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Reduction of False-positive Bilirubin Results on the CLINITEK Novus (Version 1.1) Automated Urine Chemistry Analyzer*

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Abstract

Background: Bilirubin, a waste product of red blood cell breakdown, is excreted in feces, although small amounts may be found in urine. Trace or higher amounts may suggest underlying pathology and indicate the need for further clinical investigation. Unfortunately, even the most established methods can generate a high percentage of false-positive bilirubin results, often due to interfering substances and/or abnormal urine color. The CLINITEK Novus® Automated Urine Chemistry Analyzer (Version 1.1) employs a unique algorithm to decrease false-positive bilirubin results. Utilizing camera-based detection technology, this algorithm allows for the improved detection of true bilirubin, as confirmed by Ictotest® reflex testing. We assessed false- positive CLINITEK Novus analyzer bilirubin results versus incidence on the CLINITEK Atlas® analyzer, and correlation of CLINITEK Novus analyzer (Version 1.1 software) bilirubin results with results on the CLINITEK Atlas system.

Methods: An internal Siemens investigation was conducted to assess false-positive incidence. 270 clinical and contrived samples were run on three CLINITEK Novus analyzers and one CLINITEK Atlas analyzer, with each analyzer using one reagent lot. Ictotest tablet reflex testing was employed to identify false-positive results. Ictotest-negative results (35) were eliminated from further statistical analysis to assess true bilirubin concordance. Results were compiled in frequency tables. Positive agreement, negative agreement, exact agreement, and within-one-level agreement were calculated.

Results: Compared to the CLINITEK Atlas analyzer, the CLINITEK Novus analyzer (Version 1.1) reduced the bilirubin false-positive rate by 7%, with 0.4% false negatives. CLINITEK Novus analyzer (Version 1.1 software) test results correlated well with CLINITEK Atlas analyzer bilirubin results, with 95% exact block agreement.

Conclusions: The CLINITEK Novus analyzer (Version 1.1) showed improved detection of bilirubin. True bilirubin results were concordant with those generated on a reference analyzer. Greater accuracy (fewer false positives with 0.4% false negatives) in routine bilirubin urinalysis with the CLINITEK Novus analyzer (Version 1.1) serves to decrease the time and costs associated with potentially unnecessary follow-up bilirubin testing.

Background

False-positive bilirubin results have been reported by customers using the CLINITEK Novus® Automated Urine Chemistry Analyzer and CLINITEK Atlas® Urine Chemistry Analyzer. Samples that test positive for bilirubin during routine urinalysis testing are reflexed to Ictotest®, where the sample is then determined to be negative for bilirubin. This is not a risk to patient health when confirmatory testing is performed as the next required step and the clinical value is determined from this reference method. However, customers have expressed concerns about workflow, extra labor/time, unnecessary responsibility, and cost of the reference method to support reflex testing. A bilirubin algorithm improvement for the CLINITEK Novus (Version 1.1) system targeting a reduction in the rate of false positive results is possible and will provide a reduction in the amount of false-positive results observed by customers. Improved detection of bilirubin is achieved by adding a confirmatory step that measures the color deposited by the sample on the color pad and compares this measurement to the absorbance spectra for bilirubin. Only if the color is consistent for bilirubin does the instrument present a positive result.

To demonstrate the improved performance of bilirubin detection on the CLINITEK Novus (Version 1.1) system, a two-step protocol was conducted in which performance was compared against the predicate analyzer, the CLINITEK Atlas analyzer, and against Siemens Ictotest tablets.

Materials and Methods

Clinical samples were obtained from the University of Louisville Hospital and from Siemens Healthcare Diagnostics K.K. (Tokyo, Japan), which acquired the samples from a customer site in Japan. Sample selection from these sites had been shown in the past to include samples that were false-positive for bilirubin. The expectation was that these sample populations would also contain an appropriate subset of negative samples. True bilirubin-positive samples were also obtained from the University of Louisville; these samples were confirmed positive for bilirubin by the site. To help increase positive sample numbers, contrived samples were also prepared internally: 15% of the population was contrived for bilirubin.

A total of 270 clinical samples were tested on the CLINITEK Novus analyzer (Version 1.1), the CLINITEK Atlas system, and with Siemens Ictotest.

One replicate of each sample was tested on the CLINITEK Atlas analyzer and Ictotest tablets. One replicate of each sample was tested once on three CLINITEK Novus analyzers (Version 1.1). One reagent lot was implemented for each analyzer and Ictotest tablets.

For data analysis, the Ictotest result was taken as truth and used to identify discrepant samples—samples in which the CLINITEK Atlas analyzer result did not match the Ictotest result. For assessment to predicate, truth tables comparing the performance of CLINITEK Novus analyzer (Version 1.1) to CLINITEK Atlas analyzer were compiled. These truth tables were also compiled after the discrepant samples were removed from the sample population in the performance comparisons. For measurement of the reduction in false-positive bilirubin results, truth tables comparing the performance of Ictotest tablets to the CLINITEK Novus analyzer (Version 1.1) and the performance of Ictotest tablets to the CLINITEK Atlas analyzer were compiled.

Results

The initial analysis comparing the performance of CLINITEK Novus (Version 1.1) to CLINITEK Atlas with all samples included is shown in Table 1.

Table 1. Truth table analysis comparing the bilirubin results of the CLINITEK Novus (Version 1.1) to the CLINITEK Atlas. 270 total samples were tested on each of three CLINITEK Novus analyzers and one Atlas instrument.

Bilirubin	CLINITEK Atlas Result, All Samples				
CLINITEK Novus (Version 1.1) Result	NEGATIVE	SMALL	MODERATE	LARGE	Grand Total
Negative	441	18	27		486
Small	5	99	21		125
Moderate		3	108	13	124
Large				74	74
Grand Total	**446**	**120**	**156**	**87**	**809**
% Exact Match	98.9%	82.5%	69.2%	85.1%	–
% Within 1 block	100.0%	100.0%	82.7%	100.0%	–

Sensitivity 87.6%
Specificity 98.9%
Exact Agreement 89.2%
Within One Block 96.7%

The second analysis comparing the performance of CLINITEK Novus to CLINITEK Atlas with all discrepant (i.e., Atlas-positive, Ictotest-negative) samples – Atlas positive, Ictotest negative - removed is shown below in Table 2.

Table 2. Analysis comparing the bilirubin results of the CLINITEK Novus* (Version 1.1) to the CLINITEK Atlas after removal of discrepant results.

Bilirubin	CLINITEK Atlas Result, Ictotest Discrepant Samples Removed				
CLINITEK Novus (Version 1.1) Result	NEGATIVE	SMALL	MODERATE	LARGE	Grand Total
Negative	441		3		444
Small	2	57	15		74
Moderate		3	96	13	112
Large				71	71
Grand Total	**443**	**60**	**114**	**84**	**701**
% Exact Match	99.5%	95.0%	84.2%	84.5%	–
% Within 1 block	100.0%	100.0%	97.4%	100.0%	–

Sensitivity 98.8%
Specificity 99.5%
Exact Agreement 94.9%
Within One Block 99.6%

The analysis comparing the performance of the CLINITEK Novus (Version 1.1) bilirubin to Ictotest is shown in Table 3. There was a false-positive rate of 12%.

Table 3. Analysis comparing the bilirubin results of the CLINITEK Novus to Ictotest.

Bilirubin	Ictotest		GRAND TOTAL
CLINITEK Novus (Version 1.1) Result	NEGATIVE	POSITIVE	
Negative	483	3	486
Small	53	72	125
Moderate	12	112	124
Large	3	71	74
Grand Total	**551**	**258**	**809**

False-positive Rate 12%
Sensitivity 99%
Specificity 88%

The results of CLINITEK Atlas bilirubin performance compared to Ictotest are shown in Table 4. There was a false-positive rate of 19%.

Table 4. Analysis comparing the bilirubin results of the CLINITEK Atlas to Ictotest.

Count of Sample ID	Ictotest		GRAND TOTAL
CLINITEK Atlas Result	NEGATIVE	POSITIVE	
Negative	149		149
Small	20	20	40
Moderate	14	38	52
Large	1	28	29
Grand Total	**184**	**86**	**270**

False-positive Rate 19%
Sensitivity 100%
Specificity 81%

Conclusions

- The improved bilirubin algorithm for the CLINITEK Novus (Version 1.1) analyzer demonstrated a decreased rate in false-positive results, when referenced to the Ictotest, compared to the CLINITEK Atlas.
- The CLINITEK Novus (Version 1.1) analyzer demonstrated strong agreement to the CLINITEK Atlas analyzer.

*Under FDA review. Not available for sale in the U.S. Product availability varies by country.

A91DX-POC-140596-GC1-4A00