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Evaluation of a novel in-vitro diagnostic device for the detection of urinary tract infections in diaper-wearing children

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Summary

QUESTIONS: Is the novel in-vitro diagnostic device U-Test® reliable and secure for urine collection in diaper-wearing children and simultaneous evaluation of the urine collected for the presence of leucocytes and nitrite?
METHODS: The qualitative and functional performance of U-Test® was evaluated in a multicentre prospective clinical trial. The diagnostic performance of the novel in-vitro diagnostic device was determined in reference to the established procedure involving urine sampling by urine-bag, clean-catch, catheterisation and suprapubic aspiration followed by dipstick analysis and urine culture, and in an in-vitro study.
RESULTS: U-Test® proved to be comfortable and secure for the child and well accepted by the persons responsible for the participating children. No undesired side-effects were seen and in 75.8% (95% CI ± 10.5%; n = 66) of the tests used, enough urine was collected within the permitted time for immediate and successful urine analysis by the integrated test card. Diagnostic performance was found to be comparable to the established procedure using dipstick analysis (leucocytes: κ-coefficient 0.86; nitrite: κ-coefficient 0.74; n = 150). Sensitivity of the U-Test® for leucocyte detection was found to be 96.7% and specificity 100.0%. For nitrite detection sensitivity of 90.0% and specificity of 98.3% were found.
CONCLUSIONS: The evaluation shows that U-Test® is a safe and reliable device of high functionality and diagnostic performance for the detection of leucocytes and nitrite directly and without time delay in a child's diaper. This statement is based on a comprehensive comparison of the novel device with accepted diagnostic test systems and procedures based on the same dry chemistry technology. Due to its simplicity of use, U-Test® can be considered an alternative to the cumbersome procedures of urine collection by the bag-method or clean-catch followed by dipstick analysis for the presence of leucocytes and nitrite.

Key words: *urinary tract infection; diaper-wearing children; urine collection; diaper; leucocytes; nitrite; dry chemistry technology*

Introduction

Urinary tract infection (UTI) is a common condition in children. Approximately 1 in 10 girls and 1 in 30 boys will have a UTI by the age of 16 years [1]. The risk of renal scarring as a result of a UTI is higher in children than in adults, and, if repeatedly undiagnosed and not appropriately treated, UTI may lead to hypertension, decreased renal function, proteinuria and end-stage renal diseases [2].
In fact UTI is a most challenging condition in primary care of children, since in the early stage the symptoms may be minimal or not very specific. Additionally, urine samples are difficult to obtain [2].
Generally speaking there are various accepted strategies for urine collection in children, as outlined in the different national clinical practice guidelines and recommendations. In 2008 the expert group for paediatric nephrology in Switzerland (SAPN) published their recommendation for the treatment of UTI in children [3]. The authors point out that the use of urine collected by bag in children aged below 12 months is only significant if the urine culture is negative. Generally speaking, suprapubic aspiration and catheterisation is the "gold standard" to be used with small children. In children aged over 12 months urine collection by bag is acceptable. The NICE guidelines of 2007 [4] do generally recommend trying to obtain a clean-catch urine specimen, followed by other non-invasive strategies such as urine collection pads. Only if urine-sampling by non-invasive strategies does not prove successful should catheterisation and suprapubic aspiration be considered. In 2011 the American Academy of Paediatrics published an update of the clinical guideline for diagnosis and management of the initial UTI in febrile infants and children of 2–24 months [5]. The authors recommend deciding on the urine collection methodology on the basis of the physician's judgement of the urgency of antibiotic therapy. If antibiotic therapy is not urgent urine collection by bag for urinalysis is acceptable. Urine samples for urine culture purposes should be collected by catheterisation or suprapubic aspiration.
At the non-potty-trained age the paediatrician or general practitioner usually prefers the urine-bag method or, if possible, collection of a clean-catch sample. Catheterisation

and suprapubic aspiration are commonly used by hospital wards and emergency departments [6]. There is little literature evaluating a urine collection pad [7–10], which is generally preferred by parents due to its comfort and ease in use [11].

As a rule clinical guidelines recommend doing a urine culture for the final diagnosis of a urinary tract infection. If a child presents in a condition which does not require immediate antimicrobial therapy, urinalysis by dipstick and microscopy are acceptable to support a UTI diagnosis, taking into account the limitations of the methods as outlined in the different clinical guidelines [3–5]. Various methods are available for in-depth follow-up to diagnose the site of infection; e.g. pyelonephritis [6].

The aim of the study was a prospective performance and functionality evaluation of a novel in-vitro diagnostic device, U-Test® (fig. 1), which combines a self-adhesive fleece pad for urine collection in diaper with a diagnostic test card for the detection of leucocytes and nitrite. In a third indicator-field in the test card it is possible to judge the validity of the test performance. All indicators are based on the well established and accepted dry chemistry technology as found in various marketed dipsticks, which are frequently used by healthcare professionals for urine analysis. The design of U-Test® facilitates guidance of the voided urine by a fleece fabric directly to the diagnostic indicators for immediate processing of the chemical reaction. The indicators are included in the integrated test card which automatically seals off after sufficient urine for the indicator reaction has entered. This test design avoids incubation of the urine between voiding and diagnostic assessment, and therefore alteration of the urine sample due to incubation in the child's diaper. The stability of the test results is shown in the in-vitro study described in the methods and results section.

The novel in-vitro diagnostic device is intended to enable easy and comfortable evaluation for the possibility of a present UTI directly in the babies' diaper. The clinical and in-vitro studies were done in order to evaluate the potential of U-Test® for use as an alternative strategy to urine collection by bag or clean-catch followed by dipstick-analysis, in children presenting in a condition for which the physician finds these methods appropriate.

Methods

The multi-centre study was conducted at the Children's Hospital Lausanne (CHUV) and 15 private paediatrician's offices in Lausanne and surroundings. The study design was approved by the Ethical Committee of the Canton of Vaud and by Swissmedic.

Figure 1

The front side of U-Test® facing the patients' body is shown on the left side. On the right side the back side of U-Test® is shown with the adhesive tape serving to fix the device into the baby's diaper.

The functionality and wearing comfort of the test device was evaluated with diaper-wearing children under the age of five for whom written consent for participation was given by the authorised person, who is responsible for and taking care of the child. Children presenting at the hospital or at the private doctor's office with an indication for urine diagnosis for UTI first underwent the diagnostic procedure, on which the physician in charge decided according to the condition in which the child presented. The physicians included mid-stream clean catch, urine bag, catheter or suprapubic aspiration for urine collection, followed by dipstick urine analysis and urine culture, if considered appropriate. Either Combur^{10} Test® (Roche Diagnostics GmbH) or Multistix® 10 SG (Siemens Healthcare Diagnostics Inc.) were used and read automatically (Clinitek status® reader; Siemens AG) or manually.

The genital area of the child was then washed and a new diaper attached to the baby in which the U-Test® device was fixed. The diaper was removed again after three hours at the latest. If urine was visible and faeces were not present or present to an extent allowing the test to be read, the test results were interpreted either by a medical professional or by the lay person responsible and taking care of the child. If micturition did not occur within three hours, a second test could be administered and the procedure repeated.

Evaluation of the test card results involved reading the validity indicator, showing that enough urine had entered the test card and therefore ensuring reliable results for the other indicators. Thereafter the result for the leucocyte and nitrite indicators is read. All indicators give a qualitative result, confirming the presence or absence of the analytes. The result of the novel test device was compared to the result in the reference procedure and, if available, to the results of the urine culture.

The diagnostic performance of the novel test device was also assessed in an in-vitro study. This was done in view of the fact that the required design of the clinical study did not allow investigation of the same urine sample with the reference method and U-Test®, the device under evaluation. Since two consecutively collected urine samples would have to be compared for determination of the diagnostic performance parameters, the results would not have been unambiguous since natural differences in the urine status would be considered as incorrect performance of the U-Test®.

Samples of pool-urine were prepared, containing various concentrations of the analytes. Those samples were used to assess the sensitivity, specificity and accuracy of U-Test®. Nitrite was added to the pool-urine as $NaNO_2$ (Sigma Aldrich Co.) in the appropriate concentrations. Leucocyte esterase, the enzyme with which the leucocytes are indirectly detected by dry chemistry technology, is available as lyophilized standard material (Analyticon® Biotechnologies AG) and was handled according to the supplier's instructions. The correct preparation of the various urine samples was confirmed by their examination by Multistix® 10 SG (Siemens Healthcare Diagnostics Inc.) and automatic reading by a Clinitek status® reader (Siemens AG) done by the monitor of the in-vitro study.

Lay-people, students from the Lausanne area, were asked to perform the assessment of the reference method and the U-Test® using the prepared urine samples. The participants did not have knowledge of the urine samples' composition and were not experienced in the handling of dipsticks and U-Test®. Combur^{10} Test® dipsticks (Roche Diagnostics GmbH) were used as a comparative device. To avoid biased reading a participant would not do more than one test for each urine sample. Both test devices were read by eye. The reference chart on the box of the Combur^{10} Test® dipsticks was used for interpretation of the results. In U-Test® the interpretation chart is integrated into the test card. Performance of both methods was assessed in reference to the Multistix® 10 SG reading.

Results

Figure 2 shows the results of the clinical study. 75 test devices were used and for none of the applied tests were undesired effects such as skin irritation and wearing discomfort reported. 37% of the babies included in the study were boys and 63% girls. Also, 63% of the babies included were aged below 1 year. The average age of the babies was 0.9 years (maximum 3.2 years and minimum 9 days). However, 6 report forms were excluded from evaluation due to non-adherence to the study-protocol. In 18 of the applied tests stool was present at the time of evaluation. For 66 tests administered information was provided on the presence of urine within the permitted application duration of 3 h. The application duration of maximum 3 h was sufficient in 57 applications to collect urine, while in 9 applications micturition did not occur during this period. The mean application duration of U-Test® was 103 minutes with a minimum of 10 min and a maximum of 180 minutes. Exact duration from micturition to reading of the test could however not be assessed. For 56 applied tests the information about the reading of the validity indicator was given on the report form. The validity indicator showed a posit-

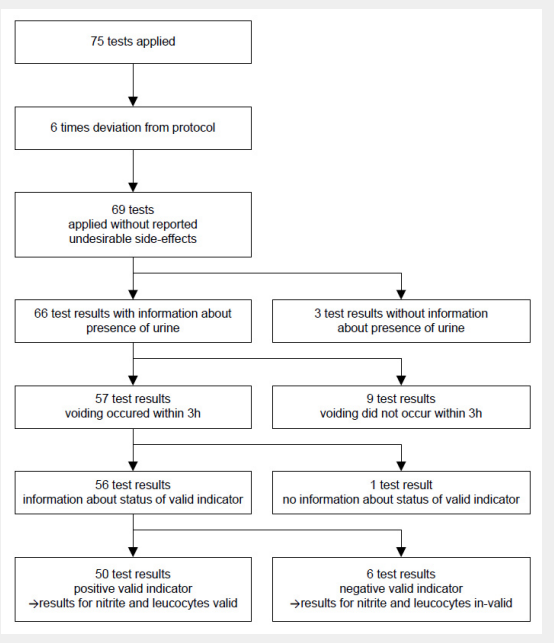

Figure 2

Results of the clinical study for the qualitative parameters evaluated.

ive result in 50 of the applied tests, meaning that enough urine entered the test card, and therefore test results for nitrite and leucocytes were also valid. In summary the clinical evaluation showed that in 75.8% (95% CI ± 10.5%) of applications urine is present within the permitted application duration of 3 hours and the conduct of the test is correct according to a positive validity indicator.

The diagnostic performance of U-Test® within the clinical study in comparison to the dipstick results (Combur[10] Test® and Multistix® 10 SG) is shown in table 1. In total 42 patients had urine consecutively collected and evaluated by dipstick (24 negative for both nitrite and leucocytes; 18 positive for either one or both nitrite and leucocytes) and U-Test®. If the U-Test® was administered without indication for urine collection, the procedure for reference urine collection was not done and only qualitative parameters were assessed. For 35 children, the physician in charge decided on the bag-method to be the most appropriate for urine collection and therefore represents the vast majority. Suprapubic aspiration was employed once, midstream-catch twice and catheterisation for four of the patients.

U-Test® proved to exhibit a sensitivity of 71.4% for nitrite and 82.4% for leucocytes. The specificity of U-Test® was found to be 85.7% for nitrite and 76.0% for leucocytes. The κ-coefficient for nitrite detection is 0.57 and for leucocyte detection 0.67. All values are determined in reference to the dipstick results by the study centres. In addition to the fact that two consecutively collected urine samples had to be evaluated, the limited number of 42 samples must be taken into consideration in rating the results.

According to the physician's decision, for 25 of the conventionally collected urine samples an additional urine culture was done (11 positive and 14 negative). A positive urine culture was considered to be equal to a present urinary tract infection. The results of the dipsticks and U-Test® readings were considered to be true positive if nitrite and/or leucocyte indicators were positive in case of a positive urine culture. If both, the nitrite and leucocyte indicators, were negative the result would be true negative in case of a negative urine culture. The performances of the dipsticks and U-Test® based on urine culture as reference method are shown in table 2. The performance of the devices shows a high level of agreement in reference to urine culture, which is verified by a κ-coefficient of 0.80 [12]. The results also show that the dipsticks and U-Test® were suitable to rule out a urinary tract infection safely, since none of the samples was found to provide a false negative result for either of the devices. However, the limited number of 25 samples should be taken into consideration.

The in vitro study comprised 150 prepared urine samples, containing various concentrations of nitrite and leucocytes (table 3). U-Test® was read 30 min and 180 min after urine application. The reading of Combur[10] Test® dipsticks was done according to the time requirements specified in the instructions for use.

Detailed results of the diagnostic performances of U-Test® and Combur[10] Test® for the detection of nitrite are shown in table 4 and the results for the detection of leucocytes are given in table 5, both based on the results of Multistix® 10 SG as reference values. The agreement of the two devices in their diagnostic performance is reflected in a κ-coefficient of 0.86 for the determination of nitrites and 0.74 for the determination of leucocytes. If the κ-coefficient is calculated in reference to Multistix® 10 SG independently for the two tested devices, U-Test® shows a coefficient of 0.87 for the determination of nitrite and 0.97 for the determination of leucocytes. Combur[10] Test® exhibits a κ-coefficient of 0.99 for the determination of nitrite and 0.76 for the determination of leucocytes. The statistical significance of the differences seen in the diagnostic performance between the two devices was evaluated by a two-sided t-test (tables 4 and 5). Results of U-Test® for reading of the leucocyte indicator 30 minutes after urine application shows a statistically significantly closer agreement with the reference values than the Combur[10] Test®. The contrary can be found for nitrite detection. All false negative nitrite results of U-Test® are found within the cut-off range. Exclusion of those samples from calculation results in identical performance by the two test systems.

Reading of U-Test® 180 minutes after urine application does result in a less significant difference in the performance parameters for the detection of nitrite, meaning that fewer false negative results are generated. In contrast, the specificity of U-Test® for the detection of leucocytes does decrease due to more false positive results. However, all samples with a false positive result do contain 15 L/µl, which is within the cut-off range of the leucocyte indicator. In fact, the most significant difference in diagnostic performance of the three devices compared was found in the cut-off region for determination of leucocytes. A preset difference due to design of the test devices can be observed. Due to the differences in sensitivity of the cut-off range for leucocyte detection by the two dipsticks, the performance of U-Test® is more in agreement with either of the systems depending on the reading time.

Discussion

Despite the recommendation by the clinical guidelines of catheterisation and suprapubic aspiration as the gold standard for urine collection in small children, in this study the physicians decided on urine collection by bag as the most appropriate strategy for the majority of patients. 60% of the urinalysis by dipstick was backed up by urine culture. This

Table 1: Performance parameters of U-Test® determined in the clinical study based on the reference of Combur[10] Test® and Multistix® 10 SG (both were used) and two consecutively collected urine samples for each participant.

n = 42	Nitrite	Leucocytes
sens. %	71.4	82.4
spec. %	85.7	76.0
acc. %	83.3	78.6
κ-coeff.	0.57	0.64

n = total number of samples; sens. = sensitivity; spec. = specificity; acc. = accuracy.

deviation from the general recommendations by the clinical guidelines was reported before and is therefore not uncommon, but displays the status in practice and may be related to the patient population of this study [2, 6, 13].

The demand for an easy and comfortable method for urine collection in the child's diaper was already discussed previously [11]. The use of a urine pad for urine collection is also discussed in the NICE guidelines of 2007 (National Institute for Health and Clinical Excellence, Great Britain) [4]. The guideline points out that the urine pad is used as alternative to urine-bag and clean-catch urine collection, since those procedures often fail for urine collection in very small children. Despite the use of urine collection pads in practice in Great Britain, thus far few data are available on this methodology. Thus recommendation of the urine pad for urine collection in small children by the NICE guidelines is so far not based on scientific evidence, but rather on general practical experience. The novel device U-Test® is a step towards easy and direct urine collection combined with the immediate evaluation of urine for the presence of nitrite and leucocytes.

Besides their ease of use, urine collection pads were evaluated for the suitability of urine collected by this method for urinalysis. It was found that leucocytes and blood cells are destroyed by the pad material. But the concentrations of leucocyte esterase and blood, both determined by dipstick, were not altered [7, 14]. These results could be verified in this study, since in-vitro evaluation of U-Test® in comparison to Combur^{10} Test® and in reference to Multistix® 10 SG showed comparable diagnostic performance amongst these test systems. If retention or alteration of the analytes in the pad materials of U-Test® had occurred, the diagnostic performance parameters of the test system evaluated would not have shown such high compliance with the established reference methods.

The suitability of the dry chemistry technology applied in dipsticks for the diagnosis or exclusion of urinary tract infections in children was thoroughly evaluated in a meta-analysis conducted by Whiting et al. including 38 studies. The sensitivity for nitrite detection was generally found to be poor, with values of 16.2% to 88.1%. On the contrary, specificity was found with high values of 75% to 100% and only two values below 90%. Specificity (69.3% to 97.8%)

Table 2: Performance parameters of U-Test® and the dipsticks determined in the clinical study based on the result of the urine culture as reference method.

n = 25	U-Test®	Dipstick
sens. %	100.0	100.0
spec. %	78.6	85.7
acc. %	88.0	92.0
κ-coeff.	0.80	

n = total number of samples; sens. = sensitivity; spec. = specificity; acc. = accuracy.

Table 3: Constitution of urine samples evaluated in the in-vitro study by Multistix® 10 SG (SM), which served as reference method for the comparative evaluation of the performance parameters of U-Test® (UT) and Combur^{10} Test® (CT). For UT and CT the general interpretation of such values is given as according to the supplier.

Nitrite [mg/l]	Number of samples	SM	UT	CT	Leucocytes [L/µl]	Number of samples	SM	UT	CT
0	60	–	–	–	0	60	–	–	–
0.75	30	+	+	+	15	30	trace	+	+
1.5	30	+	+	+	25	30	+	+	+
2	30	+	+	+	75	30	+	+	+

Table 4: Performance parameters for the detection of nitrite by U-Test® (UT) and Combur^{10} Test® (CT) determined in the in-vitro study based on the result of the Multistix® 10 SG as reference method and the two-sided significance (p) in differences between the two tests.

Nitrite								
n = 150	CT (1)	UT 30 min (2)	p_1-p_2	p	CT (1)	UT 180 min (3)	p_1-p_3	p
sens. %	100.0	90.0	0.10	0.002	100.0	93.3	0.67	0.012
spec. %	98.3	98.3	0.00	1.000	98.3	100.0	–0.02	0.315
acc. %	99.3	93.3	0.06	0.005	99.3	96.0	0.03	0.055
κ-coeff.	0.86				0.91			

n = total number of samples; sens. = sensitivity; spec. = specificity; acc. = accuracy.

Table 5: Performance parameters for the detection of leucocytes by U-Test® (UT) and Combur^{10} Test® (CT) determined in the in-vitro-study based on the result of the Multistix® 10 SG as reference method and the two-sided significance (p) in differences between the two tests.

Leucocytes								
n = 150	CT (1)	UT 30 min (2)	p_1-p_2	p	CT (1)	UT 180 min (3)	p_1-p_3	p
sens. %	95.0	96.7	–0.02	0.648	95.0	100.0	–0.05	0.078
spec. %	81.1	100.0	–0.19	0.0001	81.1	70.0	0.11	0.082
acc. %	86.7	98.7	–0.12	0.001	86.7	82.0	0.05	0.266
κ-coeff.	0.74				0.73			

n = total number of samples; sens. = sensitivity; spec. = specificity; acc. = accuracy.

for the determination of leucocytes was generally higher than sensitivity (37.5% to 100%) [6]. Generally, dipstick analysis is considered to supplement the clinical information, helps to answer the question whether a child has a urinary tract infection and can be used to guide treatment. If both indicators, leucocytes and nitrite, do show a negative result, the dipstick is reported to be sufficient to rule out a UTI (specificity of 96%). In contrast, if both indicators do show a positive dipstick result, the presence of a UTI is highly likely (sensitivity 88%) and can be incorporated to initiate the appropriate additional diagnostic measure and treatment. Dipstick analysis is considered to be suitable for a rapid initial answer and to reduce the number of unnecessary urine cultures [6, 15–22]. Some publications point out that the dipstick result shows a lower performance for young children aged below 2 years than in older children. Nevertheless, it is regarded as a useful tool in diagnostic strategy if results are backed up with additional diagnostic measures [4, 15, 17, 23–25]. The sensitivity and specificity of U-Test® calculated in this in vitro study are at the upper limit of the value range published in Whiting's meta-analysis.

Reading of U-Test® after 30 min is considered to be most representative, since reading after 180 min would mean that micturition occurs immediately after U-Test® is administered and the diaper is only checked after 3 h, the maximum permitted application duration in this study. This is a highly unlikely scenario, as proven by the average application duration of 103 minutes as found in the clinical trial. In addition, the healthcare personnel or the person taking care of the child is actually waiting for the test result and will therefore watch the child closely to recognise the occurrence of micturition if possible and therefore obtain the result as soon as possible. This means that the performance of U-Test® is best described by the sensitivity, specificity and accuracy found for the reading after 30 min.

In summary, prospective evaluation of U-Test® in its application for the detection or exclusion of urinary tract infection in diaper-wearing children shows that the diagnostic performance of the novel device is equal in practice to the currently accepted procedure, which is a combination of a urine collection by urine bag, clean-catch, catheterisation or suprapubic aspiration and urinalysis by dipstick. The advantage of U-Test® in comparison to the currently used procedure is its ease of use, comfort for the child and the healthcare professional with regard to urine collection, immediate evaluation for leucocytes and nitrite without time delay and incubation times, and no mandatory reading times due to the stability of the test results. The fact that U-Test® is suitable for reading by lay people, offers further convenience, since the child does not have to stay in the doctor's office until urine sampling is successful. The person taking care of the sick child can check the test if micturition occurred and report the result to the doctor, who is then able to decide on the required subsequent steps.

The major inconvenience of the U-Test is that in the case of a positive result, further urine collection will generally be required in order to obtain a urine culture and identification of the pathogen.

Due to the performance characteristics of U-Test®, its use could be considered as a reliable and convenient alternative to the currently common practice for the assessment of a diaper-wearing child with suspected UTI. The clinician would judge the appropriateness of the method according to the condition in which the child presents, and needs to bear in mind that the negative predictive value of dry chemistry tests is not 100%.

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Figures (large format)

Figure 1

The front side of U-Test® facing the patients' body is shown on the left side. On the right side the back side of U-Test® is shown with the adhesive tape serving to fix the device into the baby's diaper.

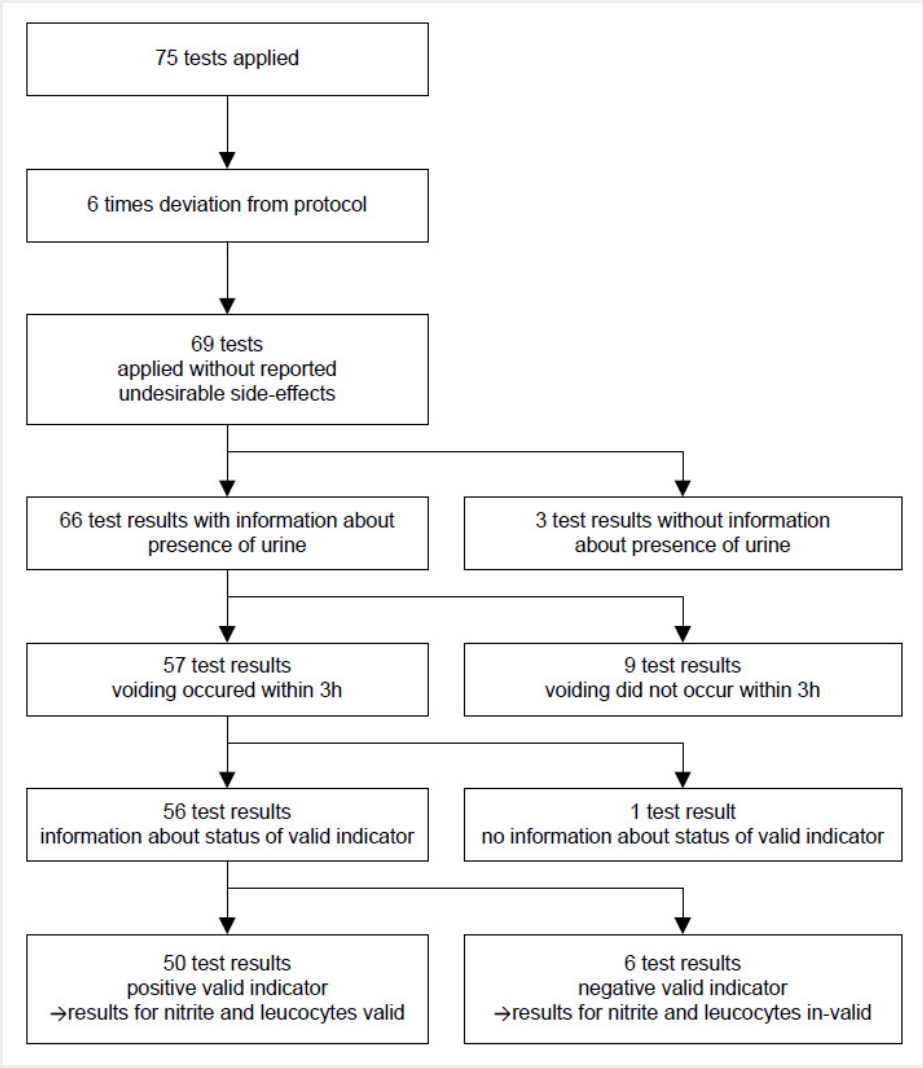

Figure 2

Results of the clinical study for the qualitative parameters evaluated.