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Substance Abuse Testing of Urine by GC/MS in Scanning Mode Evaluated by Proficiency Studies, TLC/GC, and EMIT

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ABSTRACT: Using GC/MS in scanning mode as a screening and definitive identification methodology for substance abuse testing, 4500 urine samples have been analyzed. The accuracy and sensitivity of this method was evaluated by the results of 92 proficiency sample analyses, reanalyses by TLC screening with GC confirmation of 125 samples from forensic sources and reanalysis by EMIT screening for seven groups of drugs confirmed by GC/MS of 590 samples from industrial and treatment sources. The results of these studies are presented.

KEYWORDS: toxicology, substance abuse testing, urine, spectroscopic analysis

The major thrust in laboratory testing for substance abuse has been directed to methodologies employing thin layer chromatography (TLC) or antibody-antigen reactions including radioimmunoassay (RIA), enzyme multiplied immunoassay (EMIT) and fluorescence polarization immunoassay (FPIA). Because these techniques may be associated with false-positive results, confirmation by a more specific modality, gas chromatography (GC) preferably combined with mass spectroscopy (GC/MS), is required [*1–3*]. Considering these methodologies in 1986, our concerns were that the antibody-antigen systems were limited to detecting a fixed number of substances subject to abuse and samples to be analyzed by these methodologies were vulnerable to adulteration. We considered that the "street" might become aware of methodology limitations. We considered TLC to be

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an excellent screening technology that required confirmation, great skill and experience in interpretation, which requires moderate sample preparation.

A major consideration prompting our decision to develop a GC/MS based program was that it allowed us to respond to the analytical requirements of different service needs—forensic, therapeutic and industrial. Diversification allows us the capability to be cost effective, to provide the highest quality of analytical result to a service area of 150 000 population and to permit close medical and technical consultant service.

We developed and present a GC/MS scanning method which involves hydrolysis, extraction and derivatization to screen for multiple drugs of abuse and their metabolites in urine. We have evaluated the method by duplicate forensic sample analysis by TLC/GC, industrial and treatment patient samples by EMIT/GC/MS and by proficiency sample studies.

GC/MS in scanning mode is an accurate and sufficiently sensitive method for screening and definitive identification of drugs of abuse in urine. It allows a broader spectrum of drug identification than EMIT testing.

Materials and Methods

Subjects

Urine samples were obtained from four sources: inpatient and outpatient drug treatment (N = 1934), industry (pre-employment and probable cause), (N = 1575), forensic (cause of death and sexual assault investigations) (N = 518) and others (N = 270).

Methods

Samples were subjected to two sets of extraction. One 5 mL aliquot was hydrolyzed in combination with 1 μg/mL nalorphine (an opiate antagonist not currently in therapeutic use) as internal standard. Hydrolysis was performed by adding 0.50 mL of a 6 N HCl solution with 5 mL of concentrated H_2SO_4 per liter and heating at 100°C for 1 h. The hydrolyzed sample was added to a Toxi-Lab A tube and rotated for 5 min. Following a 10 min centrifugation, the organic (top) layer was removed and 20 μL N,N-dimethylformamide (DMF) was added. This fraction was evaporated slowly to near dryness. The aqueous (bottom) layer in the Toxi-Lab tube was re-extracted using 3 to 4 mL of methylene chloride and mixing for 30 min. After centrifugation, the aqueous (top) layer was discarded and the methylene chloride (bottom) layer was added to the previous extractant [*4*].

The other 5 mL urine aliquot was extracted in the same manner, without hydrolysis. All of the extracts were pooled and evaporated, nearly to dryness. The samples were derivatized by adding 50 μL bis [trimethylsilyl] trifluoroacetamide (BSTFA) with 1% trimethlychlorosilane (TMCS) and heated at 90°C for 1 h.

The samples were then analyzed using a Hewlett-Packard 5890 gas chromatograph coupled to a 5970B mass spectrometer (GC/MS) run in scan mode (40 to 600 AMU). A HP Ultra 2 (5% phenyl methyl silicone, 12 meter by 0.2 mm by 0.33 μM film thickness) column was used. The injector was operated in the split mode (30:1). The flow rate was 0.7 mL/min (measured at 180°C). A temperature ramp from 105°C to 285°C was used. The total run time was 65 min [*5,6,7*].[6]

The mass spectra were matched using the probability based matching (PBM) algorithm (developed by Hewlett-Packard based on McLafferty) against our laboratory-generated library containing approximately 430 compounds including 140 parent drugs, metabolites and derivatives.

[6]Sawyer, P. R., "Gas Chromatography in the Detection of Drugs in Urine," Seattle, V.A. Hospital, March 1986, unpublished.

Quality control was achieved by weekly analysis of Lyphochek Urine Toxicology Control (Biorad) and the nalorphine internal standard.

Marijuana was detected and quantified using selected ion monitoring for 11-nor-9-carboxy-delta-9-THC. The internal standard was 11-nor-delta 8-THC-9-THC. THC was reported as ng/mg of creatinine.

The full scan GC/MS system was evaluated by analysis of samples from four sources by three different studies: 1) the results of proficiency sample analyses; 2) comparison of the results of forensic sample (death and sexual assault) analyses by thin layer chromatography (TLC) plus gas chromatography where indicated (Washington State Toxicology Laboratory); and 3) comparison of the results of samples from treatment programs and industry by EMIT screening and GC/MS confirmation (Mayo Toxicology Laboratory). Drugs identified in the work environment are also reported.

Thin layer chromatography assays were performed at the Washington State Toxicology Laboratory using Toxi-Lab methodology [*4*]. Positive results were confirmed by gas chromatography appropriate to the analyte detected by TLC.

Immunoassays were performed in the Mayo Toxicology Laboraotry using EMIT reagents (Syva, Co., Palo Alto, CA) adapted to the Hitachi 717 Automated Chemistry Analyzer (Boehringer Mannheim, Indianapolis, IN) according to Syva applications designed for this instrument. The following threshold cutoffs were used to differentiate positive from negative specimens: amphetamines (1000 ng/mL as methamphetamine), barbiturates (300 ng/mL as secobarbital), benzodiazepines (300 ng/mL as oxazepam), benzoylecgonine (300 ng/mL), opiates (300 ng/mL as morphine), phencyclidine (25 ng/mL) and THC-COOH (20 ng/mL). A negative control was included with each batch, and in those cases where the EMIT response was below the threshold cutoff but significantly higher than the negative control, the specimen was retested by the appropriate GC/MS confirmation assay described in the following.

In cases where discrepancies were observed between scanning GC/MS analysis and immunoassay, the specimens were retested (Mayo) using GC/MS confirmation methods specific for the drug or drug category in question. All methods used SIM detection mode except the barbiturate confirmation which was conducted in full scan mode. The benzodiazepine method was designed to confirm the presence of oxazepam, nordiazepam, lorazepam, temazepam, flurazepam (as hydroxyethylflurazepam), alprazolam and triazolam (the latter two as their alphahydroxymetabolities). The barbiturate method was capable of detecting allobarbital, amobarbital, aprobarbital, butabarbital, butalbital, mephobarbital, pentobarbital, phenobarbital, secobarbital and thiopental.

Results

Proficiency Studies

The analytical method has been evaluated using external quality control since 1987 by subscription to the Urinary Toxicology program sponsored by the College of American Pathologists. The Forensic Urine Drug Confirmation was added in 1989. The results of 92 samples are listed in Table 1.

False Positives—To date, no false positive results have occurred.

False Negatives—The identification of the parent drug cocaine is not specifically requested by CAP and space for reporting cocaine is not provided. The presence and quantity of cocaine is reported in the summary reports. In one instance, although benzoylecgonine was identified, cocaine was not recognized until the sample volume was doubled. The retention time of cocaine was being masked by that of propoxyphene. The incident occurred in 1987 and the analytical system was modified to correct this problem by increasing the sample volume and extending the chromatographic run time.

TABLE 1—*Drugs detected by GC/MS in scanning mode in proficiency studies.*

Number of samples: 92
Number of false positives: None

Analyte	Det'd	Miss	Analyte	Det'd	Miss
Marijuana	11		Antihistamines		
Adrenergics			Chlorpheniramine	5	
Ephedrine	1		Diphenhydramine	3	
Phenylpropanol.	6	2	Pyrilamine	3	
Analgesics/Antitussives			Sedative/Hypnotics		
Acetaminophen	9		Amobarbital	2	1
Pentazocine	3		Butalbital	2	2
Salicylates	9		Glutethimide	1	
Anesthetics			Pentobarbital	2	
Cocaine	2		Phenobarbital	1	
Benzylecgon.	16		Secobarbital	2	
Ecogn. Me Ester	3		Narcotic Analgesics		
Lidocaine	1		Codeine	13	
Phencyclidine	9		Hydromorphone	3	
Antidepressants			Meperidine	3	
Amitriptyline	4		Methadone	2	
Amoxapine		2	Morphine	8	
Cyclobenzaprine	1		Oxycodone	1	
Desipramine	3	2	Propoxyphene	6	
Doxepin	4		Opiates	1	
Imipramine	1		Tranquilizers		
Loxapine	1	1	Oxazepam	4	
Nordoxepin	1		Stimulants		
Nortriptyline		4	Amphetamine	9	2
			Caffeine	2	
			Methamphetamine	8	1

Even though amoxapine was being detected in patients' urine samples, it was originally missed in a survey sample because the metabolite used in the proficiency sample was different from that entered in the library. Nortryptyline and desipramine remain difficult drugs to detect. In each instance where nortriptyline was not detected, amitriptyline was present and identified. Nortriptyline has been identified seven times from patient samples. (Currently confirmation of antidepressant drugs is accomplished by HPLC.)

Loxapine and metabolites were originally not in the library. Since being added, loxapine can be detected.

It is our experience that low levels of barbiturates may be missed. We identified 12 of 15 barbiturates in these samples.

After missing the first amphetamine, the "keeper solvent" (DMF) addition in the methodology was modified. This change appears to have corrected the loss of analyte due to volatilization.

In 1989, at a time when we were experiencing hardware and software problems and were not testing patient samples, we attempted to report out a survey sample. All three analytes—amphetamine, methamphetamine and desipramine—were missed. The results should not have been reported. They are included in the summary.

GC/MS Scanning Compared to Thin Layer Chromatography + Gas Chromatography

From May, 1987 through October, 1990, 238 death investigations, and the urines of alleged victims of sexual assault and assailants warranted toxicological analysis. Of these, 195 samples had enough urine to allow for analysis by GC/MS in scanning mode and quantitative SIM analysis for marijuana metabolites. Of these, 125 samples were rean-

alyzed at the Washington State Toxicology Laboratory by TLC with confirmation by GC where indicated. The comparative results of these groups of forensic samples are summarized in Table 2.

The metabolite, 6-monoacetylmorphine, specifically identifies heroin which may be of assistance in identifying the source of the opiate. It is easily added to the library for computer identification in the GC/MS analytical system [*8*].

Until recently, marijuana was not routinely identified nor reported by the Washington State Toxicology Laboratory. The pharmacological significance of this drug in urine is not clearly understood. One accidental death involving a skier apparently related to recent use of marijuana occurred in this series. A hunting accident death occurring prior to implementation of this testing program has also been observed. Marijuana and alcohol are frequently found with other drugs. We believe that the presence of marijuana has been underreported.

Methylmorphinan was included in our library to detect dextromethorphan which is a replacement drug for codeine in "over the counter" antitussive. It is subject to abuse but is not recognized to be associated with death.

The GC/MS system may miss low level barbiturates. One year after development of the method, with documentation of excellent recovery, tolybarb was eliminated as an internal standard because it was interfering with identification of other barbiturates. (Currently barbital is used as internal standard for recovery of acidic drugs).

Comparison GC/MS Scan to EMIT Screen Plus GC/MS Confirmation

In a collaborative study, 590 samples that had been stored frozen at −30°F were reanalyzed by the Toxicology Laboratory of the Mayo Clinic. Thirteen of the samples had originally been tested for marijuana only. Results are summarized in Table 3.

TABLE 2—*Thin layer chromatography + GC confirmation compared to GC/MS scanning.*

Number of Samples	Death Investigation		Sexual Assault		Total
	79		46		125
Analyte	GC/MS	TLC + GC	GC/MS	TLC + GC	
Cocaine	7	6	0	0	7/6
Cocaine Metabs	13	13	2	2	15/15
Morphine/Opiates	4	4	0	0	4/4
6-Monacetyl Morph[a]	2	0	0	0	2/0
Oxycodone	0	0	1	0	1/0
Amphetamine/Methamphetamine	1	1	0	0	1/1
Benzodiazepines	4	4	1	2	5/6
Barbiturates	0	1	0	2	0/3
Meprobamate	1	1(bl)	0	0	1/1
Tricyclic Antidepressants	1	1	0	0	1/1
Phenothiazine	0	1	0	0	0/1
Marijuana[a]	15	4	18	3	33/7
Anticonvulsants	3	0	2	0	5/0
Antihistamines	2	0	1	0	3/0
Phenylpropanal.	3	3	2	0	5/3
Ephedrine & Metabolites	3	0	1	1	4/1
Methylmorphinan	1	1	0	0	1/1
Acetaminophen	10	8	7	3	17/11
Salicylates	4	4	0	0	4/4
Quinidine/Quinine	2	2	0	0	2/2
Trimethoprin	0	2	0	0	0/2
Lidocaine	0	0	1	0	1/0

[a]see text
bl = blood

TABLE 3—*EMIT Screen + GC/MS confirmation compared to GC/MS scanning.*

Samples compared: 577
No Drugs Detected: 381

Positive	Agree	EMIT pos GC/MS neg	EMIT neg GC/MS pos
Amphetamines	2	1	0
Barbiturates	6	2 (1)[a]	0
Benzodiazepines	11	4 (2)[a]	2
Cocaine	21	6 (3)[a]	0
Marijuana	95	0	1
Opiates	7	3 (2)[a]	0
Phencyclidine	0	0	0
Other	see text		

[a](below threshold)

Amphetamine—The sample that was negative by GC/MS scan was retested by the originating laboratory. It tested positive by Abbott TDX fluorescence polarization immunoassay methodology. Retesting by GC/MS in scanning mode was negative. Employing SIM technic, a retention time peak suggestive of amphetamine was present. A peak indicative of methamphetamine could not be demonstrated.

Barbiturates—Of the two samples negative by GC/MS, one contained less than 300 ng/mL; the other contained less than 500 ng/mL. Low levels of barbiturates may not be detected by GC/MS using the extraction methodology employed.

Benzodiazapines—Two of the four samples containing benzodiazapines not detected by scanning GC/MS technique were below the 300 ng/mL threshold level. One contained 194 ng/mL of a-hydroxyalprozolam, and the other 194 ng/mL of temazepam, 137 ng/mL of oxazepam and 69 ng/mL of nordiazepam. An additional sample detected by the EMIT system contained hydroxyethylflorazepam but was of insufficient volume to quantitate. Although triazolam and metabolites have been recovered and identified utilizing the GC/MS system described, repeat analysis of one sample by the originating laboratory failed to identify this drug quantified to be 534 ng/mL. Lorzaepam at a level of 4496 ng/mL was not detected by EMIT. The reason for the false negative of this level is not known. A sample containing 334 ng/mL of oxazepam was also not detected by the EMIT system.

Cocaine—Three samples containing 217 ng/mL, 162 ng/mL, and 117 ng/mL benzoylecognine respectively were not identified by GC/MS in scanning mode. Two samples initially negative by GC/MS scan analysis containing 687 ng/mL and 4410 ng/mL of benzoylecognine respectively were retested using half quantities and were positive. The reason for the original false negative results are not known.

Marijuana—Fourteen samples measured less than 20 ng/mL by the originating laboratory employing GC/MS using SIM technology gave positive results by EMIT presumably due to cross reactivity of marijuana metabolites other than THC-COOH in the EMIT assay. One sample containing 75 ng/mL of THC was not detected by the EMIT system.

Opiates—Two samples containing morphine below threshold levels, 167 ng/mL and 128 ng/mL, were not detected by GC/MS scan. One sample containing 565 ng/mL of codeine and 699 ng/mL of morphine was retested by GC/MS scan. The background interfering peaks were particularly intense at high molecular levels and the two opiates were not detected by computer. In retrospect they are visible by manual inspection.

Phencyclidine—Phencyclidine was not detected by either methodology in any of the samples.

Other—The EMIT system was not programmed to detect drugs other than the groups reported above. We believe it of interest to note additional drugs that GC/MS in scanning mode detected in the 577 samples: Oxycodone (2), Propoxyphene (1), Methadone (1), Naltrexone (9), Meprobamate (9), Nortryptyline (1), Antihistamines (8), Anticonvulsants (2), Phenylpropanalamine (17), Ephedrine and/or Pseudoephedrine (9), and methylmorphinan (8). The incidence of these possibly significant drugs of abuse is not great in this group of samples originating from employment (70%), treatment programs (23%), law enforcement (2.6%) and individual requests (4.4%). Emergency room activity and medical examiner sources are not represented. The identification of this group of drugs was particularly well received by health care providers involved in treatment programs.

One example involved a subject being followed in an out-patient treatment program. A first sample had urine THC of 838 ng/ml (1309 ng/mg creatinine). One month later he was tested again with a random, unannounced sample to check abstinence. This repeat sample had a marijuana level decrease as indicated by the lower equivalent relative mass (per unit mass creatinine). Unexpectedly, four additional drugs including cocaine and codeine metabolites, hydrocodone and hydromorphone were detected. The latter two would probably not have been detected by EMIT or RIA testing technologies. They were considered significant to the management of the patient.

Industrial Source Analytes

(Pre-employment and Cause)

From March, 1987 through June, 1990 1575 samples obtained from industrial sources were analyzed. These results are summarized in Table 4. An example of a typical report is shown in Fig. 1. Several of these drugs would not have been detected by EMIT. Those detected would have had to be confirmed to identify the drug present.

The reporting of nicotine and metabolites is used by some Employee Assistance Administrators to implement counseling or treatment for nicotine addiction or habituation.

The vast majority of industrial samples were submitted for pre-employment screening. The job applicants were aware that company policies required pre-employment testing. Because most samples were collected in the laboratory, which is often of considerable distance from the job application site, there was opportunity to avoid or delay sample collection. Analytes identified do not represent the usage incidence in the general population.

Discussion

Application of GC/MS scanning methodology in a hospital setting has been previously reported [*9*] but has apparently not been widely applied or reported. Testing by GC/MS has several advantages when compared with immunoassay. Important is the ability to detect and identify an individual drug rather than a drug class. Dependent on the immunoassay employed, different mixtures of monoclonal or polyclonal antibodies are used which provide cross-reactivity to detect classes of compounds. For example, the Syva EMIT polyclonal amphetamine assay will give a positive response for samples which contain 0.3 μg/mL amphetamine or 1.0 μg/mL phenylpropanolamine. The marketing of a monoclonal antibody reagent system specific for amphetamine or methamphetamine will miss phenylpropanolamine or pseudoephedrine unless these drugs are present in very high concentrations. This may be important in some situations. The GC/MS procedure can identify these drugs without difficulty.

Opiate EMIT assays may give a positive result for a sample with 0.6 to 1.0 μg/mL 6-monoacetylmorphine or 1.1 to 2.14 μg/mL codeine [*1*]. The significance of the report depends on the actual drug present.

TABLE 4—*Analytes identified from industrial sources March 1987–June 1990.*

Number of samples: 1575
Number of Analytes: 2091

Drug or Group	No Positive	Percent
Marijuana	191	12.1
>1000 ng/mL	5	
Ethanol	38	2.4
Cocaine and benzoylecgonine	26	1.6
Cocaine	1	
Opiates		
Codeine	15	1.0
Morphine	9	
Oxycodone	1	
Norproproxyphene	1	
Total	26	1.6
Stimulants		
Amphetamine	2	
Methamphetamine	1	
Nicotine	723	45.9
Caffeine	1157	73.5
Benzodiazepines	11	
Antidepressants	8	
Adrenergics		
Ephedrine	12	
Phenylpropanolamine	74	4.7
Pseudoephedrine	72	4.5
Total	158	10.0
Anticonvulsants	8	
Antihistamines	81	5.1
Analgesics		
Acetaminophen	199	12.6
Ibuprofen	118	7.5
Salicylates	35	2.2
Dextromethorphan met.	23	1.5

Follow-up confirmation is required following the EMIT assay to identify the particular analyte. The GC/MS scanning method screens and identifies which member of the drug family is present. The advantages of increased selectivity is gained at the expense of increased time required for the analysis. Using an automated analyzer with EMIT reagents, hundreds of samples can be analyzed each day. Scanning by a single unit GC/MS is limited to 20 to 22 samples per day. To an extent, we overestimated the throughput capacity of the system. The 65 min run time does not include time necessary for hydrolysis, extraction or derivatization. This is accomplished while prior samples are being automatically processed.

Each analyte has been documented by recovery studies to be detected at levels of 1 μg/mL. Barbiturates, amphetamines and tricyclic antidepressants are recoverable at lower concentrations. Phencyclidine, benzodiazepines, and opiates, are recovered at much lower levels.

Opiates have been recovered at 200 ng/mL and phencyclidine at less than 100 ng/mL. Specific analytes can be detected at lower levels by a quick or short scan at restricted mass spectra. These have been developed for amphetamines and phencyclidine.

In CAP urine toxicology survey set UT-C (1990), two significant problems were reported. Despite warning from the manufacturer of immunoassay kits, over 165 respondents falsely reported positive results for phencyclidine due to thimerasol, a preservative included in the samples. It would appear that these laboratories were not confirming

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TOXICOLOGY REPORT

Date of Report: 3/20/90
Name: Anon
Requested by: Pre-employment counselor
Type of Specimen: Urine
Date/Time Collected: 3/16/90 0930
Date/Time Received: 3/16/90 1820
Chain of Evidence: YES
Urine pH: 5.0 Urine Creatinine = 0.88mg/ml

Alcohol (ETOH) = None Detected

Marijuana as Urine COOH-THC = None Detected

Other Drugs Detected.

1.	Amphetamine	10.	Acetaminophen
2.	2-Amino-5-chlorobenzophenone	11.	Salicylic Acid
3.	Norpropoxyphene	12.	Salicyluric acid
4.	Codeine	13.	Salicylamide
5.	Norcodeine	14.	Nicotine
6.	Oxycodone	15.	Cotinine
7.	Dihydrocodeine	16.	Caffeine
8.	Meprobamate	17.	Paraxanthine
9.	Pseudoephedrine		

Case History: Patient was a 37 year female applicant for office manager position with an excellent resume and impressive interview. She was alert, attentive and had good appearance. When informed she was to be drug tested, she produced 5 prescriptions from 4 physicians and suggested these might produce positive results. She did not return.

FIG. 1—*Example of a toxicology report.*

with GC/MS. In this survey, cyclobenzaprine, a tricyclic muscle relaxant subject to abuse, was not detected by almost 50% of respondents employing TLC. Our methodology correctly recognized both analytes.

Proficiency testing is an excellent, albeit expensive, system for upgrading and fine tuning any analytical technology. Quantitative data in summary reports provide an index of the lower levels of analyte detection.

Other than program and labor cost, a major liability is the use of the results of proficiency tests by regulators as the major measure of the quality of a program. Chemicals used in proficiency testing products may not be those being measured in patients. When analytes added to proficiency test products are the same as that commonly used as an internal standard, the analyte will not be detected. Reagent and instrument bias to analytes added and to matrices employed in proficiency samples must be recognized. Extreme care must be exercised to ensure that results are compared between comparable testing systems. Resolution or explanation of possible errors of results in proficiency tests are usually time consuming and costly. It is more important that results reported from patient samples are accurate.

Many of the drugs identified by GC/MS scan are not necessarily indicative of abuse. They are reported because they may be of assistance in identification of "over the counter" medications or prescription medications which contain controlled drugs administered for

appropriate medical indications or which may be abused. Codeine is such a drug. While codeine with salicylate or acetaminophen may be abused, codeine without these substances is highly suspect.

The presence of drugs of abuse, including alcohol, associated with sexual assault, in some instances, was helpful in clarifying a confusing medical history and was helpful to law enforcement investigators.

The comparative study with EMIT technology would be enhanced by expanding the data base, possibly with emphasis on those areas where the full potential of GC/MS scanning can be optimally utilized such as in the treatment environment and in forensic medicine. We are considering a clinical correlative study in treatment programs. Because of the multitude of drugs identified in subjects entering and undergoing treatment, it is our impression that the most productive use of this analytical system exists in this setting.

Conclusions

GC/MS in scanning mode is an excellent alternative to immunoassay testing for drugs of abuse in urine. It provides sensitivity and better specificity without risk of false positives.

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