Urine Drug Testing in Long-term Opioid Therapy
Ethical Considerations

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Abstract: As long-term opioid analgesic therapy has gained increasing clinical and societal acceptance over the past 2 decades, morbidity and mortality related to the misuse of these drugs have increased in lockstep. Hence, monitoring for opioid-related problems, largely through urine drug testing, has become a central component of risk mitigation in long-term opioid therapy. Despite the increasing use of urine drug testing, little has been written about the ethical aspects of its application. In this paper, we analyze multiple aspects of drug testing—rationale for testing, specimen collection, ordering and interpretation, and response to inappropriate test results—through the principlist lens, using the ethical principles of beneficence, nonmaleficence, justice, and autonomy.

Key Words: urine drug testing, ethics, opioids

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Long-term opioid analgesic therapy (LOT) for the management of chronic pain has gained widespread clinical and societal acceptance over the past 2 decades. During this period, there has been at least a 10-fold increase in the prescribing of this medication class.[1] The practice has become increasingly controversial in recent years, however, due to the unintended consequences of the increased availability of prescription opioids. The Centers for Disease Control and Prevention has described unintentional prescription opioid overdose deaths as an epidemic.[2] And for each unintentional prescription overdose death, there are 9 treatment admissions, 35 opioid-related emergency room visits, 161 cases of opioid use disorders, and 461 cases of nonmedical opioid use.[3] Evidence indicates that most opioids destined for nonmedical use originate from valid prescriptions.[4] An as-yet unstudied aspect of opioid prescribing is how adverse events affect clinicians' emotional lives and their future opioid prescribing practices.

Notwithstanding the harms associated with prescription opioids and a dearth of high-quality evidence demonstrating their effectiveness in treating chronic pain, LOT benefits many patients and a consensus exists that, prescribed with requisite knowledge and skill, it has an important place in the care of properly selected patients. Components of such care include thorough initial and ongoing pain evaluations; opioid risk stratification; assessment of analgesic benefit, adverse effects, and functional levels in major life spheres; and monitoring for the development of substance use disorders. Monitoring may include measuring progress toward therapeutic goals, maintaining vigilance for the development of aberrant drug-related behaviors, querying state prescription drug monitoring databases, performing random pill counts, speaking (with patient assent) to significant others, and conducting drug testing, with urine constituting the most common biological testing matrix.

Of the various monitoring tools, urine drug testing (UDT) is the most controversial. Some patients and patient advocates contend that UDT is offensive, antitherapeutic, profit-driven, and even unconstitutional.[5–7] Some have objected that implementing a drug testing program is tantamount to assuming a "police" role. Others have criticized drug testing as lacking in outcomes data.[8]

Certainly, UDT can be offensive, antitherapeutic, and profit-driven (although clinical UDT is not a constitutional issue). Evidence that UDT serves to deter drug abuse is limited.[8] Still, the antipathy with which some clinicians regard drug testing may reflect their beliefs about the nature of substance use disorders. Those who regard these disorders as moral failings, or even crimes, may believe that it is beyond their purview to look for evidence of their existence. If they do order UDT, they may use inappropriate test results in a punitive fashion. Those who view these disorders as treatable brain disorders are likely to believe that it is within their clinical domain to search for clues that can lead to timely diagnosis and treatment.

Despite the objections to UDT, it can serve a critical role in detecting opioid and other substance use disorders that might not otherwise be apparent.[9,10] Properly ordered and interpreted, UDT gives clinicians a window into their patients' past-several-day (and sometimes longer) use of a large number of drugs. For clinicians, appropriate test results can support clinical impressions that their patients are using medications as prescribed and are abstaining from illicit and unauthorized prescription drugs. Inappropriate test results can alert clinicians to the possibility of clinical problems, such as potentially dangerous drug combinations, a substance use disorder, another form of drug misuse, or, infrequently, the crime of drug diversion. Depending solely upon patients' accounts of their drug use is an unreliable way of discerning the presence of a substance use disorder that could impact the safe and effective provision of LOT.[11–13] Moreover, relying solely on observable problematic behaviors (eg, running out of medications early, frequent opioid-related telephone calls to the clinic, unannounced opioid-related clinic visits) to identify drug-related problems will miss a substantial percentage of problems detectable by drug testing.[14,15]

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In recent years, the use of UDT in long-term opioid therapy has been advocated by, among others, the American Academy of Pain Medicine,[10] the American College of Occupational and Environmental Medicine,[16] the American Pain Society,[10] the American Society of Interventional Pain Physicians,[17] and the Department of Veterans Affairs/Department of Defense.[18]

Yet, missing from these documents is a full discussion of the ethical considerations that clinicians should take into account when UDT is used as a monitoring tool in the context of LOT for chronic pain. Four ethical principles—beneficence, nonmaleficence, justice, and autonomy—have been described as general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions.[19] Although these principles cannot always be used to definitively resolve particular ethical problems, they will be used here to provide an analytical framework with which to view the ethical issues associated with UDT in long-term opioid therapy for chronic pain.

BENEFICENCE

Beneficence refers to the ethical obligation of clinicians to act for the benefit of their patients. The idea that beneficence represents the primary obligation of clinicians in the therapeutic relationship is an ancient one, and one that some ethicists argue provides the primary goal and rationale for the practice of medicine.[19]

UDT is used to verify both the presence of prescribed controlled substances and the absence of proscribed controlled substances. It provides information that can aid in detecting substance use disorders and other forms of drug misuse. Although closely akin to other diagnostic tests, UDT differs in one important respect: it is fundamentally a test of patient veracity, and the fact that clinicians must assess their patients' truthfulness evinces an implicit lack of trust. But lack of truthfulness—to others and to oneself—about drug use, its motivations, and its consequences, is a universal feature of untreated substance use disorders. (And to describe drug diverters as truth-averse is a tautology.) It is vital, then, that clinicians regard UDT as a medical diagnostic, and not as a trap for "catching" and "firing" patients who "fail" a test. When the intent of drug testing is diagnostic and therapeutic, and when this rationale for testing is communicated to patients with tact and sensitivity, it is likely to be met with acceptance and can even enhance the therapeutic relationship.[20]

In some circumstances, UDT can be directly beneficial to patients. Appropriate drug test results can allow clinicians to persuasively advocate for patients in certain legal contexts (eg, child custody, probation, and parole). And for those patients with substance use disorders—whether active or in remission—appropriate test results can provide both positive reinforcement to the patients and reassurance that they continue to enjoy the trust and confidence of their clinicians.

NONMALEFICENCE

The ethical principle of nonmaleficence imposes an obligation on clinicians to refrain from actions that may cause harm to their patients. Some ethicists argue that nonmaleficence typically, but not invariably, overrides other ethical principles.[19]

Although not well-studied,[21] UDT constitutes a minefield of potential harms, some of which can be great and lasting. These will be categorized into issues of rationale for testing, specimen collection, test ordering and interpretation, and response to test results.

Rationale for Testing

Ordering UDT should not be done for the purpose of discovering transgressions for which undesirable patients can then be terminated from medical practices. As well, UDT decisions, including the type and frequency of testing and the choice of commercial laboratory, should not be made for purposes of financial gain. Rather, UDT should be undertaken as a tool to optimize patient care. As such, it is one strategy that can help minimize harms that may accrue to some patients who are prescribed opioids for chronic pain.

Specimen Collection

Although the greatest assurance of specimen integrity is through direct observation of urination, this must be balanced by the obligation to respect patient privacy. Because the prevalence of specimen adulteration in pain clinic settings seems to be low[22]; because drug testing is only one of several sources of information about patients' drug use; and because routine direct observation has the potential to needlessly undermine trust, in general, urine specimen collection should not be monitored or directly observed. To balance privacy and specimen integrity concerns, it is reasonable to follow a simple urine collection protocol, consisting of having the patient remove jacket, coat, and hat, and display the contents of pockets; securing the water supply to the restroom (if possible and practical); and bluing the toilet water.[23]

Urine collection devices now commonly include tests of specimen validity, including temperature, pH, specific gravity, and presence of oxidizing agents. If a specimen is invalid or appears to be adulterated, a second, "for-cause" collection should occur under monitored or directly observed conditions (and both specimens should undergo testing).[23] In individuals with a history of subverting UDT, monitored or directly observed collections become permissible for subsequent tests.

A recent study of opioid-addicted patients in the St Louis Veterans Affairs Opioid Treatment Program found that the percentage of inappropriate random urine drug screen results increased from 25% under unmonitored conditions to 41% under monitored conditions,[24] indicating that patients with substance use disorders are at elevated risk of subverting their urine specimens. Thus, there is a rationale for monitored collections in patients with substance use disorders.

In certain patients, particularly those for whom drug test results may play a role in clinicians' advocacy on their behalf in legal contexts, urine collection under monitored or directly observed conditions, with patient assent, may be desirable. Directly observed collection must always be performed by same-sex observers.

Ordering and Interpretation Errors

UDT comprises a heterogenous group of tests, including screening and confirmatory assays. Screening (or "preliminary") tests are generally immunoassays. They include "point-of-care" test cups and strips, semiautomated systems for office use, and automated laboratory-based platforms. Screening tests are inexpensive and rapid; in the

case of point-of-care devices, results are available within minutes. The trade-offs are in specificity and sensitivity, particularly for "class-specific" assays (eg, benzodiazepines, opiates), which are not designed to distinguish among members of a drug class (limited specificity) and cross-react variably with members of a drug class (limited sensitivity). Thus, for example, the Roche Diagnostics Opiates II assay, designed to detect morphine at 300 ng/mL, is 28% cross-reactive with hydrocodone (1086 ng/mL), 21% cross-reactive with hydromorphone (1425 ng/mL), and $<0.4\%$ cross-reactive with oxycodone (>75,000 ng/mL).[25]

Confirmatory (or "definitive") tests involve gas or liquid chromatographic separation paired with mass spectrometric identification of specific analytes. Although more time-consuming and expensive than screening tests, confirmatory tests offer state-of-the-art sensitivity and specificity. Both screening and confirmatory techniques comprise vast combinations of test panels and reporting thresholds.

Interpretation of test results can be deceptively complex, and there is a "differential diagnosis" of factors—behavioral, genetic, analytic, and pharmacokinetic—that can account for apparently inappropriate positive and negative screening and confirmatory test results.[26] Evidence indicates that physicians are not adept at UDT interpretation.[27–29] Moreover, in a recent study involving internal medicine residents, their proficiency in UDT interpretation was poor, but their confidence in their ability to correctly interpret test results was (falsely) high.[30]

Inexpert ordering of UDT has the potential to cause harm. For example, clinicians who order opiate screens to monitor for unauthorized use of synthetic opioids may miss problems if they are unaware that opiate screens are incapable of detecting these drugs. Conversely, if clinicians are expecting to see positive opiate screening results in patients who are prescribed synthetic opioids, the negative results could lead to incorrect conclusions that patients are diverting, abusing, or addicted to the medications. Inexpert ordering can also impose financial harms, especially in patients who must bear the costs of testing with limited or no insurance coverage. UDT can be extraordinarily expensive, but when used in a patient-centered manner, it does not have to be. For example, immunoassay screening tests are relatively inexpensive. (Clinician costs for collection containers are in the range of $5, and commercial payers reimburse in the range of $10 to 18.) Often, more expensive confirmatory testing—charges for which can run into hundreds of dollars or more—can be reserved for contexts in which (1) the screening result and patient's account of drug use are at variance, and (2) selectively, when the clinician wants to verify the presence (or absence) of a specific drug/metabolite when a class-specific screening result was appropriately positive (or negative). A large retrospective study found that, with open communication between patients and clinicians and therapeutic, nonpunitive action plans, only 3% to 5% of screening results necessitated confirmatory testing.[31]

Similarly, inexpert drug test interpretation can also cause harm. For example, in patients taking certain opioids (eg, hydrocodone, morphine, oxycodone) or benzodiazepines (eg, chlordiazepoxide, diazepam, temazepam) detectable concentrations of other opioids and benzodiazepines, respectively, can—and often should—be present as metabolites of the prescribed medication. Failure to appreciate this may lead to accusations of use or abuse of unauthorized prescription medications.

When apparently inappropriate drug *screen* results are at variance with a patient's narrative of their drug use, and especially if the results will serve as the basis for clinical action, specimens must be sent for confirmatory testing. No current screening test is close enough to perfect, and as close to perfect as possible is necessary in these circumstances. When apparently inappropriate *confirmed* test results are not consistent with patients' accounts and clinicians are not certain about whether the 2 are reconcilable, they should consult with their laboratory's clinical scientist to determine whether there may be a legitimate medical explanation for apparently inappropriate test results.

Response to Test Results

Inappropriate action taken on the basis of incorrect—or even correct—drug test interpretation has the potential for devastating and enduring consequences for the patient. It may erode the patient's trust in the treating clinician (and other clinicians), and may result in loss of a valuable therapy, the therapeutic relationship itself, or worse. As medical records will likely follow the patient to subsequent clinicians, the initial harm may be perpetuated. The patient's insurance carrier may have access to records, and the misidentification of a patient as a drug abuser may have consequences for insurance coverage. Furthermore, surveys have found that some physicians, when confronted with the absence of a prescribed opioid in the urine of a patient, believe it would be appropriate to notify law enforcement for investigation of drug diversion.[27,28]

Discharging a patient from a medical practice is virtually never an acceptable response to an inappropriate drug test. The clinician should use drug test results as data points, to be integrated with the patient's history and other relevant pieces of clinical information, to determine whether a clinical problem exists, and, if so, the nature of the problem. Reflexively discharging a patient means forfeiting an opportunity to initiate a dialogue about the patient's drug use, including patterns of use and motivations for misuse, and when appropriate, to initiate or refer for evaluation and treatment of a suspected substance use disorder. Moreover, it may place patients into uncomfortable and sometimes dangerous opioid withdrawal syndromes; compel them to procure controlled substances from emergency rooms or nonmedical sources; or pass them along to new, sometimes unwitting, clinicians. If a substance use disorder is suspected, and clinicians are ill-equipped to diagnosis or manage the problem, they should offer referral to an addiction medicine physician or facility. When appropriate, continuing care using nonopioid modalities should be offered. There are few circumstances for outright discharge of a patient from a clinician's practice. One such circumstance may be verified evidence of drug diversion, but it is impossible to reach this conclusion solely on the basis of a drug test result.

Failure to act appropriately on test results because of implausible patient explanations (eg, that a confirmed cocaine-metabolite-positive test result was due to Novocain from a recent dental procedure; that an oxycodone-positive test result was due to metabolism from prescribed morphine), patient entreaties for second (and third, and fourth) chances, or wanting to be perceived as benevolent can create their own harms related to continued unaddressed substance use disorders.

JUSTICE

The ethical principle of justice requires that patients be treated fairly and equitably.[19] It means, in this context, that patients receive both appropriate pain treatment (including, when indicated, trials of long-term opioid therapy) and appropriate monitoring for the development of serious side effects related to that therapy, including the diseases of abuse and addiction.

The terms "equally" and "equitably" are important in making decisions about opioid therapy and drug testing. These terms are similar, but not the same. To treat equally means to treat all patients exactly the same way. To treat equitably means to treat all patients fairly.[19] In the context of LOT, equitable application of drug testing dictates that it is driven by patient-specific risk for development (or recurrence) of substance use disorders. Initial and ongoing assessment for these disorders can be facilitated by risk prediction instruments such as the Opioid Risk Tool, the Screener and Opioid Assessment for Patients with Pain – Revised, and the Current Opioid Misuse Measure. These instruments are highly imperfect,[32] however, and necessitate complementary monitoring strategies, of which UDT is but one. Thus, clinicians must spend time speaking with their patients about their drug use, their lives, and their progress toward therapeutic goals. They should note and address potentially aberrant opioid-related issues, such as the inability to adhere to opioid prescription instructions, requests for early refills, and lost or stolen prescriptions They should periodically check their state's prescription drug monitoring database. If indicated, they should conduct random opioid "pill counts."

There are neither empirical nor ethical justifications for differential application of UDT based on race, ethnicity, religion, or sexual orientation. Two recent studies addressed racial disparities in UDT among patients prescribed LOT. Becker et al,[33] in a retrospective study of 1612 patients, found that black patients were more likely to receive UDT than white patients (10.4% vs. 4.1%), although statistical significance was lost after adjustment for substance abuse, mental health comorbidities, and other factors. Aberrant opioid-related behaviors were not examined as a possible cause of differential testing, and UDT results were not reported. Hausmann et al,[34] in a retrospective study of 1899 patients, found that although the odds of having at least one UDT did not differ between groups, among the subset of patients who had at least one UDT, black patients underwent a significantly higher number of UDTs. As in the previous study, the authors did not examine differences in aberrant drug-related behaviors between the groups, and did not report UDT results. Data from the 2011 National Survey on Drug Use and Health on lifetime, past-year, and past-month nonmedical drug use and illicit drug use do not show consistent, meaningful race-based or sex-based differences that would support differential UDT strategies.[4] There is no evidence to justify differential UDT based on religion or sexual orientation.

Even if a particular group within a pain clinic population (or society) were shown to have a higher prevalence of opioid or other substance use disorders, it is not clear that there would be an ethical justification for differential drug testing. Generalizing from the group to the individual is always problematic. Evidence clearly showing a connection between a particular group and adjusted risk for developing a substance use disorder would be only 1 factor in a holistic assessment of individual risk. Furthermore, there continues to be disparities in access to health care for minorities across multiple contexts, including access to adequate acute and chronic pain care.[35] Access problems, coupled with punitive responses to inappropriate UDT results, could serve to exacerbate these disparities in the care of patients with chronic pain.

RESPECT FOR AUTONOMY

Autonomy refers to an individual's right to self-rule that is free from controlling interference from others and from other limitations, such as inadequate understanding, which prevent meaningful choice.[19] As a core attribute of high-quality health care systems, the Institute of Medicine has expressed this principle as care that is "patient-centered."[36] In the Affordable Care Act the principle is expressed as "shared decision-making."[37]

Respect for autonomy is operationalized through a discussion with patients about the risks, benefits, costs, and alternatives associated with LOT, and the rationale for using UDT as a component of monitoring the safety and efficacy of such therapy. This discussion, which comprises informed consent, is usually codified in an informed consent document (or treatment agreement), which is executed before beginning a trial of opioid therapy or before continuing LOT that had heretofore been prescribed by another clinician.

Some experts have questioned the ethical implications of opioid agreements, arguing that their universal application threatens the integrity of the therapeutic relationship.[38] Some have cautioned about the legal ramifications when patients are terminated from clinics and turn to the courts for relief, or when patients are harmed from clinicians' failure to adhere to the tenets of their own treatment agreements.[39] Other experts have advocated for their thoughtful adoption, arguing that they codify the tenets of the informed consent discussion and clarify mutual expectations with respect to the pain treatment plan.[40,41] The US Department of Veterans Affairs considers these documents to constitute the standard of care in the management of patients with LOT.[18]

An extensive discussion of treatment agreements is beyond the scope of this manuscript, but their mention is warranted insofar as these agreements usually contain provisions for UDT. Any such written treatment agreement should only represent a record of a clinician-patient discussion, and should never substitute for the actual discussion. Components of these discussions should include nonopioid treatment options; the expected benefits, limits, and risks of LOT; opioid risk in *this* patient, based on a personalized assessment; and details of any UDT protocols, including types of test schedules (eg, random, scheduled, for-cause), methods of collection (eg, nonmonitored, monitored, directly observed), and determinants of each method; consequences of refusal to test; and diagnostic and/or therapeutic actions to be taken in the case of confirmed inappropriate test results. Such actions might include education/discussion/counseling, closer follow-up and enhanced treatment boundaries, involvement of family or other stakeholders, substance use disorder evaluation, referral to an inpatient or outpatient treatment program, and protocols for tapering and discontinuing opioid therapy, if indicated. It should be understood that an agreement stipulating that a patient will be summarily dismissed from the clinic and deprived of useful therapy in the event of a

"violation" will discourage patient honesty about drug use. Rather than encouraging truthful disclosures that can lead to constructive discussions and rational treatment decisions, many patients will calculate the consequences of their utterances. Moreover, such stipulations have no medical or ethical basis. Rather, violations of treatment agreements as revealed by inappropriate confirmed UDT results should be treated in a patient-centered, therapeutic manner, and this should be reflected in the content of the discussion and treatment agreement.

The tone of the discussion will influence patient perception of the UDT program, so an empathic, nonjudgmental approach will be helpful. The clinician should assess for understanding and give the patient an opportunity to ask questions. Such an assessment might include having the patient "teach back" to the clinician the central tenets of the agreement and/or having patient-designated stakeholders present for discussion. Should the patient refuse drug testing, it is helpful to enquire as to the reasons, which may include a current substance use disorder, intent to divert, psychiatric or urologic issues, or negative previous drug testing experiences. Ultimately, some patients will demur at drug testing provisions of opioid treatment plans, and the clinician must decide whether or not opioid therapy can be safely prescribed. If not, nonopioid pain management plans should be designed or, if appropriate, the names of other pain management clinicians should be provided.

CONCLUSIONS

UDT in LOT has become a commonplace over the past decade and, in the face of the high morbidity and mortality associated with the abuse of prescription opioids, is emerging as a standard of care in the monitoring of patients treated with this class of medications. The primary purpose of UDT is to monitor for signs of abuse of and addiction to prescribed opioids and other drugs of abuse, which, unaddressed, are incompatible with successful pain management[20] and place the patient, and sometimes others, in harm's way.

In addition to benefits of UDT, there are also potential harms, some of which may be serious, long-lasting, and irreparable. Many, although not all, of these harms derive from inadequate knowledge regarding the technical and analytical aspects of testing and can be mitigated by proper education. Several online resources address the essentials of clinical UDT, including a free CME activity presented by the Johns Hopkins School of Medicine.[42] Live courses, such as those leading to Medical Review Officer certification, are available throughout the country and throughout the year, by the American Association of Medical Review Officers and the Medical Review Officer Certification Council. Although designed for workplace drug testing, much of the curriculum is applicable to testing in pain management.

Correctly understood, UDT is a patient-centered diagnostic tool, used with the intention of optimizing the safety and efficacy of LOT. Clinicians should sensitively communicate with their patients the clinical rationale for testing. They should use testing in an equitable manner, according to the patient risk. They should be capable of ordering tests correctly and interpreting test results with accuracy. They should have an awareness of the limits of their knowledge in this area, and should cultivate relationships with their laboratory's clinical director and/or others to assist with the interpretation of unclear or unexpected results. Finally, they should have a therapeutic action plan for patients who yield confirmed inappropriate UDT results and who are suspected of having a substance use disorder. UDT must be ordered, interpreted, and acted upon with skill and compassion or it should not be a part of an opioid monitoring program.

REFERENCES

1. Centers for Disease Control and Prevention. Prescription drug overdoses: an American Epidemic. Public Health Grand Rounds. 2011. Available at: http://www.cdc.gov/about/grandrounds/archives/2011/01-February.htm. Accessed April 23, 2013.
2. Paulozzi LJ, Jones CM, Mack RA, et al. Vital signs: overdoses of prescription opioid pain relievers—United States, 1999-2008. *Morb Mortal Wkly Rep*. 2011;60:1487–1492.
3. Paulozzi L, Baldwin G, Franklin G, et al. CDC grand rounds: prescription drug overdoses—a U.S. Epidemic. *Morb Mortal Wkly Rep*. 2012;61:10–13.
4. Substance Abuse and Mental Health Services Administration. *Results from the 2011 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-44, HHS Publication No. (SMA)*. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2012:12–4713. Available at: http://www.samhsa.gov/data/nsduh/2k11results/nsduhresults2011.htm#Fig2-14. Accessed April 21, 2013.
5. Collen M. Urine drug screens. *J Pain Palliat Care Pharmacother*. 2011;25:395.
6. Collen M. Profit-driven drug testing. *J Pain Palliat Care Pharmacother*. 2012;26:13–17.
7. Collen M. The fourth amendment and random drug testing of people with chronic pain. *J Pain Palliat Care Pharmacother*. 2011;25:42–48.
8. Starrels JL, Becker WC, Alford DP, et al. Systematic review: treatment agreements and urine drug testing to reduce opioid misuse in patients with chronic pain. *Ann Intern Med*. 2010;152:712–720.
9. Reisfield GM, Graham NA, Gold MS. Urine drug testing is still an invaluable resource for primary care. *Ann Intern Med*. 2010;153:420.
10. Chou R, Fanciullo GJ, Fine PG, et al. for the American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10:113–130.
11. Mormon A, Larriviere K, Hamill-Ruth R. Using multi-modal Information to identify patients at risk for abnormal drug-taking behavior presenting to the emergency department. *J Pain*. 2012;23:S9.
12. Fishbain DA, Cutler RB, Rosomoff HL, et al. Validity of self-reported drug use in chronic pain patients. *Clin J Pain*. 1999;15:184–191.
13. Berndt S, Maier C, Schutz HW. Polymedication and medication compliance in patients with chronic non-malignant pain. *Pain*. 1993;52:331–339.
14. Katz NP, Fanciullo GJ. Role of urine toxicology testing in the management of chronic opioid therapy. *Clin J Pain*. 2002; 18(suppl):S76–S82.
15. Ives TJ, Chelminski PR, Hammett-Stabler CA, et al. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. *BMC Health Serv Res*. 2006;4:46.
16. American College of Occupational and Environmental Medicine. Guildeines for the Chronic Use of Opioids. 2011. Available at: http://www.acoem.org/Guidelines_Opioids.aspx. Accessed April 21, 2013.
17. Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2–guidance. *Pain Physician*. 2012;15(suppl):S67–116.

18. Department of Veterans Affairs/Department of Defense. VA/DoD Clinical Practice Guideline for management of opioid therapy for chronic pain. Version 2.0, 2010. Available at: http://www.healthquality.va.gov/COT_312_Full-er.pdf. Accessed April 21, 2013.
19. Beauchamp TL, Childress JF. *Principles of Biomedical Ethics*. 6th ed. New York: Oxford University Press; 2008.
20. Heit HA, Gourlay DL. Urine drug testing in pain medicine. *J Pain Symptom Manage*. 2004;27:260–267.
21. Abadie J. How can the clinical picture guide appropriate laboratory drug testing in the treatment of pain clinic patients with opioid analgesics? *Pain Med*. 2012;13:857–859.
22. Michna E, Jamison RN, Pham LD, et al. Urine toxicology screening among chronic pain patients on opioid therapy: frequency and predictability of abnormal findings. *Clin J Pain*. 2007;23:173–179.
23. Mandatory guidelines for federal workplace drug testing programs. *Federal Register*. 2008;73:71858–71907. Available at: http://www.gpo.gov/fdsys/pkg/FR-2008-11-25/html/E8-26726.htm. Accessed April 23, 2013.
24. Mallya A, Purnell AL, Svrakic DM, et al. Witnessed versus unwitnessed random urine tests in the treatment of opioid dependence. *Am J Addic*. 2013;22:175–177.
25. Roche Diagnostics. Roche Diagnostics Opiates II package insert. Available at: http://intrashands1.umc.ufl.edu/Department%20Laboratory/Guide%20to%20Interpreting%20Drug%20Screens/Complete%20Product%20Inserts/Opiates.pdf. Accessed April 23, 2013.
26. Reisfield GM, Goldberger BA, Bertholf RL. "False positive" and "false negative" test results in clinical urine drug testing. *Bioanalysis*. 2009;1:937–952.
27. Reisfield GM, Webb FJ, Bertholf RL, et al. Family physicians' proficiency in urine drug test interpretation. *J Opioid Manag*. 2007;3:333–337.
28. Reisfield GM, Bertholf R, Barkin RL, et al. Urine drug test interpretation: what do physicians know? *J Opioid Manag*. 2007;3:80–86.
29. Levy S, Harris SK, Sherritt L, et al. Drug testing of adolescents in ambulatory medicine: physician practices and knowledge. *Arch Pediatr Adolesc Med*. 2006;160:146–150.
30. Starrels JL, Fo AD, Kunins HV, et al. They don't know what they don't know: internal medicine residents' knowledge and confidence in urine drug test interpretation for patients with chronic pain. *J Gen Intern Med*. 2012;27:1521–1527.
31. Gilbert JW, Wheeler GR, Mick GE, et al. Urine drug testing in the treatment of chronic noncancer pain in a Kentucky private private neuroscience practice: the potential effect of Medicare benefit changes in Kentucky. *Pain Physician*. 2010;13:187–194.
32. Chou R, Fanciullo GJ, Fine PG, et al. Opioids for chronic noncancer pain: prediction and identification of aberrant drug-related behaviors: a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *J Pain*. 2009;10:131–146.
33. Becker WC, Starrels JL, Heo M, et al. Racial differences in primary care opioid risk reduction strategies. *Ann Fam Med*. 2011;9:219–225.
34. Hausmann LRM, Gao S, Lee ES, et al. Racial disparities in the monitoring of patients on chronic opioid therapy. *Pain*. 2013;154:46–52.
35. Anderson KO, Green CR, Payne R. Racial and ethnic disparities in pain: causes and consequences of unequal care. *J Pain*. 2009;10:1187–1204.
36. Krumholz HM. Informed consent to promote patient-centered care. *JAMA*. 2010;303:1190–1191.
37. Lee EO, Emanuel EJ. Shared decision making to improve care and reduce costs. *N Engl J Med*. 2013;368:6–8.
38. Payne R, Anderson E, Arnold R, et al. A rose by any other name: pain contracts/agreements. *Am J Bioeth*. 2010;10:5–12.
39. Prince A. Much ado about nothing. *Am J Bioeth*. 2010;10:22.
40. Fishman SM, Gallagher RM, McCarberg BH. The opioid treatment agreement: a real-world perspective. *Am J Bioeth*. 2010;10:14–15.
41. Cheatle MD, Savage SR. Informed consent in opioid therapy: a potential obligation and opportunity. *J Pain Symptom Manage*. 2012;44:105–116.
42. Johns Hopkins University School of Medicine. Urine drug testing in clinical practice: the art & science of patient care (ed 5). Office of Continuing Medical Education. Available at: http://www.hopkinscme.edu/. Accessed April 21, 2013.

