Post-Market Surveillance of a Blood Glucose Test Strip Demonstrates No Evidence of Interference on Clinical Accuracy in a Large Cohort of People with Type 1 or Type 2 Diabetes

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Abstract

Background Regulations and industry guidance relating to testing for interference in blood glucose monitoring (BGM) systems continue to focus on in vitro laboratory bench tests. Post-market surveillance (PMS) in a clinical setting allows for BGM accuracy assessments to evaluate the impact of real-world exposure to polypharmacy in people with diabetes. This study evaluated the OneTouch Select Plus® BGM test-strip accuracy with respect to polypharmacy using a clinical registry dataset.

Methods Medication profiles were analysed for 1023 subjects (425 with type 1 (T1D) and 598 with type 2 diabetes (T2D)) attending 3 UK hospitals. Blood samples were analysed to determine clinical accuracy of the BGM test-strip against a laboratory comparator.

Results 538 different medications (48 diabetes and 490 non-diabetes) were recorded across the 1023 subjects. Patients took on average 6.9 ($n = 1$-36) individual medications and 4.1 ($n = 1$-13) unique medication classes. Clinical accuracy to EN ISO 15197:2015 criteria were met irrespective of increasing average number of individual medications, categorized from 1-3, 4-6, 7-9, 10-12 and >12 taken per subject (97.7%, 97.7%, 97.8%, 97.8%, and 98.4%, respectively). Clinical accuracy criteria were met across 15 classes of medication using the combined dataset (97.9%; 29784/30433). Surveillance Error Grid (SEG) analysis showed 98.7% (29959/30368) of readings presented no clinical risk. No individual class or combination of medication classes impacted clinical accuracy of the BGM test-strip.

Conclusions Clinical performance for the test strip under assessment demonstrated no evidence of interference from over 500 prescription medications, with clinical accuracy maintained across a range of polypharmacy conditions in people with diabetes.

Keywords

post market surveillance (PMS), accuracy, blood glucose monitoring (BGM), medications, regulations

Introduction

Industry guidance indicates that a choice of interfering compounds should be made based on: ". . .knowledge of the chemistry, the measurement procedure, and its intended use."[1] Beyond a limited list of potential interferences defined by regulatory authorities such as the FDA[2] and international standards,[3] manufacturers of glucose monitoring devices are themselves responsible for the identification of potential

interferents. Inputs such as internal complaints, monitoring processes and periodic literature reviews may detect new

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sources of interference, but the challenge for device manufacturers is to balance a need to evaluate true novel risks with a speculative approach of testing compounds that have no proposed mechanism or history of interference with established chemistries.

The assessment of interfering effects in the clinical setting is not mandated for blood glucose or continuous glucose monitoring (BGM or CGM) systems by regulators, and indeed this could prove logistically challenging to organize. However, this does not remove the responsibility for manufacturers to use the tools at their disposal to evaluate interference sensitivity in samples from the intended patient population. A practical solution to this problem may be to use ongoing clinical post market surveillance (PMS) activities to establish the real-world impact of new or existing medications on all glucose monitoring products. These surveillance activities are capable of mimicking the full range of medications taken by people with diabetes (PWDs). Evaluations of this type complement established laboratory interference tests that provide detailed assessments of a single substance at pathologic concentrations but offer limited insight about the impact of concomitant medications on the BGM or CGM device. The Clinical and Laboratory Standards Institute (CLSI)[1] guided single-substance laboratory approach (valuable and well-defined though it is) is still the only method advocated within recently finalized FDA industry guidance.[2]

Where multiple subjects are using the same prescribed medication (in a retrospective surveillance initiative with many patients) an opportunity exists to evaluate the impact of a specific medication upon the patient population. This relies upon an assumption that the range of other medications taken concomitantly would not all interact substantially with the specific compound of interest. The challenge with polypharmacy interaction with glucose measurement is well illustrated by the summing of measurement errors as described by Erbach et al,[4] where the influence on an assay from numerous interfering compounds may prove either directionally synergistic or antagonistic, such that small interfering effects are either exacerbated or concealed. Previously published data[5] has demonstrated that a BGM system may be evaluated against such cumulative effects by using clinical data to increase confidence in performance in the presence of a wide array of medications. The current study describes a robust surveillance evaluation of a different strip technology: the OneTouch Select Plus® strip platform utilizing the enzyme glucose oxidase. The accuracy of this strip platform in the presence of potential interference was evaluated over a four-year surveillance period, as part of a PMS program using a hospital-based registry.

Methods

Patient registry

The patient registry (initiated by Lifescan) started collecting in-clinic data for the specified test strip platform from May 2016. All patients attend one of the manufacturer's 3 UK NHS (National Health Service) clinics: The Highland Diabetes Institute, Inverness; The Royal Infirmary of Edinburgh; Birmingham Heartlands Hospital. Patients must first enrol in the registry, with any subsequent testing performed under UK Scotland Research Ethics Committee approval (10/S1103/2). The registry collects anonymized demographic, medical history and study participation data within the Medidata RAVE electronic data capture system (Medidata Solutions, NY). At first visit, self-reported details on medications taken by each patient are provided to trained facilitators and verified against the subject's NHS electronic medical records before being recorded within the registry. This data can therefore be cross-referenced and correlated with in-clinic patient test-strip performance data to evaluate any impact of medications on strip performance. If a patient makes a repeat visit to the clinic, they are then asked to confirm their current medications status and the patient registry is updated accordingly.

Clinic Blood Glucose Test-Strip Method

Routine performance monitoring of test-strips, manufactured by LifeScan Europe GmbH (Zug, Switzerland), is conducted through clinical accuracy assessment of representative production batches. Only clinical data specific to the test strip platform under evaluation was included in this assessment. Inclusion criteria required participants to have completed informed consent and have a diagnosis of diabetes. Although the product hematocrit claim is 30%-55%, all patient data were included, irrespective of hematocrit. During clinical assessment, the participant's finger is lanced (finger-stick) by the site staff and a drop of blood applied to up to 18 blood glucose test-strips. Hematocrit levels are recorded as the percentage volume of red blood cells (RBCs) as a proportion of the total sample volume. Reference glucose values were determined from the centrifuged plasma fraction of a 300 μl capillary blood sample collected by Microvette and analyzed, within 30 mins., on 2 separate YSI STAT PLUS™ blood glucose analyzers (Yellow Springs Instrument Co. Inc., OH). This reference analyser uses the same enzyme (glucose oxidase) as the system under test but includes a cellulose-acetate membrane that reduces the sensitivity of the analyser to many potential sources of interference.[6] However, some glucose analogues and small molecules may have been capable of interfering with both the test-strip and reference analyser using the same mechanism. If meeting acceptance criteria, the mean of the duplicate comparator values was used. Participants may have visited a clinic site on multiple occasions and been tested with more than 1 strip lot per visit, thus the clinical dataset is not entirely composed of unique subjects. Each strip lot was assessed on a minimum of 100 unique subjects with all tests performed by trained staff. The clinical accuracy of each BGM value within the patient registry dataset was evaluated against the EN ISO

Table 1. Subject Demographics of Patients Tested Using OneTouch Select Plus® Strips.

	All *N* = 1023	T2D *N* = 598	T1D *N* = 425
Sex, *n* (%)			
Male	543 (53.1%)	333 (55.7%)	210 (49.4%)
Female	480 (46.9%)	265 (44.3%	215 (50.6%)
Age in years, mean (range)	56 (14-88)	63 (17-88)	45 (14-85)
Diabetes type, *n* (%)	1023 (100%)	598 (58.5%)	425 (41.5%)
Mean diabetes duration, years	19	17	22
Duration range, years	<1 to 64 (*N* = 975)	<1 to 56 (*N* = 561)	<1 to 64 (*N* = 414)
A1c mean, % (mmol/mol)	8.5% (69)	8.3% (67)	8.7% (72)
A1c range, % (mmol/mol)	5.1-15.9% (32-150)	5.1-14.8% (32-138)	5.3-15.9% (34-150)
BGM frequency, *n*			
Mean (tests per day)	3.0	1.9	4.4
BGM range (tests per day)	0 to 15	0 to 15	0 to 15
Therapy, *n* (%)			
Insulin pump and insulin injections	457 (44.7%)	92 (15.4%)	365 (85.9%)
Oral meds + insulin	351 (34.3%)	296 (49.5%)	55 (12.9%)
Oral meds only	173 (16.9%)	173 (28.9%)	-
Oral meds + other injectables	13 (1.3%)	10 (1.7%)	3 (0.7%)
Diet and exercise	26 (2.5%)	25 (4.2%)	1 (0.2%)[a]
Other	3 (0.3%)	2 (0.3)	1 (0.2%)

[a]T1D subject attended clinic whilst in hospital after transplant surgery.

15197:2015 definition of accuracy (A minimum of 95% of BGM values to be within ±15 mg/dL (<100 mg/dL) or ±15% (≥100 mg/dL) of comparator. Data were also evaluated by surveillance error grid (SEG).

Medication Status & Test-Strip Performance

Over the assessment period (Jan 2017 to Jan 2020) the dataset included 1023 evaluable patients. Some individual patients may have visited a clinic more than once during this period, and on each occasion may have provided a blood sample for accuracy evaluation of more than one production batch, hence the number of medications and associated blood glucose reading combinations is 30,433. The maximum number of medications assigned to a patient was considered as visit-specific within this assessment (if the subject took at least one medication from a class, they were assessed against that class). This allowed for a single patient to appear in different medication classifications depending on their medication status at the time of each visit. Clinic testing was scheduled during standard daily operating hours, and it would reasonably be expected that dosages of medications were as per prescribed therapeutic levels. However, factors such as time of administration, dosage, pharmacokinetic properties and other patient-specific factors were not controlled, with patients routinely recruited directly from the diabetes clinic waiting areas. All medications reported by the patient were first classified as either a diabetes medication or non-diabetes medication, with non-diabetes further refined into 15 medication classes according to their intended physiologic or therapeutic action. Medications were then either individually assessed with respect to test-strip performance or assessed with respect to cohorts of patients taking certain medication classes (eg, anti-hypertensive, lipid lowering or anti-depressants).

Analysis

Each test-strip batch was assessed against the EN ISO 19157:2015 definition of clinical accuracy. Analyses were performed using SPSS Statistics v21 software (IBM Corp. Armonk, US) with independent statistician verification.

Results

Subject Demographics

Of the 1023 patients, a greater proportion were male (53.1%), with wide variation in age range (14-88 years) and an overall mean age of 56 years (Table 1). A high proportion of the T2D patients in our cohort (388/598; 64.9%) reported using insulin compared to international survey and registry values,[7] which reflects the fact that hospital-based clinics often have more difficult to manage or complex patients referred to them from primary care. Non-insulin-users accounted for 215/1023 (21.0%) of the cohort. Patients had significant durations of diabetes averaging 19 years with a range of <1-64 years.

Medication Classifications

A total of 538 unique medications were recorded across all 1023 patients. This included 48 individual diabetes

Table 2. Summary of Diabetes Medications with an Overall Population Prevalence of ≥0.5% for All 1023 Subjects.

	All patients N = 1023	T2D N = 598	T1D N = 425
	n (%)		
Metformin	499 (48.8)	441 (73.7)	58 (13.6)
Novorapid	329 (32.2)	87 (14.5)	242 (56.9)
Lantus	314 (30.7)	118 (19.7)	196 (46.1)
Humalog	225 (22.0)	105 (17.6)	120 (28.2)
Levemir	145 (14.2)	40 (6.7)	105 (24.7)
Gliclazide	143 (14.0)	140 (23.4)	3 (0.7)
Novomix	102 (10.0)	81 (13.5)	21 (4.9)
Sitagliptin	74 (7.2)	73 (12.2)	1 (0.2)
Humulin	71 (6.9)	49 (8.2)	22 (5.2)
Dapagliflozin	62 (6.1)	59 (9.9)	3 (0.7)
Trajenta	48 (4.7)	47 (7.9)	1 (0.2)
Liraglutide	38 (3.7)	36 (6.0)	2 (0.5)
Degludec	28 (2.7)	2 (0.3)	26 (6.1)
Empagliflozin	27 (2.6)	26 (4.3)	1 (0.2)
Tresiba	26 (2.5)	—	26 (6.1)
Trulicity	20 (2.0)	20 (3.3)	—
Fiasp	19 (1.9)	1 (0.2)	18 (4.2)
Glargine	17 (1.7)	8 (1.3)	9 (2.1)
Pioglitazone	17 (1.7)	16 (2.7)	1 (0.2)
Apidra	15 (1.5)	3 (0.5)	12 (2.8)
Bydureon	14 (1.4)	13 (2.2)	1 (0.2)
Glipizide	9 (0.9)	9 (1.5)	—
Glimepiride	8 (0.8)	8 (1.3)	—
Hypurin neutral	8 (0.8)	—	8 (1.9)
Xultophy	8 (0.8)	8 (1.3)	—
Glucagen	6 (0.6)	1 (0.2)	5 (1.2)
Canagliflozin	5 (0.5)	5 (0.8)	—
Insulatard	5 (0.5)	3 (0.5)	2 (0.5)
Saxagliptin	5 (0.5)	5 (0.8)	—

medications and 490 non-diabetes medications. Diabetes medications with an overall population prevalence of ≥0.5% (29 of 48) are presented in Table 2. Non-diabetes medications with an overall population prevalence of ≥2.5% (41 of 490) are shown in Table 3. All 538 medications were then classified according to intended physiologic or therapeutic action into 15 medication classes. The numbers of patients taking at least one medication from each of the 15 classes are shown in Table 4. The highest percentage of patients took diabetes medications (96.9%), anti-hypertensive (53.5%), lipid lowering (53.2%) or anti-depressants (32.8%). The average number of medication classes taken by all, T1D and T2D patients were 4.1, 3.3 and 4.6 respectively. Nearly a quarter of patients (23.3%) used one class of medication whereas 30.1% used 6 or more medication classes (Table 5). The mean number of individual medications taken by all, T1D and T2D patients were 6.9, 5.5 and 7.9 (medians of 6, 4, and 7) respectively with a range of 1 to 36 across all subjects (Figure 1).

Clinical accuracy of OneTouch Select Plus® Test-Strip With Respect to Medications

Clinical accuracy was assessed for all medications within each medication class (Table 6). Each accuracy subset (eg, 19,317 readings for anti-hypertensives) represents strip accuracy data from subjects who confirmed they were taking anti-hypertensives although subjects may also have been taking other medications. Therefore, each subset is defined by the fact that all subjects in that subset are taking at least that specific medication, as a minimum. For all combinations of individual medication-reference paired readings, at least 97% of glucose values were within ±15 mg/dL (<100 mg/dL) or ±15% of comparator (≥100 mg/dL). Table 7 lists clinical accuracy categorized by the number of medication classes taken by patients. No systematic effect on clinical accuracy was evident with increasing number of medication classes. Furthermore, there was no impact on clinical accuracy based upon

Table 3. Summary of Non-Diabetes Medications with an Overall Population Prevalence of ≥2.5% for All 1023 Subjects.

	All patients N = 1023	T2D N = 598	T1D N = 425
		n (%)	
Simvastatin	246 (24.0)	177 (29.6)	69 (16.2)
Atorvastatin	245 (23.9)	188 (31.4)	57 (13.4)
Aspirin	206 (20.1)	153 (25.6)	53 (12.5)
Omeprazole	169 (16.5)	114 (19.1)	55 (12.9)
Lisinopril	162 (15.8)	113 (19.9)	49 (11.5)
Alodapine	133 (13.0)	106 (17.7)	27 (6.4)
Ramipril	115 (11.2)	89 (14.9)	26 (6.1)
Co-codamol	95 (9.3)	66 (11.0)	29 (6.8)
Lansoprazole	88 (8.6)	68 (11.4)	20 (4.7)
Paracetamol	86 (8.4)	65 (10.9)	21 (4.9)
Bendroflumethiazide	84 (8.2)	71 (11.9)	13 (3.1)
Salbutamol	80 (7.8)	44 (7.4)	36 (8.5)
Amitriptyline	79 (7.7)	48 (8.0)	31 (7.3)
Bisoprolol fumerate	78 (7.6)	58 (9.7)	20 (4.7)
Levothyroxin	76 (7.4)	35 (5.9)	41 (9.6)
Furosemide	73 (7.1)	58 (9.7)	15 (3.5)
Doxazosin	72 (7.0)	56 (9.4)	16 (3.8)
Tramadol	61 (6.0)	38 (6.4)	23 (5.4)
Losartan	59 (5.8)	45 (7.5)	14 (3.3)
Gabapentin	58 (5.7)	37 (6.2)	21 (4.9)
Clopidogrel	56 (5.5)	45 (7.5)	11 (2.6)
Ferrous fumarate	51 (5.0)	36 (6.0)	15 (3.5)
Thyroxine	45 (4.4)	16 (2.7)	29 (6.8)
Atenolol	44 (4.3)	37 (6.2)	7 (1.6)
Pregabalin	44 (4.3)	32 (5.4)	12 (2.8)
Rosuvastatin	43 (4.2)	30 (5.0)	13 (3.1)
Cetirizine	41 (4.0)	24 (4.0)	17 (4.0)
Folic acid	39 (3.8)	24 (4.0)	15 (3.5)
Perindopril	37 (3.6)	31 (5.2)	6 (1.4)
Ranitidine	36 (3.5)	27 (4.5)	9 (2.1)
Duloxetine	35 (3.4)	23 (3.8)	12 (2.8)
Candesartan	34 (3.3)	27 (4.5)	7 (1.6)
Adcal	33 (3.2)	24 (4.0)	9 (2.1)
Dihydrocodeine	32 (3.1)	23 (3.8)	9 (2.1)
Fluoxetine	31 (3.0)	18 (3.0)	13 (3.1)
Setraline	30 (2.9)	14 (2.3)	16 (3.8)
Fenofibrate	28 (2.7)	24 (4.0)	4 (0.9)
Ibuprofen	28 (2.7)	18 (3.0)	10 (2.4)
Naproxen	27 (2.6)	14 (2.3)	13 (3.1)
Quinine sulphate	27 (2.6)	20 (3.3)	7 (1.6)
Indapamide	26 (2.5)	20 (3.3)	6 (1.4)

increasing average number of individual medications taken per subject, categorized from 1-3, 4-6, 7-9, 10-12, and >12 (97.7%, 97.7%, 97.8%, 97.8%, and 98.4% respectively).

Whilst the accuracy pooled by medication class indicated robust performance, certain medications may present a greater risk to BG measurement inaccuracy. The test-strip design under investigation is based on electrochemical transduction, thus potentially may be influenced by the presence of electroactive medications that may be directly electrochemically oxidized at the test-strip working electrode. Acetaminophen (paracetamol), a common electroactive medication, was recorded as being taken by 86 subjects (3186 glucose readings) but was not associated with any systematic effect on the accuracy of the test-strips. A similar outcome was recorded for salicylic acid (as a metabolite of aspirin). Both acetaminophen and salicylic acid are presented alongside the other 18 most frequently encountered

Table 4. Summary of Individual Medication Classes Used by All 1023 Subjects.

Medication classification	All patients N = 1023	T2D N = 598	T1D N = 425
		n (%)	
Diabetes medications	991 (96.9)	571 (95.5)	420 (98.8)
Anti-hypertensive	547 (53.5)	406 (67.9)	141 (33.2)
Lipid lowering	544 (53.2)	403 (67.4)	141 (33.2)
Anti-depressant, psychotic or spasmolytic	336 (32.8)	211 (35.3)	125 (29.4)
Gastrointestinal	324 (31.7)	222 (37.1)	102 (24.0)
Anti-inflammatory	293 (28.6)	210 (35.1)	83 (19.5)
Analgesic or sedative	263 (25.7)	174 (29.1)	89 (20.9)
Anti-infective or microbial	198 (19.4)	122 (20.4)	76 (17.9)
Nutritionals, minerals or supplements	183 (17.9)	116 (19.4)	67 (15.8)
Cardioprotective or anti-thrombotic	139 (13.6)	110 (18.4)	29 (6.8)
Hormonal	132 (12.9)	58 (9.7)	74 (17.4)
Asthma, COPD or allergy	119 (11.6)	68 (11.4)	51 (12.0)
Urological	76 (7.4)	61 (10.2)	15 (3.5)
Cancer or neoplastic	19 (1.9)	14 (2.3)	5 (1.2)
Ophthalmological	17 (1.7)	13 (2.2)	4 (0.9)

Table 5. Percentage of 1023 Subjects Using One or More Medication Classes.

Number of medication classes	All patients N = 1023	T2D N = 598	T1D N = 425
		n (%)	
1	238 (23.3)	93 (15.6)	145 (34.1)
2	117 (11.4)	51 (8.5)	66 (15.5)
3	117 (11.4)	72 (12.0)	45 (10.6)
4	134 (13.1)	91 (15.2)	43 (10.1)
5	108 (10.6)	75 (12.5)	33 (7.8)
6	123 (12.0)	82 (13.7)	41 (9.6)
7	69 (6.7)	44 (7.4)	25 (5.9)
8	44 (4.3)	34 (5.7)	10 (2.4)
>8	73 (7.1)	56 (9.4)	17 (4.0)
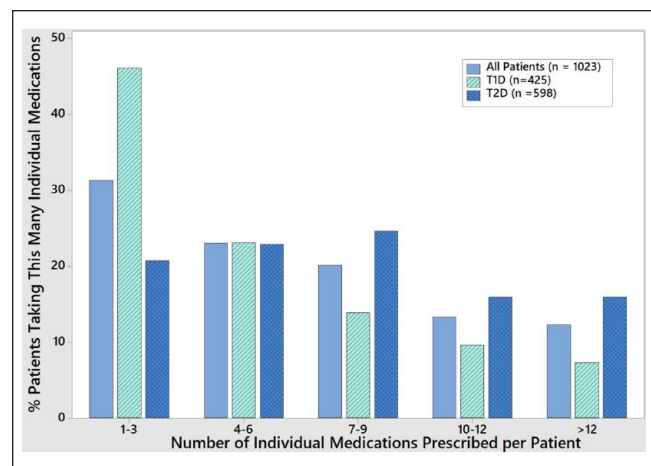
Figure 1. Number of medications prescribed to all (*n* = 1023), T1D (425), and T2D (598) subjects.

non-diabetes medications from this study in Table 8. Table 9 presents accuracy data for the 20 most frequently encountered diabetes medications.

Evaluation of Clinical Accuracy by Surveillance Error Grid (SEG)

The SEG classifies data into 15 zones according to an assigned level of risk.[8] The SEG plot for all individual medication-reference paired readings is shown (x and y axes being limited to 0-600 mg/dL (33.3 mmol/L) glucose). A total of 29959/30368 readings (98.7%) were classified as presenting no clinical risk, whilst 404/30368 of readings (1.3%) were classified as slight, lower risk and 5/30368 as slight, higher risk. No values were recorded in any other risk zones in Figure 2. Additional SEG data, classified across all 15 medication classes are shown in Table 10.

Table 6. EN ISO 15197:2015 Clinical Accuracy for All 15 Medication Classes.

Class	Medication class	Total number of medication/ reference combinations	Number of individual medication/reference combinations within ±15 mg/ dL or ±15% of comparator[a]	Percent of individual medication-reference combinations within ±15 mg/ dL or ±15% of comparator[b]
	All classes	30433	29784	97.9
1	Diabetes medications	29693	29064	97.9
2	Anti-hypertensives	19317	18914	97.9
3	Lipid lowering	19103	18693	97.9
4	Anti-depressants	11938	11723	98.2
5	Gastrointestinal	11212	10998	98.1
6	Anti-inflammatory	10725	10521	98.1
7	Analgesic or Sedative	9454	9309	98.5
9	Anti-infective	8547	8379	98.0
8	Nutritional Supplements	6849	6719	98.1
10	Cardioprotective	5364	5266	98.2
12	Asthma, COPD or allergy	4815	4716	97.9
11	Hormonal	4404	4317	98.0
13	Urological	2476	2425	97.9
14	Cancer	733	719	98.1
15	Ophthalmological	845	824	97.5

Data includes all data pairs, including those over 600 mg/dl (the upper claimed glucose limit of this BGM system).
[a]Number of capillary blood glucose readings within ±15 mg/dL (<100 mg/dL) or ±15% of comparator (≥100 mg/dL).
[b]Percent of capillary blood glucose readings within ±15 mg/dL (<100 mg/dL) or ±15% of comparator (≥100 mg/dL).

Discussion

In a continuing surveillance initiative comprising 30,433 blood samples gathered within a clinical setting on the test strip platform under evaluation, accuracy consistently met the criteria defined in EN ISO 15197:2015. Further sub-analysis of 15 medication classes and sub-analysis based on the number of medications taken by individual patients demonstrated that accuracy levels remained consistent with the primary dataset—at no point falling below 97% against the EN ISO 15197:2015 criteria. Splitting the dataset to separately evaluate diabetes and non-diabetes medications, or by diabetes type produced values ≥97% in all cases. SEG analysis supported these findings, with 98.7% of results assigned as 'no clinical risk', a pattern that was again sustained across all 15 medication classes.

When considering individual medications, the top 20 most prevalent in the diabetes and non-diabetes categories were assessed, and all met EN ISO 15197:2015 accuracy criteria. Although most of these compounds had no known mechanism of interference with the system under test, the list did include the common analgesics acetaminophen and salicylic acid that are mandated for assessment using laboratory methods by both regulators and international standards.[2,3] Acetaminophen has been specifically identified as a risk compound for some earlier CGM devices[9,10] and remains a risk when present in excessive levels or with repeated dosing on at least one current generation CGM device.[11,12]

The system under evaluation has been demonstrated to be insensitive to a panel of recommended compounds at non-pathologic physiological or therapeutic concentrations, including acetaminophen, ascorbic acid and salicylic acid[1,3] as part of laboratory testing for regulatory clearances.

The value of laboratory evaluations is their ability to evaluate potential interfering compounds when tested in isolation, but the limitations of testing single interferents are highlighted by the degree of polypharmacy encountered in this dataset. Bauer and Nauck[13] provide a comprehensive assessment of polypharmacy using a dataset of over 300 people with diabetes. Some salient observations were that both type 1 diabetes (T1D) and type 2 diabetes (T2D) groups were prescribed multiple medications, with T2Ds and older patients of both types prescribed more medications. Our data confirms such observations, particularly the clinically significant differences in medication exposure between people with T1D and T2D. However, there may be a confounding effect of age and diabetes type (mean age of T1D of 44.6 years compared to T2D of 63.4 years), given that polypharmacy has also been found to increase with age independently of diabetes as a disease condition.[14] This may also contribute to the differences in number of classes of medications prescribed (mean classes T1D=3.3, T2D=4.6), and is consistent with the lower (1-3 individual medications) group being younger for both T1D and T2D populations.

Diabetes as a condition is generally associated with comorbidities. Research has indicated that multimorbidity affecting T1D patients is common, including disorders such

Table 7. EN ISO 15197:2015 Clinical Accuracy Per Number of Medication Classes Taken.

Number of medication classes	Total number of medication/reference combinations	Number of individual medication-reference combinations within $\pm$15 mg/dL or 15% of comparator	Percent of individual medication-reference combinations within $\pm$15 mg/dL or 15% of comparator
1	4530	4420	97.6
2	2395	2343	97.8
3	3499	3405	97.3
4	4404	4298	97.6
5	3891	3821	98.2
6	4416	4322	97.9
7	2334	2291	98.2
8	1605	1585	98.8
>8	3359	3299	98.2

Table 8. EN ISO 15197:2015 Clinical Accuracy for 20 Most Frequently Encountered Non-Diabetes Medications.

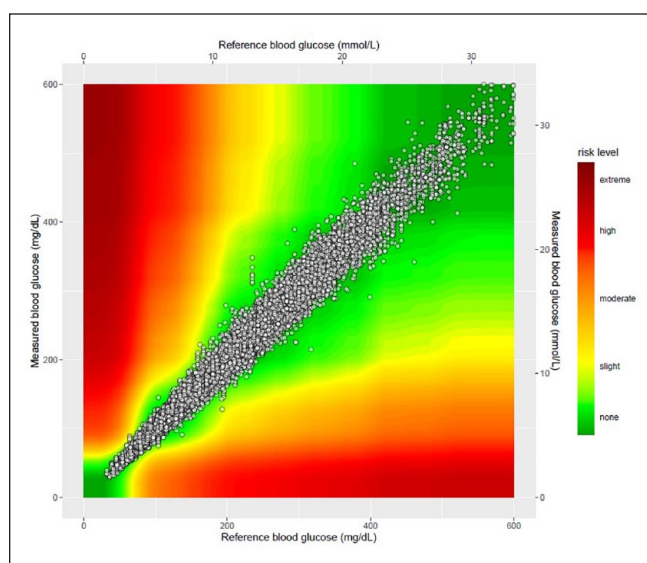|	Total number of medication/reference combinations	Number of individual medication-reference combinations within 15 mg/dL or 15% of comparator	Percent of individual medication-reference combinations within 15 mg/dL or 15% of comparator
Simvastatin	9431	9204	97.6
Atorvastatin	8028	7865	98.0
Aspirin	7227	7094	98.2
Omeprazole	6224	6113	98.2
Lisinopril	6106	6005	98.3
Alodapine	5594	5478	97.9
Ramipril	3621	3544	97.9
Co codamol	3663	3598	98.2
Lansoprazole	2967	2910	98.1
Paracetamol	3186	3130	98.2
Bendroflumethiazide	3111	3053	98.1
Salbutamol	2990	2932	98.1
Amitriptyline	3265	3197	97.9
Bisoprolol fumerate	2907	2821	97.0
Levothyroxin	2637	2589	98.2
Furosemide	2343	2293	97.9
Doxazosin	2790	2750	98.6
Tramadol	2624	2591	98.7
Losartan	2535	2476	97.7
Gabapentin	1959	1932	98.6

as hypertension, dyslipidemia and depression.[15] If it is assumed that each of these conditions is treated alongside diabetes, this may consequently add a further 3 medication classes, even before considering other common prescribed drug classes such as anti-inflammatories, analgesics and gastrointestinal medications. Our dataset does indicate that the anti-hypertensive, lipid-lowering and anti-depressant classes are respectively second, third, and fourth most prescribed (after diabetes medications). A similar picture emerges for T2D patients, with a rapid increase in prescribed medications for comorbidities after diagnosis of diabetes.[16]

One of the principal expectations of a patient using a glucose monitoring system (BGM or CGM) should be that it is robust in the context of these real-world conditions and that manufacturers are actively collecting and analysing long term data to elaborate on any potential impact of new medications on product performance in this challenging heterogenous environment. Common comorbidities of diabetes require specific medications, and these may either interfere directly with a glucose monitoring system or interact with one another to produce unanticipated increases in interference effects due to drug interactions that may not have been evaluated in the mandatory laboratory testing. It should therefore be incumbent on manufacturers to provide their patients with assurances that products are effective outside of a controlled in vitro laboratory environment, using blood

Table 9. EN ISO 15197:2015 Clinical Accuracy for 20 Most Frequently Encountered Diabetes Medications.

	Total number of medication/reference combinations	Number of individual medication-reference combinations within 15 mg/dL or 15% of comparator	Percent of individual medication-reference combinations within 15 mg/dL or 15% of comparator
Metformin	16868	16513	97.9
Novorapid	9397	9183	97.7
Lantus	8820	8614	97.7
Humalog	6881	6738	97.9
Levemir	5384	5269	97.9
Gliclazide	6054	5935	98.0
Novomix	3154	3085	97.8
Sitagliptin	2321	2289	98.6
Humulin	2368	2324	98.1
Dapagliflozin	2634	2579	97.9
Trajenta	1507	1475	97.9
Liraglutide	1379	1362	98.8
Degludec	612	590	96.4
Empagliflozin	1245	1227	98.6
Tresiba	537	524	97.6
Trulicity	796	777	97.6
Fiasp insulin	467	446	95.5
Glargine	416	412	99.0
Pioglitazone	752	742	98.7
Apidra	525	514	97.9

Figure 2. Surveillance error grid plot of all individual paired medication-reference readings.

samples from volunteers without diabetes, spiked with solutions of a small number of common medications. Increasing advocacy for the collection and use of real-world data (RWD) and real-world evidence (RWE) is clear in publications from both regulatory[17] and academic sources.[18] This is also in agreement with increasing legislative control to incorporate observations made during post-market surveillance (PMS)

activities into a feedback system for product improvement and safety reporting as part of updates made to the Medical Devices Regulation (MDR) and In Vitro Medical Device Regulation (IVDR) in Europe.[19] Such an approach is supported by independent commentary on the necessity for PMS for BGM devices.[20]

A systematic, longitudinal PMS program based on randomly selected batches and representing the full variation of both production processes and manufacturing materials has previously been demonstrated to be an effective means to assess product performance.[21] When a glucose monitoring system PMS program engages with healthcare providers (such as the NHS in the UK), additional patient prescription data should be available to assess performance against new criteria, such as polypharmacy burden. There is reason to be optimistic that improved data collection infrastructure will allow better synchronization with patient health records and thus create more widely adopted and transparent BGM and CGM surveillance activities, with consistently robust assessments of the impact of polypharmacy.

There are limitations to this type of study. Subjects in our hospital setting could perhaps be on more medications than the primary care recruited population of people with diabetes. There may be potential gaps or errors within the NHS records used, despite these being the patients' primary healthcare records, and in addition, to verify data against NHS records the medications themselves must be prescribed, which results in a limited ability to assess other supplements such as ascorbic acid (vitamin C) which may not be routinely

Table 10. Surveillance Error Grid (SEG) Data Categorized for All 15 Medication Classes.

Class	Total number values	No clinical risk (%)	Slight, lower clinical risk (%)	Slight, higher clinical risk or greater (%)
All data[a]	30368	98.7	1.3	0.02
Diabetes medications	29628	98.6	1.3	0.02
Anti-hypertensive	19261	98.7	1.2	0.03
Lipid lowering	19052	98.7	1.3	0.01
Anti-depressant	11925	98.8	1.2	0.01
Gastrointestinal	11172	98.8	1.2	0
Anti-inflammatory	10699	99.0	1.0	0
Analgesic or Sedative	9431	99.0	1.0	0
Nutritional supplements	6840	98.8	1.1	0.01
Anti-infective	8518	98.7	1.3	0
Cardioprotective	5350	98.8	1.2	0
Hormonal	4390	98.3	1.7	0.02
Asthma, COPD or allergy	4802	98.1	1.9	0
Cancer	733	98.4	1.6	0
Ophthalmological	845	98.6	1.4	0
Urological	2468	98.9	1.1	0

[a]SEG software excludes data pairs with results over 600 mg/dl, the resulting dataset represents 30368 readings.

recorded by the health care team. It is also not possible, in the real world, to assume compliance to medication regimens, with the possible outcome that therapeutic concentrations were not present in all blood samples collected. In addition, pharmaceuticals may vary in their rates of prevalence across different territories worldwide, and a PMS program may only represent national conditions in that healthcare system. These compromises are a natural consequence of a real-world study, and we accept that their presence generates a level of uncertainty, despite our best efforts to maintain clinical integrity of the analysis by virtue of leveraging a substantial clinical dataset. A final limitation is that the findings of this study should not be interpreted as exhaustive—medications not encountered within the study may still be a source of interfering effects.

Conclusion

Clinical performance for the test strip platform under assessment demonstrated no evidence of interference from over 500 prescription medications, with clinical accuracy maintained across a broad range of polypharmacy conditions in people with diabetes.

Abbreviations

BG, Blood Glucose; BGM, Blood Glucose Monitoring; CGM, Continuous Glucose Monitoring; CLSI, Clinical and Laboratory Standards Institute; FDA, Food and Drug Administration; ISO, International Standards Organisation; IVDR, In Vitro Devices Regulation; MDR, Medical Device Regulation; NHS, National Health Service; PMS, Post Market Surveillance; PWD, People with Diabetes RWD, Real-World Data RWE, Real-World Evidence; SEG, Surveillance Error Grid; YSI, Yellow Springs Instruments.

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