Validation study for the Alertgy non-invasive continuous glucose monitor (ANICGM)

Investigators

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Study sponsor

Cleveland Clinic Innovations

External personnel

Required to set up the device:

Marc Rippen – CEO of Alertgy

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Introduction

Diabetes mellitus (DM) affects 30 million people in the United States. To achieve glucose control, most patients are prescribed glucose meters by their physicians. Obtaining glucose levels in this manner necessitates cleaning the fingers, attaching a lancet to a device (or simply using a lancet if a device is not available), pricking the finger with a lancet, placing a drop blood on a strip, and awaiting the readout that results after some chemical reactions. Thereafter, the lancet has to be disposed of in a safe receptacle and the finger has to be blotted to stop the blood from oozing.

The anxiety, pain, and tedious process have led researchers to develop other means of checking glucose levels. There are now continuous glucose monitoring systems (CGMS) that entail inserting a subcutaneous sensor that sends readings through a transmitter. These CGMs may or may not need calibration with a fingerstick glucose reading, and the subcutaneous sensor still has to be changed every 10 -14 days.

The Alertgy non-invasive continuous glucose monitor (ANICGM) is a device that does not entail any subcutaneous insertion of a sensor. It is strapped on to the wrist, and glucose readings are given based on subcutaneous signals (see Description of technology and Description of device below). In 2001, a non-invasive device called Glucowatch Biographer was introduced that also involved subcutaneous signals without needing a subcutaneous insertion. However, for various reasons such as long calibration period and reading inaccuracies, the product did not take off. The ANICGM is a promising device that might overcome the limitations of existing and previous methods of non-invasive glucose measurement.

General aim

This study aims to validate the glucose readings taken from the ANICGM with an approved outpatient glucose meter in patients with type 2 diabetes

Specific aim

1) To determine the correlation between glucose readings using the ANICGM an AccuChek Inform II blood glucose meter in patients with type 2 diabetes at baseline and after ingestion of a glucose load throughout a complete glucose excursion

   -Rationale: a continuous glucose monitor needs to capture rapid postprandial glucose increases and returns to baseline levels

2) To ascertain if the ANICGM calibration is maintained up to 14 days

   -Rationale: the ANICGM is being developed for use for multiple days

Note: The results from the ANICGM meter will not be used to guide any aspect of the patient's treatment course.

Description of the technology

The ANICGM uses a weak electromagnetic field generated by its wrist band sensor to look into the body to produce a spectrum that provides a measurement of blood glucose present in the wrist area of the body. The core sensing technology used is dielectric spectroscopy, and has been shown capable of measuring blood glucose, non-invasively, in a laboratory environment (1-3). The system uses proprietary and patented dielectric materials and signal processing to enhance performance in both selectivity and sensitivity for blood glucose measurement.

Much like how a MRI uses a strong magnetic field and its interaction with the body to create a picture of what is inside, the ANICGM uses a safe weak low frequency radiofrequency field to take a picture of a person's chemical spectrum, some of it specific only to blood glucose.

The device sends and receives back signals from the wrist area that are used to generate a dielectric spectrum once every 6 seconds. This spectral data is stored on the device, and then downloaded wirelessly or through USB port to an Alertgy laptop. The POC BG using the Accuchek Inform II will be used to provide calibration values for the ANICGM every 5 minutes in mg/dL, during the calibration process. The POC BG levels will be entered into the Alertgy laptop and a proprietary calibration program will be used to analyze the spectral data collected and will generate a calibration algorithm. The Alertgy support team will provide the ANICGM data to compare to the POC BG data they collected concurrently during the tests.

Description of the device

The present band is about 5 inches long made out of inert plastic material. It is applied to the wrist area and adjusted to a snug fit. All of the materials that make contact with the body are inert. A photo is included below.

(This is the current model. An improved version may be available at the time of the study).

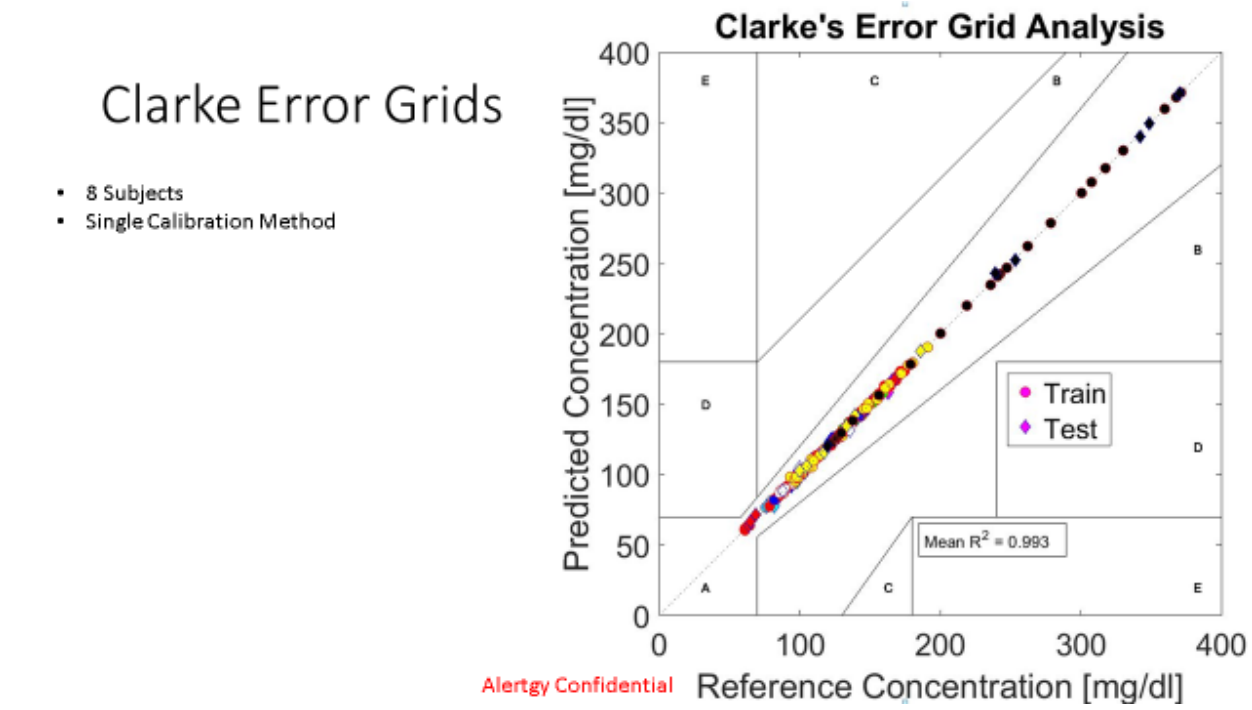
Cleveland Clinic staff will be trained by a written instruction manual in the application and use of the device by Alertgy staff on site. As the device is automated and noninvasive, it is anticipated that the training period will take no longer than two hours maximum.

Preliminary data

Data from Alertgy in the graph below shows testing of 8 subjects in their lab showing correlation between the ANICGM (y-axis) and the Abbott Freestyle Neo glucometer (x-axis).

Of the 8 subjects, 3 had type 2 diabetes (2 of whom are on insulin), 2 had prediabetes, and 3 did not have prediabetes or diabetes.

Pearson's correlation was used, R^2= 0.993.



Inclusion Criteria

Type 2 diabetes on diet or on pharmacologic treatment for diabetes

Hemoglobin A1c (HbA1c) 7.5-10.0%

- below 7.5%, there may not be a demonstrable blood glucose spike
- above 10.0%, subjects are more likely to be symptomatic from hyperglycemia and require treatment during the study

Age 18-75 years old

Exclusion Criteria

Patients taking prandial insulin

Fasting blood glucose by fingerstick <70 mg/dL or >250 mg/dL. Hypoglycemia <70 mg/dL will be treated according to clinic protocol.

Pregnancy

ESRD

Decompensated or acute heart failure

Medications that might cause false readings with glucose meters: acetaminophen, ascorbic acid, dopamine, maltodextrin, mannitol

Conditions that limit the ANICGM such as lesions on the forearms

Other conditions that the investigators deem will affect the conduct of the study

Protocol

There are 3 study visits: Visit 1, Visit 2 (3-14 days after Visit 1) and Visit 3 (5-14 days after Visit 1)

Alertgy personnel will undergo the onboarding process utilized by CCF Innovations called Silkroad/Red Carpet. Personnel undergoing this process complete 8 Comet modules (code of conduct, corporate complains, HIPPA overview and HIPPA & IS Security Awareness, Emergency Management, Environment of Care, Patient Safety and Energy Savings).

Study Calendar

	Visit 1	Visit 2	*Visit 3*
	Day 1	*3-14 days*	*5-14 days*
Informed Consent	X		
Inclusion/Exclusion	X		
Medical History	X		
Urine Pregnancy Test *	X	X	X
Vitals	X	X	X
Comorbidities	X		
Adverse Events Assessment	X	X	X
Medication Review	X	X	X
Ingest GlucoCrush	X	X	X
Glucose Collection (Fingersticks)	X	X	X

Women with childbearing potential

For all study visits

The timing of the fingerstick blood glucose checks outlined below are approximate, as there might be occasions where the fingerstick might not be performed at the exact minute specified (for example, patient needing to go to restroom, issues with the Accuchek Inform II glucose meter, etc). Every effort will be made to do the fingerstick at the specified time.

Subject fasts overnight, then proceeds to Cleveland Clinic Main Campus Adult Endocrinology clinic at F20.

Vital signs will be taken.

Women with childbearing potential will have a urine pregnancy test before each study.

Patients will be asked to bring diabetes medications (and related devices) if requiring injections) to F20.

If a subject is on basal insulin, the subject will take the basal insulin as close to the usual time as possible.

A baseline fingerstick blood glucose (BG) will be taken using the clinic's Accuchek Inform II glucose meter (time -60 min); this is needed to determine eligibility.

If BG 70-150 mg/dL subject will hold their morning medications or delay taking their diabetes medication until after the procedure (except for basal insulin as above) upon instructions of the investigator.

If BG 151-250 mg/dL, subject will take their diabetes medication at the usual time to prevent symptomatic hyperglycemia.

The ANICGM will be placed on the wrist. Measurements from the ANICGM start immediately. There will be a period of 20 minutes to allow the ANICGM to stabilize to body temperature.

Fingerstick BG will be repeated at time -30 min, -15 min, and 0 min for baseline validation.

At time 0 min, subjects ingest 75 g oral glucose drink (GlucoCrush)

For Visit 1:

Since the ANICGM is using new technology that depends on calculating the slope of the fingerstick glucose change to individualize the calibrations, it is crucial to have frequent fingersticks during Visit 1 for the first hour after the glucose challenge (GlucoCrush).

After the GlucoCrush, fingerstick BG will be done every 5 minutes for 2 hours.

Other continuous glucose devices have done monitoring as frequently as this (see attachment, figure 7, from Choi H, Naylon J, Luzio S, Beutler J, Birchall J, Martin C, Porch A. Design and *In Vitro* Interference Test of Microwave Noninvasive Blood Glucose Monitoring Sensor. IEEE Trans Microw Theory Tech. 2015 Oct 1;63(10 Pt 1):3016-3025)

For Visit 2 and Visit 3:

Fingerstick BG will be taken every 15 minutes for 2 hours after ingestion of GlucoCrush

Other continuous glucose devices have done monitoring as frequently as this (see attachment, figure 8, from Choi H, Naylon J, Luzio S, Beutler J, Birchall J, Martin C, Porch A. Design and *In Vitro* Interference Test of Microwave Noninvasive Blood Glucose Monitoring Sensor. IEEE Trans Microw Theory Tech. 2015 Oct 1;63(10 Pt 1):3016-3025)

For all study visits

Wrist device is removed after each study visit. In-between patients, either same or different day, the device will be cleaned by using Super Sani Cloth wipes, which are the disinfectants we have in the endocrine clinic (active ingredients: dimethyl ethylbenzyl ammouinum chloride, isopropyl alcohol)

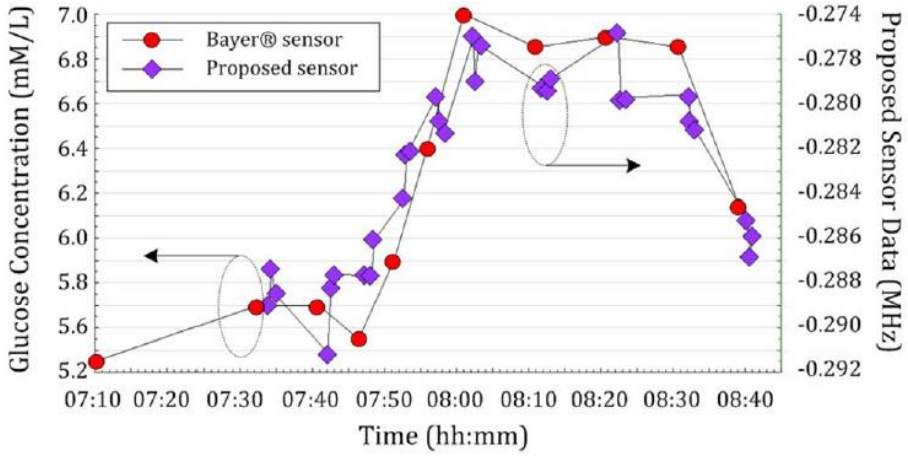


Fig. 7. OGTT I. The sensor response (here the change in bandwidth) is compared with blood glucose levels measured using a "blood-strip" glucometer (Bayer CONTOUR).

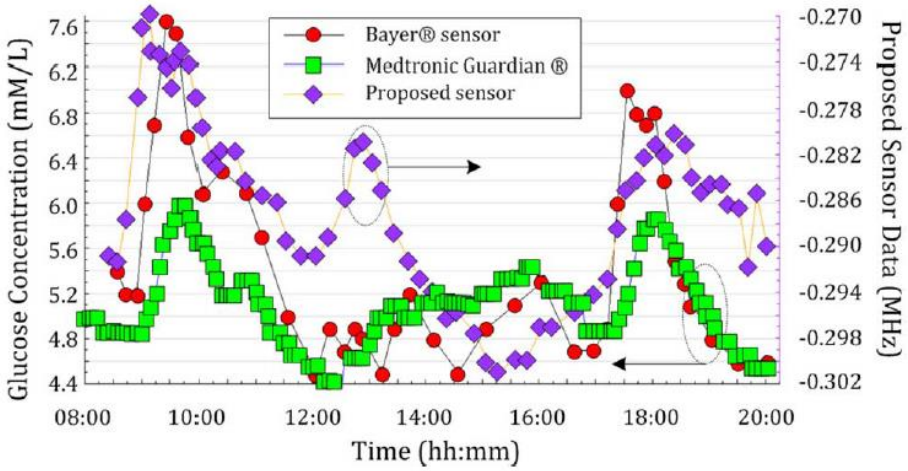


Fig. 8. OGTT II. Sensor data (change in bandwidth) are measured over a continuous 12-h period involving three food ingestions, and are compared with data from a continuous glucose meter (Medtronic Guardian CGM) and blood-strip glucometer (Bayer CONTOUR), after [27].

Sample Size

It is expected that 10-15 subjects will be enrolled, and that there will be up to 24 paired measures on Visit 1 (every 5 minutes for 2 hours), and 8 paired measures (every 15 minutes for 2 hours) each of the follow-up days. If no errors on the Clarke error grid are observed (as in the preliminary data), the error rate based on the "rule of three", will be constrained to be no more than 0.5% overall (based on 600 total measures), and no greater than 5% within subject (Jovanovic and

Levy, 1997). Confidence limits for the agreement will depend on the within and between subject variability measures, so formal power calculations on this measure of agreement is not possible.

Statistical analysis

Agreement between glucose measures between systems will be evaluated graphically using Bland-Altman plots, and Clarke error grids. Error rates from the Clarke error grid will be calculated, and 95% confidence limits will be calculated overall, by subject and by day within subject. Similarly, limits of agreement from the Bland-Altman plots will be adjusted to account for repeated measures, as described by Bland and Altman (2007). Analysis will be performed using SAS software (version 9.4; Cary, NC).

Possible adverse effects

The materials for the wrist band are inert and the potential for allergy is low.

Fingersticks can cause pain and discomfort.

The Accucheck Inform II needs a small drop of blood for each fingerstick.

Ingesting GlucoCrush may cause high blood glucose if diabetes is not in optimal control

Should a patient develop acute hyperglycemia with symptoms such as increased thirst/vision changes/headache, patients will be hydrated and assessed for the need for insulin. The F20 clinic has regular insulin and/or fast-acting insulin.

As with any patient who comes to the clinic and develops hypoglycemia, a hypoglycemia protocol is in place for study participants. Signs and symptoms of hypoglycemia include, but are not limited to: weakness, restlessness, nervousness, hunger, and sweating. If a patient develops hypoglycemia during the study follow up period (defined as blood sugar < 70 mg/dL), he/she will be administered 4 oz. (120ml) of juice. If the patient is unable to consume carbohydrate sources by mouth, he/she will receive an intramuscular glucagon injection, which is readily available in the clinic.

Due to the potential risk for hypo- and hyperglycemia during the study period, patients will be strongly encouraged to have assisted transportation to and from the visit. In the event that this is not possible, the investigators will assess the subjects individually which might include recommendations to check fingerstick blood glucose at home prior to the visit, taking glucose tablets, staying after the study for observation and fingerstick blood glucose checks.

Compensation

Each study participant will be compensated $300 for each completed visit, with a total potential to earn $900 if all three visits are completed.

Informed Consent

Written informed consent will be obtained from the subjects.

Relationship between Alertgy and Cleveland Clinic

Cleveland Clinic, along with University Hospitals and JumpStart, is a founding partner in the Cleveland location of the Silicon Valley headquartered organization called PlugNPlay platform. The company has a Cleveland location which opened in 2018 and is located at the Global Innovation Center (downtown Cleveland).

Alertgy, was a company that was accepted into the first batch PlugNPlay companies. Numerous meetings were held with Cleveland Clinic, Metro & University Hospitals to show the technology. Subject Matter Experts were convened to learn more about the technology and provide feedback as to how the technology could be enhanced and used in the market.

Cleveland Clinic (Innovations & Endocrinology and Metabolic Institute) and Alertgy agreed to work together to validate the effectiveness of the company's initial noninvasive blood glucose monitoring wristband. Cleveland Clinic will recruit 15 people to determine if the product characteristics are functioning and are reliable.

Cleveland Clinic will be performing product viability and design work. Additionally, Cleveland Clinic Innovations is performing market analytics, business plan development support and STTR application review support. Cleveland Clinic is being compensated for their work.

Alertgy is remunerating $57,000 to Cleveland Clinic for services. Cleveland Clinic will also receive a convertible note from Alertgy for $23,000. Should the proof of concept work validate that the technology works, Cleveland Clinic will exercise the convertible note. If the testing proves that the device does not work, Cleveland Clinic will not exercise the note.

References

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