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REVIEW ARTICLE

A New Test Strip Technology Platform for Self-Monitoring of Blood Glucose

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Abstract

In the management of diabetes, accuracy of devices used for self-monitoring of blood glucose (SMBG) is critical because SMBG results can affect patient diabetes-related health outcomes. A new blood glucose monitoring system (BGMS) platform has been developed that is based on the new CONTOUR® NEXT (CN) test strip. This BGMS platform uses a proprietary electron mediator and algorithm to minimize errors at different steps in the testing process, thus minimizing outliers and significantly improving accuracy from prior-generation blood glucose meter systems. As demonstrated by questionnaire results from clinical studies with the new BGMS platform, accuracy and ease of use are important considerations for people with diabetes and their health care professionals when selecting an SMBG device. This article provides an overview of laboratory studies and clinical trials in the hands of lay users involving the performance of the portfolio of blood glucose meters that uses the new test strip. Each BGMS in the platform, which includes the CONTOUR XT (CONTOUR NEXT EZ in the United States), CONTOUR NEXT LINK, CONTOUR NEXT USB, and CN systems, demonstrated advanced accuracy both in the laboratory and in the hands of subjects (people with diabetes) and trained health care professionals. All systems met and exceeded International Organization for Standardization accuracy criteria (both ISO 15197:2003 and ISO 15197:2013). Each system in the new BGMS platform delivers advanced accuracy, which is essential to people who utilize SMBG for improved management.

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Introduction

Self-monitoring of blood glucose (SMBG) is a key technology enabling people with diabetes to achieve near-normoglycemia. Thus, it is important for SMBG devices to deliver reliable results.[1] Glucose readings that are higher than the actual blood glucose value can conceal hypoglycemia and/or result in incorrect treatment decisions such

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Abbreviations: (ACA) ACCU-CHEK Aviva, (AST) alternate site testing, (BGMS) blood glucose monitoring system, (CN) CONTOUR NEXT, (CNEZ) CONTOUR NEXT EZ, (CNL) CONTOUR NEXT LINK, (CNUSB) CONTOUR NEXT USB, (CXT) CONTOUR XT, (FFL) FreeStyle Freedom Lite, (HCP) health care professional, (ISO) International Organization for Standardization, (MARD) mean absolute relative difference, (OTU2) OneTouch Ultra2, (OTV) OneTouch Verio, (SMBG) self-monitoring of blood glucose, (TT) TRUEtrack, (YSI) Yellow Springs Instruments

Keywords: accuracy, blood glucose monitoring, diabetes management, self-monitoring of blood glucose

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as an insulin overdose; conversely, falsely low results can mask hyperglycemia.[2] Delayed or incorrect treatment can exacerbate glycemic excursions, leading to worsening hyperglycemia and hypoglycemia.[3,4] A number of studies have demonstrated a relationship between the use of SMBG and improved outcomes among people with diabetes, including decreased glycated hemoglobin levels and fewer disease-related complications.[5–7] However, in order to fully realize the benefits of SMBG, the values must be accurate and patients (people with diabetes) and health care professionals (HCPs) need to act on the SMBG information and incorporate it into therapy and self-care plans.[3,8,9] Therefore, it is imperative that SMBG results are accurate and precise.

The importance of accuracy in *in vitro* diagnostic medical devices has been recognized by several regulatory agencies and organizations, including the International Organization for Standardization (ISO), as evidenced by the call for more stringent standards and guidelines for the assessment of SMBG devices.[10–12] While blood glucose monitoring systems (BGMSs) demonstrate a high level of accuracy in the laboratory setting, it is critically important that people with diabetes and HCPs are able to achieve a similar high level of accuracy with BGMSs where they are most commonly used, in the home as well as in the HCP office. Ease of use is also an important consideration for patient adherence. A system that is easy to use will assist both trained medical professionals and people with diabetes who are naive to the system in obtaining accurate results using the BGMS.

The CONTOUR® NEXT (CN) test strip (Bayer HealthCare LLC, Diabetes Care, Tarrytown, NY; hereinafter referred to as new test strip) in conjunction with a new portfolio of Bayer meters[13–23] achieves advanced performance in blood glucose monitoring both when used by trained laboratory personnel or during routine use by medical professionals or people with diabetes. The new test strip uses a flavin adenine dinucleotide-glucose dehydrogenase (FAD-GDH) enzyme and a proprietary phenothiazine electron mediator and algorithm to minimize errors during the testing process. This article will provide an overview of research studies involving the performance of the new test strip and the portfolio of blood glucose meters with which it is compatible.

The studies included in this article evaluated several BGMSs, each consisting of a blood glucose meter designed for use with the new test strip. The new platform includes the CONTOUR XT (CXT) BGMS [CONTOUR NEXT EZ (CNEZ) in the United States and Canada], the CONTOUR NEXT LINK (CNL) BGMS, the CONTOUR NEXT USB (CNUSB) BGMS, and the CN BGMS (Bayer HealthCare LLC, Diabetes Care, Tarrytown, NY; **Table 1**). Each meter has customizable "HI/LO" settings, premeal and postmeal markers, and the ability to track blood glucose patterns over time. In addition, each meter has a different set of features so that HCPs and their patients can select a system that can provide benefit tailored to each patient's diabetes management needs (**Table 1**). Each of these systems utilizes the new test strip to provide a similar level of advanced accuracy.

Table 1.
Meter Systems and Features

Meter system	Features
CXT	CXT and CNEZ have the ability to be set to basic testing (L1) or to enable additional features (L2)
CNEZ	
CNUSB	Direct USB connection capability and onboard diabetes management software Uses plain language text without error codes Autolog for intuitive meal marking Lighted test strip port
CNL	Transmits glucose values to Medtronic MiniMed Paradigm® REAL-Time Revel insulin pumps or Guardian® REAL-Time monitors Uses plain language text without error codes Lighted test strip port
CN	Uses plain language text without error codes

Assessment Across the Test Strip Platform

The new platform of BGMSs that use the new test strip includes features such as underfill detection and provides the user with the ability to reapply blood when the test strip is underfilled ("second chance" sampling). Studies were conducted to evaluate the accuracy of blood glucose results obtained with the new test strip after a second application of blood was added to the test strip.[24] The new test strip results were accurate under conditions of blood sample reapplication, with 99.1% of results meeting the then-proposed ISO 15197:2013 accuracy criteria (discussed later).[24]

Results obtained with the new test strip are unaffected by physiological/therapeutic concentrations of many common interfering substances as shown by test strip results demonstrating ≤1% bias (relative to a sample with no interferent

present) in the presence of the maximum therapeutic concentration or upper reference value of the six most common endogenous and exogenous interfering substances (acetaminophen, uric acid, bilirubin, galactose, maltose, and ascorbic acid; **Table 2**).[25] However, the new test strips should not be used during or soon after xylose absorption testing, as xylose in the blood will interfere with the testing process (i.e., accuracy of the result).[26]

The new test strip includes a special correction electrode that, in conjunction with an algorithm, allows the meter to compensate for a wide range (0–70%) of hematocrit levels. The results of laboratory tests conducted to demonstrate the accuracy of the new test strip over a wide range of hematocrit levels are shown in **Figure 1** as the bias of test results at different levels of hematocrit relative to Yellow Springs Instruments (YSI) reference results (data on file). Fresh venous blood samples were adjusted to hematocrit levels of 0%, 40%, and 70% and tested using three lots (n = 24 per lot per glucose level) of test strips. The results showed <10 mg/dl bias at plasma glucose levels of 50 mg/dl and <10% bias at plasma glucose levels of 120 and 450 mg/dl over the hematocrit range of 0% to 70% (**Figure 1**). The BGMSs using the new test strip are also functional over a wide range of humidity (10–93% relative humidity) and temperature [41–113 °F (5–45 °C)], as specified in their respective labeling.[27–30]

Analytical Performance (ISO 15197:2003 Section 7 and ISO 15197:2013 Section 6.3)

Laboratory studies were conducted to assess the analytical accuracy of each meter system that includes the new test strip based on the ISO 15197:2003 section 7 protocol and the ISO 15197:2013 section 6.3 protocol.[31,32] In each study, capillary finger stick blood samples from 100 subjects were tested by laboratory professionals in duplicate using each of three lots of test strips to obtain a total of 600 blood glucose test results.[13–16] Each blood sample was tested in parallel on a YSI glucose analyzer equipped with automatic calibration and linearity checks (YSI Life Sciences Inc., Yellow Springs, OH) to produce reference values for comparison. The YSI analyzer was calibrated against standards and confirmed using National Institute of Standards and Technology-traceable serum controls. Target glucose levels for the controls had previously been determined using a reference method traceable to the National Institute of Standards and Technology Standard Reference Material 965a, Glucose in Frozen Human Serum, and aqueous New England Reagents Laboratory Glucose Standards.

Table 2.
Effect of Exogenous and Endogenous Interfering Substances on Test Strip Results[25]

Interfering substance	Therapeutic or reference range, mg/dl	Bias at maximum therapeutic concentration or upper reference value	Limiting concentration,[a] mg/dl
Acetaminophen	1.0 to 2.0	≤±1%	35
Ascorbic acid[b,c]	0.4 to 2.0	≤±1%	10
Bilirubin[b]	0.3 to 1.2	≤±1%	54
Caffeine	0.5 to 2.0	≤±1%	7
Cholesterol[b]	150 to 300	≤±1%	1168
Creatinine hydrochloride	0.8 to 1.7	≤±1%	34
Dopamine hydrochloride	0.04	≤±1%	4
Ephedrine	0.005 to 0.01	≤±1%	11
Galactose	5.0	≤±1%	336
Glutathione	0.11	≤±1%	17
Hemoglobin	0.1 to 0.2 (g/dl)	≤±1%	2 (g/dl)
Ibuprofen	1.7 to 7.8	≤±1%	56
Icodextrin	0.5 (g/dl)	≤±1%	2 (g/dl)
L-Dopa	0.02 to 0.3	≤±1%	5
Maltose	120	≤±1%	336
Methyldopa	0.1 to 0.75	≤±1%	3
Sodium gentisate	0.2 to 0.7	≤±1%	112
Sodium salicylate	11.5 to 34.7	≤±1%	112
Tetracycline	0.2 to 0.5	≤±1%	4
Tolazamide	3.0	≤±1%	112
Tolbutamide	5.4 to 10.8	≤±1%	112
Triglycerides[b]	190	≤±1%	4709
Uric acid[b]	2.5 to 8.0	≤±1%	59
Xylose	57	51%	6

[a] The concentration of the interfering substance resulting in a ±10% bias of test results as determined by interpolation using linear regression analysis. If a substance did not have a concentration that created a ±10% bias, then the limiting concentration is listed as the highest level tested.
[b] Ascorbic acid, bilirubin, cholesterol, triglycerides, and uric acid occur naturally in the body, so the effect at the limiting concentration was calculated with respect to the normal concentration rather than 0 mg/dl.
[c] At five times the maximum therapeutic concentration, results showed a 10% assay bias at 80 mg/dl plasma glucose.

Accuracy was assessed according to ISO 15197:2003 performance criteria (i.e., ≥95% of results shall fall within ±15 mg/dl or ±20% of the reference result for samples with glucose concentrations <75 and ≥75 mg/dl, respectively).[31] Accuracy was also assessed based on the then-proposed ISO 15197:2013 accuracy criteria (i.e., ≥95% of results shall fall within ±15 mg/dl or ±15% of the reference result for samples with glucose concentrations <100 and ≥100 mg/dl, respectively)[32] as well as the percentage of BGMS results that fell within tighter specific error limits of the YSI reference results (e.g., ≥95% of results shall fall within ±10 mg/dl or ±10% of the reference result for samples with glucose concentrations <100 and ≥100 mg/dl, respectively).

The results of the analytical performance evaluations are summarized in **Table 3**. When compared with YSI reference results, 100% of results obtained using the new test strip platform with various types of meters met the ISO 15197:2003 section 7 accuracy criteria across all four studies (**Table 3**).[13–16,33] Similarly, 100% of results obtained using the CXT/CNEZ BGMS, the CNL BGMS, or the CNUSB BGMS and 99.8% of results obtained using the CN BGMS met the then-proposed ISO 15197:2013 accuracy criteria (**Table 3**).[13–16,33] YSI plasma-referenced blood glucose values for all studies ranged from ≥23 to ≤551 mg/dl (data on file), showing that test strip results are accurate across a wide analytical range of glucose values. Regression analyses demonstrated strong correlation between BGMS results and YSI reference results (R^2 >0.99 across all four studies; **Table 3** and **Figure 2**).[14–16,33] Evaluation of clinical accuracy using Parkes consensus error grid analysis[34] showed that 100% of results were within zone A with all meter types used in the study (**Table 3**).[14–16]

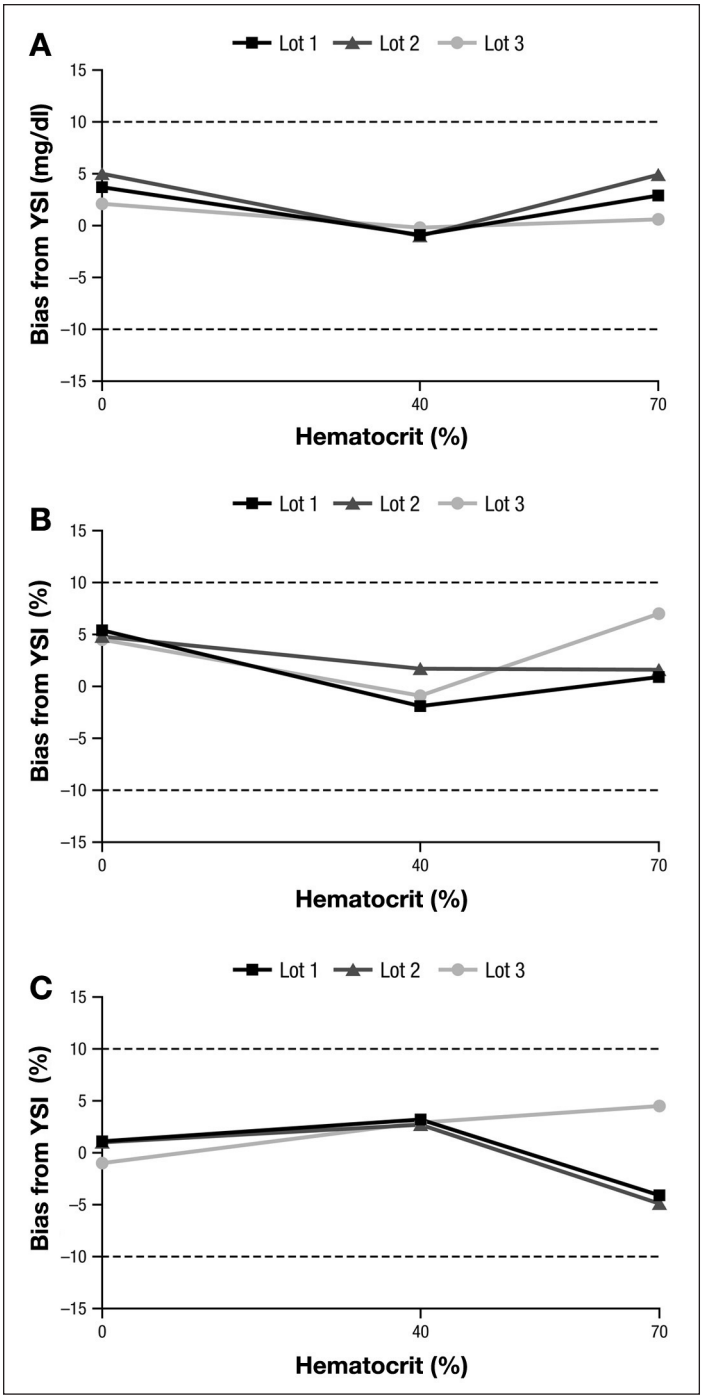

Figure 1. Effect of hematocrit levels on test strip results at plasma glucose levels of **(A)** 50, **(B)** 120, and **(C)** 450 mg/dl. (Data on file.)

The percentage of BGMS results that fell within specific error limits of the YSI reference result for each study is shown in **Table 4**. For samples with glucose concentrations <75 mg/dl, ≥98.7% of results were within ±10 mg/dl of reference results across all four studies (**Table 4**).[33] For samples with glucose concentrations ≥75 mg/dl, ≥98.1% of results were within ±10% of reference results for all systems (**Table 4**).[33] Using combined glucose concentration thresholds of <75 and ≥75 mg/dl, ≥98.3% of results were within ±10 mg/dl or ±10%, respectively, of the reference result (**Table 4**).[33] Similar results were observed using combined glucose concentration thresholds of <100 and ≥100 mg/dl; ≥98.5% of results were within ±10 mg/dl or ±10%, respectively, of the reference result (**Table 4**).[33]

The new test strip was also evaluated against laboratory instruments more commonly used outside the United States. The test strip also demonstrated advanced accuracy when comparing the CXT/CNEZ BGMS with a Dimension EXL chemistry analyzer (Siemens Healthcare Diagnostics, Deerfield, IL) that uses the hexokinase reference method for

Table 3.
Summary of Analytical Performance Evaluation of the Test Strip (ISO 15197:2003 Section 7 and ISO 15197:2013 Section 6.3)

Meter system	Reference method	Readings within specified error limits (N = 600)		R^2	Parkes consensus error grid analysis
		ISO 15197:2003 criteria[a]	ISO 15197:2013 criteria[b]		
CXT/CNEZ[16,33]	YSI	100%	100%	0.9964	100% in zone A
CNL[13,33]	YSI	100%	100%	0.9961	100% in zone A[c]
CNUSB[14,33]	YSI	100%	100%	0.9957	100% in zone A
CN[15,33]	YSI	100%	99.8%	0.9959	100% in zone A

[a] Within ISO 15197:2003 accuracy criteria (i.e., ≥95% of results shall fall within ±15 mg/dl or ±20% for samples with glucose concentrations <75 and ≥75 mg/dl, respectively).
[b] Within ISO 15197:2013 accuracy criteria (i.e., ≥95% of results shall fall within ±15 mg/dl or ±15% for samples with glucose concentrations <100 and ≥100 mg/dl, respectively).
[c] Data on file.

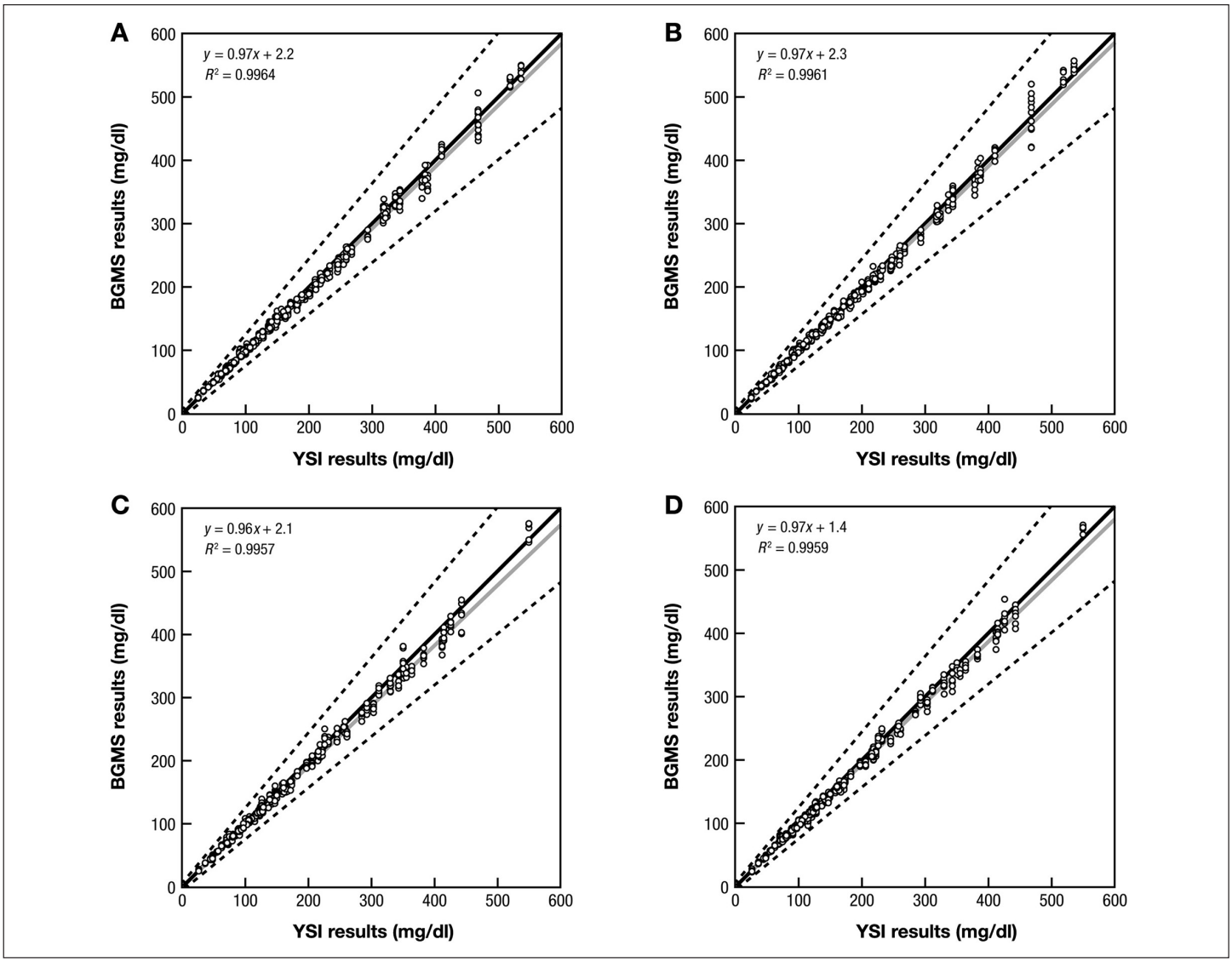

Figure 2. Regression analysis of the test strip results compared with YSI reference results from the analytical performance evaluations (ISO 15197:2003 section 7 and ISO 15197:2013 section 6.3) for **(A)** the CXT/CNEZ BGMS, **(B)** the CNL BGMS (data on file), **(C)** the CNUSB BGMS, and **(D)** the CN BGMS.[14–16] Dashed lines represent ISO 15197:2003 accuracy criteria. Solid gray line denotes regression line.

Table 4.
Accuracy of the Test Strip in the Laboratory Based on ISO 15197:2003 and ISO 15197:2013 Criteria

Meter system	Glucose concentration	Number of readings within specified error limits			
CXT/CNEZ[33]	<75 mg/dl (*n* = 102)	±5 mg/dl	±10 mg/dl	±15 mg/dl	±20 mg/dl
		97 (95.1%)	102 (100%)	102 (100%)[a]	102 (100%)
	≥75 mg/dl (*n* = 498)	±5%	±10%	±15%	±20%
		417 (83.7%)	493 (99.0%)	498 (100%)	498 (100%)[a]
	Total (*N* = 600)	±5 mg/dl or ±5%	±10 mg/dl or ±10%	±15 mg/dl or ±15%	±20 mg/dl or ±20%
		514 (85.7%)	595 (99.2%)	600 (100%)	600 (100%)
	<100 mg/dl (*n* = 186)	±5 mg/dl	±10 mg/dl	±15 mg/dl	±20 mg/dl
		167 (89.8%)	183 (98.4%)	186 (100%)[b]	186 (100%)
	≥100 mg/dl (*n* = 414)	±5%	±10%	±15%	±20%
		348 (84.1%)	412 (99.5%)	414 (100%)[b]	414 (100%)
	Total (*N* = 600)	±5 mg/dl or ±5%	±10 mg/dl or ±10%	±15 mg/dl or ±15%	±20 mg/dl or ±20%
		515 (85.8%)	595 (99.2%)	600 (100%)	600 (100%)
CNL[33]	<75 mg/dl (*n* = 102)	±5 mg/dl	±10 mg/dl	±15 mg/dl	±20 mg/dl
		97 (95.1%)	102 (100%)	102 (100%)[a]	102 (100%)
	≥75 mg/dl (*n* = 498)	±5%	±10%	±15%	±20%
		414 (83.1%)	495 (99.4%)	498 (100%)	498 (100%)[a]
	Total (*N* = 600)	±5 mg/dl or ±5%	±10 mg/dl or ±10%	±15 mg/dl or ±15%	±20 mg/dl or ±20%
		511 (85.2%)	597 (99.5%)	600 (100%)	600 (100%)
	<100 mg/dl (*n* = 186)	±5 mg/dl	±10 mg/dl	±15 mg/dl	±20 mg/dl
		169 (90.9%)	185 (99.5%)	186 (100%)[b]	186 (100%)
	≥100 mg/dl (*n* = 414)	±5%	±10%	±15%	±20%
		343 (82.9%)	412 (99.5%)	414 (100%)[b]	414 (100%)
	Total (*N* = 600)	±5 mg/dl or ±5%	±10 mg/dl or ±10%	±15 mg/dl or ±15%	±20 mg/dl or ±20%
		512 (85.3%)	597 (99.5%)	600 (100%)	600 (100%)
CNUSB[14,33]	<75 mg/dl (*n* = 78)	±5 mg/dl	±10 mg/dl	±15 mg/dl	±20 mg/dl
		65 (83.3%)	78 (100%)	78 (100%)[a]	78 (100%)
	≥75 mg/dl (*n* = 522)	±5%	±10%	±15%	±20%
		390 (74.7%)	512 (98.1%)	522 (100%)	522 (100%)[a]
	Total (*N* = 600)	±5 mg/dl or ±5%	±10 mg/dl or ±10%	±15 mg/dl or ±15%	±20 mg/dl or ±20%
		455 (75.8%)	590 (98.3%)	600 (100%)	600 (100%)
	<100 mg/dl (*n* = 180)	±5 mg/dl	±10 mg/dl	±15 mg/dl	±20 mg/dl
		160 (88.9%)	180 (100%)	180 (100%)[b]	180 (100%)
	≥100 mg/dl (*n* = 420)	±5%	±10%	±15%	±20%
		299 (71.2%)	412 (98.1%)	420 (100%)[b]	420 (100%)
	Total (*N* = 600)	±5 mg/dl or ±5%	±10 mg/dl or ±10%	±15 mg/dl or ±15%	±20 mg/dl or ±20%
		459 (76.5%)	592 (98.7%)	600 (100%)	600 (100%)

Continued →

Table 4. Continued

Meter system	Glucose concentration	Number of readings within specified error limits			
CN[15,33]	<75 mg/dl (*n* = 78)	±5 mg/dl	±10 mg/dl	±15 mg/dl	±20 mg/dl
		74 (94.9%)	77 (98.7%)	78 (100%)[a]	78 (100%)
	≥75 mg/dl (*n* = 522)	±5%	±10%	±15%	±20%
		390 (74.7%)	513 (98.3%)	521 (99.8%)	522 (100%)[a]
	Total (*N* = 600)	±5 mg/dl or ±5%	±10 mg/dl or ±10%	±15 mg/dl or ±15%	±20 mg/dl or ±20%
		464 (77.3%)	590 (98.3%)	599 (99.8%)	600 (100%)
	<100 mg/dl (*n* = 180)	±5 mg/dl	±10 mg/dl	±15 mg/dl	±20 mg/dl
		167 (92.8%)	179 (99.4%)	180 (100%)[b]	180 (100%)
	≥100 mg/dl (*n* = 420)	±5%	±10%	±15%	±20%
		319 (76.0%)	412 (98.1%)	419 (99.8%)[b]	420 (100%)
	Total (*N* = 600)	±5 mg/dl or ±5%	±10 mg/dl or ±10%	±15 mg/dl or ±15%	±20 mg/dl or ±20%
		486 (81.0%)	591 (98.5%)	599 (99.8%)	600 (100%)

[a] ISO 15197:2003 accuracy criteria.
[b] ISO 15197:2013 accuracy criteria.

glucose measurement.[35] One hundred samples were analyzed by both meters, and evaluation of accuracy showed that 100% of results obtained with the CXT/CNEZ BGMS met ISO 15197:2003 accuracy criteria and ≥99% of results met the then-proposed ISO 15197:2013 accuracy criteria. Similar to results obtained using the YSI reference method, the regression analysis R^2 for the comparison with the hexokinase method was >0.99.[35]

User Performance Evaluation (ISO 15197 Section 8)

It is critical that BGMSs perform well in the hands of the intended user population, people with diabetes and their HCPs, as well as under controlled laboratory conditions. Lay user performance evaluations of the new test strip were conducted in several clinical trials, which assessed the accuracy of the system when used by untrained lay people with diabetes and HCPs.[17–23] In each study, subjects who were naive to the system learned how to use the BGMS by reading the user and quick reference guides provided with the device and tested their own blood. Health care professionals also tested blood samples from subjects on the BGMS following the subject-performed testing. All BGMS results were compared with YSI reference results. Accuracy was assessed based on ISO 15197:2003 accuracy criteria and the then-proposed ISO 15197:2013 accuracy criteria.

Results of the clinical trials evaluating user performance are summarized in **Table 5**. The CXT/CNEZ BGMS and the CNL BGMS were each evaluated in two clinical studies, while the CNUSB BGMS and the CN BGMS were each evaluated in a single clinical study.[17–23] In all six studies, subjects tested their own capillary finger stick blood samples; ≥98.9% and ≥97.2% of results met ISO 15197:2003 and ISO 15197:2013 accuracy criteria, respectively (**Table 5**).[17,19–23,36] Three studies evaluated the accuracy of palm alternate site testing (AST) with the CNL BGMS, the CNUSB BGMS, or the CN BGMS.[19,21,22] In all three studies, ≥97.3% and ≥96.3% of palm AST results met ISO 15197:2003 and ISO 15197:2013 accuracy criteria, respectively (**Table 5**).[19,21–23]

The new BGMS platform also demonstrated enhanced accuracy when used by HCPs to test capillary blood samples from subjects. In studies that evaluated the CXT/CNEZ BGMS or the CNL BGMS, ≥99.5% of results from HCP testing of subject finger stick blood met both ISO 15197:2003 and ISO 15197:2013 accuracy criteria (**Table 5**).[17,20,22,23] In studies that evaluated the CXT/CNEZ BGMS, the CNUSB BGMS, or the CN BGMS, HCPs also tested venous samples from subjects and compared the results with venous blood measured on the YSI.[19–21] In all three studies, 100% of venous results met both ISO 15197:2003 and ISO 15197:2013 accuracy criteria (**Table 5**).[19–21]

Table 5.
Summary of User Performance Evaluation of the Test Strip (ISO 15197 Section 8)

National Clinical Trials identifier[a]	Meter system	Subjects, *n*	Sample type	User	Readings within specified error limits		R^2	Parkes consensus error grid analysis
					ISO 15197:2003 criteria[b]	ISO 15197:2013 criteria[c]		
NCT01264016	CXT/CNEZ[20]	96	Capillary finger stick	Subject	98.9%	98.9%	0.988	98.9% in zone A[d]
				HCP	99.5%	99.5%	0.986	99.5% in zone A[d]
			Venous	HCP	100%	100%	0.996	100% in zone A
NCT01447121	CXT/CNEZ[17,37]	116	Capillary finger stick	Subject	100%	99.1%	0.988	100% in zone A
				HCP	100%	100%	0.982	100% in zone A
NCT01268267	CNL[18,36]	93	Microlet®2 capillary finger stick	Subject	≥99.4%	≥97.2%	Not reported	99.4% in zone A[d]
			Tenderlett® capillary finger stick	Subject	100%	≥99.3%	Not reported	100% in zone A
NCT01410773	CNL[22,23]	110	Capillary finger stick	Subject	100%	99.1%	0.993	100% in zone A
				HCP	100%	100%	0.993	100% in zone A
			Palm AST	Subject	97.3%	96.3%	0.983	97.2% in zone A[d]
NCT01466075	CNUSB[19]	207	Capillary finger stick	Subject	99.5%	98.5%	0.984	99.0% in zone A[d]
			Palm AST	Subject	99.5%	99.0%	0.976	100% in zone A
			Venous	HCP	100%	100%	≥0.991	100% in zone A
NCT01474317	CN[21]	226	Capillary finger stick	Subject	99.5%	99.1%	0.985	99.5% in zone A[d]
			Palm AST	Subject	99.1%	96.8%	0.968	99.1% in zone A[d]
			Venous	HCP	100%	100%	0.987	100% in zone A

[a] Per ClinicalTrials.gov.
[b] Within ISO 15197:2003 accuracy criteria (i.e., ≥95% of results shall fall within ±15 mg/dl or ±20% for samples with glucose concentrations <75 and ≥75 mg/dl, respectively).
[c] Within ISO 15197:2013 accuracy criteria (i.e., ≥95% of results shall fall within ±15 mg/dl or ±15% for samples with glucose concentrations <100 and ≥100 mg/dl, respectively).
[d] All remaining results were within zone B.

Regression analyses of BGMS results demonstrated strong correlation with reference results for the five studies for which regression analysis results were reported (R^2 >98% for finger stick and venous blood samples and >96% for AST samples; **Table 5**).[17,19–23] Evaluation of clinical accuracy using Parkes consensus error grid analysis[34] showed that the majority of BGMS results (≥98.9% of finger stick results, ≥97.2% of AST results, and 100% of venous results) were in zone A (i.e., no effect on clinical action) for all six studies (**Table 5**).[17,19–22,36] All remaining BGMS results (≤1.1% of finger stick results and ≤2.8% of AST results) were within zone B (i.e., altered clinical action with little or no effect on clinical outcome); there were no results in zones C, D, or E (i.e., altered clinical action with increasingly severe effect on clinical outcome) for any of the systems.[17,19–22,36]

Subjects in the six clinical studies reported that the new BGMS platform was easy to use. Additionally, the six clinical studies assessed meter features. Also, four of the six studies evaluated subject opinions regarding BGMS accuracy and diabetes management in general via subject questionnaires. Subject ease of use ratings from the clinical studies of the new BGMS platform are summarized in **Figure 3**. In all four studies, most subjects responded that they agreed or strongly agreed that the BGMS was easy to use (≥92%), the user guide instructions were easy to understand (≥86%),

the meter display was easy to read (≥96%), and it was easy to see and understand the test results (≥95%; **Figure 3**).[17,19,21,22] In the CN BGMS study, 93.8% of subjects agreed or strongly agreed that the meter summary screen could help them understand how they are doing with their diabetes.[21] The CXT/CNEZ BGMS and CNL BGMS studies also assessed overall satisfaction with the BGMS, and the majority of subjects (98.9% and 99%, respectively) rated their overall satisfaction with the BGMS as "good" to "excellent" on subject questionnaires.[18,20] The majority of subjects rated specific features of the CNL BGMS as "good" to "excellent," including ease of using the autolog feature (100%), ability to adjust target ranges (96%), lighted test strip port (96%), and ease of accessing (100%) and usefulness (98%) of the TRENDS menu.[18]

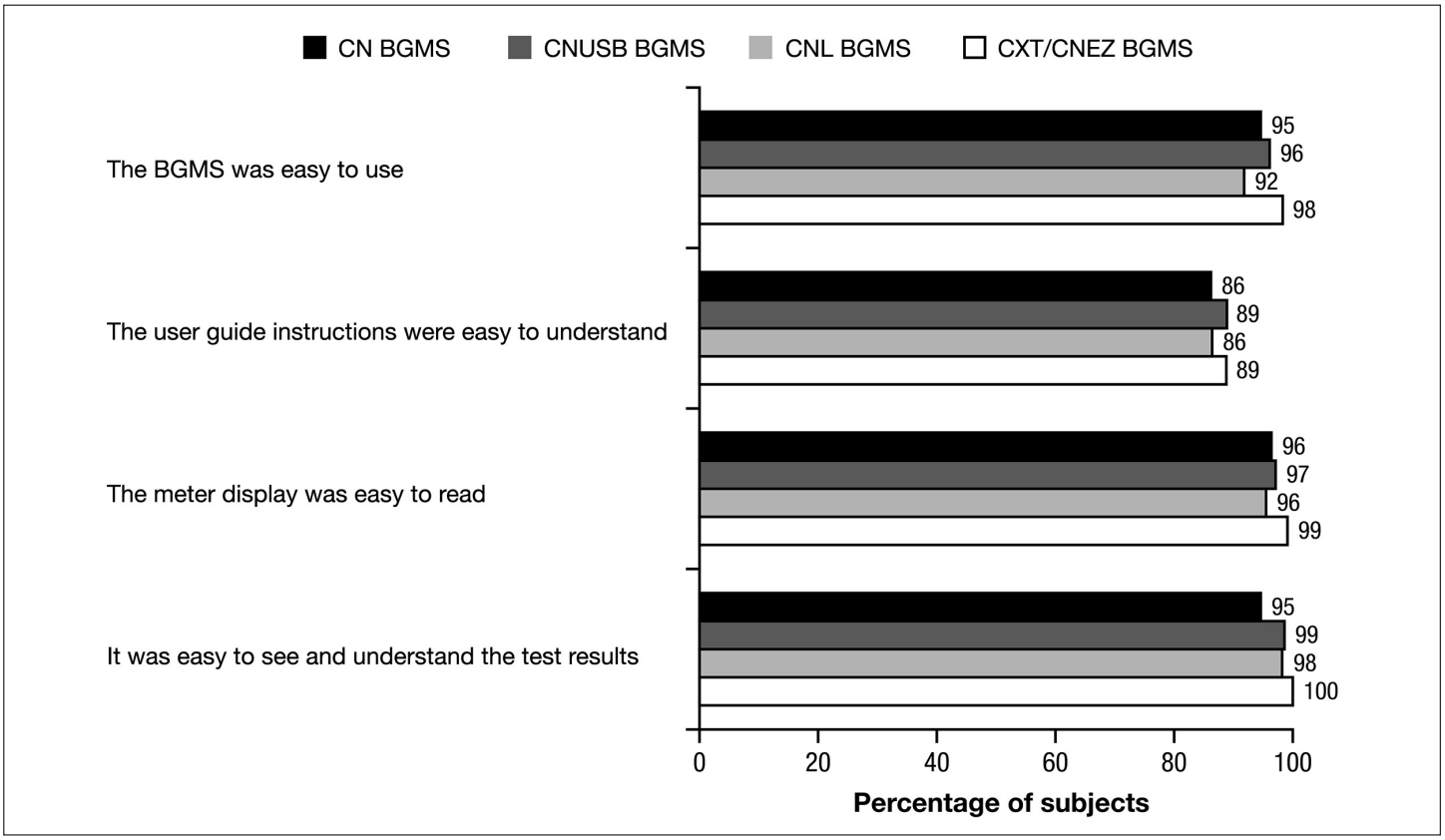

Figure 3. Ease of use of the new BGMS platform as assessed by subject questionnaire.[17,19,21,22]

Subjects in four of the six clinical studies completed a second questionnaire that assessed general attitudes regarding BGMS accuracy. In each study, most subjects agreed or strongly agreed that accuracy is important to help with: their ability to manage their diabetes (≥94%); preventing low blood sugar (89%); and using their results to manage their diabetes (≥96%; **Figure 4**).[19,21,37] Approximately half of subjects in each study indicated that they would continue to use the meters and test strips for which they are reimbursed by their insurance company even if a more accurate meter was available, thus implying that the other half of subjects consider accuracy a more important factor than cost when selecting a meter (**Figure 4**).[19,21,23,37] In addition, in studies that evaluated the CNL BGMS or the CNUSB BGMS, 70% and 79% of subject questionnaire respondents, respectively, agreed or strongly agreed that they would switch meters for a more accurate meter.[19,23]

Comparative Accuracy

The accuracy of the CXT/CNEZ BGMS was evaluated in comparison with the hexokinase reference method in a study conducted at the Quakenbrück Hospital in Germany.[38] The secondary objective of the study was to compare the accuracy of the CXT/CNEZ BGMS with the ACCU-CHEK® Aviva (ACA; Roche Diagnostics, Indianapolis, IN) and

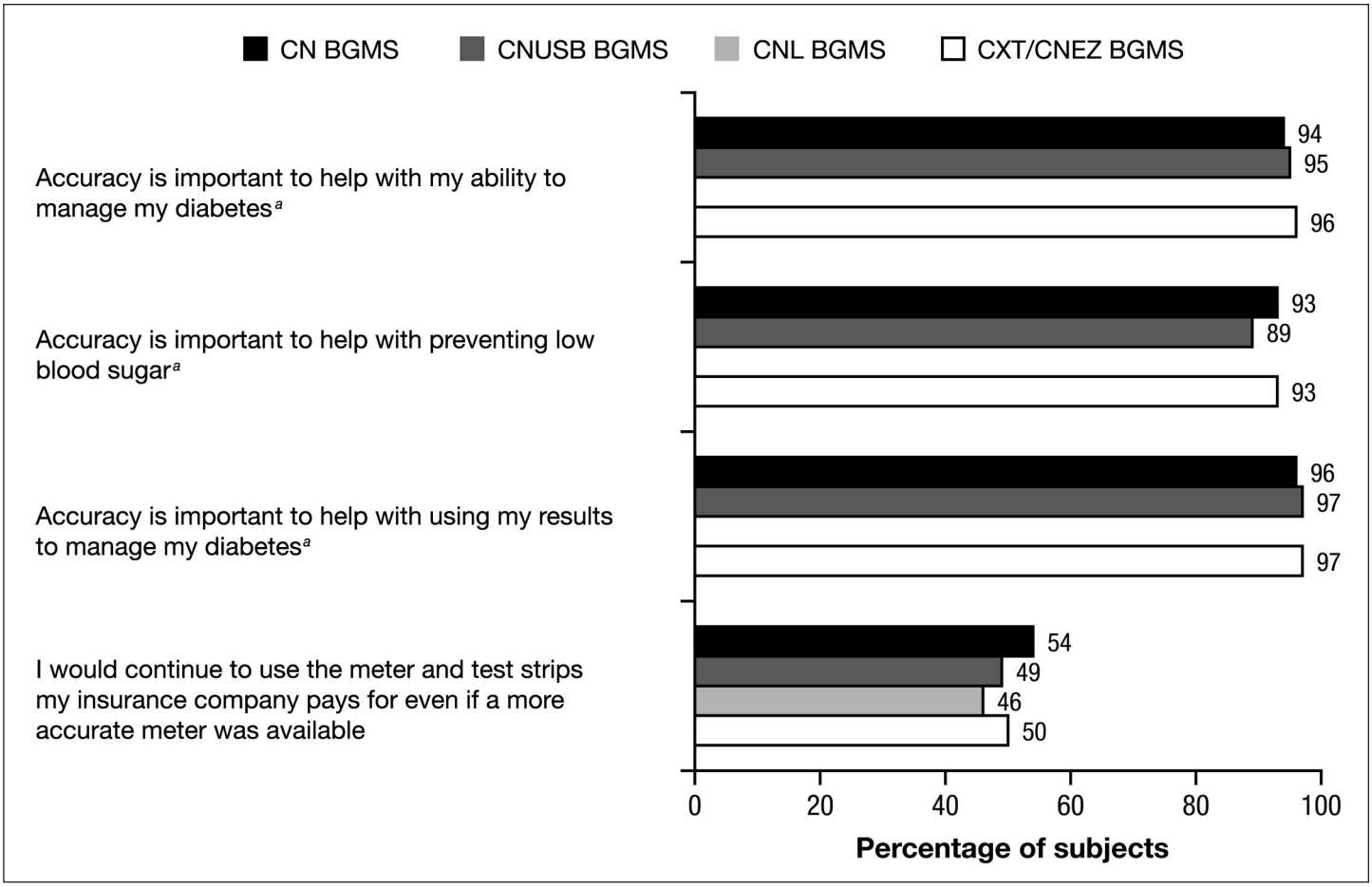

Figure 4. Subjects' general attitudes about BGMS accuracy based on questionnaire results from the clinical studies of the new BGMS platform.[19,21,23,37] [a]This question was not asked in the CNL BGMS study.

OneTouch® Verio® (OTV; LifeScan Inc., Milpitas, CA) systems.[38] In this study, a trained HCP tested capillary finger stick samples that were previously collected from 110 subjects using each of the meter systems.[38] Accuracy was assessed according to the then-proposed ISO 15197:2013 accuracy criteria. Results of the comparative accuracy evaluations are summarized in **Table 6**. Overall, 100% of results obtained using the CXT/CNEZ BGMS met the ISO 15197:2013 accuracy guidelines, compared with 98.2% of ACA results and 96.4% of OTV results (**Table 6**).[38] Analysis of variance results showed that the CXT/CNEZ BGMS had lower mean absolute relative differences (MARDs) versus reference results than the OTV system and the ACA system (**Table 6**).[38] Lower MARD values indicate less variation from the reference value and thus greater comparative accuracy. These differences were statistically significant for two of the three test strip lots used versus the ACA system and for all three test strip lots used versus the OTV system.[38]

Another study conducted using the YSI reference method evaluated the CXT/CNEZ BGMS in comparison with the TRUEtrack® (TT; Nipro Diagnostics Inc., Fort Lauderdale, FL), FreeStyle Freedom Lite® (FFL; Abbott Diabetes Care Inc., Alameda, CA), OneTouch Ultra®2 (OTU2; LifeScan Inc., Milpitas, CA), and ACA systems (data on file). In this sponsor-investigator study, a trained operator tested unmodified capillary blood samples from 146 subjects using each of the five systems. One sample per subject was tested without modification, and up to two additional blood samples were glycolyzed to safely lower blood glucose to <70 mg/dl; 242 glycolyzed samples were tested with each of the five BGMSs. The accuracy of the BGMSs was compared using MARD. The CXT/CNEZ BGMS had the lowest MARD versus reference results of 4.7%, while the TT, FFL, OTU2, and ACA systems had MARD estimates of 26.2%, 18.3%, 23.4%, and 6.3%, respectively, across the overall tested glucose range (24–386 mg/dl; **Table 7**). In addition, for samples with glucose concentrations <70 mg/dl, the CXT/CNEZ BGMS had the lowest MARD versus reference results of 0.7% compared with the TT (33.2%), FFL (18.3%), OTU2 (22.4%), and ACA (2.5%) systems (**Table 7**). Of note,

glucose-oxidase-based BGMSs (TT and OTU2) may be affected by glycolysis-induced changes in oxygen concentration, and thus unmodified samples were also evaluated. The CXT also had the lowest MARD values in all glucose ranges in unmodified samples (**Table 7**).

Table 6.
Summary of Comparative Accuracy Evaluation of the Test Strip Using the Hexokinase Reference Method

Meter system	Number of results within ISO 15197:2013 criteria[a]	Number of results within ±5 mg/dl[b] or ±5%[c] of the reference result	*P* value[d] versus ACA	*P* value[d] versus OTV	MARD from reference results (%)	Standard error (%)
CXT/CNEZ (test strip lot 1; *n* = 110)	110 (100%)	97 (88.2%)	<0.0001	<0.0001	2.76	0.29
CXT/CNEZ (test strip lot 2; *n* = 110)	110 (100%)	86 (78.2%)	0.0177	<0.0001	3.18	0.29
CXT/CNEZ (test strip lot 3; *n* = 110)	110 (100%)	98 (89.1%)	<0.0001	<0.0001	2.79	0.29
ACA (*n* = 110)	108 (98.2%)	69 (62.7%)	Not applicable	0.1336	4.31	0.29
OTV (*n* = 110)	106 (96.4%)	57 (51.8%)	0.1336	Not applicable	6.12	0.29

[a] At least 95% of results shall fall within ±15 mg/dl or ±15% for samples with glucose concentrations <100 and ≥100 mg/dl, respectively.
[b] For samples with blood glucose concentrations <100 mg/dl.
[c] For samples with blood glucose concentrations ≥100 mg/dl.
[d] Fisher exact test.

Table 7.
Summary of Comparative Accuracy Evaluation of the Test Strip Using the YSI Reference Method[a]

	Overall glucose concentration (23.5–386 mg/dl)									Glucose concentration <70 mg/dl (*n* = 190)[b]			Glucose concentration ≥70 mg/dl (*n* = 198)		
	All samples (*N* = 388)			Unmodified samples (*n* = 146)			Glycolyzed samples (*n* = 242)								
Meter system	MARD, %	95% CI	SE, %	MARD, %	95% CI	SE, %	MARD, %	95% CI	SE, %	MARD, %	95% CI	SE, %	MARD, %	95% CI	SE, %
CXT/CNEZ	4.7	-2.0 to 11.4	3.4	8.9	4.5 to 13.3	2.2	11.2	4.8 to 17.5	3.3	0.65	-5.5 to 6.8	3.1	5.5	0.7 to 10.3	2.4
ACA	6.3	-0.4 to 13.0	3.4	10.3	5.9 to 14.7	2.2	12.9	6.5 to 19.3	3.3	2.5	-3.6 to 8.7	3.1	6.9	2.1 to 11.6	2.4
FFL	18.3	11.6 to 25.0	3.4	18.5	14.1 to 22.9	2.2	27.2	20.8 to 33.5	3.3	18.3	12.1 to 24.4	3.1	15.3	10.5 to 20.0	2.4
OTU2	23.4	16.7 to 30.1	3.4	24.5	20.2 to 28.9	2.2	31.6	25.3 to 38.0	3.3	22.4	16.2 to 28.6	3.1	21.3	16.5 to 26.1	2.4
TT	26.2	19.5 to 32.9	3.4	17.7	13.3 to 22.1	2.2	40.3	33.9 to 46.7	3.3	33.2	27.1 to 39.4	3.1	16.3	11.5 to 21.1	2.4

CI, confidence interval. SE, standard error.
[a] Data on file.
[b] Of the 190 blood samples with glucose concentrations <70 mg/dl, 6 samples were unmodified and 184 samples were glycolyzed.

Conclusions

In diabetes management, both patients and HCPs need to incorporate SMBG data into therapy and self-care plans in order to maximize the benefits of SMBG. One study, which assessed differences between self-reported estimates of blood glucose values and those measured on a blood glucose meter, reported that 58% of subjects estimated blood glucose values were more than ±15 mg/dl or ±15% of meter glucose values <100 and ≥100 mg/dl, respectively.[39]

It is critical for SMBG devices to be accurate because the use of SMBG results to make therapeutic decisions has the potential to affect patient outcomes. The new test strip and its associated BGMSs enable a high level of accuracy. Based on questionnaire results from clinical studies with the new BGMS platform, accuracy in blood glucose monitoring is a common desire for people with diabetes and a very important consideration when selecting a device for SMBG. Further, the majority of people in these studies agreed or strongly agreed that BGMS accuracy is very important to assist with the management of their diabetes. Each BGMS in the platform that utilizes the new test strip met and exceeded both ISO 15197:2003 and ISO 15197:2013 accuracy criteria in the laboratory regardless of the laboratory reference method used—YSI or hexokinase. Additionally, BGMSs using the new test strip demonstrated 98% of results that were within ±10% or ±10 mg/dl of the reference result, meeting even more stringent accuracy criteria. In the hands of users (people with diabetes and HCPs), results with each BGMS in the platform were similar to results from the laboratory studies regardless of whether testing was performed by trained HCPs or subjects who were naive to the system. Each BGMS in the new platform also demonstrated ease of use and the ability to use the meter based upon the user guide provided, without additional training. In comparative accuracy evaluations, the CXT/CNEZ BGMS demonstrated an enhanced level of accuracy compared with available branded blood glucose meters.

Optimal glycemic control will improve long-term outcomes in many patients with diabetes.[40,41] Tools such as new therapeutics and advanced technology, including highly accurate BGMSs, will help patients, working with their diabetes teams, to achieve the goal of improved glucose control.

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References:

1. Bode BW. The accuracy and interferences in self-monitoring of blood glucose. US Endocrine Rev. 2007;2:46–8.
2. Hellman R. Glucose meter inaccuracy and the impact on the care of patients. Diabetes Metab Res Rev. 2012;28(3):207–9.
3. Klonoff DC, Blonde L, Cembrowski G, Chacra AR, Charpentier G, Colagiuri S, Dailey G, Gabbay RA, Heinemann L, Kerr D, Nicolucci A, Polonsky W, Schnell O, Vigersky R, Yale JF; Coalition for Clinical Research-Self-Monitoring of Blood Glucose Scientific Board. Consensus report: the current role of self-monitoring of blood glucose in non-insulin-treated type 2 diabetes. J Diabetes Sci Technol. 2011;5(6):1529–48.
4. American Diabetes Association. Standards of medical care in diabetes--2012. Diabetes Care. 2012;35 Suppl 1:S11–63.
5. Fera T, Bluml BM, Ellis WM. Diabetes Ten City Challenge: final economic and clinical results. J Am Pharm Assoc (2003). 2009;49(3):383–91.

6. Martin S, Schneider B, Heinemann L, Lodwig V, Kurth HJ, Kolb H, Scherbaum WA. Self-monitoring of blood glucose in type 2 diabetes and long-term outcome: an epidemiological cohort study. Diabetologia. 2006;49(2):271–8.
7. Karter AJ, Ackerson LM, Darbinian JA, D'Agostino RB Jr, Ferrara A, Liu J, Selby JV. Self-monitoring of blood glucose levels and glycemic control: the Northern California Kaiser Permanente Diabetes Registry. Am J Med. 2001;111(1):1–9.
8. Franciosi M, Lucisano G, Pellegrini F, Cantarello A, Consoli A, Cucco L, Ghidelli R, Sartore G, Sciangula L, Nicolucci A; ROSES Study Group. ROSES: role of self-monitoring of blood glucose and intensive education in patients with type 2 diabetes not receiving insulin. A pilot randomized clinical trial. Diabet Med. 2011;28(7):789–96.
9. Polonsky WH, Fisher L, Schikman CH, Hinnen DA, Parkin CG, Jelsovsky Z, Axel-Schweitzer M, Petersen B, Wagner RS. A structured self-monitoring of blood glucose approach in type 2 diabetes encourages more frequent, intensive, and effective physician interventions: results from the STeP study. Diabetes Technol Ther. 2011;13(8):797–802.
10. American Diabetes Association. Self-monitoring of blood glucose. Diabetes Care. 1994;17(1):81–6.
11. Klonoff DC. The Food and Drug Administration is now preparing to establish tighter performance requirements for blood glucose monitors. J Diabetes Sci Technol. 2010;4(3):499–504.
12. Klonoff DC. Regulatory controversies surround blood glucose monitoring devices. J Diabetes Sci Technol. 2010;4(2):231–5.
13. Brown D, Schachner HC, Castro R, Chu A. Accuracy assessment of a new blood glucose monitoring system. Abstract presented at: 21st Biennial Congress of the International Diabetes Federation, December 4–8, 2011, Dubai, United Arab Emirates.
14. Harrison B, Schachner HC, Brown D. Accuracy evaluation of a new blood glucose monitoring system. Presented at: 15th Annual Meetings of the Canadian Diabetes Association/Canadian Society of Endocrinology and Metabolism, October 10–13, 2012, Vancouver, British Columbia, Canada.
15. Harrison B, Dunne N. Accuracy and precision evaluation of the CONTOUR® NEXT blood glucose monitoring system. Presented at: 12th Annual Meeting of the Diabetes Technology Society, November 8–10, 2012, Bethesda, MD.
16. Pflug B, Warchal-Windham ME, Goldy A, Chu A. Analytical accuracy evaluation of the CONTOUR® XT blood glucose meter. Presented at: 12th Annual Meeting of the Diabetes Technology Society, November 8–10, 2012, Bethesda, MD.
17. Bailey TS, Tideman A, Greene C, Viggiani M, Yu J, Pardo S, Parkes JL. User performance evaluation of a new blood glucose monitoring system. Diabetes. 2012;61 Suppl 1:A223. Abstract 880-P.
18. Bailey T, Wallace JF, Greene C, Pardo S, Parkes JL, Schachner HC. Performance evaluation of a novel blood glucose monitoring system. Pediatr Diabetes. 2011;12 Suppl 15:129. Abstract P/255/WED.
19. Baum J, Robinson SJ, Pardo S, Yu J, Parkes JL. Performance evaluation of a new blood glucose monitoring system in the hands of users. Presented at: 15th Annual Meetings of the Canadian Diabetes Association/Canadian Society of Endocrinology and Metabolism, October 10–13, 2012, Vancouver, British Columbia, Canada.
20. Bailey TS, Wallace JF, Parkes JL, Pardo S, Yu J, Schachner HC, Simmons DA, Chu A. Performance of a new blood glucose monitoring system in the hands of intended users. Diabetes Technol Ther. 2012;14(9):783–9.
21. Bernstein R, Caswell M, Frank J, Fullam J, Pardo S, Wallace JF. User performance evaluation of the CONTOUR® NEXT blood glucose monitoring system with the CONTOUR® NEXT test strip. Presented at: 12th Annual Meeting of the Diabetes Technology Society, November 8–10, 2012, Bethesda, MD.
22. Wallace J, Yu J, Pardo S, Brown D, Parkes JL. Accuracy of a new blood glucose monitoring system in the hands of users. Diabetes. 2012;61 Suppl 1:A590. Abstract 2340-PO.
23. Wallace J, Yu J, Pardo S, Brown D, Parkes JL. Accuracy of the Contour Next Link blood glucose meter system (BGMS) in the hands of users. Presented at: 12th Annual Meeting of the Diabetes Technology Society, November 8–10, 2012, Bethesda, MD.
24. Harrison B, Maurer E, Wu HP. Performance of a new algorithm for sample re-application during blood glucose test strip underfill conditions. Abstract presented at: Clinical Diabetes Technology Meeting, April 20–21, 2012, Los Angeles, CA.
25. Chu A, Tudor B. Interference evaluation of the CONTOUR® NEXT test strip. Presented at: 12th Annual Meeting of the Diabetes Technology Society, November 8–10, 2012, Bethesda, MD.
26. Bayer Healthcare LLC. CONTOUR NEXT reagent insert. Revised February 2011.
27. Bayer Healthcare LLC. CONTOUR NEXT EZ user guide. Revised November 2011.
28. Bayer Healthcare LLC. CONTOUR NEXT LINK user guide. Revised February 2013.
29. Bayer Healthcare LLC. CONTOUR NEXT user guide. Revised May 2012.
30. Bayer Healthcare LLC. CONTOUR NEXT USB user guide. Revised March 2012.
31. International Organization for Standardization. ISO 15197:2003: In vitro diagnostic test systems -- requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus. Geneva: International Organization for Standardization; 2003.
32. International Organization for Standardization. ISO 15197:2013: In vitro diagnostic test systems -- requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus. Geneva: International Organization for Standardization; 2013.
33. Harrison B, Brown D, Warchal-Windham ME, Schachner HC, Parkes JL, Pardo S. Accuracy evaluation of a new platform of blood glucose monitoring systems with the CONTOUR® NEXT test strip. Presented at: 12th Annual Meeting of the Diabetes Technology Society, November 8–10, 2012, Bethesda, MD.
34. Parkes JL, Slatin SL, Pardo S, Ginsberg BH. A new consensus error grid to evaluate the clinical significance of inaccuracies in the measurement of blood glucose. Diabetes Care. 2000;23(8):1143–8.

35. Alcaraz J, Rico N, Petruschke T, Bedini JL. Performance evaluation of a novel blood glucose monitoring system: Contour® XT. Poster presented at: 5th Annual International Conference on Advanced Technologies and Treatments for Diabetes, February 8–11, 2012, Barcelona, Spain.

36. Bailey T, Wallace J, Greene C, Pardo S, Parkes JL, Schachner HC. Performance evaluation of a novel blood glucose monitoring system. Poster presented at: 37th Annual Scientific Meeting of the International Society for Pediatric and Adolescent Diabetes, October 19–22, 2011, Miami Beach, FL.

37. Bailey T, Tideman A, Greene C, Viggiani M, Yu J, Pardo S, Parkes JL. User performance evaluation of the CONTOUR® NEXT EZ (CONTOUR® XT) blood glucose monitoring system. Poster presented at: 72nd Scientific Sessions of the American Diabetes Association (ADA), June 8–12, 2012, Philadelphia, PA. Abstract 880-P.

38. Lemke C, Petruschke T, Wallace JF, Pardo S, Parkes JL, Matthaei S. Comparative accuracy evaluation of the CONTOUR XT® blood glucose monitoring system. Poster presented at: 47th Annual Diabetes Congress of the Deutsche Diabetes Gesellschaft (DDG), May 16–19, 2012, Stuttgart, Germany.

39. Pettus J, Greer J, Stenger P, Schachner HC, Dunne N, Parkes JL, Edelman S, Pardo S. Differences between perceived versus measured blood glucose test results in people with type 2 diabetes. Diabetes. 2012;61 Suppl 1:A218. Abstract 861-P.

40. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977–86.

41. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837–53.