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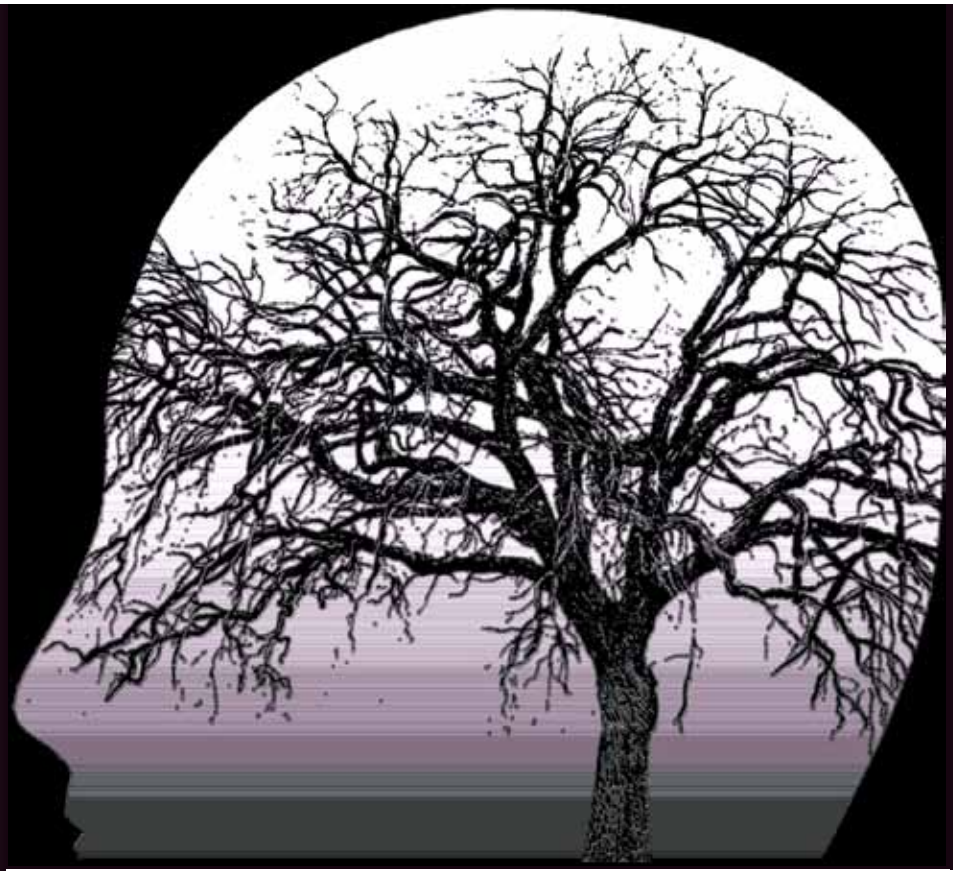

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Urine Labelling Marker System for Drug Testing Improves Patient Compliance

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Summary

Urine drug testing plays an important role in substance abuse treatments. When strictly controlled, as it often is, urine sampling creates a humiliating situation and ties up resources. A new sample labelling method has been developed to make supervision unnecessary. This innovation is achieved by labelling the urine with polyethylene glycols. In this study, 57 patients who required urine sampling were randomized into two groups, the traditional supervised (TS) group and the new marker (NM) group. The urine test return rate was 98.3% in the NM group and 100% in the TS group. Attempts to manipulate the urine samples were discovered in 2% of the NM group and 0% of the TS group. Most patients preferred the NM testing method. The personnel too preferred the NM system, and estimated that it reduced their workload dedicated to drug screening by 50%. We conclude that the NM method is more acceptable to patients and personnel, and may increase compliance as a result.

Key Words: Drug Testing; Urine Samples; Drug Addiction; Marker System

1. Background

Urine drug testing, performed regularly or randomly, plays an important role in substance abuse treatments [1-3]. Drug testing can be used to measure compliance or treatment outcome, and can also ensure the safe administration of medication. Drug testing is also used in many other areas, such as child welfare [4], occupational health care, and imprisonment. In every case, the major challenge is to ensure that the urine being analysed can undoubtedly be connected to the correct person [5, 6]. To ensure this, urine sampling is often strictly controlled, which can be a humiliating situation and ties up human resources [7, 8]. This strict control may have a negative impact on mutual trust and reduce patient compliance.

Recently, a new marker method that makes supervision unnecessary for urine sample labelling was introduced [9, 10]. This outcome can be achieved by labelling the urine with modified polyethylene glycols, which are taken orally, quickly excreted through the kidneys, and do not occur in natural urine. The different molecular weight marker solutions can be identified and linked to the person to whom it was given. In this procedure, only the consumption of the marker solution must be supervised. Drug testing is performed using normal, standard methods. In earlier studies [11] NM urine testing had a significantly higher sensitivity for the detection of concomitant drug use, and a high prevalence of urine manipulation in conventional urine screening methods was also observed. The most used manipulation method is dilution or mixing of the urine with other liquids, for example, water, for which attempts at manipulation can be checked by determining the urine creatinine concentration. When the urine labelling method is used, the marker concentration normally drops below the limit of detection before the drug reaches this limit. Screening tests with marker solutions can themselves be manipulated, most commonly by spitting a marker solution into clean urine from a different person. This, however, can be avoided by giving the marker together with sucrose, which never occurs in normal urine. Patients have also tried adding acids, alkalines and other chemical

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substances to their urine samples. Such manipulations affecting the enzymatic drug analysis can be detected by applying CEDIA sample checks.

The aim of this study was to compare two different urine screening methods, the traditional sampling (TS) method and the new marker (NM) method, with respect to compliance, patient satisfaction, unfulfilled samples, and estimated time spent on sampling.

2. Methods

2.1 Subjects

The study began on November 10, 2008 and ended on January 19, 2009. It included volunteer patients undergoing treatment at the Espoo Treatment and Rehabilitation Centre, A-clinic Foundation. Subjects were from the opioid dependence maintenance treatment unit, the detox department, and outpatient department. They were asked if they would like to become volunteer participants in the study if urine testing was part of their treatment programme. Prior to participation, the procedures, benefits, and shortcomings of the methods were carefully explained to them. The patients in maintenance treatment were required to have a history of treatment for at least 1 month prior to the study. Patients were excluded if they were disabled, less than 18 years of age, pregnant, nursing women, or prisoners, or if they had a record of kidney disease. In total, 57 subjects were included, of which 29 were in maintenance treatment, 26 were in detox, and 2 were outpatients.

2.2 Randomization

The study subjects were randomized into two groups, the NM and the TS group. Randomization was conducted by a computer programme (Vassar Statistics).

2.3 Urine testing

Following urine testing, subjects in both groups completed a questionnaire. The information gathered included when the urine test was requested, where it was performed, and whether the situation was pleasant or unpleasant. Each subject was asked to deliver a urine sample once or several times, depending on the treatment phase and visits. In the NM test group, information was also gathered on the given marker, whether the patient took the urine test at home, and, if so, whether the sample was delivered. For each NM group sample, the laboratory bar code label was added to the data.

2.3.1 New marker test group

Marker substances were provided by RUMA GmbH (Cologne, Germany). Three different molecular weight markers were used and were given to the patients in a random fashion. The patients did not know the molecular weight of the solution they received. The marker vials, which contained 30 ml of the marker solution, were individually labelled. The marker was then mixed with approximately 100 ml of a sweet soft drink. Patients were asked to drink this solution 30 min prior to delivery of urine. They were then allowed to urinate without supervision in the clinic or to take the urine test tube home and return it to the clinic within 1 week. After patients submitted the urine sample (20–50 ml), the test tube was identified with a bar code label according to the routine procedure of the Central Laboratory in Cologne. An accompanying order sheet was labelled with the patient's name, the type of drug analyses requested (amphetamine/methamphetamine, barbiturates, benzodiazepines, cannabis, EDDP/methadone, cocaine and/or opiates), and the type of marker substance that was used. Samples were then sent to the Central Laboratory in Cologne via shuttle service. Prior to shipping, the samples were stored in a refrigerator in a closed room. At the Central Laboratory, order sheets were read by an automatic chart reader. Urine samples were centrifuged and directly transported to the analytical site for determination of marker substances and drug analyses. The cost for the marker and analysis, including sample collection material and transportation to Germany, was approximately 20 Euros per sample.

2.3.2 Traditional supervised test group

Standard direct inspection of patients while urinating was conducted by trained clinical staff. The patients were asked to provide the sample using a test toilet, which had mirrors on the walls to ease supervision. Patients were asked to undress sufficiently, which was determined by the person supervising. After depositing the sample in the test tube, the patient closed the test tube and gave it to the supervisor. The urine was then quickly screen tested in a separate closed room immediately, or later the same day; in the latter case, the sample was stored in a refrigerator before testing. The testing included cannabis, amphetamine, opioids, benzodiazepines, methadone and cocaine. The qualitative immunochromatographic screening test used was from ANL Produkter AB, a Swedish-registered medical device manufacturer, and was supplied by Pragmatic Oy. The cost for one immunological rapid screening test was 7.9 Euros.

2.4 Study measures

Background information included gender, age, and time in treatment. Patient satisfaction with the method used was recorded by the personnel soon after each urine test. A questionnaire was created that included background information,

two questions measuring satisfaction on a 1-6 scale, and the patient's preferred testing system. The questionnaire was given to the subjects at the end of the study period, or earlier if the patient was unlikely to return to treatment during that period, for example, if the patient was in detox treatment.

2.5 Primary and secondary outcomes

The primary outcomes were return rate of the urine samples, detected manipulation of urine samples, and patient satisfaction. The secondary outcomes were patient and staff satisfaction, estimated time used for the sampling and controlling procedure, and economic tradeoff.

2.6 Laboratory analysis of the marker substance, drugs and manipulation

2.6.1 Marker

Polyethylene glycols were determined in urine after a protein precipitation and centrifugation with HPLC. The samples were transferred to a guard column in an automatic dispenser, where most urine components were separated from the markers, which were then transferred onto the actual separating column. After separation, the chromatograms were obtained. Each signal in the chromatogram is characteristic of a polyethylene glycol of a specific chain length. The qualitative test analysis was performed by comparing the samples with Marker C and the controls A and B. The detection limit was at 0.2 ml marker/l urine. False negative results occurred when the time between intake of the marker and delivery of the urine was too short. Delayed excretion of the marker led to a negative result in < 0.5% of the patients, in whom the waiting period was extended to 45 min.

2.6.2 Drug testing

Tests for drug analyses were performed with reagents from Microgenics (Passau, Germany) on an automatic analyzer AU400 from Olympus (Hamburg, Germany). To cleave glucuronic acids from benzodiazepines, 0.3 U-glucuronidase/arylsulfatase from helix pomatia (EC 3.2.1.31 and EC 3.1.6.1; Merck, Darmstadt, Germany) and 0.5 U of a recombinant ß-glucuronidase from E. coli (EC 3.2.1.31; Roche, Mannheim, Germany) in 20 ml of 2 mol/l sodium acetate buffer (pH 4.8) were added to 1 ml urine and incubated for 30 min at room temperature prior to investigating benzodiazepines. Urine samples that were positive were retested on a gas chromatography/mass spectrometry (GC/MS) system (Hewlett Packard, 5790 Series II, connected with a mass selective detector 5972; Hewlett Packard, Palo Alto, USA) according to a previously described procedure[12]. For sample preparation, Bond Elute-Certify (130 mg/3 ml) solid-phase extraction columns from Varian Inc. were used. The extraction procedures were carried out as described in the Certified Methods manual by Varian Germany GmbH, Darmstadt.

2.6.3 Manipulation attempts

Urine samples were further investigated for creatinine, sample check reaction, and sucrose. To measure sucrose concentration, 3 μl of urine were first incubated with 50 μl of 48 μg/ml invertase (46 U/ml) (EC 3.2.1.26) (Sigma, Deisenhofen, Germany, EC 3.2.1.26, Grade VII, 960 U/mg) in citrate/phosphate buffer (pH 4.5). The mixture was incubated at 37° C for 5 min. Then, 350 μl of the glucose reagent [13], prepared as described by Sigma, were added. The absorbance was measured at 505 nm at the beginning and end of a 5-min incubation at 37° C. Calibration was done with

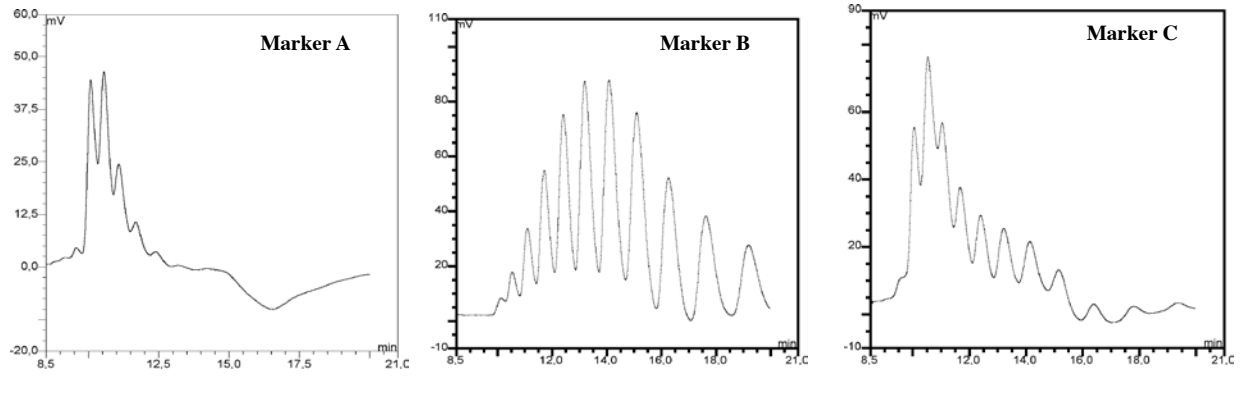

Figure 1. HPLC chromatograms of the three different markers

2–500 mmol/l sucrose solutions. This protocol was applied to an AU400 analyzer. Urine samples that were positive for sucrose were retested for glucose without pre-incubation with invertase by automatic reflex testing. Only samples that were positive for sucrose and negative for glucose were reported as ''positive'' for sucrose.

2.7 Statistical analyses

Subject and staff background information and questionnaire responses were manually entered into a Microsoft Excel spreadsheet and then analyzed using Excel.

2.8 Ethical conduct of study

The study was coordinated by the Department of Mental Health and Alcohol Research of the National Public Health Institute in Finland. The study was approved by the independent Hospital District of Helsinki and Uusimaa, Ethical Committee (permission 347/13/03/00/08). The study was conducted in accordance with the ICH Guidelines for Good Clinical Practice and the 1964 Declaration of Helsinki. All patients were required to have the ability to read and understand the patient information sheet and sign the informed consent. The patients were not paid or reimbursed for participation. Patient data were collected by the treating physician at each treatment site. Data protection was ensured throughout in accordance with the regulations of the National Public Health Institute.

3 Results

3.1 Subject disposition

The subject population comprised 65% males (n = 37) and 35% females (n = 20). There was no gender difference between the two study groups. The mean age was 36 years in the NM test group and 40 years in the TS test group. The average time in treatment was 32.4 months in the NM group compared to 16.5 months in the TS group. In the NM group, one study subject discontinued the study after three samples, and another discontinued the study after three samples but returned to the study 2 days later. Both completed the study questionnaire.

3.2 Unfulfilled urine samples and urine sample return rate

In total, 168 samples were requested; 116 for the NM test group, and 52 in the TS test group. In the NM group, the total return rate was 98.3% (n = 114). When the samples were taken home, which was done in 87% (n = 101) of the NM cases, the return rate was 97% (n = 98) (Fig. 2). In the TS group, all urine samples were returned.

3.3 Urine manipulation

In the NM test group, the marker was missing in only two cases, demonstrating that manipulation attempts occurred in less than 2% of the returned samples. In the TS test group, no manipulation attempts were reported by the supervising employees.

3.4 Patient satisfaction

Of the 57 patients, 53 returned the questionnaire (93%). Subjects were also asked if they had experience with the method to which they had not been assigned during randomization. In the NM test group, 88.8% (n = 32) answered this question, and 87.5% (n = 28) stated that they had also given TS urine samples. In the TS test group, 84% (n = 21) answered the question, and 52% (n = 11) said they had experienced the NM test system.

In the NM group, 94% (n = 31) answered the question of whether "taking the marker was an unpleasant experience", and 83.9% (n = 26) stated that it was not unpleasant. Four study subjects indicated that the marker solution tasted bitter and, therefore claimed it was an unpleasant experience. On a 1-6 point scale (1 being not unpleasant and 6 being very unpleasant), the question "How unpleasant is the waiting time after taking the marker before giving in the urine sample?" was answered by 96.7% (n = 32) of the NM group. The mean score of their answers was 1.9. In the TS group, 84% answered the question "How unpleasant is it to provide a urine sample under supervision?", which was rated on a 1-6 point scale (1 being not unpleasant and 6 being very unpleasant). The mean score of their answers was 2.9.

When asked which method the subjects would prefer, 96.7% (n = 32) of the NM test group answered the question; in this group, 71.9% (n = 23) preferred marker testing, 18.7% (n = 6) supervised testing, and 9.4% (n = 3) had no preference. In the TS test group, 80% (n = 20) answered the question; 60% (n = 12) preferred the marker system and 40% (n = 8) preferred supervised testing (Fig. 3).

In answering the questionnaire, staff members stated that urine sample collection was unpleasant only with the traditional, supervised method due to the low level of patient cooperation or the long urination time.

3.5 Use of work time and employee satisfaction

All personnel members (n = 10) completed the questionnaire, which included 12 multiple-choice questions and two open-ended questions. All employees were experienced in the addiction field and were, on average, 40 years old. All of them had had experience in collecting TS urine tests. In

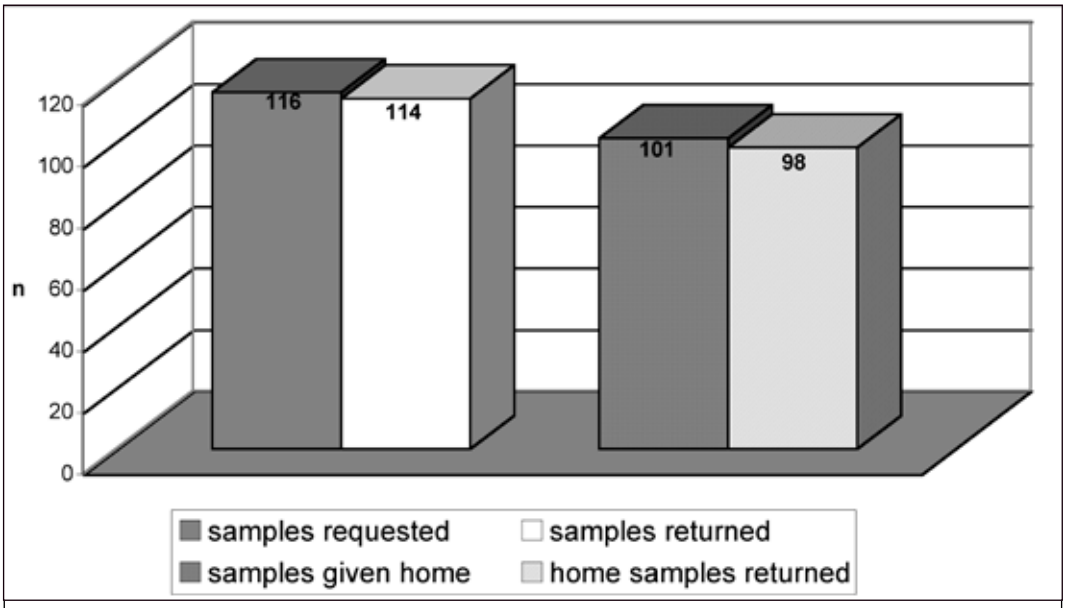

Figure 2. Urine sample return rate in the new marker group

addition, 60% (n = 6) had performed over 20 NM tests, 10% had performed between 10 and 20 tests, 20% had performed between 5 and 10 tests, and 10% had performed less than 5 tests. On a 1-6 point scale (1 being not unpleasant and 6 being very unpleasant), the personnel rated the unpleasantness of preparing and giving the NM test as 1.2 (mean). The unpleasantness of supervising patients (TS group) was rated at 3.4. All employees preferred to administer the NM test.

The employees were also asked to estimate the total average working time (in minutes) that they needed for one urine sample. For TS urine samples, 40% took 5-10 minutes, 50% took 10-20 minutes, and 10% required over 20 minutes. When using the NM test, 30% needed less than 5 minutes and 70% took between 5 and 10 minutes. When asked to

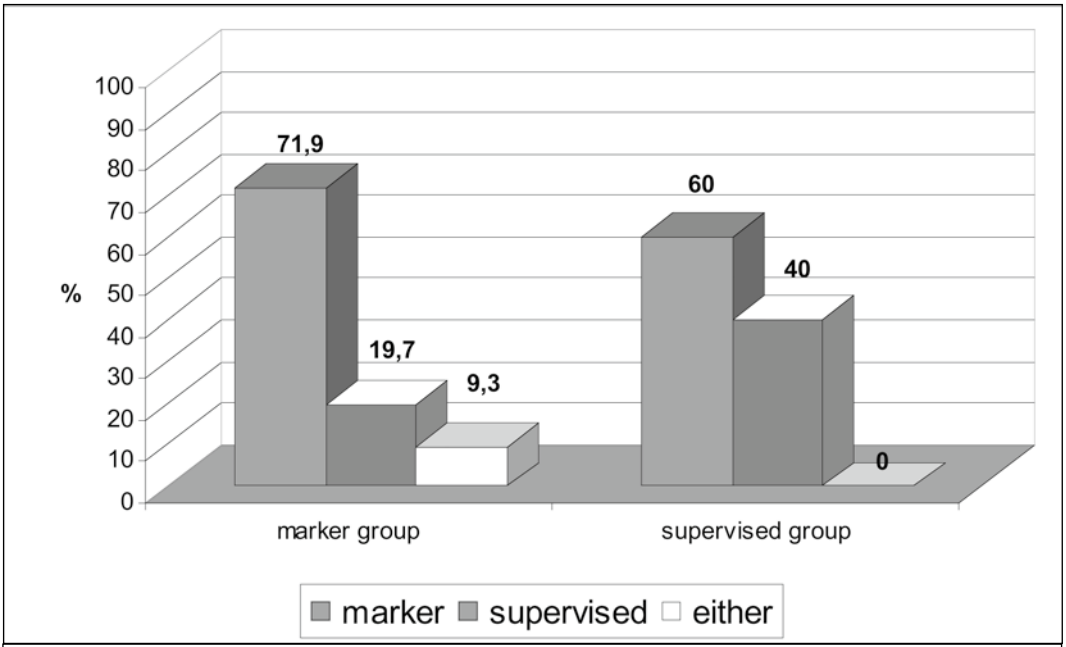

Figure 3. Methods preferred by subjects

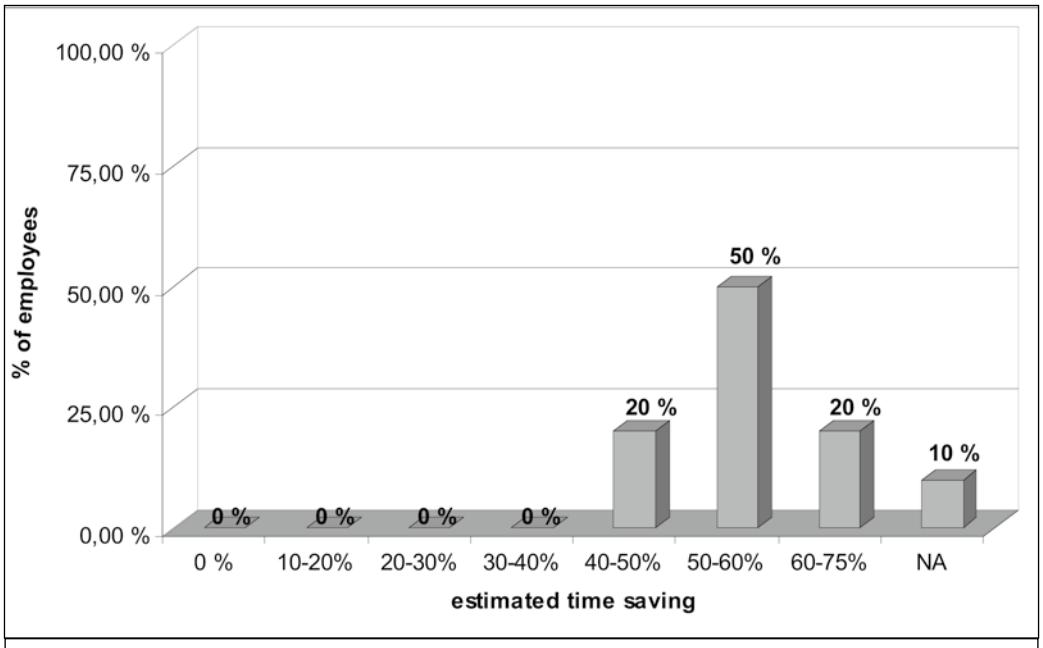

Figure 4. Employee estimation of how much working time was saved by using the new marker method

estimate how much working time the NM test saves, two employees specified a 40-50% time saving, five estimated a 50-60% time saving, and two a 60-75% time saving (Fig 4.). One staff member was unable to estimate the time saved due to limited experience with the method.

Eight employees also commented on the effects of urine testing on the staff-patient relationship. Most (n = 7) stated that TS urine sample testing has a negative impact on openness in therapeutic treatment, especially if the supervisor is also the patient's therapist. Many employees expressed the opinion that supervising may lead to manipulation attempts, due to the mistrust felt by patients. Interestingly, there were several comments that using the NM test also includes a therapeutic element, as the patient is given responsibility for his/her own treatment. A majority of comments referred to the work time saved and ease of applying the NM test.

4 Discussion

The current study has some limitations. The study sample was collected from two different patient groups (maintenance treatment and detox), and may thus have some selection bias. The number of reported attempts at manipulation could be biased, as patients in different phases or treatments have a different motivation to manipulate their urine depending on the advantages they might obtain. The focus of this study, however, was on analysing the risk of manipulation when using the new marker method. As a result, this factor may have had little impact on the outcomes.

Few patients refused to participate in the study. Those who refused expressed the view that the NM test method was complicated, and others were not asked by the treating personnel to participate in the study due to their low cognitive capacity.

In most cases, arranging for the delivery of a urine sample under supervision is an unpleasant experience both for patients and employees; this finding was again confirmed in this study. It is therefore not surprising that most of the patients and all of the employees preferred the NM test. What was surprising was that a certain proportion of patients preferred the traditional supervised urine testing because they felt incapable of adequately providing unsupervised urine samples. One explanation could be that patients are concerned that mistakes could occur (e.g., sample mixing) when the process is not under their control. Another reason why patients may feel concern is that they might make mistakes that would lead to sample testing failure and, therefore, unwelcome consequences during treatment. On the other hand, only two sample collections failed in this study, demonstrating that the real risk of testing failure is very low; this finding may reassure patients.

A large number of patients in the NM test group were allowed to collect the sample outside the treatment unit (87%), and, surprisingly, a high percentage returned the sample without any attempt at manipulation. One major benefit was the working time saved as estimated by the personnel. Because urine testing is quite common, the total

working time saved is clinically significant. For example, when collecting 20 supervised samples (15 min each) every day, the total time taken would be 6 hours (on average), excluding situations when the patients cannot urinate for hours and must be supervised throughout that entire time. With an average time saving as high as 50%, the mean time required would fall to 3 hours. This 3-hour savings can be dedicated to therapeutic work, which is the most significant part of treatment. The time saved should therefore have a positive impact on treatment outcomes.

In calculating the total costs of the different methods, the new marker system clearly involved a greater expense than fast immunological drug-screening methods. Even so, considering the ethical problems arising from supervised urine sampling and the opportunity created for employees to concentrate on therapeutic work, however, it is hard to attribute a value and calculate the costs. This should be taken into account when considering the higher costs of marker drug testing.

In conclusion, the new marker urine test appears to be favoured compared to the traditional supervised urine testing. The patients preferred the NM method, and, because of this, there was also greater compliance. Because most samples can be collected by the patient outside the clinic, the personnel can focus on treatment rather than supervising non-therapeutic urine sampling. This shift in duties could have positive effects on treatment outcomes and save resources. When considering the NM test, the patient must have sufficient cognitive ability to handle the tasks of taking, storing, and returning the sample. For patients affected by certain psychiatric comorbidities that result in, for example, instability, high insecurity, or suspicions, TS urine sampling may be the better choice. In addition, when instant results are needed, saliva tests could be used; however, they have their own limitations. Nonetheless, the new marker testing technique could become the first choice in most cases.

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Authors' contributions

KS planned the study design, collected the patient data, and analyzed the data; KS drafted and revised the manuscript; KS and HA finalized the manuscript; and both authors read

and approved the final version.

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