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Diagnostic Accuracy Report

Comparative Evaluation of the Accuracy of Immunoassay with Liquid Chromatography Tandem Mass Spectrometry (LC/MS/MS) of Urine Drug Testing (UDT) Opioids and Illicit Drugs in Chronic Pain Patients

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Background: The challenge for physicians in treating chronic pain with opioids is to eliminate or significantly curtail abuse of controlled prescription drugs while assuring proper treatment when indicated. Urine drug testing (UDT) has been shown to be a useful approach in identifying patterns of compliance, misuse, and abuse. However, significant controversy surrounds the diagnostic accuracy of UDT performed in the office (immunoassay) and the requirement for laboratory confirmation with liquid chromatography tandem mass spectrometry (LC/MS/MS).

Study Design: A diagnostic accuracy study of urine drug testing.

Study Setting: The study was performed in an interventional pain management practice, a tertiary referral center, in the United States.

Objective: The objective of this study was to compare the results of UDT of immunoassay in-office testing (index test) to LC/MS/MS (reference test).

Methods: One-thousand participants were recruited from an interventional pain management program. Urine sample was collected from all the consecutive patients with demographic information. Immunoassay testing was performed by a nurse at the location, laboratory assessment was performed with LC/MS/MS.

Results of the index test were compared to the reference test in all patients. The sensitivity, specificity, false-positive, and false-negative rates, and index test efficiency (agreement) were calculated.

Results: Overall, results showed that confirmation was required in 32.9% of the specimens. Agreement for prescribed opioids was high with the index test (80.4%). The reference test of opioids improved the accuracy by 8.9% 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 by index test was 0% for cocaine, whereas it was 2% for marijuana, 0.9% for amphetamines, and 1.2% for methamphetamines.

Limitations: The limitations include a single site study utilizing a single POC kit and a single laboratory, as well as technical sponsorship.

Conclusion: The UDT with immunoassay in an office setting is appropriate, convenient, and cost-effective. Compared with laboratory testing for opioids and illicit drugs, immunoassay in-office testing had high specificity and agreement, demonstrating the value of immunoassay drug testing. Because of variable sensitivity, clinicians would be well-advised to take a cautious approach when interpreting the results.

Key words: Controlled substances, opioids, illicit drugs, abuse, liquid chromatography tandem mass spectrometry, immunoassay, urine drug testing

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The treatment of chronic pain, escalating therapeutic opioid use and abuse, and the non-medical use of prescription drugs have been topics of intense focus and debate (1-7). The present state of affairs is based on prescriptions for chronic non-cancer pain; subjective complaints of pain; recommendations from federal, state, and local governments; professional associations; massive sales promotion activities from the pharmaceutical companies; accreditation agencies; physicians promoting opioid therapy; and finally the public-at-large expecting pain relief at any cost, rather than scientific data on efficacy and safety (1,5-9). Similar states of affairs have been described in other countries including Denmark (9). However, Americans, constituting only 4.6% of the world's population, have been consuming 80% of the global opioid supply, and 99% of the global hydrocodone supply, in addition to two-thirds of the world's illegal drugs (1,2,6,7,10,11).

Retail sales of some commonly used opioid medications have increased significantly, with an increase of 866% for oxycodone and 1,293% for methadone, whereas average sales of opioids per person have increased 402% from 1997 to 2007 (1). In addition, surveys of non-prescription drug abuse (12), emergency department visits involving prescription-controlled drugs (13), unintentional deaths due to prescription controlled substances (5,14-17), therapeutic use of opioids (1,9,18-23), lack of improvement or deterioration in functional status (9,21,24-29), adverse effects (24-27,30), and opioid abuse (1-5,31-33) illustrate grave statistics. At the same time, chronic pain's prevalence and its associated disability continue to increase (34,35), while the scientific evidence for the effectiveness of opioids for chronic non-cancer pain remains unclear (5,24-27).

The challenge is to eliminate or significantly curtail abuse of controlled prescription drugs while still assuring the proper treatment of those patients with evident indications. Adherence monitoring, including urine drug testing (UDT), has been shown to be a useful approach to assist in identifying and/or predicting patterns of drug use, compliance, misuse, and abuse (36). UDT provides relatively good specificity, sensitivity, ease of administration, and cost (36). However, controversies also exist regarding the clinical value of UDT, partly because most current methods are designed for, or adapted from, forensic or occupational deterrent-based testing for illicit drug use and are not entirely optimal for application in chronic pain management settings. Further, additional issues also exist related to excessive use, misuse, abuse, and financial incentives (36-45). UDT is performed to detect the presence of prescribed medications (i.e., compliance testing) and to identify substances that are not expected to be present in the urine, such as non-prescription or illicit drugs (i.e., forensic testing). The most commonly used Current Procedural Terminology (CPT) codes for UDT, 80101 and 80102, showed 343% and 364% increases from 2004 to 2007 and an increase in allowed charges of 452% and 387%; the total allowed charges exceeded $50 million in 2007.45 The abuses related to the utilization of UDT, its value and validity, and exploding costs, led the Centers for Medicare and Medicaid (CMS) administration to impose new regulations for UDT reimbursement (37-45).

Debate surrounds the validity of in-office UDT of chronic pain patients by immunoassay methodology that has not been validated with liquid chromatography tandem mass spectrometry (LC/MS/MS). Due to multiple methodological issues, an in-office immunoassay confirmed by an independent laboratory is commonly regarded as the best and most sensitive UDT, but at the expense of escalating costs. Other issues involved are the knowledge of the physician who interprets the drug screening (including having knowledge about opioid metabolites), appropriate testing methods in an office setting, and the cost involved (37,40,41,45).

UDT manufacturers focus their marketing efforts on the value and validity of laboratory testing, and are supported by physicians who derive significant income from these tests (37,44,46,47). Others recommend in-office testing for the reasons of convenience and cost effectiveness. The absence of prescription opioids in urine specimens has ranged from 1.9% to 15% (37,44-46). Further, studies also showed an overall presence of illicit drugs in approximately 11% (37) and false-negatives of 50% for cocaine, 11% for marijuana, and 9.3% for amphetamines.

Consequently, this diagnostic accuracy study has been undertaken to evaluate the accuracy of point of care (POC) or in-office UDT (immunoassay) of chronic pain patients in a prospective analysis of LC/MS/MS.

Methods

The study was undertaken in an interventional pain management practice, a tertiary referral center, in the United States. The protocol was approved by the Institutional Review Board (IRB) of the Ambulatory Surgery Center and it has a clinical trial registration of NCT01052155. Appropriate precautions were taken to protect the privacy and identify of patients evaluated from this study in accordance with current Health Insurance Portability and Accountability Act (HIPAA) regulations.

The protocol has been described in a previous publication (36). The study was performed utilizing the Standards for Reporting of Diagnostic Accuracy Studies (STARD) established for reporting guidelines for diagnostic accuracy studies to improve the quality of reporting (48-50).

Objective

The objective of this study was to compare results of UDT of immunoassay in-office testing (index test) with LC/MS/MS (reference test).

Proposed Hypothesis

It is proposed that there is no significant difference of clinical importance between POC drug testing (index test) and laboratory drug testing (reference test).

Investigational Methodology

The investigational methodology followed the STARD checklist (48). All specimens were tested with immunoassay (index test) and LC/MS/MS (reference test).

Participants and Recruitment

Consecutive series of patients presenting for interventional pain management were recruited in a prospective manner.

Inclusion and Exclusion Criteria

Consecutive patients in chronic pain management were included. There were no exclusion criteria.

Test Methods

The index test was the in-house POC office drug testing with immunoassay; the reference standard was LC/MS/MS.

The laboratory test (reference test) was performed by Millennium Laboratories, which holds certificates for moderate and high complexity testing.

Screening Evaluation

All consecutive patients participating in the urine drug assessments diagnostic accuracy study were provided with a verbal explanation of the study. IRB-approved written informed consent to participate in the study was obtained.

Demographic details including date of birth, sex, weight, height, and drug profiles (which included a list of all prescription and over-the-counter drugs, as well as all other drugs or substances they were taking) were obtained.

Treatment Number Assignment

Participants were consecutively assigned a number.

Urine Sample

Urine and all other appropriate information were collected by a nurse participating in the study and provided to the study coordinator. POC testing was performed by a different nurse who was unaware of the patient's name, drug intake, etc. Drug testing was performed for opioids and illicit drugs including marijuana, cocaine, amphetamine, and methamphetamine.

Laboratory Assessment

After immunoassay, the samples were sent to laboratory for LC/MS/MS without any identifying information or results of the index text.

Definition and Rationale

The definition and rationale for the units, cutoffs, and categories of the results of the index test and how reference standard have been described (36).

Personnel

A sufficient number of nurses (6) received training to conduct and read the index test. The reference test was conducted by trained certified professionals at the laboratory.

Blinding

The personnel performing and reading the index tests and reference tests were blinded (masked) to the results of the other tests as well as patient demographics.

Statistical Methods

Sample Size

Sample size calculation was carried out for our primary outcome (accuracy of the POC drug testing in screening for opioids and illicit drugs) according to the previously published method (51), and previous results of drug abuse and illicit drug use by patients referred to clinics (31-33,52). The details are provided in the protocol (36). The sample size was calculated at 811 with a planned enrollment of 1,000 patients to be tested.

Analysis

Statistical analysis was performed using SPSS 9.01 (SPSS, Inc., Chicago IL, USA). A P value below 0.05 was considered statistically significant.

Results of the index test were compared to the reference test in all patients. The sensitivity, specificity, false-positive and false-negative rates, and index test efficiency (agreement) were calculated.

Results

Flow Diagram

Figures 1 and 2 illustrate the patient flow diagram per STARD for opioids and illicit drugs.

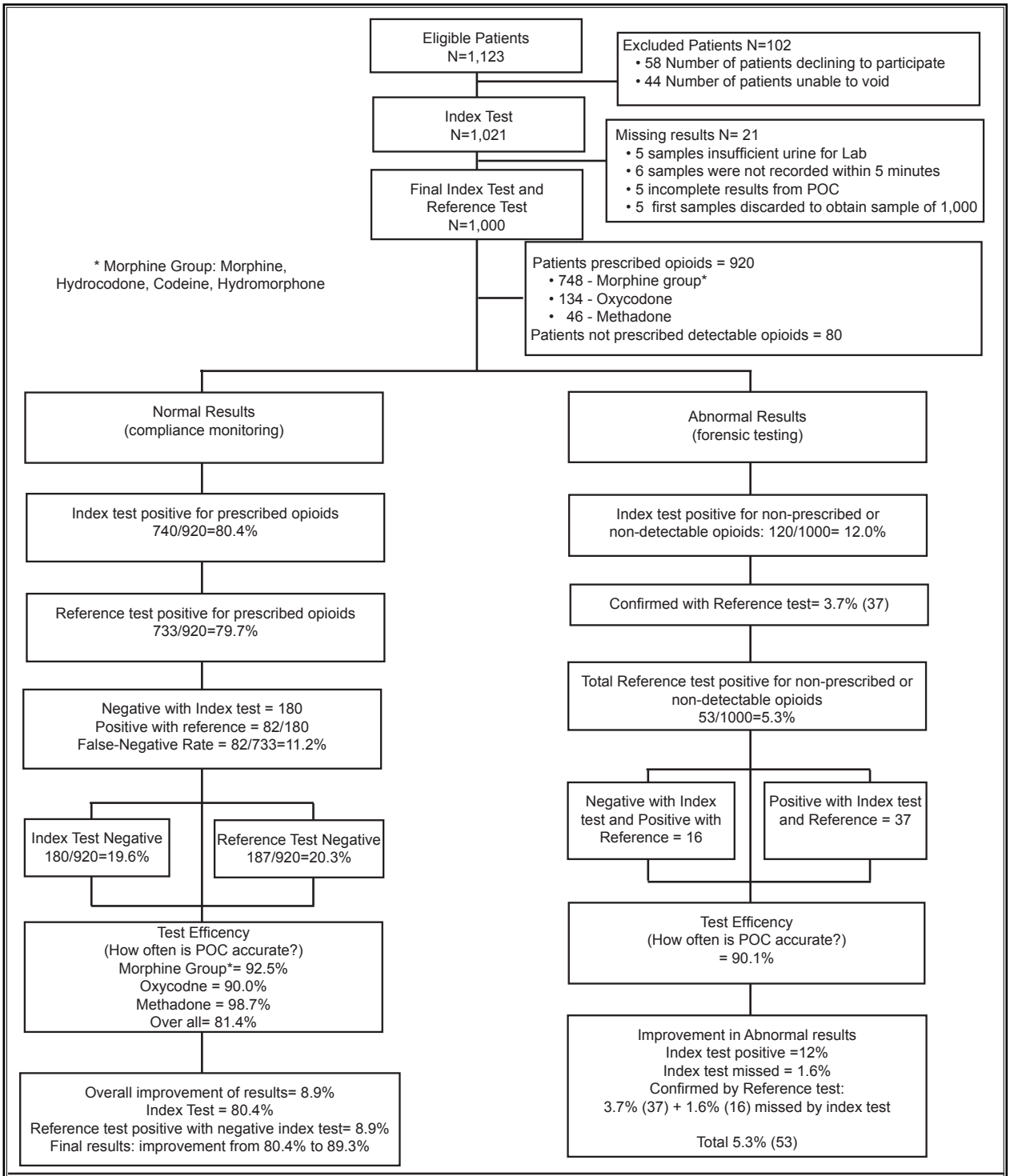

Fig. 1. *Flow diagram of diagnostic accuracy testing of opioids.*

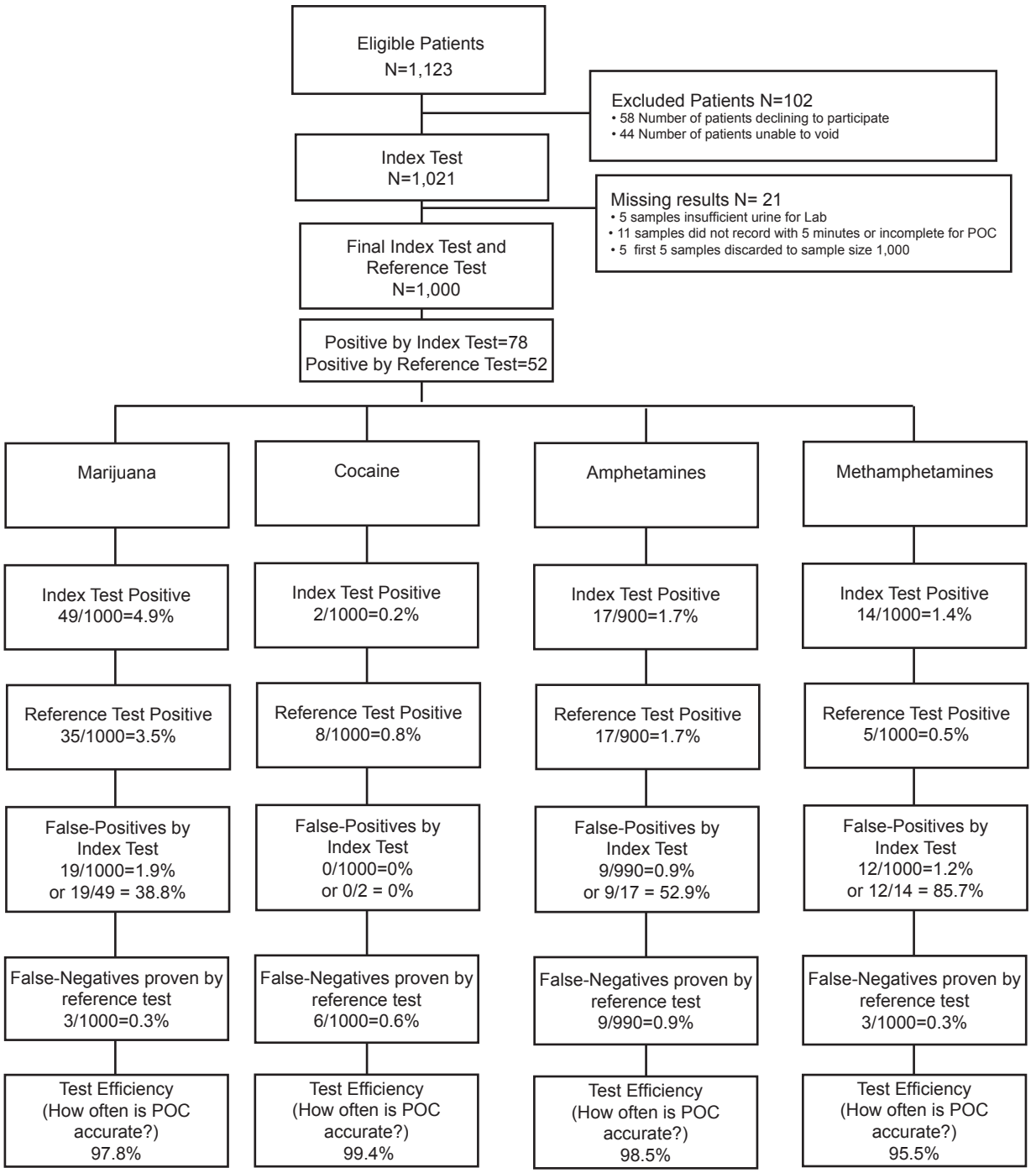

Fig. 2. *Flow diagram of diagnostic accuracy testing of illicit drugs.*

Participants

The study lasted from March 1, 2010, through June 30, 2010, with enrollment of consecutive patients. Evaluation days were selected by computerized randomization.

Demographic Characteristics

The demographic characteristics of the study population are illustrated in Table 1.

Validity and Test Reproducibility

One hundred specimens without identification or demographic data were tested for validity of the reference test. This showed perfect correlation.

Numbers Analyzed

The numbers analyzed are illustrated in Figures 1 and 2.

Time Intervals

The index test and reference test were performed on the same sample. The time interval for transporting the sample to the lab and performance of the test is estimated to have been about 72 hours.

Distribution Characteristics

The distribution of severity of disease is not applicable.

Cross Tabulation of the Results

A cross tabulation of the results of the index test and the reference test were performed.

Table 1. *Demographic characteristics.*

		Number
Gender	Male	37% (370)
	Female	63% (630)
Age (Years)	Mean ± SD	51 ± 12.6
Height		66.5 ± 4.2
Weight		184.1 ± 51.5
Insurance	Medicare	47.0% (470)
	Medicaid	25.2% (252)
	Third Party	27.8% (278)
State	Kentucky	82.9% (829)
	Others (IL, TN, MO, IN)	17.1% (171)

Adverse Events

No adverse events occurred while performing the index test or reference test.

Estimates

The estimated diagnostic accuracy and comparison were evaluated for all patients for each opioid prescribed and for illicit drugs.

Results of Accuracy of Opioids and Illicit Drugs

A summary of the diagnostic accuracy of the index test versus the reference test is illustrated in Table 2. This table illustrates the cut-off levels utilized along with sensitivity, specificity, and agreement. For opioids with morphine, hydrocodone, codeine, and hydromorphone, there was 92.5% agreement with sensitivity of 92.2% and specificity of 93.0%, with a false-negative rate of 7.8% and false-positive rate of 6.9%. The numbers were better for methadone with sensitivity of 96.1% and specificity of 98.8% with an agreement of 98.7%. However, for oxycodone sensitivity was 75.4% with false-negative rates of 24.6% and specificity of 92.3% with agreement of 90%. For all illicit drugs, test agreement was high (approximately 98% or over). However, for cocaine sensitivity was 25% with false-negative rates of 75% with specificity of 100%. Methamphetamines and amphetamines also had lower sensitivity with 40% and 47%. Consequently, these tests will show false-negative rates in 60% of the patients for methamphetamines and 53% for amphetamines even though specificity and agreement were high.

Table 3 illustrates a summary of the diagnostic accuracy of opioids with detailed data from the index test and the reference test. This table illustrates the same results as in Table 2 with detailed numbers.

Discussion

The results of this prospective, diagnostic accuracy study of UDT comparing in-office testing with immunoassay (index test) confirmed with laboratory testing of LC/MS/MS (reference test) showed significant agreement for opioids as well as illicit drugs. Specificity for opioids was 93.1% for the morphine group, 92.3% for oxycodone, and 98.8% for methadone. Sensitivity for opioids was 92.2% for the morphine group, 75.4% for oxycodone, and 96.1% for methadone. The agreement or test efficiency was 92.5% for the morphine group, 90% for oxycodone, and 98.7% for methadone. Similarly, for illicit drugs, specificity was 98% for marijuana, 100% for

Table 2. *Summary of diagnostic accuracy of opioids and illicit drugs (index test vs. reference test).*

	TP	FP	TN	FN	Cutoff levels (POC vs LC/MS/MS)	Sensitivity/ False Negative Rate	Specificity/ False Positive Rate	Test Efficiency (Agreement)
Opioids								
Morphine, Hydrocodone, Codeine, Hydromorphone	614	23	311	52	300 ng/mL vs 50 ng/mL	92.2% / 7.8%	93.1% / 6.9%	92.5%
Oxycodone	104	66	796	34	100 ng/mL vs 50 ng/mL	75.4% / 24.6%	92.3% / 7.7%	90.0%
Methadone	49	11	938	2	300 ng/mL vs 100 ng/mL	96.1% / 3.9%	98.8% / 1.2%	98.7%
Illicit Drugs								
Marijuana	30	19	948	3	50 ng/mL vs 15 ng/mL	90.9% / 9.1%	98.0% / 2.0%	97.8%
Cocaine	2	0	992	6	300 ng/mL vs 50 ng/mL	25.0% / 75%	100.0% / 0%	99.4%
Methamphetamines	2	12	983	3	NA 50 ng/mL	40.0% / 60%	98.8% / 1.2%	98.5%
Amphetamines*	8	9	964	9	1000 ng/mL vs 100 ng/mL	47.0% / 53.0%	99.1% / 0.9%	98.2%

* n=990
TP=true positive; TN=true negative; FP=false-positive; FN=false-negative; LC/MS/MS=liquid chromatography-tandem mass spectrometry; POC=point of care; NA=not applicable

Table 3. *Illustration of summary of diagnostic accuracy of opioids (index test vs. reference test).*

		Patients Prescribed Morphine, Hydrocodone, Codeine, Hydromorphone group (748)			Patients Prescribed Oxycodone (134)			Patients Prescribed Methadone (46)			Patients with non-prescribed opioids or no prescribed opioids (1000)		
		Reference Test (LC/MS/MS)			Reference Test (LC/MS/MS)			Reference Test (LC/MS/MS)			Reference Test (LC/MS/MS)		
		Positive	Negative	Totals	Positive	Negative	Totals	Positive	Negative	Totals	Positive	Negative	Totals
Index Test (POC)	Positive	594	11	605	92	3	95	44	0	44	37	83	120
	Negative	48	95	143	23	16	39	1	1	2	16	864	880
	Totals	642	106	748	115	19	134	45	1	46	53	947	1000
Test Efficiency (Agreement)		92.1%			80.6%			97.8%			90.1%		
Sensitivity		92.5% (90% - 94%)			80.0% (71% - 87%)			97.8% (88% - 99%)			69.8% (55% - 82%)		
Specificity		89.6% (82% - 95%)			84.2% (60% - 96%)			100 (2% - 100%)			93% (89% - 93%)		

LC/MS/MS=liquid chromatography-tandem mass spectrometry; POC=point of care

cocaine, 98.8% for methamphetamine, and 99.1% for amphetamine. However, the sensitivity was only 25% for cocaine, 40% for methamphetamine, 47% for amphetamine, and 90.9% for marijuana. One reason for such low sensitivity for illicit drugs is low prevalence rates. Thus, a larger sample size is needed to detect sensitivity. The agreement, or test specificity, for all illicit drugs was 95%, with 97.8% for marijuana, 99.4% for cocaine, 98.5% for methamphetamine, and 98.2% for amphetamine.

Multiple methodological issues are present in UDT, with immunoassays being based on the principle of competitive binding, detecting a particular drug group in a urine sample. In contrast, laboratory-based specific drug identification is sophisticated, but also more expensive. Thus, laboratory-based specific drug identification is needed to confirm the presence of a given drug and/or to identify drugs that cannot be isolated by a screening test. In addition, the cutoff levels for various drugs detected by urine analysis are also different between immunoassay testing and LC/MS/MS. Consequently, the capability of a particular immunoassay to detect drugs can vary according to both the drug concentration in the urine and the assessed cutoff concentration – with drug levels above cutoff being deemed to be positive. However, almost all immunoassays are subject to cross-reactivity. Some tests are highly predictive (i.e., cocaine, morphine, codeine), whereas others are very poorly predictive (i.e., amphetamine, methamphetamines, oxycodone) based on various other substances being ingested.

Previous studies performed in a prospective manner (31-33) showed the prevalence of illicit drug use to vary from 4.8% to 6.25% for cocaine, 11% to 18% for marijuana, and 2% to 3% for amphetamines and/or methamphetamine. Other studies, though not prospective and not diagnostic accuracy studies (37,44,46,47), showed false-negative rates for oxycodone, hydrocodone, methadone, and other opioids variable from 1.9% to 15% (37,44,46) and false-negative rates for illicit drugs which were not detected in 9% to 50% of patients. Further, Gilbert et al (41), in attempting to reverse CMS regulation, showed that urine drug testing represented only approximately 18.2% of professional medical services rendered in 2007, a figure considered extremely high by others (38,39). POC testing results examined in the present evaluation show an overall positive rate of 7.8%; 0.2% for cocaine, 4.9% for marijuana, 1.7% for amphetamines, and 1.4% for methamphetamines. These results differ with previous studies. Further, false-negatives were observed in 75% for cocaine, 9.1%, for marijuana, 53% for amphetamines, and 60% for methamphetamines.

The results of the present study illustrated similar results for patients with prescribed opioids, with a false-negative rate of 19.6% for the index test and 20.3% for the reference test. The improved diagnostic accuracy with the reference test is 8.9%, rising from 80.4% to 89.3%; all the samples which were tested to be negative by immunoassay were confirmed by LC/MS/MS, with 82 of 180 patients testing positive. In reference to non-prescribed opioids, 12% tested positive with the index test, with that test missing in 1.6% of the patients. However, only 37 of 120 were confirmed with the reference test, with 83 of 120 patients or 44% with false-positive results for non-opioid use with the index test performed in the office. Thus, a total of 53 patients, or 5.3%, were using non-prescribed opioids.

Multiple authors have described the utility and application of UDT in chronic pain management with opioids (31-33,36,52-54). Nafziger and Bertino (53) described that UDT, when used with an understanding of the principles of pharmacokinetics, pharmacodynamics, and pharmacogenetics of opioids, can be a useful tool in chronic pain management. Thus, clinicians must keep in mind the limitations, purpose, and value of UDT, and the inability to predict patient compliance with the drug dosages used in commercial algorithms. Pergolizzi et al (52), in a compliance survey, discussed various aspects of UDT for patients in opioid therapy including the validity of UDT with reference to index and reference tests and the implications for reimbursement. With reference to cost issues, Gilbert et al (41) discussed the cost-benefit considerations of UDT, and that testing of chronic pain patients is analogous to the federal work place drug testing program, methadone clinics, and other areas, which have shown a definite cost benefit for UDT in this complex population. It has been estimated that each UDT in the past has cost Medicare up to $220 per physician office payment, and up to an additional $600 for laboratory testing. Some physicians have stated that any patient treated with controlled substances, including stable patients, should be seen in an office every 4 weeks and be required to have a UDT (40,41,55,56). This increased frequency obviously has had a negative impact on patients and payers, as seen by new CMS guidance on this testing (45). Gilbert et al's (41) illustration of 18.2% income, the Ameritox indictment, and change of CMS coding patterns, illustrates the economic incentives for UDT (43).

The question which needs to be answered is: How many POC testing samples need to be sent to the lab? Based on our evaluation, it appears that it should be all samples testing negative for prescribed (detectable) opioids (184 patients), positive for non-prescribed opioids (123 patients), and positive for illicit drugs (68 patients), totaling 329 patients after eliminating positive duplications. However, these can be reduced based on a patient's admission of abnormal use, and the clinic's policy for controlled substances and illicit drugs. The re-

ductions could range from 20% to 60%, with a repeat of the immunoassay test during the patient's next appointment or at random. A repeat test should be much less expensive compared to sending the test to a lab; generally $25 versus as much as $600. Thus, careful analysis can save substantial amounts of health care dollars, specifically when performed judiciously without repeating during each visit in patients who do test normally, and repeating their tests only once a year and then only repeating in patients who present with abnormal results. One UDT might be more expensive than providing 2 to 3 epidural injections. Routine excessive UDT could result in annual charges as high as $10,000, which is more expensive than managing patients with common opioids or appropriately performed therapeutic interventional techniques. However, multiple interventional techniques also have been criticized for escalating use, abuse, and lack of effectiveness (38,39,57-66). Based on cost-effectiveness, numerous guidelines have been developed, which are curbing chronic pain management therapy in the era of increasing pain, including interventional techniques and surgery based on evidence-based medicine and comparative effectiveness research (34,38,39,67-99). Thus, appropriate use of immunoassay will be cost-effective with provision of appropriate care.

The present study can be criticized for limitations, which include a single site study utilizing a single POC kit and a single laboratory, as well as technical sponsorship. A multicenter study could be performed utilizing various manufacturers and different kits, etc.; however, this might provide irregular results. Consequently, as an initial diagnostic accuracy study, the present study is appropriate. Millennium Laboratories provided urine drug kits, laboratory evaluation at no cost, and expenses for employees for collecting the samples, transporting them, data entry, and analysis. However, They had no influence or interference after the protocol was designed. Further, the authors of the manuscript received no remuneration. Thus, we believe the results are valid.

Further, the results of this study illustrate practice patterns in an interventional pain management practice, rather than results generalizable to either all interventional pain medicine settings or primary care settings.

Conclusion

UDT with immunoassay in an office setting is an appropriate, convenient, and cost-effective test providing rapid results for evaluating opioid compliance. Compared with laboratory testing (LC/MS/MS) for opioids and illicit drugs, immunoassay in-office testing had high specificity and agreement, but variable sensitivity, demonstrating the value of immunoassay drug testing.

However, in patients with abnormal results, either by detection of non-prescribed opioid or illicit drugs, the results are not dependable and might have to be confirmed either by a repeat test, proper history, or confirmation by LC/MS/MS. Based on this evaluation, it appears that overall, as many as 32.9% or as few as 20% of patients could require their samples be sent for LC/MS/MS confirmation and subsequent patient management.

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Author Contributions: Dr. Manchikanti had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Manchikanti, Malla, and Wargo designed the study protocol. Dr. Manchikanti managed the literature searches and summaries of previous related work and wrote the first draft of the manuscript. All other authors provided revision for intellectual content and final approval of the manuscript.

Conflict of Interest Disclosures: All authors have no conflicts of interest to report. None of the authors of the manuscript received any remuneration. Further, the authors have not received any reimbursement or honorarium in any other manner. The authors are not affiliated in any manner with Millennium Laboratories. However, all the authors are members of the American Society of Interventional Pain Physicians (ASIPP) and practicing interventional pain physicians except for Bert Fellows, who is a retired psychologist. Dr. Manchikanti is the Chairman of the Board and founder of ASIPP, which was responsible for the National All Schedules Prescription Electronic Reporting Act (NASPER) legislation and its implementation. Vidyasagar Pampati, MSc, statistician, is an employee of Ambulatory Surgery Center.

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Physicians, a state organization, has no relevance to the study and none of the Florida members were involved in conduct of the study.

Role of Sponsor: The financial sponsor of this work had no role in the design and conduct of the study or the collection, management, analysis, and interpretation of the data. The sponsor also did not have a role in the preparation or review of the manuscript or the decision to submit.

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