is not accepted for forensic purposes(120). One study showed that approximately one-third of ethanol-positive urine samples shipped to a reference lab were falsely positive because of fermentation of glucose and that the glucose level did not indicate the likelihood of a false positive result. Therefore, the authors recommended that confirmatory testing for ethanol metabolites ethyl glucuronide (EtG) and ethyl sulfate (EtS) be performed to ensure accurate results.

FENTANYL: The performance of a relatively new qualitative automated HEIA (Immunalysis Corporation, Pomona, CA) for fentanyl was compared to LC-MS/MS. Not only was the technical performance of the assay sufficient, but the diagnostic accuracy was found to be acceptable by the authors in this study. The overall agreement of HEIA with LC-MS/MS was 99%. Three false posi-

tives and one false negative were obtained. The authors concluded that the fentanyl immunoassay was a reliable screening method with high sensitivity and specificity for assessing compliance and abuse in patients with chronic pain. However, confirmation of results by a targeted assay should be performed, particularly for positive results(103).

The oral fluid fentanyl immunoassays have been shown to also produce false positive results when compared to LC-MS/MS. Positive screening results were confirmed in 98.6% of patients, yielding a false positive rate of 1.6%(69).

METHADONE: False negative results for methadone may be obtained. One study compared the performance of the DRI methadone immunoassay to LC-MS/MS and showed that 6.1% (n=17) of results were falsely negative. However, the cutoff was 300 ng/mL for the DRI assay and 50 ng/mL for LC-MS/MS(110). Mikel et al. showed similar results, with false negative rates around 10%(111).

Unlike urine, the oral fluid methadone immunoassays can produce a high rate of false positive results compared to LC-MS/MS. In one study, positive screening results were confirmed in only 87.4% of patients, yielding a false positive rate of 12.6%(69).

MDMA: As shown in one study, the MDMA immunoassay has a high rate of false positive results, particularly in patients taking pseudoephedrine(112).

OPIATES: Opiate immunoassays have variable cross-reactivity for opioid compounds. One group of authors demonstrated that testing with an opiate ELISA alone produced only moderate agreement (55%) with LC-MS/MS. However, a combination of opiate ELISA and oxycodone ELISA had reasonable agreement (82.6%) with LC-MS/MS(65). Mikel et al. also showed a high rate of false negative opiate screens (approximately 30%) when compared to LC-MS/MS in patients being treated for chronic pain(111).

The oral fluid opiates immunoassays have also been shown to have a high rate of false positive results when compared to LC-MS/MS. Positive screening results were confirmed in only 76% of patients, yielding a false positive rate of 24%(69).

OXYCODONE: Manufacturers began offering an oxycodone-specific immunoassay when the drug increased in popularity and data showed that many opiate assays did not adequately detect oxycodone. One group compared the performance of the oxycodone DRI assay to GC-MS confirmation of free oxycodone (oxymorphone, a metabolite of oxycodone, was not measured). In a sample of approximately 50 urine specimens, there was 100% agreement between DRI and GC-MS, but this study is limited by the small number of specimens and the fact that the GC-MS assay did not detect the active metabolite of oxycodone, oxymorphone(98). Another study took a similar approach, but its GC-MS assay was designed to detect both oxycodone and oxymorphone with a detection limit of 100 ng/mL. Using 1,523 urine specimens (437 confirming positive for oxycodone and/or oxymorphone), one group of authors reported that the sensitivity and specificity of the Microgenics DRI oxycodone assay were 99.1% and 99.8%, respectively. Only four false negatives and two false positives were seen. The authors concluded that the immunoassay was highly reliable in the pain management setting(83).

Using 96 urine specimens from chronic pain patients, Gingras et al.(121) demonstrated that the oxycodone DRI immunoassay had a sensitivity of 97% and a specificity of 97% (two false positives and one false negative) when compared to GC-MS. The authors suggest that the DRI assay should be used in combination with the CEDIA opiate immunoassay to reduce confirmation of negative screens. A combination of opiate ELISA and oxycodone ELISA was also recommended by a different group of authors because this combination had reasonable agreement (82.6%) with LC-MS/MS(65). Furthermore, Mikel et al. showed a high rate of false negative oxycodone screens (approximately 10%) when compared to LC-MS/MS in patients being treated for chronic pain. The false negative rate was higher than reported by other studies(111).

The oral fluid oxycodone immunoassays can also yield a high rate of false positive results when compared to LC-MS/MS. Positive screening results were confirmed in only 88.2% of patients, yielding a false positive rate of 11.8%(69).

PCP: GC-MS is preferable to DRI immunoassay for PCP, as demonstrated by two case reports that showed that tramadol can cause false positive immunoassay results(122), along with two larger studies. One of the larger studies reported several positive PCP immunoassay results in a pain management population that could not be confirmed by GC-MS and hence were false positive results(112). In the other larger study, all positive PCP screens (Siemens Syva EMIT II) were confirmed by GC-MS, and 17.6% were found to be falsely positive. False positive PCP results were commonly associated with tramadol, diphenhydramine, and dextromethorphan use (123).

TRAMADOL: The oral fluid tramadol immunoassays can produce false positive results when compared to LC-MS/MS. Positive screening results were confirmed in 96.8% of patients, yielding a false positive rate of 3.2%(69).

Point-of-Care (POC) Testing

Urine or oral screening immunoassays are also available at the point of care. POC testing can be done in the pain clinic or physician's office using single-use dipstick or cup-based technologies and can provide immediate results for the provider and patient. Negative results are typically used to rule out drug abuse. Positive samples are usually sent for definitive laboratory-based testing to identify the drug(s) present and to determine adherence or identify abuse/diversion. POC immunoassays, similar to laboratory-based screening immunoassays, have lower sensitivity

and specificity than definitive assays. In addition, quality control, quality assurance, and result documentation are challenging with POC testing. It should also be mentioned that most, but not all POC assays indicate a negative test with the presence of a line and a positive test by the absence of a line.

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**

Note: POC devices must be performed exactly according to the manufacturer's instructions. Any deviation from this can significantly alter the POC devices ability to operate correctly and may affect the interpretation of the test result. Lastly, it should also be noted that most devices require additional confirmatory testing, especially when unexpected results are observed.

Two studies(106, 107) looked at POC urine immunoassays for opioids and benzodiazepines, respectively, and compared the results to mass-spectrometry-based testing. One thousand pain patients at a tertiary referral center and interventional pain management practice in the United States were studied. The authors concluded that the POC immunoassays were appropriate, convenient, and cost-effective. In fact, compared with laboratory based immunoassay testing for opioids and illicit drugs, POC immunoassay testing had higher specificity and better agreement with MS, demonstrating the value of POC drug testing. However, a cautious approach should be taken when interpreting POC results due to variable sensitivity. Providers should make sure they understand the limitations of their POC assays and, if appropriate, consult with laboratory personnel to assist with interpretation. The authors also recommend that abnormal or unsuspected results, such as detection of non-prescribed opioid or illicit drugs, should be confirmed either by a repeat test, proper history, or LC-MS/MS. It was estimated in this study that 20%-32.9% of patients would need their samples sent for LC-MS/MS confirmation.

Another study examining POC urine drug testing noted that the specific methodology used in immunoassay can yield varying performance characteristics, and the tests used in many primary care settings have limited sensitivity for many drugs, including hydrocodone (the most commonly prescribed opioid in the primary care setting)(14). In another study (124), they compared oral fluid POC testing to urine immunoassay with mass spectrometry-based confirmation. The study was performed in an academic interventional pain management center in patients on a stable dose of prescription opioids with or without illicit drug use. Urine and oral fluid qualitative results were similar. Both matrices offered comparable detection rates and were effective at compliance monitoring. The authors concluded that oral fluid produces results comparable to urine. However, differences in windows of detection for different drug classes should be considered.

Another study evaluated POC oral fluid testing to monitor pain management patients and compared results to urine(69). Oral fluid specimens were analyzed from 6,441 pain patients from 231 pain clinics in 20 states. Specimens were screened with 14 ELISA assays, and non-negative specimens were confirmed by LC–MS/MS for 40 licit and illicit drugs and metabolites. 83.9% of specimens screened positive for one or more drugs (n = 5401), 98.7% (n = 5329) of which confirmed (at ≥ LOQ concentrations) positive for at least one analyte. The prevalence of confirmed positive drug groups was as follows: opiates > oxycodone > benzodiazepines > methadone ≈ carisoprodol > fentanyl > cannabinoids ≈ tramadol > cocaine > amphetamines ≈ propoxyphene ≈ buprenorphine > barbiturates >methamphetamine. Approximately 11.5% of the study population used one or more illicit drugs (cannabis, cocaine, methamphetamine, and/or MDMA). Overall, the pattern of licit and illicit drugs and metabolites observed in oral fluid paralleled results reported earlier for urine, indicating that POC oral fluid testing is another viable option for use in compliance monitoring programs of chronic pain patients. However, physicians using POC testing still need to reference the POC package insert and/or consult laboratory personnel in order to accurately determine any assay's capabilities and understand the limitations for detecting specific medications within a drug class to prevent incorrect assumptions or interpretation, as well as determine when additional testing is necessary.

Timing of Urine Drug Testing

Although guidelines recommend urine drug testing as one tool to monitor compliance in pain management, the existing guidelines do not recommend how frequently patients should be tested, if baseline testing is indicated, or whether testing should be random or scheduled. This information is critical for both providers and the laboratory to successfully manage patients and predict resource use.

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**

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)

In one study, 100 patients undergoing interventional pain management and receiving controlled substances, including opioids, were randomly selected for evaluation of illicit drug use by means of POC urine drug testing(125). All included patients had no history of drug abuse as determined by history, physical examination, doctor shopping, prescription substance abuse, escalation of dosage, and appropriate response to controlled substance usage (stable without dependency). The study showed that there actually was significant use of illicit drugs in this low-risk population; 13% were positive for marijuana and 3% for cocaine. Therefore, the authors concluded that random POC urine testing, particularly for marijuana, is an inexpensive way to detect illicit drug abuse in low-risk patients on controlled substances.

In a methadone medical maintenance study (126), patients were required to leave two urine specimens for analysis each month, with at least one on a random basis. Cocaine, opiates, benzodiazepines, and methadone were measured using an enzyme-multiplied immunoassay technique followed by thin layer chromatography and fluorescence polarization immunoassay to confirm the results. In the end, only 4/73 study patients had positive urine samples.

While immunoassays for specific opioids (e.g., methadone, oxycodone, and fentanyl) are more reliable than general opiate immunoassays, which typically have little to no cross-reactivity with the synthetic and semisynthetic drugs, the synthetic opioids can still be missed in these targeted immunoassays, yielding false negative results. As a result of these concerns, it is difficult to offer simple recommendations on how frequently definitive laboratory testing (mass-spectrometry-based) should be employed. For example, laboratory testing once yearly for low-risk patients and twice yearly for higher-risk patients has been recommended, but the same recommendations call for POC screening every six months for low-risk patients and every three months for higher-risk patients[40], which is far more frequent than the previously cited ASIPP recommendations(37, 38). Therefore, due to a lack of scientific evidence to suggest that random testing is superior to scheduled testing, the committee recommends random drug testing to better assess compliance and outcomes. If testing is scheduled, patients have an opportunity to adulterate their specimen before or during the visit. Furthermore, patients who know the date of testing may adhere to their prescribed medication(s) immediately prior to their visit, only to continue abuse or diversion when testing is not scheduled.

Cost-Effectiveness of Urine Drug Testing

Cost is a concern in all areas of healthcare, but particularly with laboratory testing. Providers and laboratorians are under pressure to provide the same level of patient care at a lower cost. Therefore, there is interest in whether qualitative screening immunoassays, either in the laboratory or at the POC, are more cost-effective than MS-based assays. Any cost benefits need to be weighed with the clinical benefits and sensitivity and specificity of the most cost-effective testing options.

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 #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**

There is a lack of evidence to suggest that laboratory-based qualitative/semi-quantitative urine screening assays are more cost-effective than mass-spectrometry-based assays in detecting outcomes in pain management patients. However, Manchikanti et al.(106, 107) wrote two articles that concluded that appropriate use of urine drug screening assays at POC is more cost-effective than LC-MS/MS. The authors report a cost per test of $25 for immunoassay and a cost per test of $600 for mass spectrometry and advocate for a testing algorithm to reduce costly LC-MS/MS use. According to the authors' testing algorithm, mass-spectrometry-based assays should only be performed in patients who test negative when prescribed a drug, in patents that test positive when not prescribed the drug, or in patients who test positive for an illicit drug. However, in the latter two scenarios, mass-spectrometry-based assays should not be confirmed if the patient admits adherent use. Instead, repeat testing should be performed by POC immunoassay at their next visit or at a random time. As stated earlier in the POC section of this chapter, it is important that providers understand the limitations of POC assays and consult the laboratory if appropriate so that the lower cost is not compromising patient care, leading to incorrect interpretations.

CHAPTER 4

Quantitative or definitive assays

This section will address the role of definitive methods like HPLC, GC-MS, or LC-MS/MS in pain management testing. It will include: technologies available for definitive and quantitative assays, when a definitive test should be typically ordered, the benefits and limitations of definitive testing, the benefits and limitations of quantitative testing, and the effectiveness of using hydrolysis (e.g., acid vs. enzymatic) in this type of testing.

Definitive testing

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**

Melanson et al.(116) examined the utility of an EIA buprenorphine immunoassay for monitoring compliance and abuse relative to a CEDIA buprenorphine immunoassay using urine specimens from 149 patients treated for chronic pain or opiate addiction. The reference method for both was an LC-MS assay for buprenorphine and metabolites. In this study, the authors found that the EIA had a higher degree of agreement with LC-MS results compared to the CEDIA assay. Implicit in this study is that the LC-MS results are of higher quality compared to immunoassay results, as it is designated as the gold standard. There is no discussion of the impact of immunoassay or LC-MS methods of measurement of detection of outcomes.

A study by Pesce et al.(110) evaluated the diagnostic accuracy of LC-MS/MS vs. immunoassay for drug testing in pain patients. In this study, the authors tested 4,200 urine specimens from pain patients for amphetamine, methamphetamine, alphahydroxyalprazolam, lorazepam, nordiazepam, oxazepam, temazepam, cannabinoids, cocaine, methadone, methadone metabolite, codeine, hydrocodone, hydromorphone, morphine, propoxyphene, and norpropoxyphene. The authors compared the immunoassay results to the LC-MS/MS results. Using the drug and metabolites to define a positive result by LC-MS/MS, the authors found the following false negative results in urine by immunoassay: 9.3% for amphetamines, 22% for benzodiazepines, 10.6% for cannabinoids, 50% for cocaine, 6.1% for methadone, 1.9% for opiates, and 23.4% for propoxyphene. The authors attribute the differences to variance in cross-reactivity for immunoassays, along with lower cutoffs for the LC-MS/MS methods. The authors concluded that the use of LC-MS/MS significantly reduces the risk of false negative results. Implicit in this study is that the LC-MS results are of higher quality compared to immunoassay results, as it is designated as the gold standard. There is no discussion of the impact of immunoassay or LC-MS methods of measurement on detection of outcomes.

Dickerson et al.(127) demonstrated the use of opioid glucuronide metabolites in monitoring for chronic pain patients. In this study, the authors developed and validated an LC-MS/MS method for opioids and metabolites (including glucuronides) and then used the method to analyze 111 urine specimens from chronic pain patients that had previously been analyzed using an immunoassay (EMIT) for opiates (47 negative and 64 positive). Upon comparison using LC-MS/MS as the reference method, they found the immunoassay to have a 35% false positive rate (all attributed to oxycodone and metabolite) and an 11% false negative rate. The authors suggest the LC-MS/MS method is superior to immunoassay screening due to the increased sensitivity and specificity of LC-MS/MS, with the added benefit of detecting analytes that are not cross-reactive with the standard immunoassay screen. However, there is no discussion of the impact of this testing or LC-MS in general on determination of clinical outcomes.

A study by Backer et al.(83) evaluated the performance of the DRI oxycodone immunoassay for the detection of oxycodone in urine relative to GC-MS confirmation testing. The authors tested 1,523 consecutive urine specimens and found 435 positive results by immunoassay, with 433 confirmed by GC-MS. They report a sensitivity of 0.991 and specificity of 0.998 for the DRI immunoassay relative to GC-MS. Implicit in this report is that GC-MS is the gold standard for measurement. There is no discussion of the impact of immunoassay or GC-MS measurement on clinical outcomes in pain management patients.

A study by West et al.(128) investigated the utility of chiral analysis in differentiating illicit from medicinal methamphetamine usage in pain patients. In this retrospective study, the authors include the test results and medical histories of 485,889 urine specimens submitted for analysis from patients being treated for pain. After subjecting a limited set of specimens positive for methamphetamine to chiral analysis (and comparing to patient medication histories), they determined that medicinal

use of l-methamphetamine is underreported. The authors suggest that chiral analysis should be available on request to pain management physicians. However, there is no discussion of the impact of having this test available on clinical outcomes for this patient population.

Snyder et al.(103)examined the technical performance and clinical utility of a fentanyl immunoassay relative to an LC-MS/MS method for monitoring fentanyl use in pain management patients. In the study, the authors analyzed 307 urine specimens from pain management patients by immunoassay, and when compared to the reference LC-MS/MS method, they found a diagnostic sensitivity, specificity, and accuracy of 97%, 99%, and 99%, respectively. Implicit in the study design is that the LC-MS/MS is more accurate as the reference method, and neither approach was evaluated for its impact on clinical outcomes in pain management patients.

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**

Crews at al.(120) examined the use of EtG and EtS as urine markers for ethanol use in pain management patients. This study was driven by concern over the possibility of false ethanol positives coming from fermentation of sugars in urine during transportation. In this study, the authors examined 94 ethanol-positive urine specimens from chronic pain patients for EtG, EtS, and glucose. They found that only two-thirds of the samples (62 out of 94) contained either EtG or EtS, and suggested that in the absence of these metabolites, the ethanol present in the urine specimens is derived from fermentation of glucose. In addition, 63 of the 94 urine specimens had glucose results greater than 10 mg/dL. The authors suggest that confirmation testing for EtG and EtS is needed to determine whether the presence of ethanol in urine is due to consumption rather than fermentation in transport; the presence of elevated glucose in the urine does not establish that the ethanol is present due to fermentation.

A study by Narang et al.(129) examined the incidence of false negatives of immunoassay for THC in blood for patients taking dronabinol. The authors analyzed 228 blood samples from 27 patients enrolled in their study. The majority of samples (57.4%) showed THC as expected; however, a significant number of samples (42.6%) showed no detectable evidence of THC four and eight hours after administration of dronabinol. The authors suggest that the higher-than-anticipated number of false negative results could be explained by a lower sensitivity of the blood screening technique or in how oral cannabinoids are metabolized. There is no discussion of the impact of this screening on clinical outcomes for pain patients.

Manchikanti et al.(106) presented a comparative evaluation of a POC immunoassay kit versus LC-MS/MS for detection of UDT opioids and illicit drugs in the urine of pain management patients. In this study, the authors analyze 1,000 consecutive urine specimens submitted for analysis. The immunoassay was performed first, followed by LC-MS/MS analysis at a reference laboratory – the LC-MS/MS test was designated as the reference method. Agreement for prescribed opioids was high with the index test (80.4%). The reference test of opioids improved the accuracy from 80.4% to 89.3%. Non-prescribed opioids were used by 5.3% of patients. The index test provided false positive results for non-opioid use in 44%, or 83 of 120 patients. For illicit drugs, the false positive rate was 0% for cocaine, 2% for marijuana, 0.9% for amphetamines, and 1.2% for methamphetamines. Overall, the authors suggest that confirmation was required in 32.9% of the samples. They state that POC immunoassay is sufficient for front-line UDT in pain management, and suggest that all samples negative for prescribed opiates, positive for non-prescribed opiates, and positive for illicit drugs should be sent for confirmatory testing. There is no discussion of the impact of this testing paradigm on clinical outcomes for pain management patients. Manchikanti et al.(107) also presented data from the same study, but focused on the detection of benzodiazepines. They drew the same conclusion for benzodiazepines that they published for opiates and illicit drugs.

Quantification vs. Qualitative Definitive Tests

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**

A study by Pesce et al.(130) examined the feasibility of establishing reference intervals for urine drug testing in pain management patients. In this study, the authors analyzed 8,971 consecutive urine specimens from patients on chronic opioid therapy using non-parametric, parametric, robust, and transformed estimators to derive the upper 97.5th percentile concentration values of 31 drugs and their metabolites. By applying these statistical approaches, the authors suggest that it is possible to define an upper limit of urine concentration for a drug that will provide an alert of the possibility for abuse of that particular drug. They caution that this should be interpreted in the context of additional clinical information for the patient. There is no evidence regard-

ing the impact of this approach on the clinical outcomes of pain management patients.

Mikel et al.(111) conducted a study to look at the distribution of low concentrations of excreted drugs in the pain patient population. In this study, they analyzed approximately 8,000 urine specimens by LC-MS/MS for 19 analytes, where the nominal cutoff for the LC-MS assays was defined as the limit of quantification (LOQ), and the number of drugs detected above that cutoff was compared to the number that would be detected using SAMSHA cutoffs for each of the drugs. The authors defined "missed drugs" as those that would be detected using the LOQ cutoff, but not the SAMSHA cutoff. On their analysis, they found "missed drug" rates ranging from 4.0% (tramadol) to 53.3% (alpha-hydroxyalprazolam). Based on this analysis, they suggest that a significant number of patients being treated for pain are testing negative for their medications despite their compliance, because they excrete drugs in concentrations that are measurable by LC-MS/MS but below the nominal immunoassay screen cutoffs. For these patients, in the absence of further testing, a falsely negative result is reported. However, there is no discussion of the impact of one cutoff versus another on clinical outcomes in the pain patient population.

Larson et al.(131) conducted a study to investigate the possibility of using the ratio of urine EDDP concentration to urine creatinine concentration to develop a regression model for prediction of drug adherence in patients prescribed methadone for pain management of opiate addiction. In this study, the authors abstracted relevant clinical data, including age, gender, weight, height, methadone dose, urine creatinine concentration, urine EDDP concentration, and clinical records of compliance (or non-compliance) for two groups of patients. The first group of seven patients was used to develop the initial model (39 urine specimens over four months), and the second group of 33 patients was used to validate and refine the initial model (102 urine specimens over 28 months). In their model, the investigators state that they are able to predict urine EDDP/creatinine ratio based on the methadone dose corrected for body size, and the deviations from the predicted ratio (based on evaluations of residuals) allow identification of individuals that are likely non-compliant. When applying their regression model and a cutoff of rs>2, the sensitivity and specificity were calculated as 75% and 96.7%, respectively. When using a cutoff or rs>3, the sensitivity and specificity were calculated as 60% and 98.3%, respectively. This study was limited, however, in that it was a retrospective analysis, and the testing results used to develop the model were also used to evaluate the validity of the model.

A study by Couto et al.(132) assessed the ability of an algorithm applied to urine drug levels of oxycodone in healthy adult volunteers to differentiate among low, medium, and high doses of OxyContin (oxycodone). In this study, the urine drug concentrations were determined by LC-MS and then adjusted for urine pH, urine specific gravity, and lean body mass (proprietary algorithm). This was done for three groups of study subjects taking doses of 80, 160, or 240 mg/d of OxyContin. The distributions for the LC-MS values (adjusted and unadjusted) were plotted by dose, and when statistical analysis was performed, it was demonstrated that the median values of the distribution for each dose were statistically different, and that the confidence limits of the medians did not overlap, even when conservative adjustments were applied to account for multiple comparisons. Based on this observation, the authors state that the normalized LC-MS/MS results show excellent discrimination between the populations taking 80, 160, and 240 mg/d of OxyContin. A similar study looking at the ability of an algorithm applied to urine drug levels of hydrocodone in healthy volunteers to differentiate among low, medium, and high doses of hydrocodone was also performed(133). In this study, 20 subjects received 20, 60, and 120 mg daily doses of hydrocodone dosed to steady-state at each level while under a naltrexone blockade. Using a florescence polarization immunoassay (FPIA), two urine samples were taken at each dosing level from each participant once steady-state was reached. The concordance was calculated for raw and adjusted FPIA urine hydrocodone values within each study participant across all doses. The concordance correlation coefficient for the pairs of raw urine FPIA values was 0.339, while the concordance correlation coefficient for the pairs of normalized FPIA values using the algorithm was 0.677. While some overlap of the confidence intervals was observed using the raw FPIA values, the intervals for the adjusted FPIA levels did not overlap between any dose levels, despite the application of a Bonferroni adjustment to correct for multiple comparisons. The authors concluded that the algorithm normalized hydrocodone urine drug levels for pH, specific gravity, and lean body mass and could differentiate between all three daily doses of hydrocodone tested (20, 60, and 120 mg). However, there are several important limitations to both of these studies. The study patients were relatively homogenous with respect to cytochrome P450 2D6 – poor, rapid, and ultra-rapid metabolizers were excluded from the study. In addition, they were restricted from any medications or items in their diet that could inhibit or induce the CYP2D6 enzymes. Lastly, a careful observation of the data demonstrates significant overlap between the distributions. While the medians may be statistically differentiated between the groups, a comparison of an individual result to a population distribution would not likely be able to place the patient in one particular group or another.

Linares et al.(134) conducted a prospective, randomized, cross-sectional study to develop and validate a pharmacokinetic model to predict oxycodone in urine for the purpose of identifying patient compliance with their oxycodone-dosing regimen. In this study, the authors used existing models and published pharmacokinetic data to refine and produce a modified pharmacokinetic model that incorporates two specific changes from the existing models for oxycodone: 1) it assumes steady-state concentration in plasma, and 2) it separates the urine clearance in metabolic clearance into two discrete factors. The PK model was then validated using 20 patients treated with oxycodone; the authors predicted the urine concentration and compared the measured

concentration (from an outside reference laboratory). They were able to show that 90% (18/20) of the patients fell within 10% of their predicted value. They suggest that using a PK model, one can establish a target value based on patient-specific dosing – in other words, a patient-specific quantitative urine "normal" range. However, there is no clinical validation of this as a tool for compliance monitoring, nor is there evidence that demonstrates the impact of this approach on clinical outcomes in a pain management population.

Detection limits

The evidence in the literature is currently insufficient to determine standardized cutoffs or limit of quantifications to determine full compliance, partial compliance, or misuse/abuse of controlled drugs by pain management patients.

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**

Crews et al.(135) demonstrated the use of LC-MS/MS to detect 6-acetylmorphine (6-AM) in the absence of morphine in pain management patients. In this study, the authors analyzed 22,361 urine specimens from chronic pain patients. From these specimens, 30 tested positive for 6-AM above a cutoff of 10 ng/mL and 23% of those had a morphine concentration less than the cutoff of 300 ng/mL. The authors suggest that using a standard screening cutoff of 300 ng/mL for morphine as a threshold for confirmation (including 6-AM) will result in a missed diagnosis of heroin use in approximately 25% of the cases. It is important to note that there is no discussion of the impact of this confirmatory testing on clinical outcomes.

A study by West et al.(113) examined the comparison of clonazepam compliance as measured by immunoassay and LC-MS/MS in a pain management population. In this study, the authors selected samples from their database prescribed clonazepam only, while eliminating any patients that were prescribed a second (or more) benzodiazepine drug. From this selection, 180 urine specimens were found that met the criteria and were analyzed using an immunoassay with a cutoff concentration of 200 ng/mL, and also analyzed with an LC-MS/MS method using cutoffs of both 200 ng/mL and 40 ng/mL that detected both clonazepam and the primary metabolite 7-aminoclonazepam. The positivity rate for the immunoassay was 21%, while the positivity rates for the LC-MS/MS method were 70% and 87% for the 200 ng/mL and 40 ng/L cutoffs, respectively. The authors attributed the differences in positivity rates to the lack of cross-reactivity of the immunoassay with the clonazepam metabolite. They suggest that a much lower cutoff (e.g., 40 ng/mL) is needed to reliably monitor clonazepam adherence. There was no discussion of the impact of using either the immunoassay or LC-MS/MS assay on clinical outcomes in pain management patients.

Several articles conclude that confirmatory testing should replace drug screening in the pain management setting due to its superior sensitivity and specificity and lower cutoffs. However, there is no evidence that patient outcomes are improved with confirmatory testing. One group compared the KIMS, CEDIA, and High Sensitivity CEDIA (HS-CEDIA) benzodiazepine assays to LC-MS/MS in a pain management population(105). The authors concluded that LC-MS/MS quantification offers superior sensitivity and specificity for monitoring benzodiazepine in patients treated for chronic pain and should be used instead of screening immunoassays. In another study, the performance of the Microgenics DRI benzodiazepine assay (cutoff 200 ng/mL) was examined in patients prescribed clonazepam for chronic pain(113). If a cutoff of 200 ng/mL was used for both immunoassay and LC-MS/MS, the positivity rates were 21% and 70%, respectively. The positivity rate for LC-MS/MS increased to 87% if a limit of detection of 40 ng/mL was employed. The authors conclude that the current cutoff of the majority of immunoassays (200 ng/mL) is not sufficient to monitor clonazepam compliance and that LC-MS/MS, due to its ability to have lower limits of detection, should be performed in all pain management patients(113).

Pesce et al.(110) and Mikel et al.(111) also recommended LC-MS/MS testing in pain management. Pesce et al.(110) examined the diagnostic accuracy of LC-MS/MS versus immunoassay (DRI Microgenics) in 4,200 pain management patients. Many false negative results were obtained, most strikingly with benzodiazepines (28% falsely negative) and cocaine (50% falsely negative) leading the authors to conclude that LC-MS/MS should be the standard for urine drug screening in pain management (Level III)(110). Mikel et al.(111) demonstrated that a significant number of patients are testing negative by immunoassay but are in fact compliant with their medications, as evidenced by measurable LC-MS/MS concentrations. This group concluded that current immunoassays do not have low enough cutoffs to assess compliance and abuse in the pain management setting(111).

In psychiatric patients, POC urine drug screening (Clearview 6-panel Drug Screen Card [Inverness Medical International, Bedford UK]) was more accurate than the physician's assessment, but still missed patients with substance abuse, particularly those on cannabinoids and benzodiazepines (Level II)(136). The sensitivity and specificity of the benzodiazepine, opiate, amphetamine, cannabinoids, cocaine, and ecstasy immunoassays ranged from 76%-97% and 82%-100%, respectively. Cannabinoid results were falsely positive in 11 patients. Benzodiazepine results were falsely positive in eight patients and falsely negative in seven patients. In conclusion, chromatographic methods were recommended for routine screening of acutely admitted psychiatric patients due to the inadequacies of POC testing(136).

Pre-analytical hydrolysis (enzymatic/chemical) of urine

The evidence in the literature is inconsistent to support routine use of hydrolysis for all drug classes to more effectively detect outcomes in pain management patients.

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

Pre-analytical hydrolysis is commonly used to liberate glucuronide and sulfate conjugate metabolites of drug analytes in mass spectrometric methods such as GC-MS and LC-MS/MS. This practice is common for urine because many drugs are eliminated in a conjugated form. The consequence of pre-analytical hydrolysis is to increase the concentrations of drug analytes and thereby increase the sensitivity of an assay for the associated drug analytes. Drug analytes that will theoretically benefit from pre-analytical hydrolysis are those that are known to form glucuronide and sulfate conjugates(136). Drugs known to produce significant proportions of conjugated metabolites include many opioids such as morphine and buprenorphine, most benzodiazepines, and marijuana metabolites.

Immunoassays do not routinely employ pre-analytical hydrolysis reactions, although some commercial kit labeling suggests that detection will be improved by incorporating pre-analytical hydrolysis. Cross-reactivity to the conjugated metabolites improves detection of drug analytes in some immunoassays. The product labeling should be consulted to evaluate the sensitivity of an immunoassay to conjugated metabolites and any recommended pre-analytical processing.

Table 9. Examples of references for definitive assays that include pre-analytical hydrolysis include

Drug/drug class	Drug analytes	Method of hydrolysis	References
Heroin	Morphine, Codeine, Dihydrocodeine, 6-MAM, Meconin	β-glucuronidase	(137)
	Morphine, 6-MAM	β-glucuronidase	(135)
	Diacetylmorphine, 6-MAM, 6-monoacetylcodeine, Morphine	β-glucuronidase	(138)
Buprenorphine	Buprenorphine, Norbuprenorphine, Naloxone	β-glucuronidase	(115)
	Buprenorphine, Norbuprenorphine	β-glucuronidase	(116)
Tramadol	Tramadol, O-desmethyltramadol, N-desmethyltramadol, Hydroxytramadol, tramadol-N-oxide	β-glucuronidase	(139)
Tapentadol	Tapentadol, N-desmethyltapentadol, Tapentadol-glucuronide, N-desmethyltapentadol-glucuronide	6N HCl	(140)
Carisoprodol	Carisoprodol, Meprobamate	β-glucuronidase	(141, 142)
Clonazepam	Clonazepam, 7-aminoclonazepam	β-glucuronidase	(113)
Oxycodone	Oxycodone, Oxymorphone	β-glucuronidase	(83)
	Oxycodone, Oxymorphone, Noroxycodone	β-glucuronidase	(143)
Morphine	Morphine, Codeine	β-glucuronidase	(144)
Opioids	Buprenorphine, Norbuprenorphine, Fentanyl, Norfentanyl, Meperidine, Normeperidine, Methadone, EDDP, Propoxyphene, Norpropoxyphene	β-glucuronidase	(145)
	Morphine, Morphine-3-glucuronide, Morphine-6-glucuronide, Normorphine, 6-MAM, Noscapine, Papaverine, Codeine, Norcodeine, Codeine-6-glucuronide, Dihydrocodeine, Nordihydrocodeine, Dihydrocodeine-6-glucuronide, Dihydromorphine, Oxycodone, Hydrocodone, Hydromorphine	β-glucuronidase	(146)
	Codeine, Norcodeine, Morphine, Hydromorphone, Hydrocodone, Dihydrocodeine, Norhydrocodone, Oxycodone, Noroxycodone, Oxymorphone	β-glucuronidase	(65, 147)
	Morphine, Codeine, Methadone, EDDP	Concentrated HCl	(148)
Multi-drug panels	Therapeutic and illicit drugs	β-glucuronidase	(99, 149)

Hydrolysis reactions can be enzymatic or chemical. Enzymes used include β-glucuronidase from abalone, β-glucuronidase type H-3 from *Helix pomatia,* β-glucuronidase type L-II from *Patella vulgata,* and glusulase(115, 140). Recombinant β-glucuronidase is also now available (IMCSzyme from IMCS). A common approach to chemical hydrolysis includes incubation with concentrated hydrochloric acid. Hydrolysis conditions, such as substrate concentrations, temperature, pH, and time, should be evaluated and optimized by the laboratory. One study comparing three methods of hydrolysis (two enzymes, and 6 N HCl) with non-hydrolyzed recoveries on efficiency of tapentadol recovery demonstrated different yields for each method(140). The chemical hydrolysis method was preferred over the enzymatic methods due to better compatibility with the associated liquid chromatography columns. As such, chromatography quality and consistency were superior to the enzymatic hydrolysis products.

As suggested above, the efficiency of hydrolysis reactions may be incomplete, despite optimization of conditions. For example, a study using β-glucuronidase demonstrated that between 17%-27% of morphine-3-glucuronide was not cleaved. Similarly, between 32%-45% of morphine-6-glucuronide was not cleaved(146). When comparing hydrolyzed and unhydrolyzed urine samples collected from pain management patients prescribed tramadol, no qualitative differences in detection were observed. This study suggests that qualitative drug testing can be performed with unhydrolyzed urine, and that doing so considerably reduces matrix interferences in mass spectrometric methods. Unconjugated tapentadol (cutoff 50 ng/mL) and the n-desmethyltapentadol metabolite (cutoff 100 ng/mL) were detected when urine was unhydrolyzed. Only one of eight patient samples evaluated required hydrolysis for detection. However, concentrations of tapentadol and metabolite were significantly increased after hydrolysis. It was estimated that the average amount of tapentadol conjugated is 65%, and the metabolite is approximately 20% conjugated(140). However, the inclusion of a known concentration of conjugated metabolites should be included as quality control material to assure stability and consistency of hydrolysis efficiency.

Detection of drug analytes in unhydrolyzed urine is required for some analytes, such as ethyl glucuronide and ethyl sulfate(55). Some chemical hydrolysis methods can also reduce recovery of heroin metabolite 6-mono-acetylmorphine (6-MAM). Enzymatic hydrolysis is preferred for this application, although very little 6-MAM is eliminated in a conjugated form(135). Detection of drug analytes in unhydrolyzed urine may also require lower cutoff concentrations than those used for hydrolyzed urine, based on the proportion of drug that is conjugated(99). No evidence was found to describe appropriate cutoffs for unhydrolyzed urine.

Use of conjugated and unconjugated drug metabolites

The evidence in the literature is currently insufficient to make any recommendations at this time regarding the use or superiority of conjugated vs. unconjugated drug metabolites in definitive tests for pain management patients.

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**

Direct measurement of glucuronide or other conjugated metabolites will improve detection of drug use with or without use of pre-analytical hydrolysis. This approach also overcomes the variation in efficiency of hydrolysis reactions. One study demonstrated that detection of morphine-3-glucuronide, morphine-6-glucuronide, oxymorphone glucuronide, hydromorphone glucuronide, and norbuprenorphine glucuronide significantly increased detection of the associated drugs when evaluating medication adherence in pain management patients. Between 10%-100% of samples would have been misclassified if glucuronide metabolites were not included(127). The interpretive value of quantitative analysis of conjugated and unconjugated drug metabolites depends on the efficiency of hydrolysis and the cutoff concentration used for detection. Ratios of conjugated metabolites may provide phenotype information, although this finding is controversial(150).

A study by DePriest at al.(145) investigated the use of normetabolites as biomarkers for synthetic opiate use. In the study, the authors analyzed more than 100,000 urine specimens from a pain management population – none of the specimens were analyzed by immunoassay. The specimens were analyzed for buprenorphine, fentanyl, meperidine, propoxyphene, and methadone along with their normetabolites. Inclusion of the normetabolites increased the detection rates of the drugs as follows: buprenorphine, 10.0%; fentanyl, 42.1%; meperidine, 98.7%; propoxyphene, 113.2%; and methadone, 8.7%. The authors conclude that testing for the normetabolites of the drugs in addition to the parent drug enhances the effectiveness of monitoring programs for pain patients. However, there is no discussion of the impact of this testing or LC-MS in general on determination of clinical outcomes.

Cone et al.(147) also investigated the use of normetabolites (norcodeine, norhydrocodone, noroxycodone) as an aid in interpretation of urine drug testing in pain management patients. For this study, the authors analyzed 2,654 urine specimens for codeine, norcodeine, morphine, hydrocodone, norhydrocodone, hydromorphone, dihydrocodeine, oxycodone, noroxycodone, and oxymorphone. They found that 71.4% of the specimens contained one or more of the analytes for which they tested. However, in the specimens containing normetabolites, the prevalence of norcodeine, norhydrocodone, and noroxycodone in the absence

of parent drug was 8.6%, 7.8%, and 9.4%, respectively. Based on this observation, the authors conclude that the inclusion of normetabolites reduces potential false negatives relative to tests that don't include these metabolites. However, there is no discussion of the impact of having these tests available in clinical outcomes for pain management patients.

Heltsley et al.(65) examined the prevalence patterns of prescription opiates and metabolites in urine drug testing of chronic pain patients. In this study, the authors analyzed 20,089 urine specimens from chronic pain patients by opiate and oxycodone immunoassays, as well as performing parallel analysis by LC-MS/MS. Almost two-thirds of the specimens were positive for at least one drug or metabolite, with a range of one to eight analytes being detected. In a large number of samples, the investigators observed the presence of noroxycodone or norhydrocodone in the absence of the parent drug. The authors assert that this establishes their interpretative value as biomarkers for use of the parent drug. While there was some discussion of the performance of oxycodone immunoassays relative to LC-MS/MS assay performance, there was no direct discussion of the impact of one technique versus another on patient outcomes in this population.

CHAPTER 5

Adulterant/Specimen Validity testing

This section will discuss the clinical utility and necessity of adulterant or specimen validity testing for pain management patients and whether observed, non-observed, or chain-of-custody testing is recommended.

For drug testing results to be used appropriately in clinical decision making, the results must be valid. The goal of drug testing in the pain management population is to confirm compliance with appropriate use of prescribed medications, but also to identify aberrant behaviors and the risk of adverse outcomes. Non-compliance can include binging, use of non-prescribed and/or non-reported medications and illicit substances, as well as diversion. Press and political attention often focus on overdose deaths, but diversion is also another significant public health issue that contributes indirectly to the overdose statistics. A high percentage of chronic pain patients treated by their primary care physicians do not take their medications as prescribed(151). The authors found in an evaluation of 801 chronic opioid patients that although a positive UDT for cocaine was significantly associated with current substance use disorder (OR=5.92), the correlation for marijuana was lower but still significant (OR=3.52). The greatest yield to identify abuse disorders was the presence of four or more aberrant behaviors, including purposeful over-sedation (26%), self-escalation (39%), hoarding (12%), obtaining additional opioids from other prescribers (8%), or coincident use of alcohol (20%). Four or more of these behaviors, determined by extended interview, were highly associated with a current substance abuse disorder (OR=48.27). This paper did not compare adulteration of UDT with the risk. Clearly, the primary care physician does not have the option of a two-hour interview. UDT is an efficient and objective screening tool that can assist the busy practitioner in identifying non-compliance and aberrant drug-taking behaviors. Katz and colleagues(152) compared presence of five aberrant behaviors (report of lost or stolen prescription, consumption of more than the prescribed amount of medication, visits without appointments, multiple drug intolerances and allergies, and frequent telephone calls) to UDT results (presence of illicit drug or non-prescribed drug was defined as a positive UDT) and found that 43% of the 122 patients had a problem. 95 had no behavioral issues, but of these, 21% had a positive UDT. Of the 86 patients with a non-positive UDT, 14% had at least one behavioral issue. The authors found that monitoring of behavioral issues alone missed 49% of the aberrancies, while UDT alone missed 32%. The authors found that more patients with signed opioid agreements had a problem compared with those with no agreement (46% vs. 35%). While 61% of those less than 40 years of age had an issue, 30% of those over 60 also had a problem. Unfortunately, the authors did not report adulteration test results for the specimens. Another weakness of this study is that a urine specimen that did not contain the prescribed drug was not defined as a problem, despite the fact that GC-MS confirmations were done. Thus, the results may well underestimate the incidence of problem behaviors. In addition, the analysis of adulteration testing results, presumably done as part of the confirmatory testing, might have identified additional problem patients. A retrospective review by Turk et al.(153) evaluated studies that screened for predictors of aberrant drug-taking behaviors in chronic pain patients on opioids. They found that the strongest predictor of aberrant behavior was a personal history of illicit drug and alcohol abuse. Younger age, a history of legal problems, and positive UDT were identified as moderate predictors. Unfortunately, this study did not include adulteration testing.

While the vast majority of the available papers addressing validity testing pertain to employment screening or addiction treatment programs, the search specifically including chronic pain patients yielded two papers. It was felt that inclusion of the employment-related papers was outside of the scope of this review. In addition, despite the potential overlap between chronic pain and addiction, the original search was specifically aimed at chronic pain patients, the body of information from the addiction treatment literature was similarly excluded.

For purposes of this chapter, we define adulteration as the alteration, especially the debasement, of a substance by deliberately adding something not ordinarily a part of it (http://dictionary.reference.com, accessed 06-14-2016). Adulteration of urine drug test validity can be accomplished in a number of ways. In vitro adulteration can result from the addition of a substance to the urine. These can include water, household cleaners, pill dust or scrapings, and commercially available additives such as nitrite, pyridinium chlorochromate (PCC), and glutaraldehyde. In vivo adulterants are intended to dilute the drugs and their metabolites through diuresis, lowering levels to sub-cutoff limits. Finally, substitution of purchased or donated urine from another person can also occur. A web search identifies multiple sites where clean urine can be purchased (e.g., www.drURINE.com, www.perfecturine.com, http://www.keepshooting.com/quick-fix-fake-urine.html, all accessed 06-14-2016). Because the term adulteration

suggests deliberate action, we did not include false positive test results from cross-reactivity with prescribed or over-the-counter medications, or other dietary or herbal supplements.

Manner of specimen collection

The ease of urine sample adulteration makes it critical to address the method of collection. In an ideal world, all urine sample collections would be observed, although attempts have been made to foil this approach as well (http://realwhizzinatorxxx.com/, accessed 06-14-2016). Data regarding these more stringent standards for specimen collection can be found in the addiction and occupational screening literature, but no references were found for the pain management population. This method is time-consuming, expensive due to staffing requirements, and often not possible in a busy practice. Alternatives include specialized collection facilities in which the water can be turned off and the toilet water is colored. Some guidelines go so far as to have patients dress in gowns prior to providing the specimen to minimize risk of adulteration or specimen substitution. A more reasonable approach would be to have the patient remove jackets, sweatshirts, and heavier outerwear, empty their pockets while observed, and leave all belongings in the exam room while obtaining the specimen. The risk of an invalid specimen increases as the level of supervision diminishes. In addition, announced urine drug testing or testing performed at an off-site lab provides the opportunity not only for planned adulteration or urine specimen substitution, but also for the patient to take enough of their medication to have an appropriate test result. This fails to identify potential binging or diversion. Finally, time from request for a urine specimen to time of actual void can affect results. While review articles may make recommendations for specimen collection methods for pain patients, these guidelines are extrapolated from the addiction literature. Diuretics and excessive fluid intake provide a delayed effect on urine content, which can take an hour or more to be seen, so some guidelines go so far as to suggest a 20-minute window during which the specimen should be provided.

In general, this chapter addresses validity testing in the context of urine drug screening due to the accessibility of this type of testing. Other potential specimen types, including breast milk, meconium, hair, oral fluids, and blood are significantly more difficult to adulterate, but also less readily available. These specimens offer variable windows into drug use and may be appropriate for specific circumstances. While there are commercially available shampoos and body washes touted to interfere with hair testing (e.g., Test'in shampoo http://www.ipassedmydrugtest.com, or Two Steps A'head shampoo and conditioner www.passadrugtest.com, all accessed 06-14-2016), and saliva testing (Saliva Detox Mouthwash https://www.passusa.com/hair-drug-testing-04.htm, accessed 06-14-2016), these products are very expensive and of undetermined efficacy. Urine adulteration is much easier and more likely to occur, so it will be addressed in detail below.

Specimen Validity Testing

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**

In an evidence-based analysis looking at methadone compliance testing by the Ontario Medical Advisory Secretariat ((88)), urine temperature of 32.5 C to 37.7 C was shown to be a good indicator that a specimen was just provided by the identified donor. However, it was noted that this specimen validity method could potentially be circumvented by warming substituted urine specimens. As a result, volume collection could be used to increase the validity of temperature readings and ensure specimen validity from the donor. In addition, laboratory analysis of the urine's pH and creatinine could offer enhanced reliability of test result. The absence of drug detected in a concentrated urine specimen was found to be more reliable in terms of non-use than a negative test result in a diluted sample. pH, in a similar fashion, could affect

the amount of drug (e.g., parent methadone) in the urine and be used to better interpret inappropriate negative results in a patient who was actually taking methadone as prescribed. In the end, it was recommended that pH and creatinine should be determined on all urine specimens Another expert opinion suggested that urinary creatinine, pH, and temperature should be used to assist with result interpretation and increase specimen reliability for pain management patients(53). Further evidence in pain patients, heroin users, and marijuana/cocaine users showed that normalization of drug concentrations to specific gravity and creatinine were effective ways to cope with diluted urine specimens(154). In this study, 10,899 urine specimens were used from pain patients being chronically treated with opioids from 31 pain clinics in six states where they had concurrent specific gravity and creatinine measurements. Drug/metabolite concentrations were performed by GC-MS. Correlations of corrected drug concentrations and specific gravity/creatinine relationships were high for all 28 drug/metabolite groups. The overall average positivity rates increased (9.8% by specific gravity correction; 4.2% by creatinine correction) and took into account a large portion of variation caused by different patterns of fluid intake.

Currently in other non-pain management populations, specimen validity testing (e.g., pH) is required by guidelines (e.g., Federal Workplace Drug Testing Programs). pH is considered important since the FDA-cleared immunoassays are designed to perform optimally in a pH-dependent fashion for opiates, cocaine metabolites, marijuana metabolites, and others, and there are commercially available products sold with the intent to add to a donor's specimen to facilitate a "negative" drug test. These products contain either very low or high pH solution that can affect the immunoassay or destroy the drugs in the urine sample(155). Current urine pH cutoffs for Federal Workplace Drug Testing are established (e.g., pH <3 or ≥11 = adulterated specimen; pH ≥3 and <4.5 or ≥9 and <11 = invalid) and are being applied to other patient populations. However, Cook et al.(155) showed that the pH of urine specimens collected for federal workplace drug testing programs could be affected by the time and temperature of transport/storage prior to laboratory analysis and produce urine pH >9 but ≤9.5 without any adulteration. As a result, extended transport times and environmental temperatures should be minimized and taken into account when interpreting "invalid" results based on pH.

Specimen validity testing vs. other physician tools

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**

There were no papers identified that specifically compared efficacy of adulteration testing to physician tools (Table B, Appendix). Moore and colleagues(156) compared structured interview with the Screener and Opioid Assessment for Patients with Pain (SOAPP), the Diagnosis, Intractability Risk, and Efficacy inventory (DIRE), and/or the Opioid Risk Tool (ORT). They evaluated a cohort of 48 chronic pain patients who were subsequently discontinued from their opioids for significant aberrant drug-related behaviors. Because the authors did not include drug testing data in their paper, no conclusions can be made that are pertinent to this paper. However, psychologist interview was most sensitive (0.77), and the SOAPP was the most sensitive of the questionnaires (0.72) for identifying likelihood of aberrant behavior. Combination of the two gave a sensitivity of predicting aberrant behavior of 0.90. Hamill-Ruth(28) compared patient report to the medical record, prescription monitoring report, and POC urine drug screening in an anonymous and voluntary quality improvement project evaluating utility of POC UDT in chronic pain patients using), a 10-class test cup with temperature and internal adulteration testing. In addition, adulteration test strips were used. 4.2% of specimens had a temperature below the cutoff limit. Less than 1% showed overt adulteration, but confirmatory testing was not allowed due to the anonymity requirements of the Quality Improvement project. Consequently, the rigor of the adulteration screening was also limited. The authors did find that patient report was frequently inconsistent with the urine screen, the medical record, and/or the Prescription Monitoring Program (PMP). The addition of the UDS and PMP identified nine times as many inconsistencies than the combination of the medical record and patient report alone.

Timing of 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**

Multiple guidelines recommend UDT prior to initiation of ther-

apy, and then randomly(36), and two to four times/year for lower-risk patients, although high-risk patients may need more frequent monitoring(19, 35). Guidelines strongly support random drug testing, but none of these addresses the frequency of specimen validity testing. Random specimen validity testing, on the other hand, can be predicted to decrease the number of specimens that would be confidently considered valid. Accurate interpretation of urine drug testing is critical to clinical decisions for continued prescribing. Hence, efforts to maximize the identification of a valid specimen are paramount. Failure to perform validity testing on all specimens could lead to inappropriate and inaccurate interpretation of drug test results.

Broad vs. targeted specimen validity testing

There is no evidence in the literature to support the statement that targeted specimen validity testing is less effective than broad panel specimen validity testing at detecting outcomes in pain management patients.

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)

There is no published evidence for or against targeted specimen validity testing versus broad panel specimen validity testing relative to clinical outcomes. In the absence of evidence, the committee cannot make a recommendation for or against targeted specimen validity testing. The recommendation is that routine specimen validity testing be performed as part of a UDT program to improve the likelihood of accurate interpretation of results. 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, recognizing that these tests will not detect all forms of adulteration. As noted above, temperature and pH should be checked preferably within 5 minutes of specimen collection; creatinine and oxidants (which detects pyridinium chlorochromate, nitrite, and glutaraldehyde) should be tested at the laboratory. At a minimum, POC testing should include onsite specimen validity testing, including temperature, pH, creatinine, and oxidant testing, either incorporated in the testing device or with validated adulterant test strips, if they are to be used for clinical decision making without definitive testing results available. POC UDT results should be interpreted with caution due to incomplete adulterant testing and limitations of this technology.

While the internet is replete with ways to foil urine drug test results, presence or absence of adulteration is not reported in studies evaluating aberrant drug-taking behaviors. In the end, very little data exists regarding specimen validity testing in the pain management population. Additional research is needed to determine if a sequential or tiered approach to specimen validity testing would be more cost-effective in a chronic pain population. For example, should initial screening include pH, creatinine, specific gravity, and temperature? Can testing for oxidants, nitrite, or glutaraldehyde be reserved for urine specimens with abnormal screens? What percentage of urine specimens that pass the initial screen would show evidence of adulteration with more complete screening? Is the cost of a tiered approach significantly less than a more comprehensive specimen validity screening protocol? Until more information is available specifically pertaining to chronic pain patients, the practitioner and laboratory personnel should be guided by the addiction and workplace literature.

CHAPTER 6

Pharmacogenomic considerations

This section addresses the role of genetic and genomic testing for pain management patients.

Understanding the details of the human genome supports research designed to identify heritable causes of disease and response to medications. As such, genetic and genomic testing are rapidly evolving tools for achieving personalized, precision medicine. In pain and addiction medicine, genomic variation has been studied to identify associations between gene variants and the pathophysiology of pain sensation, rare pain disorders, pain threshold, as well as patterns of response to pain medications and likelihood for drug addiction. Evidence-based outcome studies are currently lacking for routine clinical application of genomic or genetic testing to guide diagnosis, characterization and management of chronic pain and drug addiction. However, genetic information is sometimes used to guide drug and dose selection; this application of genetic testing is referred to as pharmacogenetics. Pharmacogenetic testing is generally designed to detect only targeted gene variants that predict discrete aspects of pharmacokinetic and/or pharmacodynamic processes. Associations have been established between relatively common genetic variants and risk of adverse drug reactions or risk of therapeutic failure for specific drugs, and are used to qualify or disqualify a patient for the associated drug(s). Pharmacogenetic testing can also predict a drug response phenotype (e.g., intermediate metabolizer) that may be used to predict whether a person is likely to require non-standard dosing (e.g., lower or higher doses than a standard dose). Most clinical studies were not performed with chronic pain management patients, but observations with cancer pain patients, surgery patients and psychiatric patients may have relevance to chronic pain patients based on commonly used medications. Two primary topics are worthy of discussion and recommendations.

Use of pharmacogenetics to guide drug and dose selection

Drug response requires a coordinated effort between the two major processes of pharmacology: pharmacokinetics and pharmacodynamics. Pharmacokinetics describes the absorption, distribution, metabolism, and elimination of a drug, while pharmacodynamics describes the mechanisms of both desirable and undesirable drug effects. Pharmacodynamic effects may be dose-dependent or may occur independent of dose and may involve various aspects of cell signaling pathways, such as enzymes, receptors, ion channels, and immune mediators. Because genes that code for proteins associated with these processes may contain variants that impact protein expression or function, genetic variants have been associated with well-characterized drug response phenotypes. The overlying hypothesis investigated was whether pre-therapeutic testing may identify genetic variants that can be used to predict the drug response phenotype for an individual patient, and thereby guide drug and dose selection.

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**

The vast majority of evidence for pharmacogenetics associations comes from retrospective or observational studies as opposed to randomized prospective clinical trials. One retrospective study evaluated rates of abnormal pharmacogenetics findings in a pain practice for 104 adult patients, with a focus on four genes that code for drug metabolizing enzymes(157). Overall, 42.3% of test results were normal, 25.5% suggested intermediate metabolizer phenotypes, 7% were poor metabolizers, and 7.2% were ultra-rapid metabolizers. Only three patients had normal metabolizer phenotypes for all four genes. The authors acknowledge a need for large prospective studies conducted with diverse populations to evaluate the generalizability of these results. Another study evaluating the effect of pharmacogenetics on opioid therapy outcomes in an outpatient pain clinic found that the frequency of genetic variants was equivalent to average population frequencies, and only modest associations with opioid dose requirements were observed(158). Nonetheless, gene-based dosing guidelines have been published for select gene-drug pairs, many of which are relevant to chronic pain management. A commonly cited source of gene-based dosing guidelines is the Clinical Pharmacogenomics Implementation Consortium (CPIC). The CPIC assigns a level of evidence to each gene-drug pair ranging from "A" (highest level of evidence in favor of changing prescribing of an affected drug) to "D," wherein evidence is limited and may be con-

flicting. However, the CPIC does not advocate or recommend testing. The guidelines provide expert review of associated literature and guidance for translation of results into actions, when testing is performed. All gene-drug pairs represented by a published guideline have achieved the "A" level of evidence. CPIC guidelines are available publicly through its website: https://cpicpgx.org/ (accessed 06-14-2016).

Table 10. Examples of gene-drug pairs relevant to chronic pain management, with guidelines published by the Clinical Pharmacogenetics Implementation Consortium (CPIC)

Gene(s)	Drug(s)	References
CYP2D6	Codeine, Tramadol, Oxycodone, Nortriptyline, Desipramine	(159), (160), (161)
CYP2D6 and *CYP2C19*	Amitriptyline, Clomipramine, Doxepin, Imipramine, Trimipramine	(161)
*HLA-B*15:02*	Carbamazepine	(162)

The Dutch Pharmacogenomics Working Group and the Canadian Pharmacogenomics Network for Drug Safety have published similar guidelines(163, 164). Guidelines for gene-based dosing are available for many other drugs that may be used in the management of chronic pain, but were not identified by the literature search, and are not discussed here. Implementation of pharmacogenetics testing services is not discussed here, either, although models for implementation were identified in the literature search associated with this guideline(165, 166).

The gene-drug pairs identified in Table 10 are discussed in more detail below. The fundamental principles for the pharmacogenetics implications of these gene-drug pairs apply to many other gene-drug pairs.

Cytochrome P450 (CYP) genes

The cytochrome P450 (CYP) genes code for proteins of the same name. These proteins are enzymes that mediate oxidative reactions important to Phase I drug metabolism. Examples of CYPs that are commonly involved in Phase I metabolism of prescribed drugs include *CYP2D6, CYP2C19, CYP3A4,* and *CYP3A5.* The metabolic phenotype for CYP enzymes can be predicted by genetic testing designed to target known variants that affect expression or function of the enzyme. Using international consensus nomenclature (http://www.cypalleles.ki.se/, accessed 06-14-2016), the targeted genetic variants detected are used to predict star (*) alleles that are associated with enzyme function or expression, as well as diplotypes that are used to predict the metabolic phenotype. CYP phenotype predictions include poor, intermediate, normal, rapid, and ultra-rapid metabolizers. The CYP phenotype may affect dose requirement, the duration of drug response, the risk of dose-related adverse drug reactions, risk of drug-drug interactions, and specific pharmacokinetic parameters. To apply CYP phenotypes to drug and dose decisions, one must know whether the CYP mediated reaction generates active or inactive metabolites, and the relative potency of parent drug and associated metabolites. Many gene-drug applications are complicated by drug-drug interactions and alternate metabolic pathways. As such, many gene-drug applications studied to date have produced controversial results, and consensus for interpretation and/or application of pharmacogenetic testing results has not been achieved(167-170). Examples of gene-drug pairs with evidence for consensus of pharmacogenetics implementation strategies are described below.

1. *CYP2D6* and opioids codeine, tramadol, and oxycodone

Evidence is well described to link genetic variation in *CYP2D6* and drug-drug interactions to altered metabolism of codeine, tramadol, and oxycodone. There are more than 100 variant alleles described for *CYP2D6,* the frequency of which varies substantially among different ethnic groups. A poor metabolizer phenotype is predicted when two non-functional alleles (e.g., *3, *4, *5) are detected(159, 160). *CYP2D6* poor metabolizers are associated with reduced formation of the potent active metabolites, including morphine from codeine(171-173), o-desmethyltramadol from tramadol (174, 175), and oxymorphone from oxycodone(176, 177). Further, *CYP2D6* poor metabolizers experienced less pain relief from these drugs, and typically required rescue medication. Conversely, *CYP2D6* ultra-rapid metabolizers, predicted by detection of more than two functional alleles, may produce an excess of active metabolite and be at risk for unintentional overdose. This latter phenomenon is best described for codeine in children, wherein several accidental deaths have been described. Both US FDA and European Medicine Agency advise against use of codeine in children(178). Breastfeeding mothers are also discouraged from use of codeine when *CYP2D6* phenotype is not known, due to the potential for neonatal toxicity when mothers are *CYP2D6* ultra-rapid metabolizers(179). However, no randomized clinical trials were found to evaluate the benefits of genetic testing prior to therapy.

2. *CYP2D6, CYP2C19,* and antidepressants

Antidepressant medications are used in the treatment of chronic pain, both to manage pain and to manage psychiatric co-morbidities. Many tricyclic antidepressants are metabolized by *CYP2D6* and/or *CYP2C19*. For example, amitriptyline is converted to the active metabolite nortriptyline by a reaction mediated primarily by *CYP2C19*. Both amitriptyline and nortriptyline are converted to inactive metabolites by a reaction mediated by *CYP2D6*. The same metabolic scheme is observed with imipramine and desipramine. Imipramine dose requirements were significantly associated with *CYP2D6* genotype in a retrospective study of

181 psychiatric patients(180). Doxepin is converted to an active metabolite by *CYP2C19* and is inactivated by *CYP2D6*-mediated reactions. The combined impact of impaired phenotypes for both CYP enzymes, along with several well-described drug-drug interactions, could lead to life-threatening accumulation of active drugs and/or metabolites, although the impact is less severe with low doses(161). *CYP2D6* and *CYP2C19* phenotypes also are relevant to metabolism of selective serotonin reuptake inhibitors (SSRIs) and potentially other drugs wherein gene-based dosing and drug-drug interactions should be considered(169). However, no randomized clinical trials were found to evaluate the benefits of genetic testing prior to therapy.

3. *CYP2C19* and diazepam

Diazepam is metabolized primarily by a reaction mediated by *CYP2C19* to nordiazepam, an active metabolite. Patterns of diazepam metabolites have been characterized and are subject to variation based on the *CYP2C19* metabolic phenotype(181, 182). The most common reduced-function alleles for *CYP2C19* are the *2 and *3 alleles; the *17 is an increased-function allele. Detection of one reduced-function *CYP2C19* allele predicts the intermediate metabolizer phenotype, while detection of two reduced-function alleles predicts a poor metabolizer phenotype. The reduced-function alleles are relatively common in people of Asian descent and have been best studied relative to diazepam. A study of 63 Japanese subjects undergoing general anesthesia demonstrated significantly larger area under the curve for diazepam, lower clearance, and longer emergence time in *CYP2C19* intermediate and poor metabolizers as compared to the normal metabolizers(183). However, no randomized clinical trials were found to evaluate the benefits of genetic testing prior to therapy.

4. *CYP3A4, CYP3A5,* and fentanyl

An observational study conducted with 60 Japanese cancer patients found that the plasma concentrations of fentanyl were highest in patients with the *CYP3A5 *3/*3* diplotype, as was the incidence of dose-related adverse effects(184). In another study, the *CYP3A4*1G/*1G* diplotype was associated with lower dose requirements of fentanyl due to higher plasma concentrations than patients without the variant alleles(185). A third study evaluated fentanyl consumption during gynecological surgery for 203 Chinese women, relative to *CYP3A4* and *CYP3A5* genotypes(186). Consumption was lower for *CYP3A5* intermediate and poor metabolizers *(CYP3A5 *1/*3* and *CYP3A5 *3/*3)* than for normal metabolizers, when *CYP3A4*1G* was also present. As such, the gene-drug effects appeared additive. However, no significant effects of *CYP3A4/5* were observed on post-operative fentanyl dose requirements in a study of Korean gynecologic patients(187). No randomized clinical trials were found to evaluate the benefits of genetic testing prior to therapy.

*HLA-B*15:02* and carbamazepine

Carbamazepine is a common drug used to treat neuropathic pain, but is associated with serious cutaneous adverse reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis. These adverse reactions are not dose-dependent and can be life-threatening. Multiple studies have demonstrated an association between the variant human leucocyte antigen (HLA) allele, *HLA-B*15:02,* and carbamazepine hypersensitivity(188, 189). The *HLA-B*15:02* is most prevalent in Han and central Chinese, Thai, and Indian populations. A case-controlled study of 74 Thai patients showed that a hypersensitivity reaction occurred in 10.8 ± 1.4 days after initiation with carbamazepine in 94.1% of patients that were positive for *HLA-B*15:02* (odds ratio of 75.4), and in 17.5% of control patients(190). In the Han Chinese population, the absence of *HLA-B*15:02* is associated with 100% negative predictive value(191). While other risk alleles are under investigation for the carbamazepine-associated hypersensitivity reaction, multiple regulatory and professional organizations recommend that screening for this allele be performed prior to initiation of carbamazepine in naïve persons of Asian descent(162). However, no randomized clinical trials were found to evaluate the benefits of genetic testing prior to therapy.

Other genes

Many additional associations between response to drugs and genetic variation have been identified. The Pharmacogenomics Knowledgebase (https://www.pharmgkb.org/, accessed 06-14-2016) provides summaries of many such associations, along with clinical annotations that are categorized based on the level of evidence surrounding the association. Examples of genes that were identified in 10 or more studies to have associations with opioid response and/or dose are summarized in Table 11.

Table 11. Genes associated with opioid responses and/or dosages

Gene symbol (full name)	Description of protein function and potential role in pain management	Examples of associated drug(s)	References
ABCB1 (ATP-binding cassette, subfamily B, member 1, also known as multi-drug resistance, MDR 1)	Codes for p-glycoprotein (P-gp), which transports drugs from intracellular to extracellular domains, in various tissues. Variants may affect dose requirements, response, and risk of adverse effects for P-gp substrates due to changes in the amount of drug absorbed, eliminated, and/or transported into the compartments such as the central nervous system.	Morphine Methadone Fentanyl	(192, 193) (184, 187, 194-201)
COMT (catechol-O-methyltransferase)	*COMT* mediates the transfer of a methyl group from S-adenosylmethionine to catecholamines such as neurotransmitters, and catechol drugs. Variants may be associated with pain sensitivity, dose requirements, risk of adverse effects such as nausea and vomiting or sedation, as well as risk of heroin addiction.	Morphine Triptans	(194, 197, 198, 202-209)
OPRM1 (μ-opioid receptor, exon 1)	The μ-opioid receptor is a principal target for opioid analgesics. Variants are thought to play a role in dose requirements, response, and risk of adverse effects, such as nausea and vomiting or sedation from opioids. In addition, addiction to opioids, alcohol, nicotine, and other drugs, as well as response to addiction treatment, has also been associated with *OPRM1* variants.	Morphine Hydrocodone Fentanyl Oxycodone	(187, 192, 194, 195, 197, 198, 200, 203, 204, 208, 210-223)
UGT2B7 (UDP-glucuronosyltransferase family 2, member B7)	*UGT2B7* is a Phase II drug metabolizing enzyme responsible for conjugating drugs and drug metabolites with glucuronides. Glucuronide conjugates are usually eliminated more readily than unconjugated counterparts. Function of *UGT2B7* could affect elimination kinetics and dose requirements.	Morphine NSAIDs	(197, 200, 204, 222, 224-227)

Recognizing that the optimal dose of a single drug is likely to be affected by multiple proteins, coded by many potentially variant genes, efforts to study the multi-gene effects (e.g., pharmacogenomics) on optimal drug and dose selection are required. While studies identified here included more than one gene, most included only two or three genes, and none was comprehensive. Further, the combinations of genes, protocols, and patient populations that were studied were not consistent, making results difficult to compare between studies. No randomized clinical trials were found to evaluate the benefits of genetic testing prior to therapy.

Supportive testing of pharmacogenetics

Results of pharmacogenetic testing could impact optimal dose and dosing of a specific drug for an individual patient. The impact of the variant metabolic phenotype may be characterized and/or illustrated by metabolic ratios determined with quantitative urine or serum drug testing. Recognizing metabolic patterns and how they may be affected by pharmacogenetic variability is important for interpretation of drug testing results, and for detecting drug-drug interactions. For example, a poor metabolizer may not generate a metabolite that is common to normal metabolizers and could be viewed as non-compliant due to the lack of metabolite in the urine. Likewise, a rapid metabolizer may not realize the benefit of a drug, and may request higher doses because of accelerated elimination; such a patient could be inappropriately viewed as a drug seeker. Drug-drug interactions can produce or change a variant CYP metabolic phenotype, such as by inhibition of CYP enzyme function. As such, directed quantitative urine or serum drug testing, and evaluations of metabolic ratios may help evaluate and monitor the effects of abnormal drug metabolism on drug testing results.

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**

Gene-dose guidelines often recommend therapeutic drug monitoring to optimize dose when impaired metabolic phenotypes are predicted(161, 163). For example, therapeutic drug monitoring was used in combination with *CYP2D6* genotyping to more quickly attain therapeutic plasma concentrations and metabolic ratios of imipramine/desipramine(180). The plasma

concentrations ratios of several antidepressants were shown to be higher in *CYP2D6* poor metabolizers, and often exceeded the therapeutic ranges in a retrospective study of 62 hospitalized psychiatric patients(228). The ultra-rapid metabolizer phenotype for *CYP2D6* has been associated with steady-state concentrations of methadone, normalized for dose and patient weight, that were 54% of the concentrations observed in poor metabolizers, suggesting that individualization of methadone dose could be based on plasma concentrations(229). Therapeutic drug monitoring with plasma has also been proposed as a complementary tool for optimizing dose of many other drugs when variant metabolic phenotypes are recognized through pharmacogenetics testing(173, 230-232).

Urine testing results may reflect variation in CYP phenotypes as well. For example, hydromorphone is an expected metabolite of hydrocodone. The ratio of hydromorphone:hydrocodone may represent a patient phenotype that could be explained by variation in *CYP2D6* activity(233). In a retrospective evaluation of 25,200 urine samples that contained both hydrocodone and hydromorphone, the median metabolic ratio calculated with creatinine-corrected concentrations (mg/g creatinine) was 0.162, and the central 50% range (25th and 75th percentile) was 0.074 – 0.351. The authors suggest that low metabolic ratios could reflect *CYP2D6* metabolic phenotype, although this was not specifically tested. Theoretically, *CYP2D6* poor metabolizers would not produce hydromorphone, whereas ultra-rapid *CYP2D6* metabolizers would produce higher-than-expected amounts of hydromorphone. Monitoring metabolic ratios could identify *CYP2D6* metabolic phenotype and could also detect drug-drug interactions that affect the phenotype for an individual patient. Studies have demonstrated that CYP metabolic status is reflected in the urine metabolic ratios for several other opioids such as meperidine, oxycodone, buprenorphine, fentanyl, methadone, and propoxyphene and the benzodiazepine drug diazepam(145, 182, 234, 235).

CHAPTER 7

Reporting, interpretation, and communication of laboratory results with physicians

As discussed in the Introduction of this guideline, the testing used to support pain management evolved, in part, from workplace drug testing (WPDT) when clinical laboratories adopted and adapted the samples and methods for clinical use. The post-analytical phases involving the release, reporting, and interpretation of urine drug testing results in WPDT are heavily regulated and well defined. For example, all presumptive positive results obtained through screening must be confirmed using mass spectrometry prior to release. Results undergo a post-analytic review by a medical review officer who renders the final interpretation. The process may take several days to weeks to complete. Understandably, the clinical setting has very different needs and expectations reflected in each aspect of testing. Interfaces linking instruments, including mass spectrometers, to hospital and laboratory information systems (LIS) not only facilitate data entry, but permit many results to be transmitted within fractions of seconds of completion, without human intervention, to the electronic medical record (EMR) where they are available to both provider and patient. Although some have suggested that the testing conducted for pain management should be more in line with testing conducted for forensic purposes in light of the growing legal issues, others have countered that this would poorly serve patients, delay care, and add unnecessary burdens to providers and laboratories already encumbered by regulations. In this chapter we address several important post-analytical issues and make recommendations for addressing these issues to best serve the pain management community. Sixty-five manuscripts were initially identified as pertinent to the questions developed for this chapter.

General Reporting Requirements

Standards specified by various regulatory agencies, such as the Centers for Medicare and Medicaid Services (CMS) through the Clinical Laboratory Improvement Act (CLIA), the College of American Pathologists (CAP), and the Joint Commission (TJC) define critical elements that are common to all testing reports. (http://www.ecfr.gov/cgi-bin/text-idx?SID=1248e3189da5e5f936e55315402bc38b&node=pt42.5.493&rgn=div5, accessed 06-14-2016, Laboratory General Checklist, College of American Pathologists, 07-28-2015 Edition) Outside of these required elements, there is not a standard, uniform format agreed upon or in use specifically related to the reporting of UDT results for clinical purposes. A review of reports from a variety of laboratories conducting this testing shows a range of formats in use, not dissimilar to the variations observed for any other test report. Reporting formats range from the very simple to the inclusion of colorful graphics and interpretative "aids." These variations represent differences in information services support and marketing, and do not represent the quality of the laboratory testing.

Despite the variety in reporting, there are some unique features to consider when configuring a format for reporting UDT results:

- The test name should clearly identify the test performed by the drug or drug class as well as purpose or methodology to avoid confusion. For example, naming testing for opiates as "opiate class, screening (immunoassay)" or "opiates, confirmation (LC-MS/MS)" reduces confusion as to what the end user should expect. Today's EMR and LIS should not be encumbered by overly restrictive character limitations.
- Reference intervals in the traditional sense are not applicable, and clinical laboratories, in order to comply with the requirement to provide a reference, or "normal," range, use a variety of comments in this field, from "not detected" to "not applicable." It is important to note that the term "not detected" or "negative" may be appropriate for some drugs, e.g., cocaine, and in some situations, but not universally. Certainly, one expects to detect the prescribed medications discussed in this guideline in the urine specimens of compliant patients.
- The cutoff(s) employed should be defined. For screening methods, these are typically established by the assay manufacturer, and many manufacturers make several cutoff options available to accommodate the various settings in which these assays are used, e.g., many opiate screening immunoassays have the option of using a cutoff of either 2,000 ng/mL or 300 ng/mL. Where the testing method is developed by the laboratory, as is typically the case when LCMSMS or GCMS methods are used, the cutoff is based upon validation data, such as the limits of detection (LOD) and quantification (LOQ). As will be discussed below, there is no evidence that reporting the cutoff improves the accuracy of the interpretation, but the committee believes it is important. Cutoff values may be set high to avoid false positive results, and providers should take that into account when interpreting a result below the cutoff.
- If test(s) are not FDA-approved, that should be noted with the result. Furthermore, CAP-accredited laboratories should clearly state if the method was internally developed and validated by the laboratory.

Additional information regarding the method and testing may be helpful to the interpretation, but impractical to provide or maintain as part of the report. This information should be maintained as part of the laboratory formulary, handbook, testing menu, or other similar resource.

While there is not a standard format in which UDT results for pain management are reported, the committee agrees that the laboratory should use a format that conveys the results in a clear, concise, and understandable manner, and that this is especially important both when done through an EMR system. Additional details regarding reporting are found in CLSI C63, Laboratory Support of Pain Management.

Qualitative or Screening Results

The manner in which results are reported should be considered carefully. The use of the terms positive and negative in the reporting of qualitative results may mislead the reader who sees these terms as definitive, that is, drug is present and drug is absent from the sample. As an alternative, some laboratories have adopted the use of the assay cutoff (< 300 ng/mL or ≥ 300 ng/mL) in hopes that such would convey to the reader that a less than result could range from not detected to just below the reported number (e.g. 0-299 ng/mL) and thus facilitate interpretation. Unfortunately, the literature searches revealed that while this is an often-discussed issue, there have been no studies conducted to demonstrate if either manner of reporting, or an alternative, is effective.

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**

Turnaround Time of Reporting Screening Results

There has also been considerable debate as to how quickly screening results are needed and if such results should be held until confirmatory testing is completed. At the center of this debate is the concern that the release of unconfirmed results could lead to a negative patient care outcome, such as inappropriate dismissal from a facility based on a false positive screening result.

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**

There may be circumstances where reporting presumptive immunoassay results may be clinically useful. Other providers may prefer all testing be complete prior to reporting. The committee recommends that laboratories and healthcare providers communicate and determine which pattern of reporting is important to their specific clinical setting. When screening results are reported without confirmation or definitive testing, a reminder should be appended that additional, i.e., confirmatory or definitive, testing is available upon request when unexpected results are obtained (unexpected results may include both negative and positive screening results).

Quantitative Results

The application of mass spectrometry-based methods to UDT permits both the identification of the compounds present in the sample and the quantification of the result. What to report and how to use the data for patient care warrants discussion.

Reporting patterns of drug and drug metabolites to infer compliance and non-compliance

The literature readily supports that identification of an excreted drug and/or drug metabolite is useful in detecting recent exposure to a drug. Not all drugs are metabolized, but when metabolites are known, detection of common metabolites assures that the drug has been processed by the body, which would infer drug ingestion and possibly compliance.

During metabolism, many commonly used drugs are conjugated with a glucuronide or sulfate molecule to yield a metabolite that is more water-soluble than its unconjugated counterpart, promoting renal elimination of that drug. As such, the conjugated metabolites often represent the majority of drug present in the urine. In preparing urine samples for testing, pre-analytical hydrolysis will cleave the conjugated metabolite, which increases the amount of the unconjugated counterpart in the urine and may improve detection of that drug. This scenario reflects "total" drug. Some laboratories detect and report only the unconjugated, or "free," drug, typically with a lower cutoff than would be observed when an assay is designed to detect total drug. Other laboratories report both the free drug and conjugates independently. The committee investigated whether there was evidence to support the reporting of total drug, free drug, or both conjugated and unconjugated drug concentrations and whether reporting such concentrations would be more effective at assessing compliance with drug therapy in pain management patients.

Patterns of parent drug and drug metabolite concentrations may reflect aspects of pharmacokinetics for a specific patient, such as major versus minor routes of metabolism, and individual drug elimination patterns. The presence of a large amount of parent drug and no appreciable metabolites could also suggest the direct addition of the compound to a urine sample to simulate medication compliance. In addition, a large amount of one drug and a very small amount of a closely related but different drug (e.g., not an expected metabolite) may suggest pharmaceutical impurity.

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**

1. Opioids in General

Dickerson et al. found that direct measurement of glucuronide metabolites in urine improved detection of opioids including codeine, morphine, hydromorphone, oxymorphone, and buprenorphine(127). Of significance, no patients were positive for buprenorphine parent only, suggesting that either hydrolysis or direct measurement of glucuronides was required to evaluate adherence to buprenorphine in this population.

In a retrospective study, Cone et al. concluded the determination of total normetabolites for codeine, hydrocodone, and oxycodone (after hydrolysis) facilitated the assessment of compliance(147). In their study, a retrospective evaluation of 1,895 urine samples positive for one or more of 10 opioid analytes (total, cutoff 50 ng/mL) demonstrated that normetabolites were detected in the absence of parent drug in 8.6% of codeine-positive samples, 7.8% of hydrocodone-positive samples, and 9.4% of oxycodone-positive samples. Both parent drug and normetabolite were observed in 25.7% (codeine), 70.0% (hydrocodone), and 69.1% (oxycodone) of positive samples, and only parent drug was detected in 65.7% (codeine), 22.2% (hydrocodone), and 21.5% (oxycodone) of positive samples. Common patterns of parent drug and/or metabolites were also evaluated. When oxycodone and noroxycodone was detected, oxymorphone was commonly detected (n=418 of 1060). Oxymorphone was detected with oxycodone but not noroxycodone in 9.3% (n=99) of samples positive for oxycodone or noroxycodone (n=1060); noroxymorphone was not included in this evaluation. Oxymorphone was also detected with noroxycodone in 4.1% of samples (n=44). Several patterns of parent and/or metabolites observed in samples positive for hydrocodone or norhydrocodone (n=753). The most common pattern was hydrocodone/norhydrocodone/hydromorphone/dihydrocodeine (n=134, 17.8%). Many other patterns were observed. A second study from the same lab reported similar findings in a larger cohort of 13, 126 samples positive for one or more of the 10 opioid analytes (total) at concentrations >49 ng/mL(65). A third retrospective study of 108,923 urine results for which the pharmacy history was known(143) showed noroxycodone to be the major metabolite of oxycodone. Mole fractions of noroxycodone were significantly higher in women than in men, and mole fractions of oxycodone and oxymorphone were lower in women than in men. Higher oxycodone and oxymorphone mole fractions were observed with advanced age.

2. Morphine and codeine

In a retrospective case-controlled study, the prevalence of hydromorphone as a metabolite of morphine was evaluated relative to morphine dose and gender(236). Patients were included if the urine drug screen and chart review indicated that the patient was only taking morphine. Of the 32 patients meeting the inclusion criteria, 11 patients did not show evidence of hydromorphone and were designated as the controls. The remaining 21 patients showed evidence of both morphine and hydromorphone (prevalence 66%). The assay reporting limit was 50 ng/mL. Hydromorphone was observed in 87% of positive urine samples collected from women and 47% of positive samples collected from men, but the ratio of hydromorphone to morphine in urine was not significantly different between genders. In general, the concentration of hydromorphone was approximately 2% of the total morphine concentration, suggesting that hydromorphone occurs as a minor metabolite of morphine. Detection of hydromorphone is likely to be associated with the detection limit of the assay employed. A similar relationship has been described for hydrocodone as a minor metabolite of codeine in both controlled administration and postoperative patient studies(237). The concentration of hydrocodone could appear in urine at up to 11% of the parent (codeine) concentration.

In a retrospective study of urine drug test results wherein pharmacy history was known, a small amount of codeine was observed in the urine collected from patients prescribed only morphine. (144)Fifteen samples of 535 samples evaluated were described to contain total morphine concentrations in the range of 10,000 – 150,000 ng/mL, and total codeine concentrations between 20-50 ng/mL. Using average concentrations of morphine (94,000 ng/mL) and codeine (40 ng/mL), it was estimated that the fraction of codeine nearly approximates the estimated impurity observed in pharmaceutical morphine (0.04%). The authors conclude that their data suggest evidence of pharmaceutical impurity rather than a minor route of metabolism.

3. Meperidine

In a retrospective study, the mean metabolic ratio of normeperidine:meperidine was 5.07 in urine from men (n=291) and 6.97 in women (n=508)(238). The central 50% (25th and 75th percentile) ranged from 2.24-14.8 and 2.75-17.4 for the two populations, respectively. A weak but positive relationship was also found between urine pH and metabolic ratio, suggesting that acidification of urine could increase urinary excretion of meper-

idine. As with several other drugs, targeting normetabolites is important for maximizing detection of drug use.

4. Buprenorphine

In a retrospective study, 216 urine samples from 70 patients prescribed buprenorphine were evaluated (115). Buprenorphine was found in only 33 samples, whereas norbuprenorphine was found in all samples. There was strong evidence that nine samples were adulterated. Of the adulterated samples that could be further evaluated (n=6), the norbuprenorphine/buprenorphine ratio was less than 0.02 as compared to ratios of >0.99 for typical samples. Four of the samples had buprenorphine concentration in the 10,000 – 50,000 ng/mL range and naloxone concentrations between 4,000 – 15,000 ng/mL. Because the expected ratio of the pharmaceutical product Suboxone is 4:1, these data suggest that the patients who provided these urine samples had added drug directly to the urine after voiding to mimic compliance.

5. Diazepam

The proportions of total diazepam metabolites were determined retrospectively in 22,509 urine samples, in which oxazepam was the predominant metabolite and nordiazepam was the smallest(182). The mean fractions of excreted nordiazepam, temazepam, and oxazepam were 0.16, 0.34, and 0.47. All three metabolites were observed in 86.8% of samples, and 92% of samples had a larger amount of temazepam than nordiazepam. Fractions of nordiazepam were 4.8% lower in females than in males, whereas the temazepam fraction was 7.4% higher in females than in males. Similarly, the oxazepam fraction in females was 4% lower in females than in males. Age and urine pH did not affect fractions of metabolites. CYP3A4 substrates and inhibitors were evaluated and shown to affect the fractions, whereas CYP2C19 substrates and inhibitors did not.

6. Heroin

High concentrations of morphine in urine is traditionally recognized as an indicator of either morphine or heroin use. An unusual finding that has been replicated many times now is the presence of the unique heroin metabolite, 6-monoacetylmorphine (6-MAM), but no morphine in urine from pain management patients(138). This study evaluated the patterns of heroin, 6-MAM, and the 6-monoacetylcodeine (6-MAC) metabolite in 2871 urine samples positive for at least one of the heroin-specific analytes. Morphine and codeine were present in 76.4% and 42.4%, respectively. Specimens negative for morphine (n=677) represented 23.6%, of which 50 contained all three heroin analytes, 161 contained heroin only, 217 contained 6-MAM only, 92 contained 6-MAC only, and 145 contained the combination of heroin and 6-MAM. The reason for the variant metabolism is not known.

Approximation of the time of last dose

Some laboratories have applied therapeutic drug monitoring principles appropriate to serum, plasma, or blood concentrations to the quantified urine results with claims of such permitting a more effective assessment of the approximate time of the patient's last dose.

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

In a retrospective study of 161 patients prescribed transdermal fentanyl, the medial metabolic ratio of norfentanyl:fentanyl in urine was 6 with the central 50% range (25th and 75th percentile) 3-12(239). However, the study also acknowledged that the metabolic ratio could vary in a single subject by 10-fold, and between subjects by 37-fold. No pattern was demonstrated between the total amount of drug excreted and the metabolic ratio, suggesting that metabolic ratio does not correlate with dose. Studies with oxycodone and hydrocodone in urine have suggested that use of a proprietary algorithm can predict dose compliance (132, 133), but these data were challenged based on substantially overlapping distributions of urine concentrations by dose. Misclassification of dose estimates occurred in more than 25% of patients(240, 241).

Normalization of Quantitative Results to Creatinine or Specific Gravity

The reporting of quantitative urine drug testing results normalized to creatinine (ng drug/mg creatinine) or to specific gravity stems from the use of the practice in the testing of other urinary analytes, especially hormones, where it serves as a means of assessing the completeness of a 24-hour collection and accounting for variations between random sample collections.

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**

Two papers were identified related to the normalization of results. In the first, Pesce et al.(130) used mathematical modeling to assess the upper limits of drug excretion observed for 8,971 patients and to define reference intervals for the measured opiates. The distribution pattern obtained was minimally affected when the excreted drug concentrations were normalized to creatinine. Insufficient data were provided to fully assess the impact of this transformation. Barakat et al.(233) investigated the utility of the excretion of urinary hydrocodone concentrations and urinary hydromorphone concentrations to assess the variability of hydrocodone metabolism. Concentrations were normalized to

creatinine before modeling, but non-normalized data were not provided.

Interpretation of Results

Laboratory medicine consultations to assist with test interpretation

Much has been written and discussed about the ability of physicians and other healthcare providers to consistently and correctly interpret urine drug testing results. Urine results for any analyte are among the most complicated to interpret, and those for drug analysis are no exception. One must begin with sound knowledge of the pharmacology of the drugs (including the expected metabolic profiles), appreciate the variation in renal function over the course of the day and between individuals, recognize the inherent limitations of a randomly collected urine sample, and tie all of these together in light of the limitations and strengths of the analytical methods used to generate the result. Unfortunately, the data show that many clinical providers have insufficient knowledge and expertise to correctly interpret urine laboratory test results for pain management patients.

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**

To assess physician knowledge on UDT interpretation, Reisfield et al. developed a questionnaire consisting of seven multiple-choice questions(42, 43). The questions included assessment of knowledge regarding the metabolism and excretion patterns expected for codeine, morphine, and heroin, the interpretation of unexpected negative screening results, the effects of poppy seed ingestion, and implications of second-hand exposure to marijuana smoke. The authors administered the assessment to 170 physicians attending two conferences: one an opiate education conference(43), the second a family medicine conference(42). Of the 114 physicians attending the opioid education conference who completed the questionnaire, 77 reported using UDT as part of their management, while 37 did not. None of the physicians achieved a score of 100%, and only 30% answered more than 50% correctly. The performance of the physicians who performed UDT was the same as those who did not. Of the 60 family medicine physicians who participated in the second assessment, 44 reported using UDT and 16 did not. Again, none achieved a score of 100%, and only 20% answered more than half the questions correctly. For this group, the highest score was five out of seven questions correct, or 71%, and those who self-identified as routinely ordering UDT performed better on only four of the seven questions compared to those physicians who indicated they did not routinely order the testing. A new question was added surveying who would consult the laboratory director when abnormal or unexpected findings were reported and found only 23% of physicians indicated they would contact the laboratory director. For each group, the authors concluded that physician knowledge of UDT interpretation is inadequate, that physicians are making important clinical decisions without understanding how to interpret the results, which could have severe consequences for both the patient and physician when tests are misinterpreted, and that efforts should be made to increase physician knowledge and encourage laboratory consultation.

One additional study administered the aforementioned survey developed by Reisfield et al. to internal medicine residents in an academic training setting. In addition to the seven questions cited previously, the survey included elements to assess level of training and experience, attitudes, and behaviors in terms of testing utilization when caring for a patient receiving opiates and opioids(44). The mean score was three of the seven questions correct (n=99 residents), with individual scores ranging from none correct to six correct. The scores of the residents were discrepant with the confidence of the residents in interpreting the results, as 56% felt confident they had the knowledge to interpret test results. In conclusion, the residents were unaware of the complexities underlying the "simple" positive or negative result, which can lead to diagnostic errors.

Although there are a few papers that demonstrate that physicians are not proficient in interpreting UDT, there is no evidence that clinical pathology/laboratory medicine consultations are more effective for correct interpretation of urine test results for any drug given in pain management patients. This is most likely because providers are unaware of their knowledge gap and do not currently contact the laboratory director. Therefore, the studies cannot be performed. Despite the lack of evidence of the efficacy of laboratory medicine consultations, we strongly recommend that laboratories offering pain management testing have

knowledgeable personnel to assist clinicians. Laboratories, in all aspects of testing, are responsible for providing accurate results, and assisting with interpretation and pain management testing should be no exception. At a minimum, laboratories should provide educational resources and detailed reports, including whom to contact with questions regarding interpretation.

Utility of Clinical Algorithms

Quantitative UDT results have been used alone or in combination with clinical data (e.g., drug dose, clinical presentation) to predict drug efficacy and side effects, guide drug dosing, and/or assess compliance. However, the utility and accuracy of these clinical-based algorithms is unclear.

> 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**

There are a few articles that describe the use of quantitative testing and clinical algorithms, but none demonstrate how their use improved outcomes. Therefore, there is no evidence that the reporting of quantitative drug concentrations is more effective in facilitating the assessment of any outcomes for pain management patients(58, 130, 146, 182, 239, 242, 243).

According to one study, use of reference interval models in a pain management population (n=8971) may be effective at determining which patients are non-compliant with their drug regimen (e.g., taking a higher dose than prescribed or abusing drugs) (130). Samples were analyzed for 31 drugs and metabolites using LC-MS/MS. Distribution of results for all 31 drugs using several statistical methods was plotted and the upper 97.5th percentile for excretion was determined. The authors conclude that excretion limits, clinical history, and medication dosage can be used in aggregate to better assess compliance and construct clinic- or patient-specific excretion patterns. However, the study is limited by the lack of information regarding dosage, time after drug ingestion, and other demographic data. Furthermore, as recommended earlier in this chapter, there is no evidence that quantitative results can approximate the time of last dose.

Another study examined the benzodiazepine urinary excretion pattern in 22,509 specimens from unique subjects(182). Most patients (86.8%) had all three metabolites detected in urine. Oxazepam accounted for the largest fraction of urine diazepam metabolites, and nordiazepam was the smallest. The metabolite distribution was similar among patients, suggesting that the patterns presented by the authors could be extrapolated to the general population. Therefore, quantitative measurement of diazepam metabolites in the urine may be useful to monitor patients for compliance, drug-drug interactions, and adverse effects and utilized to adjust therapy. Of note, inhibitors of CYP3A4 and CYP2C19 altered the metabolic pattern slightly. The study was limited by lack of dosage information and lack of correlating plasma concentrations.

In contrast to the above studies, one study showed that quantitative methamphetamine and amphetamine results may be seen in patients taking the analgesic famprofazone, a major ingredient of Gewolen, making it challenging to use quantitative levels to predict methamphetamine or amphetamine abuse(242). In six healthy subjects given one tablet of Gewolen containing 25 mg of famprofazone, concentrations of methamphetamine by GC-MS ranged from 901 to 2670 ng/mL and concentrations of amphetamine by GC-MS ranged from 208 to 711 ng/mL. 18% of urine specimens within 48 hours would have been positive by immunoassay using 500 ng/mL cutoff. Therefore, a famprofazone user may be misinterpreted as an illicit methamphetamine abuser. The medication has been banned in Korea and the United States, and it has been banned by the World Anti-Doping Agency since 2005. According to the authors, other countries such as Taiwan should consider banning this drug.

Although not the focus of these guidelines, a few papers have been published on the use of serum or plasma drug concentrations and post-mortem samples to assist with patient outcomes. Three studies examined the utility of plasma drug levels to predict clinical efficacy(243), dosing requirements(58) and side effects(239). Another study used quantitative post-mortem drug concentrations to determine the cause of death(146). Similar to urine, there was lack of evidence that plasma or post-mortem analysis, alone or in combination with clinical variables, could improve outcomes.

APPENDIX A

Tables Used for PICO(TS) Questions

Table A. Drug/drug class and outcomes

Drug/drug class	Outcomes
Amphetamines (Amphetamine, Methamphetamine, Methylenedioxyethylamphetamine [MDEA], Methylenedioxymethamphetamine [MDMA], Methylenedioxyamphetamine [MDA])	Adverse drug reactions (ADRs)
Acetaminophen	Abuse
Alcohol	Addiction
Anticonvulsants (Carbamazepine, Felbamate, Gabapentin, Lacosamide, Lamotrigine, Levetiracetam, Oxcarbazepine, Phenytoin, Phenobarbital, Pregabalin, Rufinamide, Tiagabine, Topiramate, Valproic acid)	Adherence/compliance
Antidepressants (TCAs, SSRIs, SNRIs) (Amitriptyline, Desipramine, Imipramine, Clomipramine, Nortriptyline, Doxepin, Duloxetine, Citalopram, Fluoxamine, Paroxetine, Fluoxetine, Sertaline, Venlafaxine)	Altered pharmacokinetics (PK)
Antihistamines (Certirizine, Chlorpheniramine, Diphenhydramine, Loratadine)	Appropriate interpretation
Antipsychotics (Amisulpride, Amoxapine, Chlormethiazole, Clopenthixole, Chlorpiprazine, Chlorpromazine, Chlorprothixene, Cloxazepine, Clozapine, Distraneurine, Dixyrazine, Chlorpromazine, Flupentixol decanoate, Fluphenazine, Haloperidole, Loxapine, Melperone hydrochloride, Methotrimeprazine, Olanzapine, Oxilapine, Perphenazine, Pimozide, Quetiapine, Risperidone, Sulpiride, Thioridazine, Tiapride, Trifluoroperazine, Ziprsasidone, Zotepine, Zuclopenthixole)	Death
Barbiturates (Amobarbital, Butalbital, Pentobarbital, Phenobarbital, Secobarbital)	Dependence
Bath salts (Cathinones: Mephedrone, Methylone, 3,4-Methylenedioxypyrovalerone [MDPV])	Diversion
Benzodiazepines (Alprazolam, Chlordiazepoxide, Clonazepam, Clorazepate, Diazepam, Estazolam, Flurazepam, Halazepam, Lorazepam, Medazepam, Midazolam, Oxazepam, Prazepam, Temazepam, Triazolam)	Drug sensitivity
Buprenorphine	Drug-drug interactions
Cannabinoids/Tetrahydrocannabinol (THC)	Driving under the influence of drugs (DUID)
Cocaine (Cocaine, Benzoylecgonine)	Emergency Department (ED) visits
Dextromethorphan	Hospitalization
Ketamine	Lack of efficacy
Lysergic acid diethylamide (LSD)	Misuse

Table A *continued*

Drug/drug class	Outcomes
Methadone	Overdose
6-monoacetylmorphine (6-MAM)	Therapeutic failure
Muscle relaxants (Carisoprodol, Meprobamate,)	Violent crimes
Opiates/Opioids (Codeine, Dihydrocodeine, Heroin, Hydrocodone, Hydromorphone, Morphine, Oxycodone, Oxymorphone)	
Phencyclidine (PCP)	
Phenothiazine	
Propoxyphene	
Salicylates	
Synthetic THC (K2, Spice, etc.)	
Tapentadol	
Tramadol	
Non-steroidal anti-inflammatory drugs (NSAIDs) (Aspirin, Ibuprofen)	
Fentanyl	

Table B. Physician tools/matrix

Physician Tools	Matrix
CAGE	Breast milk
Medical record review	Dried blood spots
Physician interview	Hair
Prescription monitoring program (PMP)	Meconium
Self-report	Oral fluid
Screener and Opioid Assessment for Patients with Pain (SOAPP)	Plasma
TIC	Serum
	Umbilical cord
	Whole blood

Table C. Targeted screening methods

Targeted Screening Methods
Liquid chromatography-time of flight mass spectrometry (LC-TOF-MS)
High performance liquid chromatography (HPLC)
Liquid chromatography-mass spectrometry (LC/MS)
Liquid chromatography-tandem mass spectrometry (LC/MS/MS)
Gas chromatography-mass spectrometry (GC/MS)

Table D. Adulterants

Adulterant
Creatinine
Specific gravity
pH
Oxidant
Pyridinium chlorochromate
Nitrite
Temperature
Glutaraldehyde
Zinc

Table E. Genes and DNA sources

Genes	DNA Source
ABCB1	Buccal swab
CNA1B	Hair
CNR1	Oral fluid
COMT	Serum/plasma
CYP1A2	Tissue
CYP2B6	Urine
CYP2C19	Whole blood
CYP2C8	
CYP2C9	
CYP2D6	
CYP2E1	
CYP3A4	
CYP3A5	
KCNQ2	
OPRM1	
SCN9A	
SULT	
UGT1A1	
UGT1A3	
UGT1A8	
UGT1A9	
UGT2B15	
UGT2B7	
5-HT receptor (serotonin)	
Dopamine receptors	
POR (cytochrome P450 oxidoreductase)	

Table F. Alternate wording for "positive" or "negative"

Positives	Negatives
Presumptive positive	Absent
Present	Not detected
Detected	Less than cutoff
Greater than cutoff	Negative
Positive	Low
High	Abnormal
Normal	

APPENDIX B

Summary tables of the evidence-based LMPG recommendations and consensus-based expert opinions

Table G. Summary of Evidence-based LMPG Recommendations

#	Recommendation	Grading: Strength of recommendation, Quality of evidence	Target Group		
			Lab	Clinician	Policy¥
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.	A, I	X	X	X
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.	A, II		X	X
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.	A, III (pain management) II (substance abuse disorder monitoring population)		X	X
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.	A, II		X	X
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.	B, II		X	X
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.	B, II		X	X
7	Qualitative definitive tests should be used over 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.	A, II	X	X	X

Table G *continued*

#	Recommendation	Grading: Strength of recommendation, Quality of evidence	Target Group		
			Lab	Clinician	Policy[¥]
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.	A, II	X	X	X
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.	B, II		X	X
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.	B, II		X	X
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.	B, II		X	X
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.	A, II	X	X	X
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.	A, III		X	X
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).	A, II	X	X	X
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.	A, I (workplace drug testing) II (pain management)	X	X	X

Table G *continued*

#	Recommendation	Grading: Strength of recommendation, Quality of evidence	Target Group		
			Lab	Clinician	Policy[¥]
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 using 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.	A, I (workplace drug testing) III (pain management)	X	X	X
17	Clinicians should consult the laboratory regarding proper collection, storage, and transportation of urine specimens to maintain specimen validity.	A, III		X	
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.	A, II		X	
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.	A, I (workplace drug testing) III (pain management)	X	X	X
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.	A, II		X	X
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.	B, II	X	X	X
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.	I, II	X	X	X
23	Urine drug testing (quantitative or qualitative) is not recommended for approximating the time of last dose.	B, II		X	
24	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.	A, I		X	
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.	A, III	X		

Table G *continued*

#	Recommendation	Grading: Strength of recommendation, Quality of evidence	Target Group		
			Lab	Clinician	Policy[¥]
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.	A, III	X		

[¥]Policy: Includes policy makers, regulatory bodies, and health insurance companies.

Table H. Summary of consensus-based expert opinions

#	Expert Opinion	Grading: Strength of recommendation/ Quality of evidence	Target Group		
			Lab	Clinician	Policy
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.	A, II		X	X
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).	A, III	X	X	X
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.	A, III (pain management), II (substance abuse disorder monitoring population)		X	X
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.	B, II	X	X	
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.	I, III		X	
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.	I, III	X		
7	Specimen validity testing should be performed on every urine drug test for pain management patients.	A, II	X	X	X

[¥]Policy: Includes policy makers, regulatory bodies, and health insurance companies.

APPENDIX C

Search strategy used for MEDLINE database

Introduction, background and scope

1. exp pain/dt or pain clinics/ or "pain management".mp. or "chronic pain".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
2. exp clinical chemistry tests/
3. specimen handling/ or blood specimen collection/ or urine specimen collection/
4. exp Chemistry Techniques, Analytical/
5. medication adherence/
6. exp Immunoassay/
7. monitoring, physiologic/ or medication adherence/ or substance abuse detection/
8. "sensitivity and specificity"/ or reproducibility of results/ or exp diagnostic errors/ or "false negative".mp. or "false positive".mp. or cross reaction*.mp. or "predictive value".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
9. exp Substance-Related Disorders/bl, cf, di, pc, ur
10. exp analgesics/ or exp analgesics, non-narcotic/ or exp analgesics, opioid/
11. 1 or 10 or exp pain/ur, ae, co, ch
12. 9 and 11
13. 8 and 12
14. 11 and (2 or 3 or 4 or 5 or 6 or 7)
15. exp analgesics/an, bl, cf, ct, me, pk, pd, tu, to, ur, ad, ae or exp analgesics, non-narcotic/an, bl, cf, ct, me, pk, pd, tu, to, ur, ad, ae or exp analgesics, opioid/an, bl, cf, ct, me, pk, pd, tu, to, ur, ad, ae
16. 14 and 15
17. 8 and 16
18. ..l/ 17 hu=y and lg=en
19. limit 18 to (clinical conference or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or consensus development conference or consensus development conference, nih or controlled clinical trial or legal cases or legislation or meta analysis or multicenter study or patient education handout or practice guideline or randomized controlled trial or systematic reviews)
20. ..l/ 13 lg=en
21. limit 20 to (clinical conference or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or consensus development conference or consensus development conference, nih or controlled clinical trial or legal cases or legislation or meta analysis or multicenter study or patient education handout or practice guideline or randomized controlled trial or systematic reviews)
22. 19 or 21
23. (13 or 18) and (legislation, drug/ or lj.fs. or mandatory*.mp. or drug monitoring/ or liability, legal/ or adultera*.mp. or "screening assays".mp.) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
24. ..l/ 23 lg=en
25. 22 or 24
26. remove duplicates from 25
27. (18 or 13) and (review.pt. or "evidence-based".mp. or cohort*.mp. or retrospective study/ or prospective study/) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
28. ethanol/ad, ae, an, bl, cf, ct, me, ge, pk, pd, tu, ur or alcohol drinking/
29. exp anticonvulsants/ad, ae, an, bl, ch, cf, ct, me, ge, pk, po, pd, tu, ur
30. exp amphetamines/ad, ae, an, bl, cf, ct, me, ge, pk, pd, po, tu, ur
31. exp antidepressive agents/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
32. exp histamine antagonists/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
33. exp antipsychotic agents/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
34. exp barbiturates/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
35. exp benzodiazepines/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
36. exp narcotics/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur or exp antitussive agents/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
37. exp cocaine/ or street drugs/ or designer drugs/ or "bath salts".mp. or tetrahydrocannabinols/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword

heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

38. exp hallucinogens/ or exp muscle relaxants, central/ or phencyclidine/ or phencyclidine abuse/ or exp antiinflammatory agents, non-steroidal/
39. 14 and 38
40. 39 and (drug interactions/ or drug monitoring/ or prescription drug misuse/ or screening*.mp. or monitor*.mp.) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
41. limit 40 to (english language and (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or consensus development conference or consensus development conference, nih or controlled clinical trial or guideline or legal cases or legislation or meta analysis or multicenter study or patient education handout or practice guideline or randomized controlled trial or "review" or systematic reviews or validation studies))
42. or/28-37
43. 14 and 42
44. 43 and (drug interactions/ or drug monitoring/ or prescription drug misuse/ or screening*.mp. or monitor*.mp.)
45. limit 44 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or consensus development conference or consensus development conference, nih or controlled clinical trial or evaluation studies or legal cases or legislation or meta analysis or multicenter study or patient education handout or practice guideline or randomized controlled trial or "review" or systematic reviews or validation studies)
46. 43 and (review.pt. or "evidence-based".mp. or cohort*.mp. or retrospective study/ or prospective study/)
47. 41 or 45 or 46
48. 47 not (25 or 27)
49. remove duplicates from 48
50. 14 and ("point of care".mp. or point-of-care systems/) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
51. limit 50 to (english language and humans)
52. 49 or 51
53. 52 not (letter or editorial or news).pt.
54. limit 53 to humans
55. limit 54 to english language
56. exp *pain/dt or *pain clinics/ or *"pain management"/ or *"chronic pain"/ or (exp pain/ti or pain clinics/ti or "pain management"/ti or "chronic pain"/ti)
57. 56 or *analgesics, opioid/
58. exp Substance-Related Disorders/co, ep, pc, px, st, sn [Complications, Epidemiology, Prevention & Control, Psychology, Standards, Statistics & Numerical Data]
59. 57 and 58
60. 59 and drug monitoring/
61. 59 or 60
62. ..l/ 61 yr=2013-2015
63. exp medical errors/ and 62
64. 59 and (exp pain/ep, sn or exp pain management/sn or pain clinics/)
65. exp Total Quality Management/ or exp Quality Assurance, Health Care/
66. 62 and 65
67. 62 and effective*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
68. 67 and review.pt.
69. 62 and hi.fs.
70. 63 or 64 or 66 or 68 or 69
71. remove duplicates from 70

Common Classes of medications prescribed and abused by pain management patients

1. exp pain/dt or pain clinics/ or "pain management".mp. or "chronic pain".mp. or exp analgesics, opioid/ or pain/ur, ae, co, ch [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
2. exp Government Agencies/ or exp Federal Government/ or exp Government Regulation/
3. exp "Drug and Narcotic Control"/ or exp Legislation, Drug/ or exp Drug Prescriptions/
4. exp "United States Food and Drug Administration"/
5. societies, medical/
6. (academy adj5 pain).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
7. ((association or society) adj5 pain).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8. or/5-7
9. or/2-4
10. exp Drug Interactions/
11. Drug Monitoring/
12. prescription drug misuse/ or monitor*.mp. or screen*.mp. or medication adherence/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
13. exp *substance-related disorders/co, ep, pc, px, st, sn, di, bl, ur
14. or/10-13
15. 1 and (8 or 9) and 14
16. 1 and 14

17. 16 and (confirm* or regulat* or mandator* or screen* or safe).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
18. exp clinical chemistry tests/ or specimen handling/ or blood specimen collection/ or urine specimen collection/ or exp chemistry techniques, analytical/ or exp immunoassay/ or monitoring, physiologic/ or substance abuse detection/
19. 17 and 18
20. 17 and ("point of care".mp. or point of care, systems/) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
21. 15 or 19 or 20
22. 17 and testing.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
23. 21 or 22
24. 21 and ((adultera* or screen*).mp. or liability, legal/ or documentation.mp. or witness*.mp. or requirement*.mp. or timing.mp. or schedul*.mp. or frequen*.mp.) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
25. 23 or 24
26. 25 and (recommend* or consensus or guideline* or "evidence-based").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
27. limit 25 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or consensus development conference or consensus development conference, nih or controlled clinical trial or evaluation studies or legal cases or legislation or meta analysis or multicenter study or patient education handout or practice guideline or randomized controlled trial or "review" or systematic reviews)
28. exp case-control studies/ or exp cohort studies/ or exp cross-sectional studies/ or exp clinical trials as topic/ or exp feasibility studies/ or exp intervention studies/ or exp pilot projects/
29. 25 and 28
30. 26 or 27 or 29
31. ..l/ 30 lg=en
32. remove duplicates from 31
33. exp *pain/dt, ae, co, ur, bl, ch or exp *analgesic, opioid/ or prescription drug misuse/ or 13
34. 32 and 33
35. 32 and controlled.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
36. 34 or 35

Specimen types and detection times

1. exp analgesics/ or exp analgesics, non-narcotic/ or exp analgesics, opioid/
2. ethanol/ad, ae, an, bl, cf, ct, me, ge, pk, pd, tu, ur or alcohol drinking/
3. exp cocaine/ or street drugs/ or designer drugs/ or "bath salts".mp. or tetrahydrocannabinols/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
4. exp hallucinogens/ or exp muscle relaxants, central/ or phencyclidine/ or phencyclidine abuse/ or exp antiinflammatory agents, non-steroidal/
5. exp pain/dt or pain clinics/ or "pain management".mp. or "chronic pain".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
6. exp clinical chemistry tests/
7. specimen handling/ or blood specimen collection/ or urine specimen collection/
8. exp Chemistry Techniques, Analytical/
9. medication adherence/
10. exp Immunoassay/
11. monitoring, physiologic/ or medication adherence/ or substance abuse detection/
12. "sensitivity and specificity"/ or reproducibility of results/ or exp diagnostic errors/ or "false negative".mp. or "false positive".mp. or cross reaction*.mp. or "predictive value".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
13. exp analgesics/ or exp analgesics, non-narcotic/ or exp analgesics, opioid/
14. 5 or 13 or exp pain/ur, ae, co, ch
15. 14 and (6 or 7 or 8 or 9 or 10 or 11)
16. exp *pain/dt or *pain clinics/ or *"pain management"/ or *"chronic pain"/ or (pain/ti or pain clinics/ti or "pain management"/ti or "chronic pain"/ti)
17. drug abuse/di, pc or drug misuse/di, pc
18. exp statistics/
19. exp case control study/ or exp case study/ or exp clinical trial/ or exp "clinical trial (topic)"/ or exp community trial/ or exp intervention study/ or exp major clinical study/
20. exp substance abuse/ or exp addiction/ or exp drug dependence/ or exp drug abuse/
21. exp cocaine/ or exp addiction/ or exp drug abuse/ or exp substance abuse/ or exp drug dependence/
22. exp anticonvulsive agent/ae, an, cr, it, to [Adverse Drug Reaction, Drug Analysis, Drug Concentration, Drug Interaction, Drug Toxicity]
23. exp amphetamine derivative/ae, an, cr, do, it, to, pk [Adverse Drug Reaction, Drug Analysis, Drug Concentration, Drug Dose, Drug Interaction, Drug Toxicity, Pharmacokinetics]
24. exp antidepressant agent/ae, ad, an, cr, do, it, to [Adverse Drug Reaction, Drug Administration, Drug Analysis, Drug Concentration, Drug Dose, Drug Interaction, Drug Toxicity]

25. exp antihistaminic agent/ae, an, do, it, to, pk [Adverse Drug Reaction, Drug Analysis, Drug Dose, Drug Interaction, Drug Toxicity, Pharmacokinetics]
26. exp neuroleptic agent/ae, an, cr, do, it, to [Adverse Drug Reaction, Drug Analysis, Drug Concentration, Drug Dose, Drug Interaction, Drug Toxicity]
27. exp barbituric acid derivative/ae, an, cr, do, it, to, pk [Adverse Drug Reaction, Drug Analysis, Drug Concentration, Drug Dose, Drug Interaction, Drug Toxicity, Pharmacokinetics]
28. exp benzodiazepine derivative/ae, an, cr, do, it, to, pk, pd [Adverse Drug Reaction, Drug Analysis, Drug Concentration, Drug Dose, Drug Interaction, Drug Toxicity, Pharmacokinetics, Pharmacology]
29. exp narcotic agent/ae, an, cr, do, it, to, pk, pd [Adverse Drug Reaction, Drug Analysis, Drug Concentration, Drug Dose, Drug Interaction, Drug Toxicity, Pharmacokinetics, Pharmacology]
30. or/2-4
31. or/20-29
32. 30 or 31
33. or/6-12
34. 16 or 17
35. 32 and 33
36. 34 and 35
37. 35 and (drug misuse/ or drug abuse/ or safe*.mp.)
38. 16 and 37
39. 36 or 38
40. 39 and (18 or 19)
41. methodology/ or exp cohort analysis/ or exp cross-sectional study/ or exp evidence based practice/ or exp intermethod comparison/ or exp multimethod study/ or exp qualitative research/ or exp quality control/
42. 39 and 41
43. 40 or 42
44. limit 43 to (human and english language and yr="2000 - 2013")
45. remove duplicates from 44

Qualitative screening assays

1. exp pain/dt or pain clinics/ or "pain management".mp. or "chronic pain".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
2. exp clinical chemistry tests/
3. specimen handling/ or blood specimen collection/ or urine specimen collection/
4. exp Chemistry Techniques, Analytical/
5. medication adherence/
6. exp Immunoassay/ or exp clinical laboratory techniques/ or diagnostic tests, routine/ or "drug surveillance".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
7. monitoring, physiologic/ or medication adherence/ or substance abuse detection/
8. "sensitivity and specificity"/ or reproducibility of results/ or exp diagnostic errors/ or "false negative".mp. or "false positive".mp. or cross reaction*.mp. or "predictive value".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
9. or/2-8
10. exp Substance-Related Disorders/an, bl, cf, di, me, mo, px, pc, ur
11. exp analgesics/an, bl, cf, ct, me, pk, pd, tu, to, ur, ad, ae or exp analgesics, non-narcotic/an, bl, cf, ct, me, pk, pd, tu, to, ur, ad, ae or exp analgesics, opioid/an, bl, cf, ct, me, pk, pd, tu, to, ur, ad, ae
12. ethanol/ad, ae, an, bl, cf, ct, me, ge, pk, pd, tu, ur or alcohol drinking/
13. exp anticonvulsants/ad, ae, an, bl, ch, cf, ct, me, ge, pk, po, pd, tu, ur
14. exp amphetamines/ad, ae, an, bl, cf, ct, me, ge, pk, pd, po, tu, ur
15. exp antidepressive agents/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
16. exp histamine antagonists/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
17. exp antipsychotic agents/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
18. exp barbiturates/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
19. exp benzodiazepines/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
20. exp narcotics/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur or exp antitussive agents/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
21. exp cocaine/ or street drugs/ or designer drugs/ or "bath salts".mp. or tetrahydrocannabinols/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
22. exp hallucinogens/ or exp muscle relaxants, central/ or phencyclidine/ or phencyclidine abuse/ or exp antiinflammatory agents, non-steroidal/
23. or/11-21
24. drug interactions/ or drug monitoring/ or prescription drug misuse/ or substance abuse detection/

Quantitative or confirmatory assasys

1. exp pain/dt or pain clinics/ or "pain management".mp. or "chronic pain".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
2. exp clinical chemistry tests/
3. specimen handling/ or blood specimen collection/ or urine specimen collection/
4. exp Chemistry Techniques, Analytical/
5. medication adherence/
6. exp Immunoassay/ or exp clinical laboratory techniques/ or diagnostic tests, routine/ or "drug surveillance".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

7. monitoring, physiologic/ or medication adherence/ or substance abuse detection/
8. "sensitivity and specificity"/ or reproducibility of results/ or exp diagnostic errors/ or "false negative".mp. or "false positive".mp. or cross reaction*.mp. or "predictive value".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
9. or/2-8
10. exp *Substance-Related Disorders/
11. exp *analgesics, opioid/
12. *ethanol/ or *alcohol drinking/ or exp *alcoholism/
13. exp *anticonvulsants/
14. exp *amphetamines/
15. exp *antidepressive agents/
16. exp *histamine antagonists/
17. exp *antipsychotic agents/
18 exp *barbiturates/
19. exp *benzodiazepines/
20. exp *narcotics/ or exp *antitussive agents/
21. exp cocaine/ or street drugs/ or designer drugs/ or "bath salts".mp. or tetrahydrocannabinols/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
22. exp hallucinogens/ or exp muscle relaxants, central/ or phencyclidine/ or phencyclidine abuse/ or exp antiinflammatory agents, non-steroidal/
23. or/11-21
24. drug interactions/ or drug monitoring/ or prescription drug misuse/ or substance abuse detection/
25. 1 or 11 or exp pain, an,bl,ae,co,ch,cf,me,mo/
26. 9 and 10 and 25
27. 23 and 25 and 24
28. 27 and (drug monitoring/ or prescription drug misuse/ or substance abuse detection/)
29. 26 or 28
30. 9 and 27
31. urinalysis/
32. 30 and 31
33. limit 32 to (human and english language and yr="2000 - 2014")
34. (patient monitoring/ or drug screening/) and 27
35. limit 34 to (human and english language and yr="2000 - 2014")
36. 33 or 35
37. 27 and drug urine level/
38. 37 not 36

Adulterant testing

1. exp pain/dt or pain clinics/ or "pain management".mp. or "chronic pain".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
2. exp clinical chemistry tests/
3. specimen handling/ or blood specimen collection/ or urine specimen collection/
4. exp Chemistry Techniques, Analytical/
5. medication adherence/
6. exp Immunoassay/ or exp clinical laboratory techniques/ or diagnostic tests, routine/ or "drug surveillance".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
7. monitoring, physiologic/ or medication adherence/ or substance abuse detection/
8. "sensitivity and specificity"/ or reproducibility of results/ or exp diagnostic errors/ or "false negative".mp. or "false positive".mp. or cross reaction*.mp. or "predictive value".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
9. exp *Substance-Related Disorders/
10. exp *analgesics, opioid/
11. *ethanol/ or *alcohol drinking/ or exp *alcoholism/
12. exp *anticonvulsants/
13. exp *amphetamines/
14. exp *antidepressive agents/
15. exp *histamine antagonists/
16. exp *antipsychotic agents/
17. exp *barbiturates/
18. exp *benzodiazepines/
19. exp *narcotics/ or exp *antitussive agents/
20. exp cocaine/ or street drugs/ or designer drugs/ or "bath salts".mp. or tetrahydrocannabinols/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
21. exp hallucinogens/ or exp muscle relaxants, central/ or phencyclidine/ or phencyclidine abuse/ or exp antiinflammatory agents, non-steroidal/
22. or/10-20
23. drug interactions/ or drug monitoring/ or prescription drug misuse/ or substance abuse detection/
24. or/2-6
25. 24 and 22 and (7 or 23)
26. 25 and (8 or confirm*.mp. or quantif*.mp.) [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
27. limit 26 to (english language and yr="2000 - 2015")
28. 27 and (ur.fs. or urinalysis.mp. or urine.mp.) [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
29. 27 and (ec.fs. or "costs and cost analysis"/ or "cost-benefit".mp.) [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

30. 27 and (cutoff or "cut adj off").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
31. 28 or 29 or 30
32. limit 31 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or observational study or randomized controlled trial or validation studies)
33. 31 or 32

Pharmacogenomic considerations

1. exp pain/dt or pain clinics/ or "pain management".mp. or "chronic pain".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
2. exp clinical chemistry tests/
3. specimen handling/ or blood specimen collection/ or urine specimen collection/
4. exp Chemistry Techniques, Analytical/
5. medication adherence/
6. exp Immunoassay/ or exp clinical laboratory techniques/ or diagnostic tests, routine/ or "drug surveillance".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
7. monitoring, physiologic/ or medication adherence/ or substance abuse detection/
8. "sensitivity and specificity"/ or reproducibility of results/ or exp diagnostic errors/ or "false negative".mp. or "false positive". mp. or cross reaction*.mp. or "predictive value".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
9. exp *Substance-Related Disorders/
10. exp *analgesics, opioid/
11. *ethanol/ or *alcohol drinking/ or exp *alcoholism/
12. exp *anticonvulsants/
13. exp *amphetamines/
14. exp *antidepressive agents/
15. exp *histamine antagonists/
16. exp *antipsychotic agents/
17. exp *barbiturates/
18. exp *benzodiazepines/
19. exp *narcotics/ or exp *antitussive agents/
20. exp cocaine/ or street drugs/ or designer drugs/ or "bath salts". mp. or tetrahydrocannabinols/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
21. exp hallucinogens/ or exp muscle relaxants, central/ or phencyclidine/ or phencyclidine abuse/ or exp antiinflammatory agents, non-steroidal/
22. or/10-20
23. drug interactions/ or drug monitoring/ or prescription drug misuse/ or substance abuse detection/
24. or/2-6
25. 24 and 22 and (7 or 23)
26. 25 and (adulterant* or adulterat* or deception or deceiv* or substitut*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
27. 25 and custody.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
28. 25 and (creatinine or ph or oxidant or pyridinium or pcc or nitrite* or glutaraldehyde or peroxid*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
29. 26 or 27 or 28
30. 29 and (ur.fs. or urine.mp. or urinaly*.mp.) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
31. 23 and 29
32. 30 or 31
33. limit 32 to (english language and yr="2000 - 2014")
34. 29 and (urine specimen collection/ or specimen handling/)
35. ..l/ 34 lg=en and yr=2000-2014
36. 33 or 35
37. 36 not (letter or editorial).pt.

Regulatory and DEA issues and considerations for labs and physicians

1. exp pain/dt or pain clinics/ or "pain management".mp. or "chronic pain".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
2. exp clinical chemistry tests/
3. specimen handling/ or blood specimen collection/ or urine specimen collection/
4. exp Chemistry Techniques, Analytical/
5. medication adherence/
6. exp Immunoassay/ or exp clinical laboratory techniques/ or diagnostic tests, routine/ or "drug surveillance".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
7. monitoring, physiologic/ or medication adherence/ or substance abuse detection/

8. "sensitivity and specificity"/ or reproducibility of results/ or exp diagnostic errors/ or "false negative".mp. or "false positive".mp. or cross reaction*.mp. or "predictive value".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
9. or/2-8
10. exp Substance-Related Disorders/an, bl, cf, di, me, mo, px, pc, ur
11. exp analgesics/an, bl, cf, ct, me, pk, pd, tu, to, ur, ad, ae or exp analgesics, non-narcotic/an, bl, cf, ct, me, pk, pd, tu, to, ur, ad, ae or exp analgesics, opioid/an, bl, cf, ct, me, pk, pd, tu, to, ur, ad, ae
12. ethanol/ad, ae, an, bl, cf, ct, me, ge, pk, pd, tu, ur or alcohol drinking/
13. exp anticonvulsants/ad, ae, an, bl, ch, cf, ct, me, ge, pk, po, pd, tu, ur
14. exp amphetamines/ad, ae, an, bl, cf, ct, me, ge, pk, pd, po, tu, ur
15. exp antidepressive agents/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
16. exp histamine antagonists/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
17. exp antipsychotic agents/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
18. exp barbiturates/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
19. exp benzodiazepines/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
20. exp narcotics/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur or exp antitussive agents/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
21. exp cocaine/ or street drugs/ or designer drugs/ or "bath salts".mp. or tetrahydrocannabinols/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
22. exp hallucinogens/ or exp muscle relaxants, central/ or phencyclidine/ or phencyclidine abuse/ or exp antiinflammatory agents, non-steroidal/
23. or/11-21
24. Genetic Testing/
25. 1 and 24
26. 23 and 24
27. 10 and 24
28. 25 or 26 or 27
29. limit 28 to (english language and yr="2000 - 2015")
30. limit 29 to humans
31. exp Genotype/
32. (1 or 10 or 23) and 31
33. exp Cytochrome P-450 Enzyme System/
34. 32 and 33
35. 32 and 9
36. exp ATP-Binding Cassette Transporters/ or exp Genes, MDR/ or exp P-Glycoprotein/ or exp Multidrug Resistance-Associated Proteins/ or exp Polymorphism, Single Nucleotide/
37. 32 and 36
38. (34 or 37) and (comparative study/ or 8)
39. (34 or 37) and ec.fs.
40. ..l/ 37 lg=en and yr=2000-2015
41. 40 and 1
42. 30 or 38 or 39 or 41
43. limit 42 to (english language and humans and yr="2000 - 2015")
44. remove duplicates from 43
45. limit 44 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or guideline or meta analysis or multicenter study or observational study or practice guideline or randomized controlled trial or "review" or validation studies)
46. 44 and ((cohort* or prospective* or retrospective*).mp. or cross-sectional study/ or exp pilot studies/) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
47. 45 or 46

Reporting, interpretation, and communication of laboratory results with physicians

1. exp pain/dt or pain clinics/ or "pain management".mp. or "chronic pain".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
2. exp clinical chemistry tests/
3. specimen handling/ or blood specimen collection/ or urine specimen collection/
4. exp Chemistry Techniques, Analytical/
5. medication adherence/
6. exp Immunoassay/ or exp clinical laboratory techniques/ or diagnostic tests, routine/ or "drug surveillance".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
7. monitoring, physiologic/ or medication adherence/ or substance abuse detection/
8. "sensitivity and specificity"/ or reproducibility of results/ or exp diagnostic errors/ or "false negative".mp. or "false positive".mp. or cross reaction*.mp. or "predictive value".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
9. or/2-8
10. exp Substance-Related Disorders/an, bl, cf, di, me, mo, px, pc, ur
11. exp analgesics/an, bl, cf, ct, me, pk, pd, tu, to, ur, ad, ae or exp analgesics, non-narcotic/an, bl, cf, ct, me, pk, pd, tu, to, ur, ad, ae or exp analgesics, opioid/an, bl, cf, ct, me, pk, pd, tu, to, ur, ad, ae
12. ethanol/ad, ae, an, bl, cf, ct, me, ge, pk, pd, tu, ur or alcohol drinking/

13. exp anticonvulsants/ad, ae, an, bl, ch, cf, ct, me, ge, pk, po, pd, tu, ur
14. exp amphetamines/ad, ae, an, bl, cf, ct, me, ge, pk, pd, po, tu, ur
15. exp antidepressive agents/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
16. exp histamine antagonists/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
17. exp antipsychotic agents/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
18. exp barbiturates/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
19. exp benzodiazepines/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
20. exp narcotics/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur or exp antitussive agents/ad, ae, an, bl, ch, cf, ct, ge, me, pk, pd, po, tu, ur
21. exp cocaine/ or street drugs/ or designer drugs/ or "bath salts". mp. or tetrahydrocannabinols/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
22. exp hallucinogens/ or exp muscle relaxants, central/ or phencyclidine/ or phencyclidine abuse/ or exp antiinflammatory agents, non-steroidal/
23. or/11-21
24. drug interactions/ or drug monitoring/ or prescription drug misuse/ or substance abuse detection/
25. 1 or 11 or exp pain, an,bl,ae,co,ch,cf,me,mo/
26. 9 and 10 and 25
27. 23 and 25 and 24
28. 27 and (drug monitoring/ or prescription drug misuse/ or substance abuse detection/)
29. 26 or 28
30. 9 and 27
31. 29 or 30
32. limit 31 to (english language and humans and yr="2000–2015")
33. 32 and (lod or loq or detect* or confirm*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
34. 32 and (communicat* or report*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
35. 32 and (positive or present).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
36. 32 and (negative or absent).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
37. 35 and 36
38. 33 and (interpret* or report* or communicat*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
39. 37 or 38 or (33 and 34)
40. 33 and ((clia or cap).mp. or st.fs. or require*.mp.) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
41. 39 or 40
42. limit 41 to (english language and humans and yr="2000–2015")
43. 33 and (attitude of health personnel/ or exp physicians/ or exp specialties, medical/)
44. 42 or 43
45. 44 not (letter or editorial).pt.
46. remove duplicates from 45

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