Using Artificial Intelligence to Improve the Accuracy of a Wrist-Worn, Non-Invasive Glucose Monitor: A Pilot Study

Muhammad Rafaqat Ali Quresh PhD[a], Stephen Charles Bain MD[b,c], Stephen Luzio PhD[c], Consuelo Handy BSc[a], Daniel J. Fowles PhD[a], Bradley Love PhD[a], Kathie Wareham MPH[b], Lucy Barlow[b], Gareth J. Dunseath PhD[c], Joel Crane MEng[c], Isamar Carrillo Masso PhD[a], Julia A. M. Ryan BA[a], Mohamed Sabih Chaudhry PhD[a]

Author affiliations: [a]Afon Technology, Monmouthshire, UK; [b]Joint Clinical Research Facility, Institute of Life Science 2, Swansea University, UK; [c]Diabetes Research Group, Faculty of Medicine, Health and Life Science, Swansea University, UK.

Full author details:

Muhammad Rafaqat Ali Qureshi, Afon Technology, Unit 670 Castlegate Business Park, Caldicot Road, Caldicot, Monmouthshire, NP26 5AD, UK. 01291 442109. muhammad.qureshi@afontechnology.com

Stephen Charles Bain, Joint Clinical Research Facility, Institute of Life Science 2, Swansea University, SA2 8PP. UK. + 44 (0) 1792 530819. S.c.bain@swansea.ac.uk

Stephen Luzio, [c]Diabetes Research Group, Faculty of Medicine, Health and Life Science, Swansea University, SA2 8PP, UK. +44 (0) 1792 530819 s.luzio@swansea.ac.uk

Consuelo Handy, Afon Technology, Unit 670 Castlegate Business Park, Caldicot Road, Caldicot, Monmouthshire, NP26 5AD, UK. +44 (0) 1291 442101. Consuelo.handy@afontechnology.com

Daniel J. Fowles, Afon Technology, Unit 670 Castlegate Business Park, Caldicot Road, Caldicot, Monmouthshire, NP26 5AD, UK. +44 (0) 1291 442101. Dan.fowles@afontechnology.com

Bradley Love, Afon Technology, Unit 670 Castlegate Business Park, Caldicot Road, Caldicot, Monmouthshire, NP26 SAD, UK. +44 (0) 1291 442100. Brad.love@citalytics.com

Kathie Wareham, Joint Clinical Research Facility, Institute of Life Science 2, Swansea University, SA2 8PP. UK. + 44 (0) 1792 530819. Kathie.wareham@wales.nhs.uk

Lucy Barlow, Joint Clinical Research Facility, Institute of Life Science 2, Swansea University, SA2 8PP. UK. + 44 (0) 1792 530819. Lucy.barlow@wales.nhs.uk

Gareth J. Dunseath, [c]Diabetes Research Group, Faculty of Medicine, Health and Life Science, Swansea University, SA2 8PP. UK. + 44 (0) 1792 530819. G.j.dunseath@swansea.ac.uk

Joel Crane, [c]Diabetes Research Group, Faculty of Medicine, Health and Life Science, Swansea University, SA2 8PP. UK. + 44 (0) 1792 530819. J.h.crane@swansea.ac.uk

Isamar Carrillo Masso, Afon Technology, Unit 670 Castlegate Business Park, Caldicot Road, Caldicot, Monmouthshire, NP26 5AD, UK. +44 (0) 1291 442100. Isamar.masso@afontechnology.com

Julia A. M. Ryan, Afon Technology, Unit 670 Castlegate Business Park, Caldicot Road, Caldicot, Monmouthshire, NP26 5AD, UK. +44 (0) 1291 442100. Julia.ryan@afontechnology.com

Mohamed Sabih Chaudhry, Afon Technology, Unit 670 Castlegate Business Park, Caldicot Road, Caldicot, Monmouthshire, NP26 5AD, UK. +44 (0) 1291 442101. sabih.chaudhry@afontechnology.com

Abbreviations: AI, Artificial Intelligence; ARD, Absolute Relative Difference; CGM, Continuous Glucose Monitoring; DRS, Dial Resonating Sensor; MARD, Mean Absolute Relative Difference; MCU, Micro-Controller Unit; MC, Monte Carlo; NIGM, Non-Invasive Glucose Monitoring; PCB, Printed Circuit Board; SD, Standard Deviation; SEG, Surveillance Error Grid; SMBG, Self-Monitoring of Blood Glucose.

Keywords: Blood glucose self-monitoring; Diabetes mellitus; Microwaves; Non-invasive glucose monitoring; Radio frequency; Wearable electronic devices

Corresponding Author: Mohamed Sabih Chaudhry, Afon Technology, Unit 670 Castlegate Business Park, Caldicot Road, Caldicot, Monmouthshire, NP26 5AD, UK. +44 (0) 1291 442101. sabih.chaudhry@afontechnology.com

Figure/Table count: 5 Figures, 3 Tables

Word count: Abstract, 218; Main text, 2139

Abstract

Background:

Self-monitoring of glucose is important to the successful management of diabetes; however, existing monitoring methods require a degree of invasive measurement which can be unpleasant for users. This study investigates the accuracy of a non-invasive glucose monitoring system that analyses spectral variations in radio frequency/microwave signals.

Methods:

An open-label, pilot design study was conducted with four cohorts (N = 5/cohort). In each session, a dial-resonating sensor (DRS) attached to the wrist automatically collected data every 60 seconds, with a novel artificial intelligence (AI) model converting signal resonance output to a glucose prediction. Plasma glucose was measured in venous blood samples every 5 minutes for Cohorts 1-3 and every 10 minutes for Cohort 4. Accuracy was evaluated by calculating the mean absolute relative difference (MARD) between the DRS and plasma glucose values.

Results:

Accurate plasma glucose predictions were obtained across all four cohorts using a global sampling procedure, with an average MARD of 10.3%. A statistical analysis demonstrates the quality of these predictions, with a Surveillance Error Grid (SEG) plot indicating no data pairs falling into the higher risk zones.

Conclusions:

These findings show that MARD values approaching accuracies comparable to current commercial alternatives can be obtained from a multi-participant pilot study with the application of AI. Microwave biosensors and AI models show promise for improving

85 the accuracy and convenience of glucose monitoring systems for people with
86 diabetes.

87 **Clinical Trial Number: NCT05023798**

Introduction

Self-monitoring of blood glucose (SMBG) is an important part of managing diabetes (1). However, the invasiveness of standard finger-prick glucose tests, which must be taken several times a day, are a significant barrier to SMBG (2). Systems for continuous glucose monitoring (CGMs) – with wearable glucose sensors that provide continuous glucose readings from the interstitial fluid in the subcutaneous tissue – are therefore increasingly being utilised (3). The continuous data from such CGM systems provide insight into glycaemic patterns throughout the day, improving glycaemic control and increasing patient confidence in managing their diabetes (4). Nevertheless, CGMs require the insertion of a subcutaneous sensor which can compromise skin integrity (5). Interstitial glucose levels lag 5-10 minutes behind blood glucose levels, which may lead to underestimations of changes in glycaemic levels, particularly during activities such as exercise (6). There is thus great interest in the development of accurate, non-invasive, wearable devices for CGM (7) (8).

Many non-invasive glucose monitoring (NIGM) systems currently under investigation, such as photoacoustics (9) and near infra-red spectroscopy (10), utilise expensive instrumentation and are subject to error from physiological and environmental variables (11). Other methods such as transdermal or epidermal electrochemical sensors may still involve the use of microneedles (12), or involve monitoring glucose in sweat which can also be problematic (13).

Studies have shown that employing microwave technology is a promising area of development for such devices. For example, one study has shown that a micro-resonator using a metal-insulator-semiconductor provided a reliable indicator of glucose levels (14). Another reports promising tests of a highly sensitive resonator-based microwave biosensor for real-time blood glucose detection (15). Nevertheless,

a recent review concluded that there is a need for increased sensitivity, accuracy and stability in such sensors, some of which could be achieved through AI and machine learning (16).

The current study reports on an open-label, pilot design study of a novel, non-invasive, wrist-worn device which analyses resonance shifts in the microwave spectrum using AI. The dial-resonating sensor (DRS) uses a microwave sensor to measure bulk plasma glucose levels in the body, which are then converted to a glucose measurement. This study aims to determine the accuracy of the DRS device by comparing gold standard measures of plasma glucose to algorithmically derived measures of glucose from the DRS device.

Methods

Ethics Statement

Ethics committee approval was obtained (WoS reC4, 21/WS/0139), with all participants providing written informed consent.

Study Design

In this open-label, pilot design study, four cohorts (each comprising five participants) attended trials that were ≤7 days apart at the Joint Clinical Research Facility (JCRF) in Swansea, Wales. A total of four 2-hour sessions or two 8-hour sessions were organised for each participant from Cohorts 1-3 and Cohort 4, respectively. During each trial, DRS-derived glucose measurements were compared with plasma glucose levels measured using a YSI 2500 laboratory glucose analyser. A Random Forest algorithm applied to and trained on this DRS data was used to estimate the glucose levels on unseen subsets of this dataset. No major changes were made to the protocol during the study.

Participants

To be included in the study, participants needed to have documented Type 1 diabetes diagnosed before age 29 or have had documented Type 2 diabetes for more than one year with negative glutamic acid decarboxylase antibody test results. They were also required to be aged 18-80 years and to have a body mass index of 18-35 kg/m^2. Potential participants were then excluded if: they had another active implantable medical device (e.g., a pacemaker); were currently participating in another clinical trial for a pharmaceutical product; had a history of allergies to any materials used in the study; were females who were pregnant or lactating; had clinically significant abnormal values in clinical chemistry; had a concurrent illness or condition that may

interfere with blood glucose levels; have had an episode of diabetic ketoacidosis, hyperglycaemic hyperosmolar non-ketotic coma, or severe hypoglycaemia within one month prior; were on pramlintide; had a wrist injury; or, had severe macrovascular disease. As this was a pilot study, a sample size calculation was not performed. Instead, the target was to recruit five participants to each cohort.

DRS Device

The DRS device comprises a planar split ring resonator fabricated on the top layer of a multi-layered printed circuit board (PCB). Other system components such as the oscillator, coupler, micro-controller unit (MCU) and detector are fabricated on the other side of the PCB to realise the wearable wrist-worn monitor, shown in Figure 1. The DRS is designed to radiate high-frequency, low-power electromagnetic waves into the patient's wrist over a frequency band of 1-10 GHz. The electromagnetic signal transmitted into the wrist is susceptible to glucose induced dielectric changes in the arteries, veins, and interstitial fluid. These dielectric changes result in a shift of the absorption spectrum of the electromagnetic wave in the blood, which can then be algorithmically transformed into a prediction of the change in glucose concentration within blood.

< Insert Figure 1 about here>

Procedures

After providing informed consent, screening for eligibility was conducted by a member of the clinical team at least seven days before the first trial visit. Patient

details were reviewed by a clinical team member before approval to take part in the study was given. Upon admittance to the study a second visit (Trial 1) was scheduled.

Participants attended each session after a minimum four-hour fast to ensure low plasma glucose levels were recorded at the start of each session. Eligibility was re-confirmed at the commencement of each session. At each visit the patient had the DRS device strapped to the same wrist for calibration and a venous cannula inserted into the participants' arm. For a single patient trial, due to difficulty with inserting the cannula, the DRS device was strapped to the other wrist. Device operators were engineers who had been trained in usage of the DRS and on study procedures. Patients remained sitting or reclining on a bed throughout the trial period. Participants drank one 200 mL bottle of Ensure Plus to increase glucose levels (at T90 for Cohorts 1 and 2, T30 for Cohort 3, and T120 for Cohort 4), and were permitted comfort breaks as needed. Time was added for comfort breaks to ensure a full trial period was completed for each participant.

The first measurement from the DRS device was taken and recorded at time point 0 (T0). Within one minute, a blood sample was taken via a venous cannula for plasma glucose measurement. Thereafter, DRS measurements were automatically triggered at 60-second intervals, with blood samples for glucose measurements taken every 5 minutes throughout sessions involving Cohorts 1-3 and every 10 minutes for those with Cohort 4. Medical staff remained on hand to assist in case of any adverse reactions. At the end of the trial, participants were offered refreshments and discharged if their plasma glucose levels were acceptable. Trialling of each cohort took place over a period of approximately 5-6 weeks between July 2022 and June 2023.

Data Analysis

An AI model was built using the Random Forest algorithm, which was chosen due to its better predictive accuracies and ability to limit overfitting than has been observed from other algorithms (17). A global sampling procedure was applied to the full 4-cohort dataset involving Monte Carlo (MC) resampling with an inner 5-fold cross-validation loop. A total of 50 MC resamples were generated using a 70%/30% train/test split of the full dataset, with the final statistics obtained as an average of all MC resamples. Within each resample, the training set was separated into 5 folds for use in the cross-validation process, with model hyperparameters optimised using a full grid search of all possible parameter combinations.

Accuracy of the glucose measurement using the DRS device was calculated by obtaining the MARD (primary outcome) of the DRS device vs venous plasma glucose. The MARD is a commonly used metric for assessing the performance of glucose monitoring systems (18), and refers to the mean absolute relative deviation of the glucose value calculated by the model from the reference glucose levels. Surveillance error grids (SEGs) were used according to the methodology described by Klonoff et al. (19), to display the clinical risk of errors in the DRS generated data.

Results

Sample Characteristics

Each cohort included five participants, with one participant included in both Cohort 1 and Cohort 3 and another in Cohorts 1, 3, and 4. In each cohort, 60.0% of participants had Type 1 diabetes and 40.0% had Type 2 diabetes. Table 1 provides a breakdown of participant demographics across each cohort.

In total, there were 63 trials conducted across the 20 participants. Each trial had 31 – 50 glucose measurements taken with associated device readings. From a total of 2,370 readings across all trials, YSI plasma glucose measurements ranging from 3.2 mmol/L to 19.6 mmol/L were obtained, with a mean and median of 9.3 mmol/L and 8.8 mmol/L, respectively. Figure 2 gives the distribution of these reference glucose measurements.

< Insert Table 1 and Figure 2 about here>

Accuracy

An average MARD of 10.3% was obtained from glucose predictions across all trials for Cohorts 1-4, with individual MARDs of 10.3%, 10.1%, 9%, and 12.1% for Cohorts 1, 2, 3, and 4, respectively. Table 2 provides a breakdown of these results alongside the average median ARD and individual cohort median ARD values. The distribution of MARD values across trials is given in Figure 3, which shows a clustering of MARD values below 20% and a long-tailed distribution. A plot of reference glucose values against predictions for all test set data is given in Figure 4. Additional statistical measures of the quality of these predictions are also given in Figure 4: coefficient of determination (R^2), root mean square deviation (RMSD), bias, and standard deviation (SD). These statistics are taken as averages across all 50 MC resamples.

< Insert Table 2, Figure 3 and Figure 4 about here>

SEG analysis (Figure 5) shows that the measurements obtained were primarily (89.4%, 10.3%) within the deep green (no risk) zone and the light green (slight, low risk) zone, with small numbers (0.2%) within the yellow zones (moderate risk). No measurements were in the orange (great risk) or red (extreme risk) zones. Table 3 highlights the percentage of each data pair within these risk factor ranges.

< Insert Figure 5 and Table 3 about here>

Safety

There were no adverse events reported.

Discussion

This study compared the accuracy of a non-invasive, wearable glucose measurement system using microwave resonance technology, to standard plasma glucose monitoring. Several prior studies have established the possibility for detecting plasma glucose levels (14) (16) (20) (21). The most recent of these studies demonstrated that a MARD of 28% could be obtained from trial-specific multiple regression models trained on DRS device measurements (21). Here, it has been shown that the accuracy of the DRS device has been improved upon with a decline in MARD from 28% to the 10.3% obtained from this study. This improvement in MARD suggests the use of a more complex algorithm, combined with a global sampling procedure, offers superior results to previous device tests. Results also suggest that the DRS device under consideration here is approaching a level of accuracy comparable to commercially available glucose monitoring systems when applied within a controlled environment. In general, a system with a MARD < 10% is regarded to have good analytical performance (22). Other commercially available CGM systems such as the Freestyle Libre (Abbott Diabetes Care, Witney, UK), Minimed Enlite (Medtronic, Dublin, Ireland), and Dexcom (Dexcom Inc., California, USA) have published MARDs of 11.4% (23), 13.6% (24) and 9.3% (25) respectively.

Results also showed that no data pairs were in the higher risk categories of clinical error in SEG. The DRS device considered herein has the advantage of being non-invasive, which can be assumed to improve patient adherence to self-monitoring procedures (2), thus leading to better health outcomes (26).

A current limitation of this approach is that the AI model was built after all trial data had been collected, and not generated as data collection was occurring. It is expected that additional clinical trials involving a wider range of participants and longer test

periods will result in valuable data with which to support the development of AI models capable of real time predictions.

The study is limited by the fact that accuracy of the device was assessed under the hands of trained engineers within a controlled environment, and so may not reflect any settling period observed for an individual user with diabetes under daily life conditions. Nevertheless, the controlled, lab-based nature of the study adds to the body of evidence supporting the use of AI and machine learning to improve the accuracy of NIGM systems. The development of NIGM wearable systems that provide an accurate and sensitive glucose measurement are of great relevance given the increasing popularity of CGM systems which are frequently replacing SMBG in a variety of therapeutic situations (18).

Conclusions

This study demonstrates that a novel, non-invasive, wearable DRS device could estimate glucose levels in the body with reasonable accuracy compared with venous plasma glucose measurements. Future studies will continue to test the accuracy of subsequent iterations of the device as well as provide further data to improve the AI model.

Acknowledgements: The authors would like to thank the study participants. Dr Danielle Bodicoat and Dr. Sandra Garrido (independent consultants) provided writing assistance paid for by Afon Technology. Bodicoat and Garrido jointly produced the first draft based on previous submissions, the protocol and Clinical Investigation Report, which was then critically reviewed and updated by the authors.

Author Contribution Statement: All persons who meet authorship criteria are listed as authors. All authors have participated sufficiently in the work to take public

responsibility for the content, including participation in the concept, design analysis, writing or revision of the manuscript.

Conflict of Interest Statement: The authors declare the following relationships which may be considered as potential conflicts of interest: Dr Muhammad Rafaqat Ali Qureshi, Consuelo Handy, Dr Daniel J. Fowles, Dr Bradley Love, Dr Isamar Carrillo Masso, Julia A. M. Ryan are employees of Afon Technology, and Dr. Mohamed Sabih Chaudhry is the chief executive officer of Afon Technology.

Funding Statement: The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Welsh Government's SMARTCymru programme, backed by the EU's European Regional Development Fund [grant number 2019/ED/054].

References

1. *Self-Monitoring of Blood Glucose in Type 2 Diabetes: Recent Studies.* **Schnell O, Alawi H, Battelino T, Ceriello A, Diem P, Felton A-M, et al.** 2013, J. Diabetes Sci. Technol., Vol. 7 (2), pp. 478-488.

2. *Invasiveness as a barrier to self-monitoring of blood glucose in diabetes.* **Wagner J, Malchoff C, Abbot G.** 2005, Diabetes Technol. Ther,, Vol. 7 (4), pp. 612-619.

3. *Continuous glucose monitoring versus self-monitoring of blood glucose in the management of cystic fibrosis related diabetes: A systematic review and meta-analysis.* **Kumar S, Soldatos G, Ranasinha S, Teede H, Pallin M.** 2023, J. Cyst. Fibros., Vol. 22 (1), pp. 39-49.

4. *Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial.* **Beck R.W, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, et al.** 2017, JAMA, Vol. 317 (4), pp. 371-378.

5. *Preserving Skin Integrity with Chronic Device Use in Diabetes.* **Messer L.H, Berget C, Beatson C, Polsky S, Forlenza G.P.** 2018, Diabetes Technol. Ther., Vol. 20 (S2), pp. S254-S264.

6. *How Well Do Continuous Glucose Monitoring Systems Perform During Exercise?* **Castle J.R, Rodbard D.** 2019, Diabetes Technol. Ther., Vol. 21 (6), pp. 305-309.

7. **M, Hoskins.** 'Noninvasive' Glucose Monitoring for Diabetes: Where Is It Now? [Online] 2022. https://www.healthline.com/diabetesmine/non-invasive-diabetes-technology.

8. *Novel Microwave Based Non-Invasive Glucose Device.* **Qureshi M.R.A, Shillingford J, Handy C.M, Chaudhry M.S, DeVries J.H, Zijlstra E, et al.** 2020, GJDEMD, Vol. 1 (1), pp. 12-20.

9. *In vivo Microscopic Photoacoustic Spectroscopy for Non-Invasive Glucose Monitoring Invulnerable to Skin Secretion Products.* **Sim J.Y, Ahn C-G, Jeong E-J, Kim B.K.** 2018, Sci. Rep., Vol. 8, p. 1059.

10. *Prospects and limitations of non-invasive blood glucose monitoring using near-infrared spectroscopy.* **Yadav J, Rani A, Singh V, Murari B.M.** 2015, Biomed. Signal Process. Control, Vol. 18, pp. 214-227.

11. *Non-invasive glucose monitoring technology in diabetes management: a review.* **S.K, Vashist.** 2012, Anal. Chim. Acta., Vol. 750, pp. 16-27.

12. *Wearable hollow microneedle sensing patches for the transdermal electrochemical monitoring of glucose.* **Parrilla M, Detamornrat U,**

Dominguez-Robles J, Donnelly R.F, De Wael K. 2022, Talanta, Vol. 249, p. 123695.

13. *Comprehensive Review on Wearable Sweat-Glucose Sensors for Continuous Glucose Monitoring.* **Zafar H, Channa A, Jeoti V, Stojanovic G.M.** 2022, Sensors, Vol. 22, p. 638.

14. *Characterization of micro-resonator based on enhanced metal insulator semiconductor capacitor for glucose recognition.* **Dhakal R, Kim E.S, Jo Y-H, Kim S-S, Kim N-Y.** 2017, Med. Eng. Phys., Vol. 41, pp. 55-62.

15. *High-Sensitivity, Quantified, Linear and Mediator-Free Resonator-Based Microwave Biosensor for Glucose Detection.* **Kumar A, Wang C, Meng F-Y, Zhou Z-L, Zhao M, Yan G-F, et al.** 2020, Sensors, Vol. 20 (14), p. 4024.

16. *Radio-Frequency Biosensors for Real-Time and Continuous Glucose Detection.* **Jang C, Lee H-J, Yook J-G.** 2021, Sensors, Vol. 21 (5), p. 1843.

17. *Random Forests.* **L, Breiman.** 2001, Machine Learning, Vol. 45, pp. 5-32.

18. *A head-to-head comparison between Guardian Connect and FreeStyle Libre systems and an evaluation of user acceptability of sensors in patients with type 1 diabetes.* **Yeoh E, Png D, Khoo J, Chee Y.J, Sharda P, Low S, et al.** 2022, Diabetes Metab. Res. Rev., Vol. 38 (7), p. 3560.

19. *The surveillance error grid.* **Klonoff D.C, Lias C, Vigersky R, Clarke R, Parkes J.L, Sacks D.B, et al.** 2014, J. Diabetes Sci. Technol., Vol. 8 (4), pp. 658-672.

20. *Noninvasive in vitro measurement of pig-blood d-glucose by using a microwave cavity sensor.* **Kim S, Melikyan H, Kim J, Babajanyan A, Lee J-H, Enkhtur L, et al.** 2012, Diabetes Res. Clin. Pract., Vol. 96 (3), pp. 379-384.

21. *Noninvasive Continuous Glucose Monitoring With a Novel Wearable Dial Resonating Sensor: A Clinical Proof-of-Concept Study.* **Handy C, Chaudhry M.S, Qureshi M.R.A, Love B, Shillingford J, Plum-Morschel L, Zijlstra E.** 2023, J. Diabetes Sci. Technol., pp. 1-8.

22. *Benefits and Limitations of MARD as a Performance Parameter for Continuous Glucose Monitoring in the Interstitial Space.* **Heinemann L, Schoemaker M, Schmelzeisen-Redecker G, Hinzmann R, Kassab A, Freckmann G, et al.** 2020, J. Diabetes Sci, Technol., Vol. 14 (1), pp. 135-150.

23. *The Performance and Usability of a Factory-Calibrated Flash Glucose Monitoring System.* **Bailey T, Bode B.W, Christiansen M.P, Klaff L.J, Alva S.** 2015, Diabetes Technol. Ther., Vol. 17 (11), pp. 787-794.

24. *Accuracy and acceptability of the 6-day Enlite continuous subcutaneous glucose sensor.* **Bailey T.S, Ahmann A, Brazg R, Christiansen M, Garg S, Watkins E, et al.** 2014, Diabetes Technol. Ther., Vol. 16 (5), pp. 277-283.

25. *Performance of a Factory-Calibrated Real-Time Continuous Glucose Monitoring System Utilizing an Automated Sensor Applicator.* **Shah V.N, Laffel L.M, Wadwa R.P, Garg S.K.** 2018, Diabetes Technol. Ther., Vol. 20 (6), pp. 428-433.

26. *Evaluating the impact of self-monitoring of blood glucose frequencies on glucose control in patients with type 2 diabetes who do not use insulin: A systematic review and meta-analysis.* **Xu Y, Tan D.H.Y, Lee J.Y-C.** 2019, Int. J. Clin. Pract., Vol. 73 (7), p. 13357.

389 *Table 1 – Patient demographics for Cohorts 1, 2, 3, and 4.*

Demographics	**Cohort 1**	**Cohort 2**	**Cohort 3**	**Cohort 4**
Male/Female Ratio	3/2	4/1	2/3	(1)4/1
Age - Mean	54.4	58.8	58.6	45.4
Age - Standard Deviation	7.5	20.8	14.6	23.4
Age - Range	42 - 62	33 - 79	42 - 75	21 - 72

390

391 *Table 2 – Mean ARD and median ARDs for Cohorts 1, 2, 3, and 4.*

Accuracy	**Average**	**Cohort 1**	**Cohort 2**	**Cohort 3**	**Cohort 4**
Mean ARD	10.3%	10.3%	10.1%	9.0%	12.1%
Median ARD	7.4%	9.0%	8.8%	7.7%	10.0%

392 Abbreviations: ARD, Absolute Relative Difference

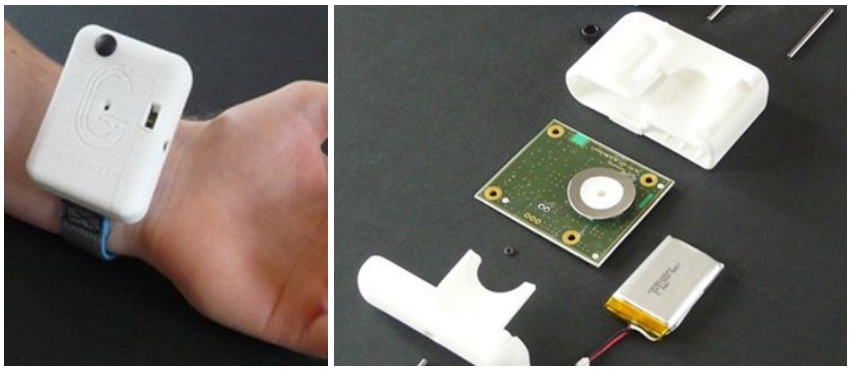
393

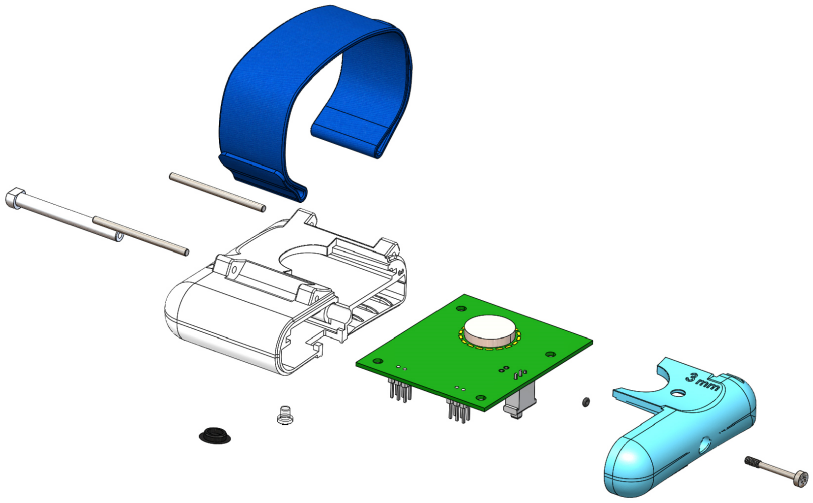
394 *Table 3 – Percentage of Pairs in each Risk Grade from SEG plot*

Risk Grade	Cohorts 1-4	Risk Factor
None	89.4%	0 – 0.5
Slight	10.3%	>0.5 - 1.5
Moderate	0.2%	>1.5 – 2.5
High	N/A	>2.5 – 3.5
Extreme	N/A	>3.5

395

Figure 1 – DRS Device

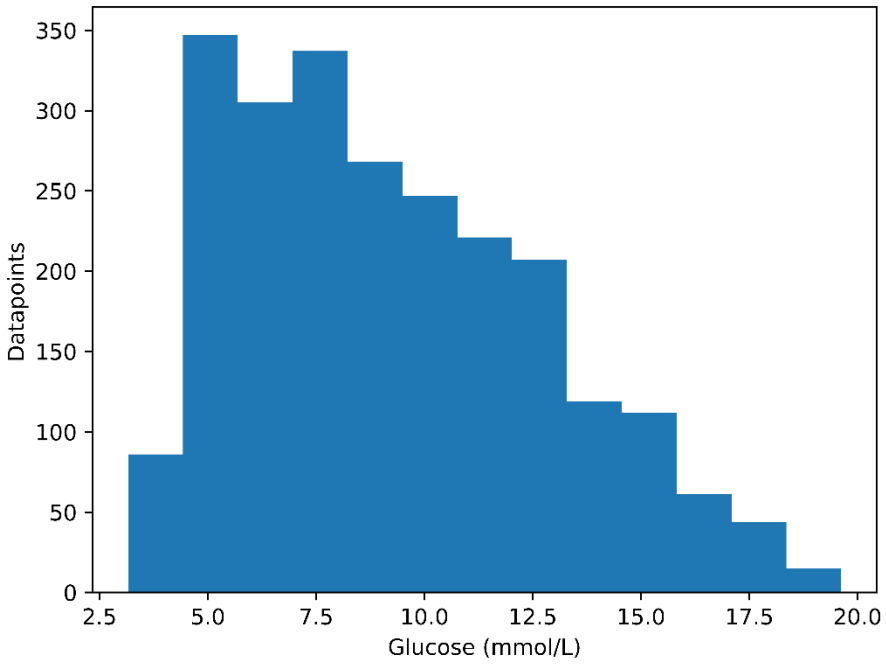




Wearable device (left) and exploded view (right)

402 *Figure 2 – Distribution of reference glucose values measured using a YSI 2500*

403 *laboratory glucose analyser.*



404

Figure 3 – Distribution of MARD values.

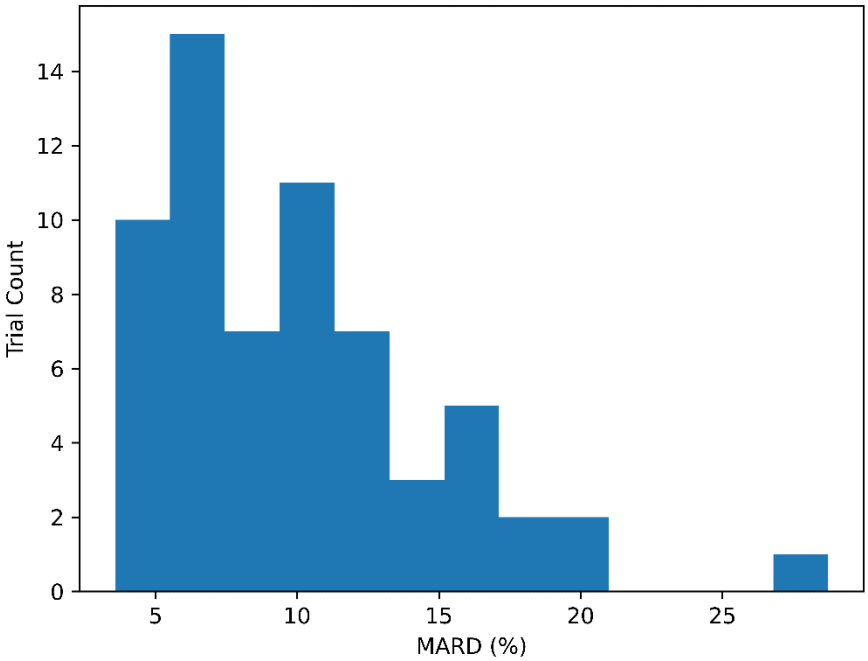
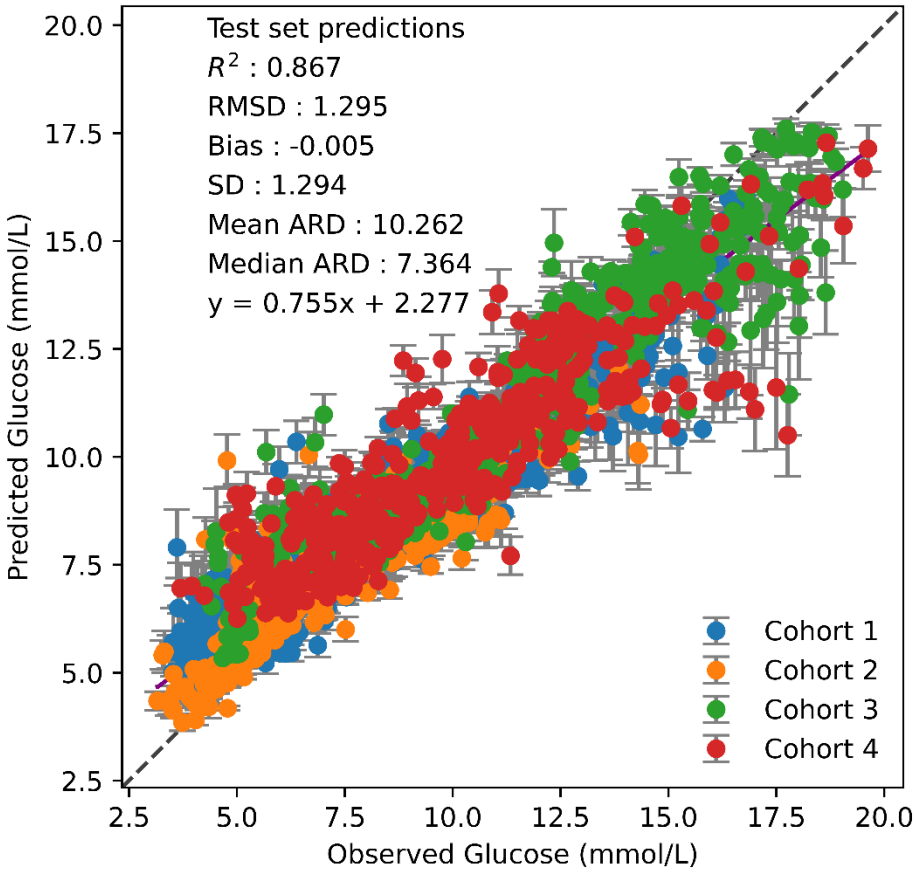
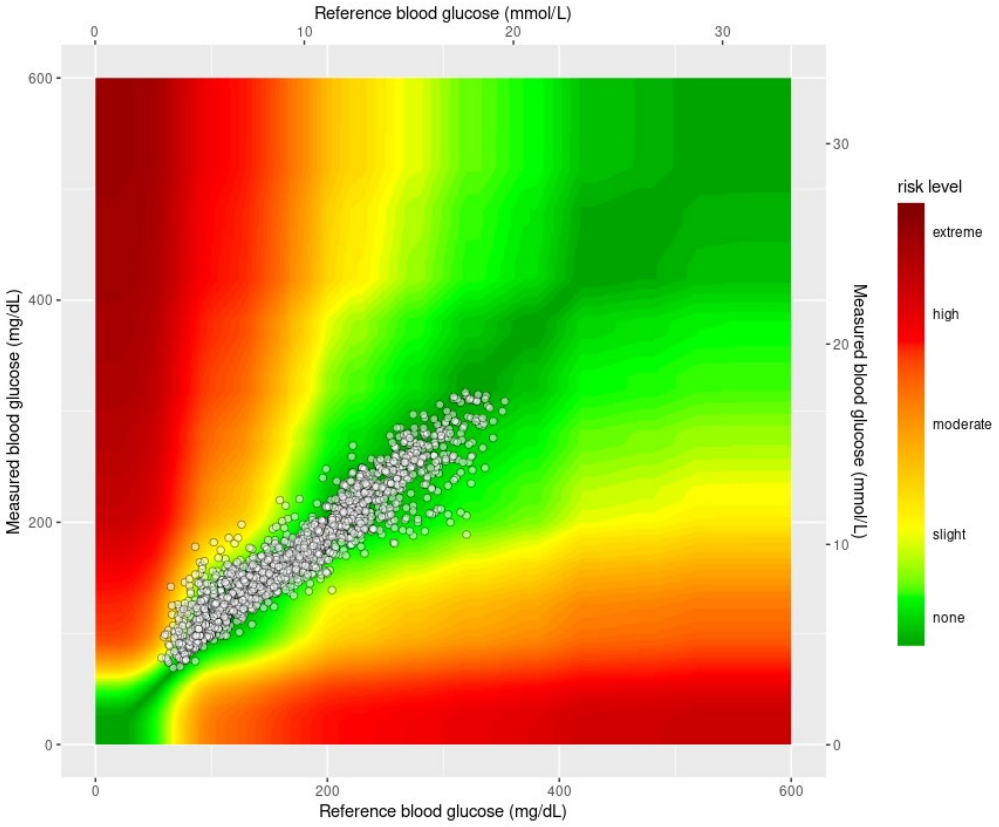


Figure 4 – Reference glucose values against predictions.



Abbreviations: R^2, Coefficient of determination; RMSD, Root Mean Square Deviation; SD, Standard Deviation; ARD, Absolute Relative Difference

413 *Figure 5 – SEG for Cohorts 1-4.*



414

415