Comparative Evaluation of Urine Reagent Strip Analytical Sensitivity for Leukocyte Esterase as an Indicator of Urinary-tract Infection

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Introduction

Pyuria, the presence of leukocytes in urine in significant numbers, is frequently indicative of a urinary-tract infection (UTI).[1] Neutrophilic leukocytes present as a result of a UTI release of leukocyte esterase (LE) into the urine, which can be easily screened for in multiple patient settings using readily available reagent strips from Siemens Healthineers and other commercial vendors.

An LE urine strip test semiquantitatively reports an amount of the enzyme in the urine proportional to the leukocyte concentration, represented by intensity of color on the test pad. Siemens Healthineers LE strip test results range from negative to differing levels of positive, including 1+, 2+, and 3+; the latter corresponds to approximately 500 cells/µL. Normal urine specimens usually generate a negative result with an LE value of less than 10 cells/µL.[2] Other manufacturers may use different indicators of results.

UTIs are relatively common; they account for as many as 8.1 million visits to healthcare providers in the U.S. every year.[3] Many UTIs are not serious if treated promptly. However, untreated infections can rapidly spread to the kidneys and cause the more-serious condition of acute pyelonephritis (APN).[4] There are around 250,000 cases of APN in the U.S. each year[5] that incur direct and indirect costs estimated at $2.14 billion.[6]

Screening for a UTI with a strip test is regarded as the physician's first recourse for initial patient evaluation.[7] A urine strip test provides an immediate result and, if accurate and reliable, can accelerate the path to diagnosis and appropriate treatment.[8] It follows that screening for LE, commonly in parallel with nitrite, on first patient assessment when UTI is suspected requires a dependable strip test.

Anecdotal reports suggest that not all commercially available LE strip tests may be robust and sensitive predictors of UTI, with underestimated and even false-negative results being found. As observed above, such results may lead to missed diagnoses, and a lack of immediate treatment can potentially result in ER visits if the patient's condition worsens. As well as affecting the quality of patient care and well-being, inaccurate urine strip results can add to an organization's cost burden if hospitalization is subsequently required for a more-advanced patient condition such as APN.

Summary

Advances in technology have led to the development of instrumentation and data-management solutions that automate the testing and reporting of results in urinalysis. These systems standardize the process by eliminating operator variability and possible risk of transcription errors.[9]

The study reported in this white paper made a comparison of four manufacturers' urine reagent strips and their reading devices, if available, targeting LE determination on both nonclinical controls and clinical urine specimens.

Multistix® 10 SG Reagent Strips from Siemens Healthineers semiquantitatively report LE and can be read on the CLINITEK Status®+ Analyzer without the subjectivity of visual color pad interpretation. More-recently introduced urine strip tests on the market offering semiquantitative LE determination and result interpretation include Clarity Diagnostics CLA-URS 10 UROCHECK strips that can be read on the Clarity UROCHECK 120 analyzer, Teco Diagnostics URS-10 strips that can be read on the TC-201 analyzer, and YD Diagnostics URISCAN 10 SGL strips that can be read on the URISCAN OPTIMA II analyzer. The Teco Diagnostics TC-201 analyzer was not available for this study.

Results demonstrated that Multistix 10 SG Reagent Strips exhibit greater analytical sensitivity for LE with nonclinical control samples than the other strips tested in this study when used in a laboratory environment. Testing with patient urine specimens encompassing a common LE reporting range confirmed this greater analytical sensitivity compared to the other strips when clinical samples are tested. These findings have implications in the point-of-care (POC) setting, where treatment decisions and clinical outcomes are highly dependent on the accuracy of initial diagnostic screening.

SIEMENS Healthineers

Multistix 10 SG Reagent Strips Report Leukocyte Esterase

Multistix 10 SG Reagent Strips can be used as an integral part of well-established POC solutions that provide disease insight through urinalysis testing. Test results indicated by color intensity on multiple pads after dipping in urine can be interpreted visually. Instrument-read test pad results on Siemens Healthineers systems including the CLINITEK Status+ Analyzer are more consistent, as they have been shown to eliminate timing errors and the variability of subjective color interpretation. Multistix 10 SG Reagent Strips report 10 clinically actionable urinary parameters: glucose, bilirubin, ketone, specific gravity, blood, pH, protein, urobilinogen, nitrite, and leukocyte esterase

Multistix 10 SG Reagent Strips Can be Interpreted Visually and/or Read on the CLINITEK Status+ Analyzer

Comparing different manufacturers' LE test pad results
There are challenges when correlating LE test pad results from different manufacturers' reagent strips, as different indicator systems are used. For visual reads, not all manufacturers' strip bottles provide the same information. Table 1 standardizes visual-read levels on a common reporting scale from 0 to 4 for information taken from Siemens Healthineers, Clarity, Teco, and YD test strip bottles. This includes block indicators, the Plus system, and cells/µL.

Siemens Healthineers reagent strips report using block indicators, the Plus system, and cells/µL, depending on country requirements. Clarity Diagnostics strips report using cells/µL and the Plus system. Teco Diagnostics provides all three measures. YD Diagnostics reagent strips report LE using cells/µL only and do not offer an equivalent to a 2+ (moderate) color block on the bottle.

The CLINITEK Status+ Analyzer can be set to report on the block indicator scale, cells/µL, or the Plus system, depending on country requirements. The Clarity UROCHECK 120 analyzer reports using both cells/µL and the Plus system. The YD Diagnostics URISCAN OPTIMA II analyzer reports using cells/µL and the Plus system. However, the YD Diagnostics analyzer does not offer an equivalent to a 2+ reporting level. Two YD analyzer reporting levels (10 and 25 cells/µL) are in the trace range of the other reagent strip types (Table 2).

It should be noted that reagent strip results exhibiting one-block or equivalent variance, whether read visually or by instrument, are considered to be equivalent indicators of the true LE amount in a control or clinical specimen.[2] A block shift* of more than one block is highlighted in the tables on the next page.

*Block shift is a term used to describe when observed test pad color intensity is less or more than expected, corresponding to a lower or higher block level result on the common reporting scale.

Table 1. Visually read LE test pad results on a common scale and their indication of measure.

Standardized Visual-read LE Level	Multistix 10 SG Reagent Strips			Clarity CLA-URS10 Reagent Strips		Teco URS-10 Reagent Strips			YD URISCAN 10 SGL Reagent Strips
	Block Indicator	Cells/µL	Plus System	Cells/µL	Plus System	Block Indicator	Cells/µL	Plus System	Cells/µL
0	Negative	0	NA	0	NA	Negative	0	NA	NA
1	Trace	15	NA	15	±	Trace	15	NA	25
2	Small	70	+	70	+	Small	70	+	75
3	Moderate	125	++	125	++	Moderate	125	++	NA
4	Large	500	+++	500	+++	Large	500	+++	500

To enable comparison of instrument-read LE test pad results, reporting information derived from analyzer printouts was related to the 0–4 common reporting scale.

Table 2. Instrument-read LE test pad results on a common scale, and their indication of measure.

Standardized Instrument-read LE Level	Multistix 10 SG Reagent Strips Read on the CLINITEK Status+ Analyzer			Clarity CLA-URS10 Reagent Strips Read on the UROCHECK 120 Analyzer		YD URISCAN 10 SGL Reagent Strips Read on the OPTIMA II Analyzer	
	Block Indicator	Cells/µL	Plus System	Cells/µL	Plus System	Cells/µL	Plus System
0	Negative	0	NA	0	NA	0	NA
1	Trace	15	Trace	15	±	10–25	±
2	Small	70	+	70	+	75	+
3	Moderate	125	++	125	++	NA	NA
4	Large	500	+++	500	+++	500	+++

Methods

Nonclinical controls

Multistix 10 SG, Clarity CLA-URS10, Teco URS-10, and YD URISCAN 10 SGL reagent strips were assessed both visually and on their respective analyzers, where available, for semiquantitative determination of LE using controls containing known amounts of leukocyte esterase. Control solutions of known concentrations of LE were prepared according to internal procedures used for product release of the CLINITEK Status+ Analyzer. Each strip type was tested in duplicate on a negative and an LE solution corresponding to a positive 2+ result according to manufacturers' instructions.

Clinical specimens

62 unaltered clinical urine specimens were tested. Specimens obtained from the Elkhart Clinic (Elkhart, Indiana)[10] were verified as containing LE across the common reagent strip reporting range according to Arkray AUTION ELEVEN AE-4022 reagent strips. Negative specimens were obtained from a local donor pool. All four reagent strip types were tested in single replicates. Testing was performed visually by comparing LE test-pad color intensity after dipping to the color chart on the respective manufacturers' bottle. Reagent strip results were also instrument-read† on the respective manufacturers' analytical device. Agreement tables were assembled from results interpreted as 0–4 block levels. Results were not compared to the reporting method used at Elkhart Clinic due to potential sample instability by the time the samples were used in the study.

In addition, five clinical urine specimens positive for LE were subject to titration through dilution with LE-negative urine specimens to further assess the analytical capability of each reagent strip, both visually and on their respective analyzers. Each strip type was tested in duplicate for all dilutions with exception of the LE-negative sample, in which only one replicate was performed. Receiver operating characteristic (ROC) curves were generated for visual and automated results for each manufacturer as well as comparative ROC curves for visual and automated readings.

†The Teco Diagnostics TC-201 analyzer was not available for this study.

Results[11]

Nonclinical controls

When read visually, all four manufacturers' reagent strips reported the negative control solution acceptably. Similarly, all reagent strip types reported a 2+ positive control within acceptable variation of one block, with Multistix 10 SG Reagent Strips reporting a 2+ and all other strips reporting one block lower (Table 3).

When instrument-read, all reagent strips tested reported the negative control accurately. Multistix 10 SG and Clarity reagent strips reported the 2+ control solution within acceptable limits. YD Diagnostics reagent strips read on the OPTIMA II analyzer underestimated the 2+ positive control by two blocks, reporting as ±, equivalent to level 1 rather than the target 3 on the standardized scale (Table 4).

Visually read clinical specimen results

When read visually, Clarity, Teco, and YD reagent strip results on clinical specimens showed overall exact agreements of 85.4%, 24.1%, and 48.3% respectively with Multistix 10 SG Reagent Strip results (Tables 5–7).

Visually read Clarity CLA-URS10 clinical specimen test result agreement with Multistix 10 SG Reagent Strip results was relatively good, demonstrating accordance with the results evidenced with control solutions.

Visually read results with Teco URS-10 reagent strips were suggestive of negative block shift indicative of LE underestimation at levels 1 through 4 on the standardized reporting scale. At level 2 on the standardized scale (equivalent to 1+/small), three patient urine specimens were reported as negative by Teco Diagnostics reagent strips. Four patient specimens were underestimated by Teco reagent strips at standardized level 3/moderate, reporting as 1/trace (see Table 6).

Similarly, visually read YD URISCAN 10 SGL reagent strip results were suggestive of negative block shift at standardized levels 1 and 2.

Instrument-read clinical specimen results

Instrument-read results on clinical specimens tested using Clarity UROCHECK reagent strips on the Clarity UROCHECK 120 analyzer and YD URISCAN 10 SGL reagent strips on the URISCAN OPTIMA II analyzer showed overall exact agreements of 58.0% and 12.9% respectively with the Multistix 10 SG Reagent Strip results read on the CLINITEK Status+ Analyzer (Tables 8 and 9).

In contrast to visually read results, instrument-read results on the Clarity UROCHECK 120 analyzer exhibited an overall negative block shift for standardized levels 1/trace and 2/small compared to the CLINITEK Status+ Analyzer, resulting in 0% agreement at level 1 with all 10 samples reporting as negative and two patient specimens reading as 0/negative at the 2/small level. In addition, a positive block shift at the 2/small level of two other patient specimens indicates poor consistency at that level.

Instrument-read results on the YD URISCAN OPTIMA II analyzer indicated poor agreement with results on the CLINITEK Status+ Analyzer, showing substantial and consistent negative block shift at 1/trace (10.0% agreement), 2/small (0.0% agreement), and 4/large (7.6% agreement) reporting levels. Twelve specimens were deemed negative at the 2/small level and one specimen was deemed negative at the 3/moderate level when tested using URISCAN 10 SGL reagent strips read on the OPTIMA II analyzer.

Table 3. Visually-read LE test pad results on control solutions.

LE Control Solution	Multistix 10 SG Reagent Strip Result		Clarity CLA-URS10 Reagent Strip Result		Teco URS-10 Reagent Strip Result		YD URISCAN 10 SGL Reagent Strip Result	
	Replicate 1	Replicate 2	Replicate 1	Replicate 2	Replicate 1	Replicate 2	Replicate 1	Replicate 2
Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Positive Plus system ++	++	++	+	+	+	+	+	+
Standardized LE Level 3	3	3	2	2	2	2	2	2

Table 4. Instrument-read LE test pad results on control solutions.

LE Control Solution	Multistix 10 SG Reagent Strip Result		Clarity CLA-URS10 Reagent Strip Result		YD URISCAN 10 SGL Reagent Strip Result	
	Replicate 1	Replicate 2	Replicate 1	Replicate 2	Replicate 1	Replicate 2
Negative	Negative	Negative	Negative	Negative	Negative	Negative
Positive Plus system ++	++	++	+++	++	±	±
Standardized LE Level 3	3	3	4	3	1	1

Table 5. Agreement of visually read LE test pad results on clinical urine specimens: Multistix 10 SG vs. Clarity CLA-URS10 reagent strips.

Clarity CLA-URS10 Test Pad LE Result	Multistix 10 SG Test Pad LE Result					
	0	**1**	**2**	**3**	**4**	**Total**
0	4	NA	NA	NA	NA	4
1	3	9	3	NA	NA	15
2	NA	2	15	1	NA	18
3	NA	NA	NA	18	NA	18
4	NA	NA	NA	NA	7	7
Total	7	11	18	19	7	62
Exact Agreement	**57.1%**	**81.8%**	**83.3%**	**94.7%**	**100.0%**	**85.4%**

Table 6. Agreement of instrument-read LE test pad results on clinical urine specimens: Multistix 10 SG vs. Clarity CLA-URS10 reagent strips.

Clarity CLA-URS10 Test Pad LE Result	Multistix 10 SG Test Pad LE Result					
	0	**1**	**2**	**3**	**4**	**Total**
0	9	10	2	NA	NA	21
1	NA	NA	3	NA	NA	3
2	NA	NA	10	2	NA	12
3	NA	NA	2	6	NA	8
4	NA	NA	NA	7	11	18
Total	9	10	17	15	11	62
Exact Agreement	**100.0%**	**0.0%**	**58.8%**	**40.0%**	**100.0%**	**58.0%**

Table 7. Agreement of visually read LE test pad results on clinical urine specimens: Multistix 10 SG vs. YD URISCAN 10 SGL reagent strips.

YD URISCAN 10 SGL Test Pad LE Result‡	Multistix 10 SG Test Pad LE Result					
	0	**1**	**2**	**3**	**4**	**Total**
0	7	2	NA	NA	NA	9
1	NA	9	11	NA	NA	20
2	NA	NA	7	14	NA	21
3‡	NA	NA	NA	NA	NA	0
4	NA	NA	NA	5	7	12
Total	7	11	18	19	7	62
Exact Agreement	**100.0%**	**81.8%**	**38.8%**	**0.0%**	**100.0%**	**48.3%**

‡YD Diagnostics URISCAN 10 SGL test strips do not offer a 3 block level (moderate) result.

Table 8. Agreement of instrument-read LE test pad results on clinical urine specimens: Multistix 10 SG vs. YD URISCAN 10 SGL reagent strips.

YD URISCAN 10 SGL Test Pad LE Result§	Multistix 10 SG Test Pad LE Result					
	0	**1**	**2**	**3**	**4**	**Total**
0	7	9	12	1	NA	29
1	NA	1	10	7	8	26
2	NA	v	NA	NA	4	4
3§	NA	NA	NA	NA	NA	NA
4	NA	NA	1	1	1	3
Total	7	10	23	9	13	62
Exact Agreement	**100.0%**	**10.0%**	**0.0%**	**0.0%**	**7.6%**	**12.9%**

§The YD Diagnostics OPTIMA II analyzer does not offer a 3 block level (moderate) result. Two YD OPTIMA II analyzer trace levels (10 and 25 cells/µL) were combined into block level 1.

Table 9. Agreement of visually read LE test pad results on clinical urine specimens: Multistix 10 SG vs. Teco URS-10 reagent strips.

Teco URS-10 Test Pad LE Result	Multistix 10 SG Test Pad LE Result					
	0	**1**	**2**	**3**	**4**	**Total**
0	7	7	3	NA	NA	17
1	NA	4	14	4	NA	22
2	NA	NA	1	12	1	14
3	NA	NA	NA	3	6	9
4	NA	NA	NA	NA	NA	0
Total	7	11	18	19	7	62
Exact Agreement	**100.0%**	**36.3%**	**5.5%**	**15.7%**	**0.0%**	**24.1%**

Titration of clinical specimen results

An additional five clinical specimens positive for LE according to Arkray AUTION ELEVEN AE-4022 reagent strips were obtained and each diluted with LE-negative urine specimens to achieve a panel of concentrations ranging from 0%, 12.5%, 25%, 37.5%, 50%, 62.5%, 75%, 87.5%, and 100%. Dilutions were analyzed visually on each manufacturer's reagent strip and also on their corresponding analyzer.

Diagnostic performance was assessed through receiver operating characteristic (ROC) curves. Comparative performance measures for visual results versus instrument-read results for each manufacturer are provided in Table 10, specifically the areas under each curve (AUC) along with their differences and *p* values associated with a test of significance. An AUC of 1 indicates the test can accurately differentiate between positive and negative samples, while a *p* value >0.05 indicates no statistical difference between AUC values of the conditions being compared. All *p* values for comparisons between the visual determinations using the Multistix 10 SG, Clarity UROCHECK, and YD URISCAN 10 SGL reagent strips versus the CLINITEK Status+, Clarity UROCHECK 120, and YD URISCAN OPTIMA II analyzers were <0.05. Although a statistically significant difference exists between the visual strip readings and instrument-read results for all comparisons, Multistix 10 SG Reagent Strips demonstrated the least difference in the ability to determine the presence of LE, whether the strip was read visually or by the CLINITEK Status+ Analyzer, with a 95% lower confidence interval slightly above 0.

Table 10. Comparative performance measures among manufacturers between visual versus instrument readings.

Test Pad	Area Under Curve		Difference (95% Confidence Interval)	*p* Value
	Visual	Instrument		
Siemens Healthineers Multistix	1.000	0.963	0.038 (0.008 to 0.067)	0.0114
Clarity UROCHECK	1.000	0.856	0.144 (0.094 to 0.194)	<0.0001
YD URISCAN	1.000	0.669	0.331 (0.279 to 0.383)	<0.0001
Teco URS-10	0.931	NA	NA	NA

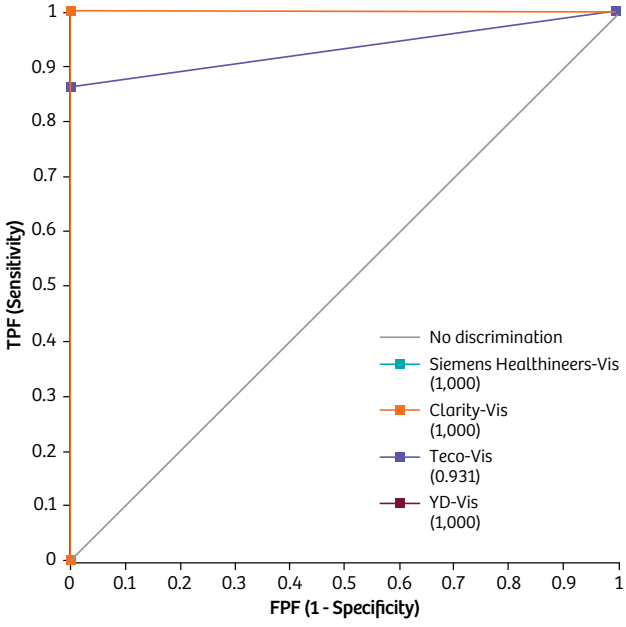

Figure 1. Comparison of ROC curves for visually read LE results for Siemens Healthineers Multistix, Clarity UROCHECK, Teco URS-10, and YD URISCAN reagent strips.

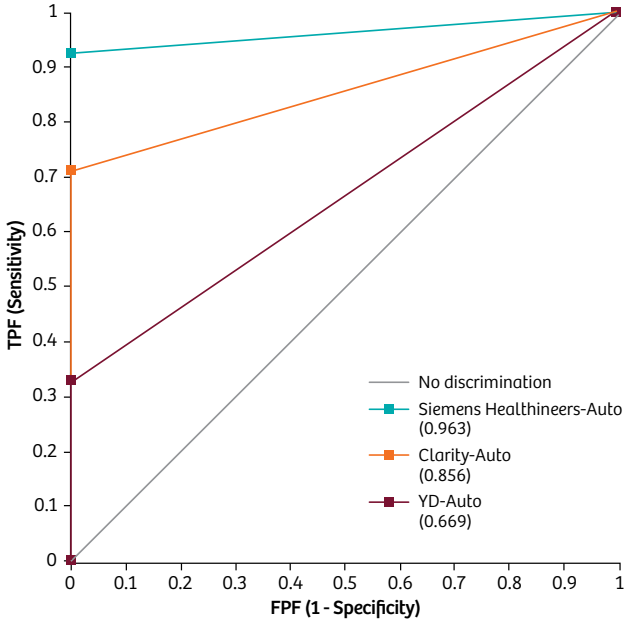

Figure 2. Comparison of ROC curves for instrument-read LE results for Siemens Healthineers CLINITEK Status+, Clarity UROCHECK 120, and YD URISCAN OPTIMA II analyzers.

Discussion and Conclusions

Results of urine strip leukocyte esterase testing serve as guidance for treatment and/or further testing in instances of suspected urinary-tract infection. Given the pivotal importance of urine strip screening at first patient evaluation, the LE strip test employed by healthcare practitioners should demonstrate good accuracy and precision to support confident, effective decision making. Inaccurate results may affect the quality of patient care and well-being.

The results reported in this study confirm anecdotal accounts suggesting that not all commercially available urine strip tests for LE offer the same analytical sensitivity, which could have a negative impact on effective clinical decision making when UTI is suspected.

Reagent strip results exhibiting one-block or equivalent variance, whether read visually or by instrument, are considered to be equivalent indicators of the true LE amount in a control or clinical specimen.[2] However, the visually read control results in Table 3 seem to suggest that the strips from Teco, Clarity, and YD report in the lower range of acceptable—one block shift lower when compared to Multistix 10 SG Reagent Strips and the target 2+/moderate control.

Clinical urine specimens are by their nature more complex than carefully manufactured, standardized controls. This may explain why the clinical samples show more deviation from the Multistix 10 SG strip results for LE level across the different test platforms compared to the control solution.

While visually read Clarity CLA-URS10 clinical specimen test result agreement with Multistix 10 SG Reagent Strip results was relatively good, there is a greater or lesser underestimation seen with both the Teco and YD reagent strips. Of particular concern were three clinical specimens that were reported as negative by visually read Teco strips but were a level 2 on the standardized scale when tested using the more sensitive Multistix 10 SG Reagent Strip.

Using instrumentation in urinalysis is a growing trend as it has many advantages, including standardizing the process by eliminating operator variability.

Instrument-read results on the Clarity UROCHECK 120 analyzer exhibited a negative block shift for standardized levels 1 and 2 in comparison to the CLINITEK Status+ Analyzer, resulting in two patient specimens reading as 0/negative at the 2/small level. In addition, a positive block shift at the 2/small level of two other patient specimens indicates poor consistency and decreased confidence of results at the 2/small level.

Instrument-read YD URISCAN 10 SGL strip results showed significant and consistent negative block shift in comparison to the CLINITEK Status+ Analyzer, with 12 specimens deemed negative at the 2/small level and 1 specimen deemed negative at the 3/moderate level.

Of the 62 clinical specimens tested, there were a total of 18 results reported as negative for the presence of LE when they should have been reported at a standardized 2 or above in comparison to Multistix 10 SG Reagent Strip results read either visually or with the CLINITEK Status+ Analyzer. This indicates that Multistix 10 SG Reagent Strips have better analytical sensitivity in the detection of LE at lower concentrations than the other reagent strips used in this study, as confirmed by titration performance, and therefore offer the potential for faster diagnosis and treatment of UTI.

Diagnostic performance was evaluated from the titration of five clinical samples. The results from the visual ROC curves demonstrated good performance from all manufacturers, with an AUC ≥0.931. When comparing the ROC curves of each analyzer, the CLINITEK Status+ Analyzer had the highest AUC, indicating greater analytical sensitivity than the Clarity UROCHECK 120 and the YD URISCAN OPTIMA II analyzers. The AUC for analyzer-read samples compared to visual decreased in all instances, with the least difference observed for the Siemens Healthineers Multistix 10 SG Reagent Strips, demonstrating the best performance in achieving the same conclusion for a result when read visually or by the CLINITEK Status+ Analyzer. The AUC of the CLINITEK Status+ Analyzer is higher than that of the Clarity UROCHECK 120 analyzer, indicating fewer instances of missed samples and faster diagnosis of patients with low-level LE by the CLINITEK Status+ Analyzer compared to the Clarity UROCHECK 120 analyzer. The YD URISCAN 10 SGL reagent strips showed poor performance when using the YD URISCAN OPTIMA II analyzer, indicating the potential to miss detection of LE in patients with UTI. The performance of instrumentation for detection of LE must be accurate for correct patient treatment and reliable to automate the process for the operator.

Any false-negative results can result in a patient not receiving the required antibiotics and puts them at risk of developing further, more-serious infections such as APN. As well as the impact on the patient, the cost burden of APN is not insignificant: an estimated $2.14 billion each year.[6] Any opportunity to reduce false-negative results should be seriously considered.

Urinalysis provides a wealth of indispensable clinical information in modern healthcare. Siemens Healthineers continues to innovate reliable POC urinalysis testing solutions that can broaden clinical insight into patient health. The Siemens Healthineers POC urinalysis portfolio of products supports the early detection, monitoring, and management of multiple disease states with the widest, most trusted range of urinalysis solutions on the market.

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Product availability may vary from country to country and is subject to varying regulatory requirements. Please contact your local representative for availability.

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