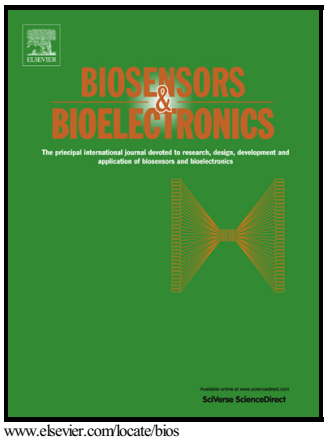
Author's Accepted Manuscript



www.elsevier.com/locate/bios

Investigating pipeline and state of the art Blood glucose biosensors to formulate next steps

Anthony G.A. Aggidis, Jeffrey D. Newman, George A. Aggidis

PII: S0956-5663(15)30169-X
DOI: http://dx.doi.org/10.1016/j.bios.2015.05.071
Reference: BIOS7735

To appear in: *Biosensors and Bioelectronic*

Received date: 16 May 2015
Revised date: 28 May 2015
Accepted date: 31 May 2015

Cite this article as: Anthony G.A. Aggidis, Jeffrey D. Newman and George A. Aggidis, Investigating pipeline and state of the art Blood glucose biosensors to formulate next steps, *Biosensors and Bioelectronic,* http://dx.doi.org/10.1016/j.bios.2015.05.071

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting galley proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

Review Investigating pipeline and state of the art blood glucose biosensors to formulate next steps

Anthony G.A. Aggidis, Jeffrey D. Newman, George A. Aggidis*

Cranfield University, College Rd, Bedfordshire MK45 4DT, UK

*Corresponding Author: G.Aggidis@lancaster.ac.uk , 0044(0)1524593052, Lancaster University, Engineering, Lancaster, Lancs., LA1 4YW, UK

Abstract

Ten years on from a review in the twentieth issue of this journal, this contribution assess the direction research in the field of glucose sensing for diabetes is headed and various technologies to be seen in the future. The emphasis of this review was placed on the home blood glucose testing market. After an introduction to diabetes and glucose sensing, this review analyses state of the art and pipeline devices; in particular their user friendliness and technological advancement. This review complements conventional reviews based on scholarly published papers in journals.

Keywords: SMBG, CGM, Non-invasive, Smartphone, Wireless

Accepted manuscript

1 Introduction

Home use blood glucose biosensors currently dominate 80% of the world market in biosensors. Of which the portable amperometric glucose biosensors are the most efficient and commercially successful. They are available in various forms such as pens and glucose displays etc. By examining Figure 1 it is visible that the biosensor market has grown at a phenomenal rate since 1985 and their applications have spread in to many sectors. Today they can be applied in many situations such as healthcare, pharma, food industry, environmental monitoring and security. The market share majority ($13 billion) however is compounded by medical diagnostics; in particular glucose biosensors and those for home use being the most common (Rustagi & Kumar, 2013, Turner, 2013).

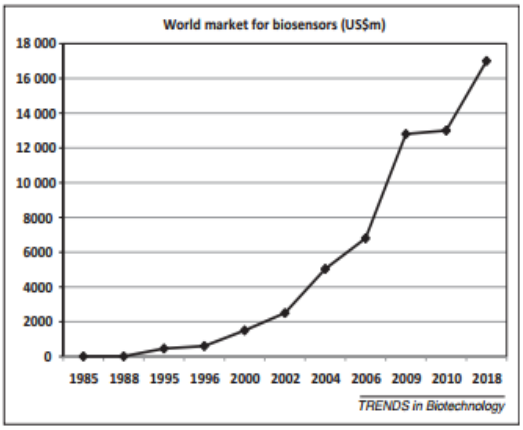


Figure 1: Estimation of biosensor world market (Turner,

ACCEPTED MANUSCRIPT

Diabetes Mellitus: Coming from the words 'siphon' and 'honey' in Ancient Greek and Greek, respectively. It is a chronic metabolic disorder affecting 347 million people worldwide (World Health Organisation, 2013); of which ~5-10% suffers from type 1 diabetes (Tuomilehto, 2013). This rate of incidence has been and is suggested to continue increasing by around 3% annually (Aanstoot, et al., 2007) to what is now predicted by 2035 to be 592 million (International Diabetes Federation, 2013). It is characterised by hyperglycaemia and disturbances in macronutrient metabolism resulting from deficits in insulin production, insulin action or both (World Health Organisation, 2011). This can be represented as venous glucose concentration or oral glucose tolerance test of >11.1mmol/l or a fasting plasma glucose concentration >7.0mmol/l. There is type 1 Diabetes characterised by a lack of insulin due to the pancreas inability to produce it (insulin dependent) and type 2 Diabetes characterised by production of insulin however there is resistance to it mainly due to poor diet and inactivity (non-insulin dependent). There is also gestational diabetes which however is temporary; only occurring during pregnancy. Type 2 is the most common of 90-95% cases worldwide.

Diabetes complications can be fatal such as hypo and hyperglycaemic coma but can also be avoided and controlled by monitoring blood glucose levels to ensure they stay within healthy levels (Holman, et al., 2008). Both the DCCT – Diabetes Control and Complications Trial, (1993) and UKPDS – United Kingdom Prospective Diabetes Study (1998) reported significant reductions in the progression of complications associated with diabetes due to tight glycaemic control. According to International Diabetes Federation, (2013) diabetes caused at least $548 billion in health costs globally by the end of 2013 ~~surmounting to~~ which was 11% of total health spending on adults. Despite the ~~grotesque~~ enormous costs an individual dies from diabetes every 6 seconds which also has its own costs (International Diabetes Federation, 2013). As a result it is crucial that blood glucose levels are monitored through blood glucose biosensors in order to save lives, improve lifestyle and save money. These are highly sensitive and selective analytical devices which inform patients of their glucose levels so they can counter elevated levels through insulin injections or oral medication if needed. Key points in glucose biosensor evolution are listed in Table ~~2~~1.

The current gold standard glucose biosensors are invasive and utilise electrochemical transducers to work in concert with microprocessors to quantitatively generate an electrical signal correlated to analyte concentration. The most common method of measurement are amperometric biosensors. Production of such biosensors is relatively cheap and easy to manufacture coupled with their rapid response make them popular (Kimmel, et al., 2012). These are highly sensitive and measure the current at a specific applied potential at a single point in a biological test sample (Ronkainen, et al., 2010). Voltametry is essentially the same thing however it measures more than one point. These changes in current are caused electrochemically by endo and exothermic reactions; increasing or decreasing applied potential until analyte reduction or oxidation occurs (Pohanka & Skládal, 2008).

Optical transduction is a popular non-invasive method using photons to measure an analyte Detection however is dependent on the enzyme converting the analyte into the product undergoing redox reactions at the working electrode (Ligler & Rowe Taitt, 2002). These are becoming increasingly prevalent due to advances in the field making them highly sensitive and specific as well as easy to miniaturise making them cost effective (Borisov & Wolfbeis, 2008). A common principle utilised in these devices is the Evanescent field detection prinicple whereby fluorophores are solely detected when in close vicinity to the optical fiber which can excite surface plasmons (Abel, et al., 1996 and Grieshaber, et al., 2008). The two main types of optical methods are colorimetric and photometric. Colorimetric measures change in light adsorption by measuring changes in refractive index e.g. optical waveguide lightmode spectroscopy, surface plasmon resonance and ellipsometry

Accepted manuscript

ACCEPTED MANUSCRIPT

(Grieshaber, et al., 2008). Photometric measures light intensity whereby luminescent or fluorescent process photon outputs can be detected utilising photomultiplier tubes and photoiodide systems.

2 Methodology

A comprehensive search of existing literature in the public domain was conducted on "state of the art and pipeline glucose biosensors". Key words were utilised (where '*' denotes a wildcard): blood, glucose, meter*, biosensor*, diabetes, technical, details, invasive, non-invasive, minimally, continuous, future, next, step*, state of the art, pipeline, current, new, develop*, amperometric, test, strip, CBG, SMBG, enzyme, wireless, internet of things, app and smartphone.

When investigating state of the art and pipeline devices, date restrictions were put in place. The relevant information obtained was initially evaluated in a meta-analysis style regarding titles, abstracts, contents and references. Additional information derived from the references of already sought literature.

Search engines utilised but not limited to include: Cranfield library, Google Patents, Google, Google Scholar, Scopus, Pub Med, Cochrane Library, Science Direct, Oxford Journals, Copac, and Mendosa.com.

3 Results

Presently five companies dominate the glucose monitoring device market as seen in Figure 2; each with a multitude of modern devices which are briefly summarised in table 3 to table 8 on their technical details.

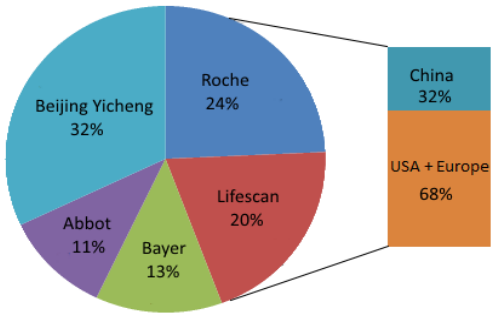


Figure 2: Market leaders in biosensor sales between the 'Big Five' companies: Roche, Lifescan, Abbott (USA), Bayer (Germany) and Beijing Yicheng (China). Adapted from (Turner, 2013).

3.1 State of The Art

In SMBG devices a test strip is inserted into the meter. Blood from the fingertip is then applied to the test strip following lancing and generates a glucose reading. In older systems strips were needed to be coded before use which ran the risk of 'miscoding' and causing inaccurate results. In more modern systems each strip can be auto-coded to the meter or some manufacturers use a single code instead thereby minimising this risk. New risk however is introduced whereby if a meter has not been calibrated properly during manufacturing the user could receive inaccurate results.

ACCEPTED MANUSCRIPT

When blood is applied on a test strip, a cascade of redox reactions occurs within it causing electrons to move from glucose towards the electron surface. This results in a measurable current representing blood glucose level. The basic concept is that immobilised enzyme catalyses the oxidation of glucose by molecular oxygen resulting in gluconic acid and hydrogen peroxide. The two main enzymes for self-monitoring glucose biosensors are GOx and GDH of which the latter may use one of three cofactors: PQQ, FAD and NAD. According to Heller & Feldman (2008), these two methods differ in redox potential, cofactors, turnover rate and selectivity for glucose (Yoo & Lee, 2010).

Glucose Oxidase

GOx is cheap, more glucose selective than GDH and more tolerable than other enzymes to pH, temperature and ions. This method utilising a two-step reaction (Equation 1) whereby GOx is catalyses glucose oxidation producing gluconic acid and hydrogen peroxide (Yoo & Lee, 2010). The presence of glucose is directly proportional to the intensity of the resultant colour and measured using spectrophotometers or reflectance photometers.

$$1)\ Glucose + H_2O + O_2 \xrightarrow{Glucose\ Oxidase} Gluconic\ Acid + H_2O_2$$

$$2)\ H_2O_2 + Chromogen \xrightarrow{Peroxidase} 2\,H_2O + Colour\ Formation$$

Equation 1: Glucose oxidase two-step reaction (Yoo & Lee, 2010).

For GOx catalysis of glucose oxidation; FAD is utilised as a redox cofactor to initially accept an electron and reduce to FADH2. It is then regenerated in reaction with oxygen leading to hydrogen peroxide as seen in Equation 2.

$$Glucose + GOx - FAD^{+} \rightarrow Glucolactone + GOx - FADH_2$$

$$GOx - FADH_2 + O_2 \rightarrow GOx - FAD + H_2O_2$$

Equation 2: Cofactor role in formation of hydrogen peroxide (Yoo & Lee, 2010).

In a glucose biosensor the resultant hydrogen peroxide is oxidised at platinum electrodes releasing electrons directly proportional to the amount of glucose in the blood represented by Equation 3. Glucose concentration can also be identified by measuring oxygen consumption and the level of hydrogen peroxide produced during the reaction (Yoo & Lee, 2010).

$$H_2O_2 \rightarrow 2H^{+} + O_2 + 2e$$

Equation 3: Glucose measurement using electrons from hydrogen peroxide (Yoo & Lee, 2010).

Glucose Dehydrogenase (GDH)

This method does not require oxygen unlike the GOx method resulting in faster electron transfer rates. GDH-PQQ (Pyrroloquinoline quinone) was marketed for around 20 years however was non-selective to glucose and so produced false high glucose results in the presence of other sugars such as maltose. The FDA reported that blood glucose biosensors report the highest adverse events than any other diagnostic device. From 1992-2009 100 deaths were associated with these biosensors as seen in Figure 12; 13 deaths were due to non-glucose interference through the use of GDH-PQQ test strips and meters leading to inappropriate insulin dosing. It was reported that 10 of these patients were receiving Extraneal (icodextrin) for renal failure and 3 were receiving maltose-containing substances (U.S. Food and Drug Administration, 2013).

ACCEPTED MANUSCRIPT

As a result the company producing Extraneal; Baxter Healthcare Corporation now advises that their product must not be used in conjunction with GDH-PQQ and GDH-glucose-dye-oxidoreductase due to false positive readings in presence of maltose (Baxter Healthcare Corporation, 2010). The remaining unaffected methods are GOx, GDH-FAD (flavin adenine dinucleotide) and Mut-Q-GDH which are now all used in the current blood glucose biosensors. FAD only has interference at very high concentrations of mannose which does not replicate real life (Hinzman, 2012).

Commoditization is where products become indistinguishable from each other and regarding test strips this is a reality. Some examples include the fact that most use similar techniques such as capillary action and use the same enzymes. Methods to counter this include technological advances such in minimally invasive glucose meters, non-invasive glucose meters and subcutaneous continuous blood glucose monitors (Nathan-Roberts & Liu, 2012).

Third generation glucose biosensors do not require a reagent and utilise electrode technology allowing direct wiring of the enzyme to the electrode through co immobilisation, thus permitting higher current due to enhanced electron transfer (Wang J. , 2008). Evolution of this technology has vastly reduced test time to few seconds and blood sample requirement from 50μL to 0.3μL (Smith, 2011). This technology has led to continuous blood glucose monitoring such as Abbot's FreeStyle Navigator CGM System released in 2006 seen in Figure 18. CGM is appealing because it lets the user know whether their blood glucose levels are increasing or decreasing which the single measurement self-monitoring blood glucose devices don't offer; as a result therapy can be conducted more promptly.

3.1.1 Roche Diagnostics

This is a division of Hoffman-La Roche Ltd established 1896 based in Switzerland; its main blood glucose devices presently on the market are summarised by Table 2.

In 2010 the worlds' first strip-free blood glucose meter was released dubbed the Accu-Chek® Mobile. It utilises replaceable cassettes of 50 test strips on continuous tape and stores used test strips. These test cassettes also contain a radiofrequency identification chip which automatically codes the meter (Roche Diagnostics, 2014). It is integrated with the Accu-Chek® FastClix finger ~~pricker~~ lancet which only needs one click to both prime and prick. It also contains replaceable drums of 6 lancets that upon release present a red line to indicate it's used. Penetration depth can be changed using the dial; the higher the number the deeper the penetration depth. Recommended starting depth is selection 3 out of maximum 6 however this may not suit all individuals. The Clixmotion® technology with 11 different settings integrated into this lancing device follows the principal of dual-guided motion. This prevents vibration and oscillation to avoid tissue damage by utilising high-speed penetration with a gentle stop and immediate retraction (Roche Diagnostics, 2014). As a result of these two integrated technologies there is less to carry around, no need for unhygienic handling and avoids clinical waste which can be safely disposed of in household waste. The device also comes with reminders and 7, 14, and 30 day averages; before or after meal can also be calculated (Roche Diagnostics, 2013).

Black code chips come with purchased test strips and needs to replace current white chip found in newly purchased meters for calibration. This ensures accuracy but is wasteful as it's one-time use only yet comes with every purchase of test strips (Roche Diagnostics, 2014).

Accepted manuscript

ACCEPTED MANUSCRIPT

The Accu-Chek® Combo includes a bolus calculator with advice and can be paired with the Accu-Chek Spirit Pump using two-way Bluetooth wireless technology with a range of 6.5 feet. It also consists of 5 pre-set time blocks to help manage insulin: Figure ~~3~~2, personalised reminders and alarms compatible with AccuChek® 360 software for result analysis. The Accu-Chek® Expert also comes with an on-board bolus advisor.

Time Block	Start Time	End Time
1. Night time	Midnight	The time you normally wake up
2. Breakfast	The time you normally wake up	1½ hours before you normally eat lunch
3. Lunch	1½ hours before you normally eat lunch	1½ hours before you normally eat dinner
4. Dinner	1½ hours before you normally eat dinner	1½ hours before you normally go to bed
5. Bedtime	1½ hours before you normally go to bed	Midnight

Figure ~~3~~2: Accu-Chek® Aviva Combo time blocks (Roche Diagnostics, 2009)

3.1.2 LifeScan

Established 1981 Their OneTouch® systems are claimed to be the most prescribed brand by Endocrinologists and Primary Care Physicians (Lifescan, 2014). Their current main devices are summarised by Table ~~5~~3.

OneTouch® Ultra® Blue and OneTouch® Verio® test strips utilise capillary action. The Ultra® Blue test strip cases have a code on the back which must match the code on the meter after insertion (Lifescan, 2014). Ultra® Blue Test Strips employ DoubleSure™ Technology which uses two isolated electrodes to make two blood measurements and compare the two. If the difference is statistically significant an error signal is provided to retake the test. OneTouch® Verio meters utilise a technology called OneTouch® GlucoFilter® ~~to iron out interfering~~ which filters out common interferences as seen in table 3 by~~. It works in a dual action mechanism (LifeScan, 2013). The filter prevents large interference substances entering and a new electrochemistry setup~~ testing~~s~~ the sample three times using one gold and one palladium sputtered opposing electrodes to isolate glucose signals (European Association for the Study of Diabetes, 2011). Ten checks are conducted to reduce interference: 1 specified system malfunction, 2 strip check failed, 3 sample applied too early, 4 user error, 5 algorithm detected errors, 6 strip removed too early, 7 temperature too high, 8 temperature too low, 9 battery voltage check failed, 10 unspecified system malfunction (LifeScan, 2010). OneTouch® Verio® Test Strip blood samples can be applied on both sides making it friendly for both right and left handed individuals. A drawback is its 18.2% reactivity to D-Xylose.

OneTouch® UltraMini® is also known as UltraEasy and in third tier markets: Horizon but uses different test strips (Lifescan, 2014).

OneTouch® Verio IQ® uses a colour indicator to communicate different glucose levels. The limitation to this is for individuals whom are colour blind and possibly those with impaired vision due to retinopathy. For consistent normal results, achievement messages appear which reinforce behaviour by acknowledging the users effort. Data can be transferred to a computer using a USB for analysis of results i.e. logbook reports, pie charts, standard day graphs and averages by meal and day

Accepted manuscript

ACCEPTED MANUSCRIPT

(Lifescan, 2014). The device utilises a backlit LCD coloured screen making it easier on the eyes having also a test port light makes night time testing easier.

OneTouch VerioSync based on the VerioIQ but stripped of some functionality and replaced with wireless Bluetooth and accompanies an app OneTouch Reveal. This allows wireless automatic transfer of results to only Apple devices for now when the application is running; not real time. Results appear in a 14-day summary showing patterns of glycaemic level and can also be opened in Microsoft Excel. These results also automatically enter a 90-day logbook which identifies the time the test was taken so it can automatically tag a test as breakfast, lunch, dinner or overnight; no need to reset times on the meter. These times are flexible as can be modified in the 'about me' section. The logbook can also be shared via text or email making it perfect for unison with their healthcare professionals. The use of this mobile application however drains the battery of the device it is running on; likely due to the use of regular Bluetooth rather than low-energy Bluetooth technology that wasn't currently available during the meters development LifeScan,(2012) and LifeScan, (2012).

The OneTouch Ping meter-remote has an on-board, customizable 500-item CalorieKing™ food database; this makes calorie counting much easier as well as more accurate. Through this it calculates bolus insulin to be taken and also wirelessly transfers data to the OneTouch Ping insulin pump from almost 10 feet away using Bluetooth (Animas & LifeScan, 2008).

OneTouch UltraLink wirelessly communicates with the MiniMed Paradigm® insulin pump and Guardian® Devices.

Accepted manuscript

3.1.3 Bayer

Bayer (~~E~~established 1863) purchased Ames and Miles which were significant precursors to Bayer diabetes. This company is based in Germany and their current leading portable devices are summarised in Table ~~6~~4. These devices come with the Microlet 2 lancing device and Microlet lancets which are different colours for each day of the week. This concept helps remind the user to change their lancets.

Contour XT (Contour EZ) utilises the new Next test strips which use capillary action to acquire a sample and employs a multi-pulse algorithm to analyse blood samples at several time points to ~~iron~~ filter out common interferences. This provides compensation for haematocrit, temperature, humidity and altitude effects (US Food and Drug Administration, 2013). These strips have the same basic technology as the Contour strips apart from the proprietary mediator which is MLB (3-(2', 5'-Disulfophenylimino-3H-phenothiazine) bis sodium salt) instead of Potassium Ferricyanide to facilitate electron transfer. This reduces background current and permits lower applied voltages. Double Dip technology allows reapplication of blood following insufficient application of <0.6µl (US Food and Drug Administration, 2013). It was recommended by the US Food and Drug Administration, (2013) that tests should not be conducted during or shortly after xylose absorption due to interference as well as cholesterol and triglyceride concentrations of >1,168 mg/dL and >4,709 mg/dL, respectively. Interference may also arise in the following compounds when concentrations exceed level stated: bilirubin, uric acid, ascorbic acid and Acetaminophen at >54, >59, >10 and >35 mg/dL, respectively (Tang, et al., 2000).

ACCEPTED MANUSCRIPT

The Countour XT target ranges which can be personalised, pre and post meal markers and provides reminders. Averages for 7, 14 and 30 days as well as weekly summaries of high and low results are provided. The display is not backlit so night tests may be difficult. Studies by the FDA expressed that xylose has a significant interference at 6 mg/dL as a result testing should be avoided during or soon after xylose absorption. They also state that some naturally occurring substances or those from therapeutic treatments such as bilirubin and Acetaminophen, respectively won't significantly disturb results (US Food and Drug Administration, 2012). The Contour Next uses Micro USB making it Mac compatible. Markers can be added using autolog to attribute a test with a symbol for pre/post meal, sick, stress and activity. Two hour reminders can be set as well as pre and post meal averages for analysis.

The Contour Next Link device has in-built software which identifies extended periods of sensor exposure to humidity and upon detecting during a test, flags up an error report; cancelling the test (US Food and Drug Administration, 2013). Bluetooth is utilised to send test information to its accompanying Medtronic insulin pump to provide personalised therapy. The Contour Next USB released June 2012 is substantially equivalent to the previously mentioned device concerning intended use, performance, safety and effectiveness. Both these devices employ an attached USB which can be directly inserted compatible devices and automatically installs GLUCOFACTS® Deluxe diabetes management software. The Contour USB again uses autolog technology to check for pre/post meal results (Bayer, 2014). In addition it is accompanied by log features providing clarity in diary of results, carbohydrates and insulin. It employs second-chance technology with Sip-in Sampling®, brightly coloured display and illuminated test port (Harrison, 2012).

The Breeze 2 permits additional testing sites including the palm and forearm as well as fingertips. The test strips changed from those used in the previous generation such as increased enzyme and substrate polymer support matrix and NoCoding technology. The FDA conducted tests to identify possible interferents of which Albumin, cholesterol, galactose, glipizide, glucosamine, maltose, metformin, salicylate, triglycerides, and xylose showed no significant bias (< ±10%) at tested concentrations (US Food and Drug Administration, 2012).

3.1.4 Abbott

Since Abbott laboratories bought MediSense along with their electrochemical blood glucose meter for $867million in 1996 and the subsidery of Therasense in 2004 they became one of the major biosensor companies globally (Abbott, 2014). Since then they have released a wide variety of new designs of which their latest can be summarised by Table ~~7~~6.

The FreeStyle InsuLinX is one of the only touch screen devices available. It utilises InsuLinX test strips which can also be used with other FreeStyle meters and is much smaller than the Accu-Chek Aviva strips. Concentrations of interfering substances for InsuLinX test strips can be summarised in table 5 along with test strips from the other companies excluding Beijing Yicheng. Despite having a back light it automatically switches off up to 10 seconds requiring the user to hold the back light button for 3 seconds. The test port however is illuminated and illuminates the test strip and finger when in contact making night time testing easier although it can't be on at the same time as the backlight. There is however computer software which allows the user to update the firmware so these lighting issues could be altered in the future. The device comes with in-built software for analysis of results on either a PC or a Mac through a micro USB. Despite an on-board insulin counter the meters analysis functions are basic compared to others out on the market with a result history filter to show those before meals are as advanced as it gets. For the calculator the units go up individually and don't have a hold button function to increase by multiples of 5 for example to make the task less tedious. You can log the insulin dose recommended into the logbook which shows an apple pre/post

Accepted manuscript

ACCEPTED MANUSCRIPT

meal and insulin markers. It also tells you how many active units of insulin are in your body and gives a timer.

FreeStyle Lite requires the smallest blood sample and has a convenient backlight and test strip port light for night time testing. It offers 7, 14 and 30 day averages and has 4 programmable reminder alerts FreeStyle Freedom Lite has a coloured port instead. FreeStyle Lite test strips allow reapplication times of 60 seconds and utilise ZipWik tabs on either side which break the meniscus of the blood drop through capillary action; as a result can be used by left and right handed people.

Figure 3: Precision Xceed Pro inside docking station alongside control solutions

Precision Xtra uses InsulinX test strip can be used with the other FreeStyle meters (FreeStyle test strips). This device is a capable of monitoring both blood glucose and β-ketone in fresh whole blood using Precision Xceed Pro Blood Glucose Test Strips, Precision PCx Plus Blood Glucose Test Strips and Precision Xceed Pro Blood β-Ketone Test Strips (Abbott Diabetes Care Inc., 2009). To calibrate the device the bar code label on each test strip foil packet must be scanned before use using the scanner on the top of the device. This also checks the expiry date to maximise accuracy and reliability. It runs on two AA alkaline batteries which are common place to find. It also comes with an optional docking station seen in Figure 3 providing wired or wireless automatic data transfer to a computer running the data management application software.

3.1.5 Beijing Yicheng

3.1.6

3.1.7 Smartphone dependant meters

These devices must plug directly into a smartphone for interfacing. They do not require batteries as they use smartphones as a power source and data connection point. As they use clouds they have unlimited memory.

The Dario by LabStyle™ (Israel) fully released in August 2014 is an all-in-one smart meter consisting of a glucose meter, an adaptor, and disposable GOx Dario™ test strip cartridge of 25 strips and lancing device utilising 30G lancets (with penetration depth lever); seen in Figure ~~5~~4. The blood sample required is 0.3µl and test time is 6 seconds ranging between 0.6-3.33mmol/l. Results

Figure 4: Dario all-in-one smart meter (LabStyle Innovations Corp., 2014).

ACCEPTED MANUSCRIPT

then logged automatically; providing alerts and actionable insights if not euglycaemic. The meter adaptor plugs into a smartphone (IOS and Android) headphone jack and upon connection syncs results to the mobile app; storing them in a cloud (LabStyle Innovations Corp., 2014).

The Gmate® SMART by Philosys, (Korea) was released on the 15th August 2014. This device is the smallest blood glucose biosensor in the world (21x42.7x8.8mm) and weighs 4.2g. It directly plugs into the headphone jack of an iPhone, iPad. Pre/post meal, exercise, medication, stress and custom written markers can be added to results. The summary for result acquisition and log can be summarised by Figure ~~6~~5. Results can be emailed or messaged in SMS and rotating the smart phone horizontally brings up a graph of results over time with choice of averages for 7, 14, 30 and 60 days. Sample size is 0.5µl with a result range of 0.6-33.3 mmol/L (Philosys, 2014).

The iBG Star by Sanofi Aventis & AgaMatrixThis is a no coding device released in April 4th 2011 (Figure ~~7~~6) with docking capabilities to iPhones and iPads. The blood sample size is 0.5µl, test time 5 seconds, result 1.11-3.33mmol/l. It also has alternate testing sites: fingertips, palms and base of forearm. It also comes with a dock connector (Sanofi Aventis & AgaMatrix, 2013).

Figure 6: iBGStar system doc agaMatrix, 2013).

Figure 5: Testing steps for Gmate SMART glucose meter and app (Philosys, 2014)

3.2 Non-Invasive

These devices are not biosensors as they work on different principles such as the absence of biological components. They don't penetrate the skin or cause pain unlike conventional meters. This encourages regular glucose monitoring; reducing complication risks. They are also economically appealing for consumers as they don't require lancets or strips. They are currently not successful enough to surpass invasive devices so investments are high risk, high return due. Success will dominate a huge sector of the glucose market (Smith, 2011).

Technologies include: near infrared spectroscopy, mid-infrared spectroscopy, optical coherence tomography, temperature-modulated localized reflectance, raman spectroscopy, polarization changes, ultrasound technology, fluorescence technology, thermal spectroscopy, ocular spectroscopy, impedance spectroscopy, electromagnetic sensing, fluid harvesting, iontophoresis, crystalline colloidal array technology (Skyler, 2012).

ACCEPTED MANUSCRIPT

3.2.1 GlucoTrack ® - Integrity Applications

This device announced its first wholesale orders in July 2014 (Integrity Applications, 2014). CE approval was given based on clinical trials at Soroka University in 2013 utilising 135 subjects and over 6,000 measurements for safety and performance between the GlucoTrack and invasive devices. 96.5% of these measurements were clinically acceptable based on the Clarke Error Grid (Integrity Applications, 2014 and Harman-Boehm, et al., 2010).

It utilises a small sensor which is clipped to the earlobe and connects to a control and display unit (Figure ~~8~~7). It measures blood glucose levels through a patented amalgamation of ultrasound, electromagnetic and thermal technologies to avoid common inaccuracies seen in other non-invasive devices. Measurements for each three methods are taken independently and simultaneously within a 1 minute window and then using a propriety algorithm which correlates and averages the data. This allows for continuous and spot glucose testing (Harman-Boehm, et al., 2010). Each individual ear clip requires monthly re-calibrations against invasive basal and postprandial fingertip measurements which may take 90-120 minutes; this can be done at home however is recommended at the clinic.

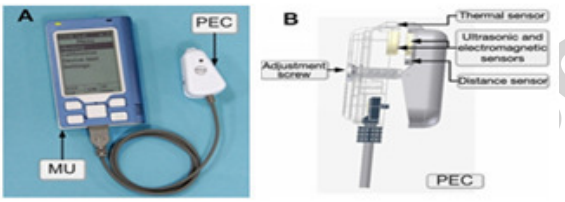


Figure 7: GlucoTrack® DF-F main unit (MU) and personalised ear clip (PEC) (Harman-Boehm, et al., 2010).

The ear clip must be replaced every 6 months and USB is used to download data and recharge the battery (Harman-Boehm, et al., 2010). It also has verbal instructions for individuals with eyesight impairment.

3.2.2 TensorTip Combo - Cnoga Medical Ltd.

This is a dual non-invasive and invasive glucose monitor where the finger is inserted into the device. It comes with an invasive add-on which uses fresh capillary whole blood for personal calibration (Cnoga Medical Ltd., 2013). The components of the device can be summarised by Figure ~~9~~8.

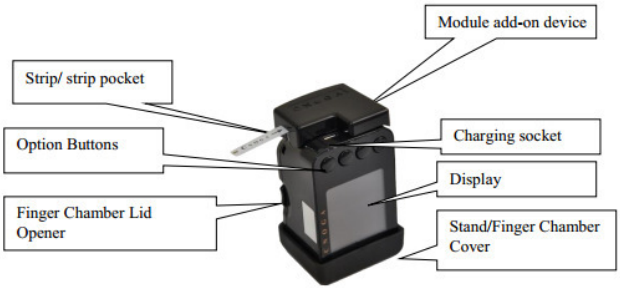


Figure 8: TensorTip Combo Glucometer component summary (Cnoga Medical Ltd., 2013)

ACCEPTED MANUSCRIPT

3.3 Pipeline Devices

Invasive

3.3.1 Dexcom G5 and G6 CGM

The Gen-5 sensor is to be released in late 2015; designed to port directly to a smart phone using low-energy Bluetooth (Gregg, 2013). This connection is protected by patent US 2014/0012118 A1. The Gen-6 is being developed for 2015-17 and will be highly resistant to ~24 drugs commonly used in hospitals; including Tylenol and Acetaminophen up to 1000mg. As a result it will be very accurate with said single digit MARD. It will also be factory calibrated and wearable for 10 days without having to calibrate with finger stick measurements. Results will be automatically sent to a smart phone. Barriers include FDA approval for connection to a smartphone and their battery life however backup external receivers will be available (Gregg, 2013). Likely that the Dexcom G4AP improved de-noising algorithms will also be applied to these newer generations (Garcia, et al., 2013).

The Dexcom Share is a docking station for the G4 Platinum and future generations is under development. It will result transmission to up to five smart phones using cloud technology. This cloud may likely be the new acquisition of SweetSpot Diabetes Care Inc. on 23rd February 2012 (Dexcom, 2012). This is an IT company with an online platform for uploading and processing data from diabetes devices. The G5 will also be compatible with the next generation of Accu-Chek® insulin pumps. This will allow blood glucose data, insulin information and also continuous glucose monitoring readings and trends to be viewable on a wireless handheld device (Dexcom, 2012).

~~*3.3.2 'Smart Tattoos'*~~

~~These are implantable fluorescent micro particle sensors for subcutaneous tissue which measure local blood glucose changes correlated to blood glucose levels through the interstitial fluid (Srivastava, Jayant, et al., 2011). Results can be monitored non-invasively using optical instrumentation (Long & McShane, 2008). These devices use competitive binding between glucose and glucose analog conjugated to donor fluorophore from Apo-GOx conjugated to acceptor fluorescent dye. Glucose displaces the latter presenting as a decrease in fluorescence resonance energy transfer (Srivastava, Jayant, et al., 2011). Dexcom were developing 'Sleeping Beauty' which would last a year under the skin in the abdomen before being replaced by a physician however was too expensive to continue~~

3.3.3 Cascade Metrix Inc.

This device utilises electrochemical glucose sensor technology. The prototype has been successfully validated in humans is expecting to acquire a European CE mark by 2015 for release in 2016. It consists of the system, a disposable cartridge of AutoSampler tube-set and a glucose sensor module (Cascade Metrix Inc., 2014). This will monitor blood parameters such as glucose, lactate, electrolytes, cholesterol, urea, and blood gases, using a "test-strip based glucose meter, an electrochemical flow-through sensor, an infrared spectroscopic flow-through sensor, and an implantable, needle-type sensor" (Kunjan & Lloyd, 2013).

Minimally Invasive

3.3.4 'Smart Tattoos'

These are implantable fluorescent micro particle sensors for subcutaneous tissue which measure local blood glucose changes correlated to blood glucose levels through the interstitial fluid (Srivastava,

Accepted manuscript

ACCEPTED MANUSCRIPT

Jayant, et al., 2011). Results can be monitored non-invasively using optical instrumentation (Long & McShane, 2008). These devices use competitive binding between glucose and glucose analog conjugated to donor fluorophore from Apo GOx conjugated to acceptor fluorescent dye. Glucose displaces the latter presenting as a decrease in fluorescence resonance energy transfer (Srivastava, Jayant, et al., 2011).

3.3.5 CGM via the eye

Google[x] miniaturised an electrochemical sensor (GOx) for measurement of glucose in tears and incorporated it and a wireless chip into a contact lens to transmit results to an app on a smartphone; Figure ~~10~~9. They plan to integrate LED lights into the contact lens to indicate hypo or hyperglycaemia (BBC, 2014). This could be used to transmit results optically or through backscatter. The device will be powered by radiation off-lens using an RF antenna or photovoltaic device striding the outside of lens (Otis, et al., 2013). On July 15th 2014 Novartis eye care division Alcon entered an agreement with Google[x] to in-licence this smart lens technology in order for development and commercialisation in 2019 (Novartis, 2014). Using an eye model ageing, temperature and biofouling effects have been studied demonstrating good sensitivity, detection limit and linear range (Bandodkar & Wang, 2014).

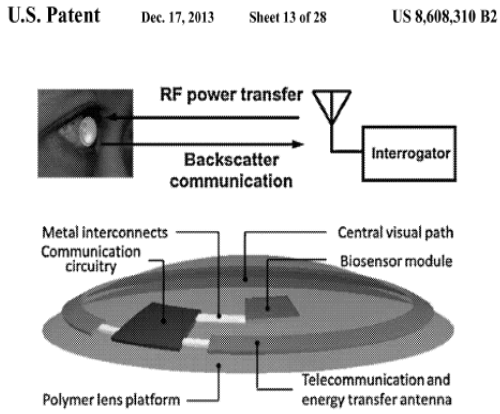


Figure 9: Google[x] Contact Lens CBG Monitoring Biosensor (Otis, et al., 2013)

NovioSense is collaborating with the Fraunhofer Institute for Microelectronic Circuits and Systems to something similar. This device uses a GOx electrochemical sensor attached to a hollow coil coated in hydrophilic gel allowing the sensor to follow the shape of the eye. The device measures 0.5x2.0mm and the circuit is encapsulated in a biocompatible resin i.e. UV curable medical adhesives to protect it from the external environment (Hanssen & Tweehuysen, 2012). An analog digital converter transforms the electrochemical signals into digital data which can be radioed to a smartphone via an antenna. The sensor consumes less than 100 microamperes allowing the sensor to be worn from weeks to months at a time and is charged using radio frequency (Fraunhofer IMS, 2012). Metabolites from lachrymal fluid could be used as biofuels to power these devices. Biofuel cells have been demonstrated to be able to produce energy from lycramal glucose and ascorbate (Falk, et al., 2012 and Falk, et al., 2013).

Akron University are developing a chemically coated contact lens (pyridinylboronic acid) that changes colour depending on blood glucose levels. From here a smartphone camera will be used to

ACCEPTED MANUSCRIPT

take a photo of each eye and analyses the difference through an app using spectrophotometry to produce a result (Hu, 2012).

The EyeSense sub-conjuctivial glucose monitoring system uses a non-invasive photometer as seen in Figure ~~11~~10 that measures blood glucose by placing it near the eye; however a minimally-invasive procedure is required to implant a tiny biochemical sensor under the conjunctiva. This is replaced annually by an ophthalmologist requiring an incision 1-2mm wide; patients reported no to little pain (Gandhi, et al., 2014 and EyeSense GmbH, 2014).

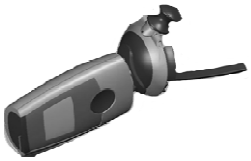


Figure 10: EyeSense Glucose Measuring Device (EyeSense GmbH, 2014).

Clinical trials suggest this technology is capable of surpassing conventional methods and improve compliance of blood glucose monitoring as seen in Figure ~~12~~11.

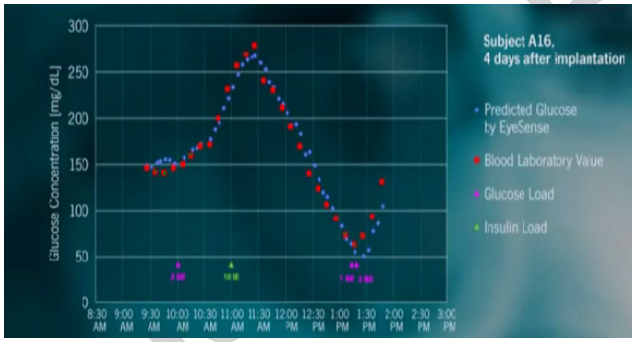


Figure 11: Clinical trial data for EyeSense (EyeSense GmbH, 2014).

The biochemical sensor is embedded on a hydrogel disk containing a chemical that reacts with glucose from the interstitial fluid below the conjunctivia to emit fluorescence. The photometer device quantifies this in less than 20 seconds.

As it's an implant there are issues with foreign body responses to the sensor. Proprietary biocompatible surface coatings have been applied to counter this however deteriorated over time. The consensus error grid at week 1 reduced from 95% zone A to 80% after 6 months. Mean absolute relative difference increased from 7% to 14% over the same period of time. Lag time was approximately 20 minutes which is still not accurate enough in times of rapid glucose fluctuations (Müller, et al., 2013). This device is aimed to launch in 2016 (EyeSense GmbH, 2014).

3.3.6 Senseonics™ CGM system

This includes an implantable micro-fluorometer sensor for insertion into the subcutaneous space of the upper arm, a Bluetooth™ low energy link transmitter and mobile medical app: Figure ~~13~~12. The fluorescent is non-enzymatic (bis-boronic acid based) glucose indicating hydrogel and measurents from the interstitial fluid are taken every 2 minutes for up to 6 months. On February 20th 2013 it was

ACCEPTED MANUSCRIPT

granted ISO 13485:2003 certification of quality management system (Senseonics, 2014 and Mortellaro & DeHennis, 2014).

An LED in the sensor excites the hydrogel causing glucose to bind reversibly to boronic acid groups causing photoinduced electron transfer disruption. This causes increased fluorescence in the presence of glucose. Results are autonomously transferred to the transmitter and then sent to the mobile app. The rechargeable transmitter is worn over the testing site using an arm band and supplies energy to the sensor. Clarke error grid analysis showed that 99% of paired data points were in the combined A and B zones (Mortellaro & DeHennis, 2014).

Figure 12: From left to right: Senseonics Sensor, Senseonics Mobile Medical Application and Senseonics Transmitter (Senseonics, 2014).

Non-Invasive

3.3.7 GlucoWise™ - MediWise Ltd

This handheld device (Figure ~~14~~13) under development expects pre orders by 2016. It can be clipped between the thumb and forefinger or on the earlobe. It measures blood glucose every 10 seconds; providing real-time readings on screen (MediWise, 2014).

Measurements are securely sent via Bluetooth 4.0 to a smartphone or tablet utilising the accompanied app. Results can be automatically uploaded to a secure Cloud or to a PC via USB cable. Cloud access is password protected so can be shared with the users' healthcare professionals. This App utilises Glucowise™ Intelligent Analytics Software allowing personalised recommendations i.e. food or medication adjustment recommendations based on measurements from exercise, diet, body mass index, medication and illness (MediWise, 2014). The company boasts unlimited testing without additional costs with accuracy exceeding industrial standards.

Measurements are derived from the transmission of low power radio waves through the hand or earlobe which are then received by a sensor on the other side. The two technologies used to achieve this include radio waves around 65 GHz to penetrate the skin and provide blood region resolutions.

Figure 13: GlucoWise™ meter and mobile application.

Non-composite films integrated in the sensor makes the skin briefly transparent to radio waves; ensuring measurements are independent of age and skin (MediWise, 2014).

Accepted manuscript

ACCEPTED MANUSCRIPT

3.3.8 Symphony™ CGM - Echo Therapeutics

This measures real-time electrical conductivity of skin. It incorporates the Prelude proprietary skin permeation device, a wireless transdermal sensor, a wireless transceiver and data display technologies (Figure ~~15~~14). The Prelude affects interstitial fluid flow and molecules across the stratum corneum Glucose levels are recorded every minute and transmit to a remote monitor which provides visual and audible alarms outside euglycaemia. This device aims to launch 2015 (Echo Therapeutics, 2014).

Figure 14: Symphony Transdermal CGM and Prelude® SkinPrep System (Echo Therapeutics, 2014).

3.3.9 Grove Glucometer - Grove Instruments

This battery powered device (Figure ~~16~~15) launching by 2016 uses optical bridge technology which has exceeded accuracy standard ISO 15197 in pilot clinical trials. This technology employs lasers that produce visible and NIR light and software algorithms to optically null background tissue and its water content and be absorbed by glucose in the vascular space (Grove Instruments, 2014). Results take ≤20 seconds after inserting earlobe and pressing the go button.

Figure 15: Grove Glucometer (Grove Instruments, 2014)

3.3.10 GlySens ICGM™ System - GlySens

Is an implantable CGM sensor (Figure ~~17~~16) that has demonstrated in preclinical testing to have a lifetime of up to 18 months. It has alerts for hypo and hyperglycaemia and is designed to expectedly function for ≥ 1 year with occasional calibration. It uses glucose-specific, oxygen-based, dual-enzyme electrode technology (GlySens Incorporated, 2013). ssues include foreign body responses to the PDMS sensor membrane; of which was tested to be mild through quantitative histologic analysis. There was insignificant difference between the mass transfer resistances of oxygen to the sensor membrane in comparison to the tissue; allowing sensitive tissue permeability estimates. Recent studies sug gest delivery of oxygen to the sensor can be sustained long term due to predictable changes in tissue permeability (Kumosa, et al., 2014).

Figure 16: GlySens ICGTM with sensor (GlySens Incorporated, 2013)

Accepted manuscript

ACCEPTED MANUSCRIPT

3.3.11 Other Devices…

These are stated as pipeline but have limited information available: LighTouch - LighTouch Medical, Inlight Solutions, MDWatch - Bio-Impedance General, SCOUT DS® - Miraculins, IvSCGM Biosensor, Multi-sensor CGM System - Biovotion AG, 5th Generation Short-Term Sensor, OrSense NBM 200, Electronic thumb-pad sensor - Baylor University and Integrated Guardian Real-Time Continuous Glucose Monitoring System (Ramchandani & Heptulla, 2012 and GBI Research, 2014).

Accepted manuscript

4 Discussion

4.1 Next Steps

Presently self-monitoring blood glucose remains the most accurate and common approach for diabetics which are becoming increasingly accurate, portable, durable and user-friendly. There are however critical limitations to this approach fuelling the research of minimally and non-invasive CGM systems (Srivastava et al., 2011). The aims of research into these fields is to make insulin administration more personalised as everyone's' body reacts differently as well as narrow fluctuations in blood glucose levels.

4.1.1 Self-Monitoring Blood Glucose

ACCEPTED MANUSCRIPT

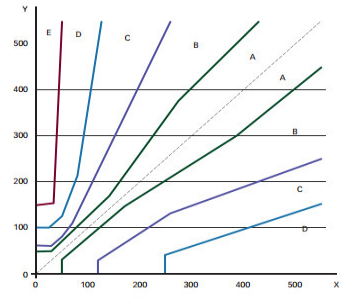
As CGM requires SMBG for calibration, accuracy needs to be improved and with the new ISO 15197:2013 criteria (Figure ~~18~~17) this research will be pursued (Garg, et al., 2013).

All current test strips are declared to be affected during or soon after xylose adsorption. Measures to

Table 1: ISO 15197 Accuracy Standards for SMBG Devices

	ISO 15197:2003[40]	ISO 15197:2013*[41]
Minimum accuracy criteria	95 % of readings: (1) within ±20 % of the reference for glucose levels >75 mg/dL; (2) within ±15 mg/dL of the reference for glucose levels ≤75 mg/dL	95 % of readings: (1) within ±15 % of the reference for glucose levels ≥100 mg/dL; (2) within ±15 mg/dL of the reference for glucose levels <100 mg/dL
Specifications for outliers	None	99 % of readings within zones A and B of the Consensus Error Grid for Type 1 diabetes
Number of reagent lots required for testing	1	3

Figure 1: Consensus Error Grid and Zone Definitions[41]



Risk Level (CEG zone)	Risk to Patient with Diabetes
A	No effect on clinical action
B	Altered clinical action – little or no effect on clinical outcome
C	Altered clinical action – likely to affect clinical outcome
D	Altered clinical action – could have significant medical risk
E	Altered clinical action – could have dangerous consequences

Figure 17: The new ISO 15197:2013 criteria for SMBG (Garg, Reed, Grey, & Westerman, 2013)

surpass this barrier should be taken. This is also to be said for a new test strip based on the Contour Next strip which attested enhanced accuracy in comparison to currently available branded blood glucose meters. It utilises FAD-GDH and a proprietary phenothiazine electron mediator and algorithm which minimises errors (Bernstein, et al., 2013).

Most current SMBGs require a USB cable for data transfer to a PC. Future SMBGs should automatically and wirelessly send information to a wireless transceiver such as a smartphone where it can then be sent to a cloud. SMBG could plug directly into a smartphone whilst conducting the test which would negate battery requirements thereby reducing weight and size. Another avenue is all in one SMBG's such as the Accu-Chek Mobile as diabetic patients currently need to carry much equipment with them. SMGs should come with backing and port lights for night tests.

A main issue regarding infrequent use of all SMBGs is emotional responses associated with finger ~~pricking~~ lancet (Ong, et al., 2014). According to Pelikan Sun, (2009) lancing is either too shallow or deep 60% of the time. Deep lancing squashes capillary loops resulting in blood pools beneath the skin and inflames nociceptors and shallow lancing extracts little to no blood. Development of a pain-free ~~pricker~~ lancer is important as SMBG testing is the most accurate method to date. A new lancing device which lances up to 4 times faster than conventional spring loaded mechanisms is the Genteel. It encourages blood draw from alternate body sites, transmits soothing vibrations to lock any pain signals to the brain and applies a vacuum to the skin in order to sooth nociceptors (Genteel, 2014). This device however does not come with a drum of lancets as the Accu-Chek FastClix does. More research and clinical trials into this field needs to be conducted.

Accepted manuscript

ACCEPTED MANUSCRIPT

4.1.2 Continuous Glucose Monitoring

Studies suggest use of real time CGM provides significant improvements in glycaemic control due to easier identification of postprandial hyperglycaemia, overnight hypoglycaemia and that in individuals unaware to it along with glucose trends (Weinzimer, et al., 2009 and Raccah, et al., 2009). The only problem is that most diabetics don't use it or don't use it continuously as these devices are sub-optimal in their usability duration, accuracy, handling, and maximal utilisation of information (Lodwig, et al., 2014).

Closed Loop

Ideally non-invasive CGMs would wirelessly and automatically send results to an insulin pump which can interpret the data and conduct an action to ensure euglycaemia. An example is that if blood glucose levels are too low the insulin pump will cease infusing basal insulin (known as low glucose suspend systems). Ly, et al.,(2012), demonstrated this reduced the number of hypoglycaemic events to zero. A more advanced example is predictive algorithms whereby the blood glucose profile can predict how long it will take to reach non-euglycaemia and can prevent infusion or administer insulin in advance (Lodwig, et al., 2014). This is otherwise known as a closed loop artificial pancreas. Future research is required to investigate whether glucagon infusions will also be necessary to make a truly artificial pancreas. An articifial pancreas would be more expensive than multiple daily injections and not everyone can afford it. Advances in CGM however will still benefit both parties as algorithms for use as bolus calculators can automatically recommend an insulin dose for conventional therapy (Lodwig, et al., 2014).

Accuracy

For a closed loop systems reliability and accuracy needs to be high as the therapeutic window for insulin dosing is narrow. As CGM devices measure interstitial fluid and not blood glucose there is a lag time to the true levels found in blood. False estimation associated with calibration issues is also a problem. Investigation of predictive algorithms for hypo and hyperglycaemia could negate glucose excursion by injecting insulin or shutting off early (Frontino, et al., 2013). The first insulin pump to implement such algorithms to prevent hypoglycaemic events is the MiniMed 530G by Medtronic; however there is still a long way to correct the inverse (Medtronic, 2014). Future CGMs will need to not only utilise hypoglycaemic avoiding algorithms but also ones for preventing hyperglycaemia however current devices need more accuracy.

Despite the fact there are few reports that electrochemical interference from substances such as acetominophen causes false readings they should still be reduced to increase accuracy. Ultimately by increasing reliability for any scenario, fingerstick ~~lancing~~ for calibration could effectively be abolished. Unfortunately the major barrier here is not technology but could potentially be physiological as sensor insertion can cause trauma to the test site leading to impaired monitoring (Lodwig, et al., 2014).

Human Error

The result gained is only as good as the skill of the individual testing; therefore teaching is important to consider. Alarms are vital to counteract limitations of human memory. An option to turn off alarms at night is beneficial as false positives can be distressing.

Using one catheter for both CGMs and insulin pumps will reduce error and increase compliance of use as it is one less puncture to conduct. Heinemann, et al., (2011) stated that this approach is feasible. According to Diabetes Digital Media Ltd., (2014) 16% of individuals wrongly calibrate

Accepted manuscript

ACCEPTED MANUSCRIPT

their meter resulting in inaccuracies up to 43% deviating from the true value. Future devices aim to be calibrated during manufacture to eliminate this source of error but patients won't know if their device is behaving normally.

Implants

These counter the cumbersome nature of conventional CGMs as the user can forget that it is there, however they come with their own issues. Biocompatibility is a problem as the body rejects foreign objects which also get coated in proteins further interfering accuracy. The Dexcom Executive Vice President of Strategy and Corporate Development stated barriers in monitoring glucose in tears include the low glucose concentration in tears, huge lag times and measurement consistency (Pacelli, 2014). Other barriers include toxicity, pH variation, selectivity (lactate) and optical detection (Pan, 2007).

4.1.3 Non-Invasive Glucose Monitoring

Drawbacks related to accuracy include variable skin properties as pigmentation, body water content, hydration, non-specificity to glucose, temperature, poor correlation between blood glucose and glucose in body fluids can interfere resulting in noise. Noise can cause false positives and negatives therefore de-noising algorithms need to be evaluated to reduce this risk thereby increasing accuracy. Next generation transducers and multi-sensor systems improve this signal to noise ratio and sensibility (Vashist, 2012). Additional research into multi sensor systems as opposed to single sensor systems will be beneficial as they provide a more comprehensive evaluation of blood glucose. They can cover various physical and chemical parameters of analysed tissue to enhance accuracy under variable conditions (Frontino, et al., 2013). This aquired sensor data can then be enhanced through employment of digital filters and data treatment techniques for example ridge regression, artificial neural networks, principal component analysis and particial least squares. GlucoTrack demonstrated multi-sensor capabilities however the downside was that the devices required individual calibration using invasive basal and post prandial blood glucose references. Future devices of this kind will need better calibration procedures (Vashist, 2012).

Currently conventional blood glucose monitoring is not only more accurate but also produce results much faster (5 seconds). Associate professor Zhi Xu from the University of Missouri-St. Louis is developing a portable non-invasive device which only takes one second to get a result (Shafferkoetter, 2011). His work discovered a cyclic pattern between light absorption in the finger and a heartbeat through photocurrent peak and layer readings which represent minimum and maximum blood in the capillaries, respectively (Figure ~~19~~18). This excludes interfering constituents in the finger such as skin, fat, bone, muscle and interstitial fluids as they aren't likely to change

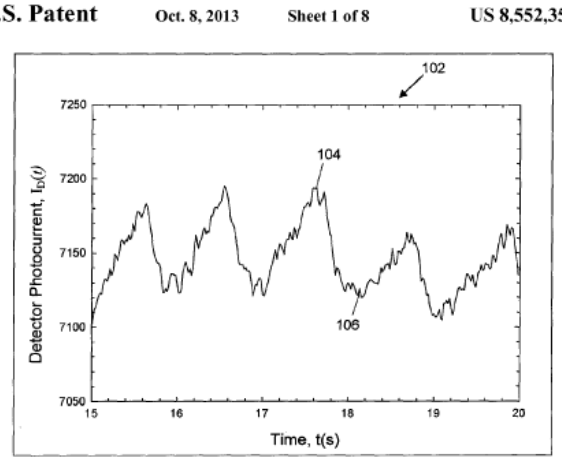


Figure 18: Peak (104) and valley (106) readings (Xu, 2013).

ACCEPTED MANUSCRIPT

during the interval of a heartbeat (Xu, 2013). This could potentially shape future non-invasive sensing.

4.1.1 Smartphones and Apps

By 2017 there will be more mobile phones in the world than people (Wu et al., 2014). Currently there are 1.75 billion smartphone users worldwide (Figure ~~20~~19) of which 83% have high speed internet connections at home (eMarketer, 2014 and Crawford, 2014).

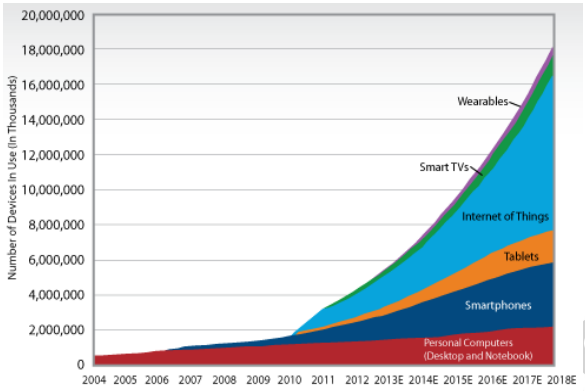


Figure 19: Global Internet Device Installed Base Forecast (BI Inteligence, 2014).

Currently some devices can wirelessly transmit results. Developing technologies aim to automatically conduct this process directly to a smartphone for analysis and then to an insulin pump. The smartphone will then automatically upload the data to a cloud for further analysis and storage; remotely supplying healthcare professionals with continuous information. This is known as smart grid technology whereby analog or digital information is automatically gathered and acted upon (Niewolny, 2013). Integration to all smartphones is a next step to developing closed loop systems and advancement of the Internet of Things.

4.1.2 The Internet of Things

China is leading the charge with 38% of patents in the field (Masood, 2014). It is the next evolutionary stage of the internet and is to connect everything with wireless connectivity to control systems which supports result collection, analysis and decision making on a global scale networks beyond machine to machine communications (Minoli, 2013). Presently ~10 billion devices are connected to the internet and by 2020 it's predicted to triple (ABI Research, 2013). Growth is also represented in Figure ~~20~~19. Regarding healthcare systems the Internet of Things is a network of interconnected devices such as a sensor and a smartphone that automatically record and share information through a secure cloud. This reduces human error and improves speed as there's no time and space between geographical space and virtual space; Figure ~~21~~20 (Minoli, 2013). As a result remote health monitoring, prompt diagnostics/ treatment and emergency warnings are possible (Niewolny, 2013).

Accepted manuscript

ACCEPTED MANUSCRIPT

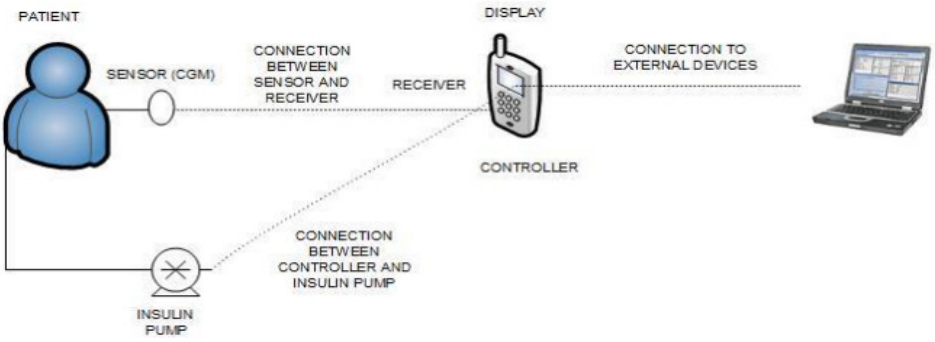


Figure 20: Artificial Pancreas Device System Connections (Burgman, 2013).

Enabling Technologies

IPv6 will provide appropriate scalability (128-bit addresses) for the unique global identification and connectivity ("plug and play") without additional reprocessing and will improve functionality towards economical and extensive characteristics. It has improved security employing payload encryption and authentication of communication source. For glucose monitoring MIPv6 will be used to allow alternative attachments to the internet without losing higher-layer connections when changing location. For cost effectiveness the best technologies for wireless physical layer communication are WiFi (802.11/n) and ZigBEE (802.15.4). This technology will save billions of dollars for the healthcare sector alone (Minoli, 2013).

Barriers

Battery life of Internet of Things devices will require low-power operation through energy harvesting using ultra-low-power DC-DC converters resulting in battery free devices; currently being researched by Freescale. Microcontrollers can support low energy Bluetooth connectivity (Niewolny, 2013). Accurate results require lots of energy; precision-analog capabilities can reduce this impact. High graphics processing performance is necessary to support graphical user interfaces essential for easy access and clarity.

The FDA classifies mobile medical apps as mobile apps that function as an accessory to a medical device or transform a mobile platform into a medical device (U.S. Food and Drug Administration, 2014). They must meet the definition of device in section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). In 21 CFR 801.4 it states that for a mobile app to be considered a device it must either provide diagnosis of a disease/condition, a cure, mitigation, treatment, prevention or alter functions in the body (U.S. Department of Health and Human Services, 2013), Regulations for apps that act as an extension of a medical device display patient data, store or transfer the data and control medical devices, Regulations for apps that transform a mobile platform into a medical device such as attachment of a blood glucose strip reader; class II. Examples of apps which are regulated medical devices include those that can do all this and provide therapy plans (U.S. Department of Health and Human Services, 2013).

Corruption of signal between transmitters and smartphones is a problem. This can occur by operating system upgrades i.e. from IOS 5 to IOS 6 or by adding additional apps. The system needs to be kept separate from the app systems on phones however phone companies don't want to invest in this. A

Accepted manuscript

ACCEPTED MANUSCRIPT

possible solution is running medical operating systems in the background with priority (Gregg, 2013).

5 Conclusion

Notable current technologies are cassettes of test strips, no coding, bolus calculators, on-board calorie databases, pocket sized meters, port lights, Bluetooth, log books, reapplication of blood to test strips and alerts.

SMBGs are the most accurate method of monitoring glucose to date however research is steering in another direction. The future will most likely be a CGM one whether or not it is non-invasive with aims for a closed loop system. This will advance the translation medicine as patients would no longer have to manually calculate and administer bolus insulin; instead it will be done automatically for them. The main issue for both CGM and SMBG however is accuracy and as a result is likely to improve in the future by as the latter is required for current CGM calibration; more sophisticated de-noising algorithms will aid this. Smartphone integration with wireless capabilities is big step forward expanding on this is through the internet of things. Either the meter plugs directly into it or wirelessly transmits information to an app installed on it; low energy Bluetooth will be vital for this in order to sustain smartphone battery life. Hand in hand with this goes the developing internet of things whereby information will be accessible on a cloud for healthcare professionals. This will allow healthcare professionals to advance the translation medicine by being able to visualise on a real time basis the trends and patterns in glucose levels. For this dream to come true though future devices will have to employ IPv6 in order to support the vast addressable items the future will hold in store. More specifically to biosensors is MIPv6 so that devices can utilise alternative attachments to the internet without losing higher-layer connections when changing location. Wireless physical layer communications will be WiFi (802.11/n) and ZigBEE (802.15.4).Battery life issues need to be addressed for this to advance effectively.

Advancement of multi-sensor technology should be developed to reduce signal to noise ratio. Implants face biocompatibility barriers and toxicity, pH variation, selectivity (lactate) addressing. Spectroscopy could be advanced by examining cyclic patterns between light absorption in the finger and heartbeats.

Accepted manuscript

REFERENCES

Aanstoot, H., Anderson, B., Daneman, D., Danne, T., Donaghue, K., Kaufman, F., et al. (2007). "The global burden of youth diabetes: perspectives and potential" . *Pediatric diabetes*, Suppl 8:1–44, available at http://www.ncbi.nlm.nih.gov/pubmed/17767619 [accessed 04 June 2014].

Abbott. (2014). *About*. Retrieved August 12, 2014, from Abbott: http://abbott.co.uk

Abbott Diabetes Care Inc. (2009). Precision Xceed Pro Operators Manual. Oxon, USA: Abbott Diabetes Care Inc.

ACCEPTED MANUSCRIPT

Abbott Diabetes Care Inc. (2010). FreeStyle Freedom Lite Owner's Booklet. Alameda, USA: Abbott Diabetes Care Inc.

Abbott Diabetes Care Inc. (2012, January 20). FreeStyle InsuLinx Owner's Booklet. Abbott.

Abel, A., Weller, M., Duveneck, G., Ehrat, M., & Widmer, M. (1996). " Fiber-optic Evanescent Wave Biosensors for the Detection of Oligonucleotides". Anal. Chem, 68:2905-2912.

ABI Research. (2013, May 09). *More Than 30 Billion Devices Will Wirelessly Connect to the Internet of Everything in 2020*. Retrieved August 15, 2014, from ABI Research: https://www.abiresearch.com/press/more-than-30-billion-devices-will-wirelessly-conne

Animas & LifeScan. (2008, July 07). OneTouch Ping Glucose Management System Owners Booklet. Animas.

Bandodkar, A., & Wang, J. (2014). "Non-invasive wearable electrochemical sensors: a review". *Trends in Biotechnology*, 32(7):363-371.

Bayer. (2014). *Contour Next USB*. Retrieved August 12, 2014, from Bayer Diabetes: http://www.bayerdaibetes.co.uk

Bayer HealthCare. (2006, November). Ascensia Breeze 2 User Guide. Mishawaka, USA: Bayer.

Baxter Healthcare Corporation. (2010). EXTRANEAL (icodextrin) Peritoneal Dialysis Solution. Deerfield: Baxter Healthcare Corporation.

BBC. (2014, January 17). *"Google unveils 'smart contact lens' to measure glucose levels"*. Retrieved August 16, 1014, from BBC News Technology: http://www.bbc.com/news/technology-25771907

Beijing Yicheng. (2014). *Our Products*. Retrieved August 25, 2014, from Beijing Yicheng: http://www.beijingyicheng.com.cn/

Bernstein, R., Parkes, J., Goldy, A., Brown, D., Harrison, B., Chu, A., et al. (2013). "A New Test Strip Technology Platform for Self-Monitoring of Blood Glucose". *Journal of Diabetes Science and Technology*, 7(5):1368-1399.

BI Inteligence. (2014, July 21). *"The 'Internet Of Things' Will Be Bigger Than The Smartphone, Tablet, And PC Markets Combined"*. Retrieved August 22, 2014, from Business Insider: The

Accepted manuscript

ACCEPTED MANUSCRIPT

'Internet Of Things' Will Be Bigger Than The Smartphone, Tablet, And PC Markets Combined

Bio Impedance General. (2014). *BIO IMPEDANCE GENERAL*. Retrieved August 18, 2014, from Madein-Israel: http://www.madein-israel.com/selectedProduct.aspx?ProductId=184&CategoryId=37&subCategoryName=Medical&productName=Non-Invasive+Glucose+Monitor

Borisov, S., & Wolfbeis, O. (2008). "Optical Biosensors". Chemical Reviews, 108(2)423–461.

Burgman, T. (2013). "A Guideline for Smart Implant Systems Supporting Patients with Diabetes Type 1". *19th Twente Student Conference on IT*, 19.

Cascade Metrix Inc. (2014). *Automating Critical Care Blood Analysis*. Retrieved August 20, 2014, from Cascade Metrix Inc.: http://www.cascademetrix.com/products

Clarke, S., & Foster, J. (2012). "A history of blood glucose meters and their role in self-monitoring of diabetes mellitus". *British Journal of Biomedical Science*, 69(2):83-93.

Cnoga Medical Ltd. (2013, February 20). TensorTip™ Combo-Glucometer™ User Guide. London, UK: Cnoga Medical Ltd.

DCCT – Diabetes Control and Complications Trial. (1993). New England Journal of Medicine, 329(14).

Dexcom. (2012). *Dexcom's History with Continuous Glucose Monitoring*. Retrieved August 15, 2014, from Dexcom: http://www.dexcom.com/en-gb/about-dexcom

Diabetes Digital Media Ltd. (2014). *Importance of Coding*. Retrieved August 22, 2014, from Diabetes.co.uk: http://www.diabetes.co.uk/diabetes_care/the-importance-of-coding.html

Echo Therapeutics. (2014). *Needle-free monitoring and drug delivery*. Retrieved August 18, 2014, from Symphony CGM System: http://www.echotx.com/symphony-cgm-system.shtml

eMarketer. (2014, Jan 16). *"Smartphone Users Worldwide Will Total 1.75 Billion in 2014 -Users Worldwide Will Total 175 Billion in 2014"*. Retrieved August 22, 2014, from eMarketer: +6+http://www.emarketer.com/Article/Smartphone-Users-Worldwide-Will-Total-175-Billion-2014/1010536

Accepted manuscript

ACCEPTED MANUSCRIPT

EyeSense GmbH. (2014). *Product Video Eye Sensor*. Retrieved August 17, 2014, from EyeSense: http://en.eyesense.com/product/eyesense-technology-precise-glucose-monitoring-at-the-eye/product-video-eye-sensor/

Falk, M., Andoralov, V., Blum, Z., Sotres, J., Suyatin, D., Ruzgas, T., et al. (2012). "Biofuel cell as a power source for electronic contact lenses". *Biosensors and Bioelectronics*, 37:38-45.

Falk, M., Andoralov, V., Silow, M., Toscano, M., & Shleev, S. (2013). "Miniature biofuel cell as a potential power source for glucose sensing contact lenses". *Analytical Chemistry*, 85:6342-6348.

Fraunhofer IMS. (2012, 09 04). *News: Measuring glucose without needle pricks*. Retrieved August 16, 2014, from Fraunhofer IMS: http://www.ims.fraunhofer.de/en/news/detail/article/blutzucker-messen-ohne-pieks.html

Frontino, G., Meschi, F., Bonfanti, R., Rigamonti, A., Battaglino, R., Favalli, V., et al. (2013). "Future Perspectives in Glucose Monitoring Sensors". *US Endocrinology*, 9(1):21–6.

Garcia, A., Rack-Gomer, A., Bhavaraju, N., Hampapuram, H., Kamath, A., Peyser, T., et al. (2013). "Dexcom G4AP: An Advanced Continuous Glucose Monitor for the Artificial Pancreas". *Journal of Diabetes Science and Technology*, 7:1436-45.

Garg, S., Reed, K., Grey, J., & Westerman, A. (2013). "Possible Impacts of New Accuracy Standards of Self-Monitoring of Blood Glucose". *US Endocrinology*, 9(1):28-31.

GBI Research. (2014). *"Glucose Monitoring Device Market to 2019: Technology Adoption and Increasing Health Awareness Serve as Distinct Regional Growth Drivers"*. New York: GBI Research.

Genteel. (2014). *What Makes Genteel Pain Free?* Retrieved August 2014, 2014, from MyGenteel: https://www.mygenteel.com/support/knowledge-base/what-makes-genteel-pain-free/

GlySens Incorporated. (2013). *DEVELOPING NEXT GENERATION, CONTINUOUS GLUCOSE MONITORING SYSTEMS FOR PEOPLE WITH DIABETES*. Retrieved August 18, 2014, from GlySens Incorporated: http://glysens.com/

Grieshaber, D., MacKenzie, R., Voros, J., & Reimhult, E. (2008). "Electrochemical Biosensors - Sensor Principles and Architectures". Senors, 8:1400-1458.

Accepted manuscript

ACCEPTED MANUSCRIPT

Gregg, T. (2013, January 24). Into Tomorow Special Report. (D. Graveline, Interviewer) ITTV. Las Vegas.

Gregg, T. (2013, April 12). Live Interview with Terry Gregg, President and CEO of Dexcom, Inc. (D. H. Foundation, Interviewer)

Gregg, T. (2014, January 09). Digital Health Summit CES. (T. Reha, Interviewer)

Grove Instruments. (2014). *The dream of painless, bloodless, noninvasive glucose testing is about to become a reality - with Grove Instruments™ technology.* Retrieved August 19, 2014, from Grove Instruments: http://www.groveinstruments.com/

Hanssen, J., & Tweehuysen, R. (2012). *Patent No. US20140081105 A1.* USA.

Harman-Boehm, I., Gal, A., Reykhman, A., Naidis, E., & Mayzel, Y. (2010). "Noninvasive Glucose Monitoring: Increasing Accuracy by Combination of Multi-Technology and Multi-Sensors". *Journal of Diabetes Science and Technology*, 4(3): 583–595.

Harrison, B. (2012). Understanding the patients' needs. Bayer HealthCare LLC.

Heinemann, L., Benesch, C., & DeVries, J. (2011). "AP@home: a novel European approach to bring the artificial pancreas home". *Journal of Diabetes Science and Technology*, 5:1363-1372.

Heller, A., & Feldman, B. (2008). "Electrochemical glucose sensors and their applications in diabetes management". Chemical Reviews, 108, 2482-2505.

Hinzman, R. (2012). "Tran C-T. System accuracy evaluation for blood glucose measurements should be performed with ISO 15197:2003 and CLSI-approved guideline EP7-A2. Diabetes Technology Therapeutics, 4(4):379-380.

Holman, R., Paul, S., Bethel, M., Matthews, D., & Neil, H. (2008). "10-year follow-up of intensive glucose control in type 2 diabetes". *The New England Journal of Medicine*, 359(15):1577-89.

Hu, J. (2012). Colour changing contact lenses to help diabetes. (T. U. Arkon, Interviewer)

Integrity Applications. (2014). *Integrity Applications*. Retrieved August 14, 2014, from Gluco Track Non-Invasive Blood Glucose Monitor: http://www.integrity-app.com/

International Diabetes Federation. (2013). *IDF Diabetes Atlas 6th Ed.* Brussels: International Diabetes Federation.

Accepted manuscript

ACCEPTED MANUSCRIPT

Kumosa, L., Routh, T., Lin, J., & Lucisano, J. (2014). "Permeability of subcutaneous tissues surrounding long-term implants to oxygen". *Biomaterials*, 35:8287-8296.

Kunjan, K., & Lloyd, F. (2013). *Patent No. US 8348844 B2.* USA.

LabStyle Innovation Ltd. (2014). Dario User Guide. Caesarea, Israel: LabStyle Innovation Ltd.

LabStyle Innovations Corp. (2014). *Thriving with Diabetes*. Retrieved August 19, 2014, from Dario: http://mydario.com/

LifeScan. (2008). OneTouch UltraLink Owners Booklet. *OneTouch UltraLink Owners Booklet*. Milpitas, USA: LifeScan.

LifeScan. (2009). OneTouch Ultra2 User Guide. LifeScan.

LifeScan. (2009). OneTouch UltraMini User Guide. LifeScan.

LifeScan. (2011). OneTouch Verio IQ Owners Booklet. Zug, Switzerland: LifeScan.

LifeScan. (2012). OneTouch Reveal App Owners Booklet Instructions for use. Milptas, USA: LifeScan.

LifeScan. (2012). OneTouch VerioSync Blood Glucose Monitoring System Owners Booklet Instructions for use. Milpitas, USA: LifeScan.

LifeScan. (2013, January 24). *OneTouch Verio*. Retrieved August 08, 2014, from OnTouch: http://www.onetouchasia.com/ph/en/content.php?c=29&sc=91&p=78

Lifescan. (2014, March 13). *Lifescan*. Retrieved August 05, 2014, from Lifescan: http://www.lifescan.com

Lifescan. (2014, March 13). *Lifescan*. Retrieved August 05, 2014, from Lifescan: http://www.lifescan.co.uk/

Ligler, F., & Rowe Taitt, C. (2002). "Optical Biosensors - Present & Future". Elsevier.

Lodwig, V., Kulzer, B., Schnell, O., & Heinemann, L. (2014). "What Are the Next Steps in Continuous Glucose Monitoring?". *Journal of Diabetes Science and Technology*, 1–6.

Ly, T., Nicholas, J., Retterath, A., Davis, E., & Jones, T. (2012). "Analysis of glucose responses to automated insulin suspension with sensor-augmented pump therapy". *Diabetes Care*, 35:1462.

Accepted manuscript

ACCEPTED MANUSCRIPT

Masood, E. (2014, August 18). *"Apple and Google left behind as China powers ahead with Internet of Things"*. Retrieved August 23, 2014, from Research Professional: https://www.researchprofessional.com/0/rr/news/uk/innovation/2014/8/Apple-and-Google-left-behind-as-China-powers-ahead-with-Internet-of-Things.html

MediWise. (2014). *GlucoWise*. Retrieved August 14, 2014, from Live a healthier life with GlucoWise™: http://www.gluco-wise.com/

Medtronic. (2014). *Introducing MiniMed® 530G with Enlite®*. Retrieved August 21, 2014, from Medtronic: https://professional.medtronicdiabetes.com/minimed-530-g

Minoli, D. (2013). *"Building the Internet of Things with IPv6 and MIPv6: The Evolving World of M2M Communications"*. Hoboken: John Wiley & Sons, Inc.

Mortellaro, M., & DeHennis, A. (2014). "Performance characterization of an abiotic and fluorescent-based continuous glucose monitoring system in patients with type 1 diabetes". *Biosensors and Bioelectronics*, 61:227–231.

Müller, A., Knuth, M., Nikolaus, K., Krivánek, R., Küster, F., & Hasslacher, C. (2013). "First Clinical Evaluation of a New Percutaneous Optical Fiber Glucose Sensor for Continuous Glucose Monitoring in Diabetes". *Journal of Diabetes Science and Technology*, 7(1):13-23.

Müller, A., Knuth, M., Nikolaus, K., Krivánek, R., Küster, F., Hasslacher, C., et al. (2013). "Blood Glucose Self-Monitoring with a Long-Term Subconjunctival Glucose Sensor". *Journal of Diabetes Science and Technology*, 7(1):24-34.

Nathan-Roberts, D., & Liu, Y. (2012). "Comparison of Design Preferences for Mobile Phones and Blood Glucose Meters". Proceedings of the Human Factors and Ergonomics Society Annual Meeting, 56(1):787-791.

Newman, J., & Setford, S. (2006). "Enzymatic Biosensors". *Molecular Biotechnology*, 32:249-268.

Newman, J., & Turner, A. (2005). "Home blood glucose biosensors: a commercial perspective". *Biosensors and Bioelectronics*, 20:2435–2453.

Niazi, J. (2009). "Overview, history & types of biosensors". Sabanci University.

Niewolny, D. (2013). "How the Internet of Things Is Revolutionizing Healthcare". freescale.

Accepted manuscript

ACCEPTED MANUSCRIPT

Novartis. (2014, July 15). *Media Releases*. Retrieved August 16, 2014, from Novartis: http://www.novartis.com/newsroom/media-releases/en/2014/1824836.shtml

Ong, W., Chua, S., & Ng, C. (2014). "Barriers and facilitators to self-monitoring of blood glucose in people with type 2 diabetes using insulin: a qualitative study". *Patient Preference and Adherence*, 8:237—246.

Otis, B., Taichung, L., Amirpraviz, B., & Yao, H. (2013). *Patent No. US 8,608,310 B2.* USA.

Pacelli, S. (2014, February 05). Glucometers won't be contact lenses anytime soon. (J. Comstock, Interviewer)

Pan, X. (2007). Contact Lens Diabetes Management . *A Vision For The Future*. Cambridge: Institute of Biotechnology, University of Cambridge.

Pelikan Sun. (2009, June 19). *Pelikan Sun Technology Animation*. Retrieved August 24, 2014, from YouTube: https://www.youtube.com/watch?v=9R7HEml81_8

Philosys. (2014). *Gmate Blood Glucose Monitoring System.* Retrieved August 20, 2014, from Gmate: http://www.gmate.com/gsmart.php

Philosys. (2014). Gmate SMART User's Guide. Philosys.

Pohanka, M., & Skládal, P. (2008). "Electrochemical biosensors – principles and applications". Journal of Applied Biomedicine, 6:57–64.

Raccah, D., Sulmont, V., Reznik, Y., Guerci, B., Renard, E., Hanaire, H., et al. (2009). "Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: the RealTrend study". *Diabetes Care*, 32(12):2245-50.

Ramchandani, N., & Heptulla, R. (2012). "New technologies for diabetes: a review of the present and the future". *BioMed Central*, 2012:28.

Roche Diagnostics. (2009). "Accu-Chek Mobile: System Evaluation". Mannheim, Germany: Roche Diagnostics.

Roche Diagnostics. (2009). Accu-Chek Aviva Combo. *Advanced Owners Booklet*. Mannheim, Germany: Roche Diagnostics.

Accepted manuscript

ACCEPTED MANUSCRIPT

Roche Diagnostics. (2013, July 16). *New Accu-Chek® Mobile*. Retrieved August 02, 2014, from Accu-Chek: https://www.accu-chek.co.uk/gb/myaccuchek/newsletters/ereach-summer2012-new-Accu-Chek-Mobile.html

Roche Diagnostics. (2013, January 04). *Welcome to E-Reach Spring 2010*. Retrieved August 02, 2014, from Accu-Chek: https://www.accu-chek.co.uk/gb/myaccuchek/newsletters/e-reachSpring2010-360plainsailing.html

Roche Diagnostics. (2014, June 27). *Accu-Chek® Aviva Nano Blood Glucose Meter System*. Retrieved August 02, 2014, from Accu-Chek: https://www.accu-chek.co.uk/gb/products/metersystems/avivanano.html

Roche Diagnostics. (2014, August 07). *Global Web Site*. Retrieved August 07, 2014, from Roche: http://www.roche.com/index.htm

Ronkainen, N., Halsall, B., & Heineman, R. (2010). "Electrochemical biosensors". Chemical Society Reviews, 39(5):1747-6.

Rustagi, S., & Kumar, P. (2013). "Biosensor and It's Application in Food Industry". *Advances in Bioresearch*, 168- 170.

Sanofi Aventis & AgaMatrix. (2013, November). iBGStar Blood Glucose Monitoring System. *Owners Guide*. USA: AgaMatrix Inc.

Senseonics. (2014, June 18). *Product*. Retrieved August 18, 2014, from Senseonics: http://senseonics.com/

Shafferkoetter, K. (2011, March 29). *"Noninvasive glucose monitor closer to market"*. Retrieved August 24, 2014, from UMSL Daily: http://blogs.umsl.edu/news/2011/03/29/glucose/

SKUP. (2012, March). Contour NEXT and Contour XT. *Test strips and meter designed for self-monitoring of blood glucose*. Bergen, Norway: Bayer AS.

Skyler, J. (2012). *"Continuous Glucose Monitoring"*. University of Miami Miller School of Medicine, Division of Endocrinology, Diabetes, and Metabolism and Diabetes Research Institute, Miami.

Smith, J. (2011). "The pursuit of noninvasive glucose: Hunting the deceitful turkey". 1-134, available at www.mendosa.com/noninvasive_glucose.pdf (accessed June 2014).

Accepted manuscript

ACCEPTED MANUSCRIPT

Srivastava, R., Jayant, R., Chaudhary, A., & McShane, M. (2011). ""Smart Tattoo" Glucose Biosensors and Effect of Coencapsulated Anti-Inflammatory Agents". *Journal of Diabetes Science and Technology*, 5(1):76-85.

Tang, et al;, Z. (2000). CONTOUR XT BGMS - Reagent R&D Report for Regulatory Submission. *American Journal of Clinical Pathology*, 113:75-86.

Tuomilehto, J. (2013). "The Emerging Global Epidemic of Type 1 Diabetes". *Current Diabetes Reports*, 13:795–804, doi:10.1007/s11892-013-0433-5, available at http://download.springer.com/static/pdf/664/art%253A10.1007%252Fs11892-013-0433-5.pdf?auth66=1402258968_6a6aaacfd9e192068f10cc143580c7aa&ext=.pdf, [accessed 05 June 2014].

Turner, A. (2013, April). "Biosensors – An essential Component in a Biomedical System". Biosensors & Bioelectronics Centre IFM-Linköping University.

Turner, A. (2013). Biosensors: sense and sensibility. *Chemical Society Reviews*, 42:3184.

Turner, A. (2013). Biosensors: then and now. *Trends in Biotechnology*, 31(3):119-120.

UKPDS – United Kingdom Prospective Diabetes Study. (1998). Lancet, 352:837-853.

U.S. Department of Health and Human Services. (2013). *Mobile Medical Applications: Guidance for Industry and Food and Drug Administration Staff.* Rockville: U.S. Food and Drug Administration.

U.S. Food and Drug Administration. (2013, March 21). *FDA Public Health Notification: Potentially Fatal Errors with GDH-PQQ* Glucose Monitoring Technology*. Retrieved July 20, 2014, from U.S. Food and Drug Administration: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm176992.htm

U.S. Food and Drug Administration. (2014, June 04). *Mobile Medical Applications*. Retrieved August 23, 2014, from U.S. Food and Drug Administration: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ConnectedHealth/MobileMedicalApplications/ucm255978.htm

U.S. Food and Drug Administration and Center for Devices and Radiological Health. (2010). FDA/CDRH PUBLIC MEETING: Blood Glucose Meters FDA.

Accepted manuscript

ACCEPTED MANUSCRIPT

US Food and Drug Administration. (2012). *150(k): k062347 SUBSTANTIAL EQUIVALENCE DETERMINATION DECISION SUMMARY ASSAY AND INSTRUMENT COMBINATION TEMPLATE.*

US Food and Drug Administration. (2012). *510(k): k111268, SUBSTANTIAL EQUIVALENCE DETERMINATION DECISION SUMMARY ASSAY AND INSTRUMENT COMBINATION TEMPLATE.* US Food and Drug Administration.

US Food and Drug Administration. (2013). *510(k): k110894, SUBSTANTIAL EQUIVALENCE DETERMINATION DECISION SUMMARYASSAY AND INSTRUMENT COMBINATION TEMPLATE.* US Food and Drug Administration.

US Food and Drug Administration. (2014). *510(k): k120708, SUBSTANTIAL EQUIVALENCE DETERMINATION DECISION SUMMARY ASSAY AND INSTRUMENT COMBINATION TEMPLATE.* Food and Drug Administration.

Vashist, S. (2012). "Non-invasive glucose monitoring technology in diabetes management: A review". *Analytica Chemica Acta*, 750:16–27.

Wang, J. (2008). "Electrochemical glucose biosensors". Chemical Reviews, 108:814-825.

Weinzimer, S., Xing, D., Tansey, M., Fiallo-Scharer, R., Mauras, N., Wysocki, T., et al. (2009). "Prolonged use of continuous glucose monitors in children with type 1 diabetes on continuous subcutaneous insulin infusion or intensive multiple-daily injection therapy". *Pediatric Diabetes*, 10:91-96.

World Health Organisation. (2011). *"Global status report on noncommunicable diseases 2010".* Geneva: World Health Organisation.

World Health Organisation. (2011). "Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus". *Geneva: The World Health Organisation, Available from: http://www.who.int/diabetes/publications/report-hba1c_2011.pdf [accessed 04 June 2014].*

Wu, C., Wu, S., P, C., & Lin, Y. (2014). "An Innovative Smartphone-Based Otorhinoendoscope and Its Application in Mobile Health and Teleotolaryngology". *Journal of Medican Internet Research*, 6(3):e71. doi: 10.2196/jmir.2959.

Xu, Z. (2013). *Patent No. US 8552359 B2.* USA.

Accepted manuscript

ACCEPTED MANUSCRIPT

Yoo, E.-H., & Lee, S.-Y. (2010). "Glucose Biosensors: An Overview of Use in Clinical Practice". *Sensors*, 10:4558-4576.

Accepted manuscript

Table 2

Blood Glucose Meter	 Accu-Chek Mobile	 Accu-Chek Aviva	 Accu-Chek Aviva Expert	 Accu-Chek Aviva Nano	 Accu-Chek Aviva Combo
Test Range (mmol/l)	0.6–33.3	0.6–33.3	0.6–33.3	0.6–33.3	0.6–33.3
Test Time (sec)	5	5	5	5	5
Blood Sample	Capillary	Capillary	Capillary	Capillary	Capillary
Blood Volume (µl)	0.3	0.6	0.6	0.6	0.6
Memory (tests)	2000	500	1000	500	1000
Working Temperature (°C)	10-40	10-40	10-40	6-44	5-40
Working Humidity (%)	15-85	10-90	10-90	10-90	20-90
Assay Method	Mut-Q-GDH	Mut-Q-GDH	Mut-Q-GDH	Mut-Q-GDH	Mut-Q-GDH
Dimensions LxWxH (cm)	12.3 × 6.6 × 2.8	9.4 x 5.3 x 2.2	9.4 x 5.5 x 2.5	6.9 x 4.3 x 2	8.8 x 5.5 x 2

Accepted manuscript

ACCEPTED MANUSCRIPT

Weight with batteries (g)	129	60	103	40	110
Battery Life (tests)	500	1000	depends	1000	30, 40, 80 days
Calibration	None	Code Chip	Code Chip	Code Chip	Code Chip
Strips	Mobile Cassette	Aviva	Aviva	Aviva	Aviva
Digital	Yes	Yes	Yes	Yes	Yes
Data Port	Micro USB, Infrared	Infrared	Infrared	Infrared	Infrared
Screen	LCD	LCD	Backlit LCD	Backlit LCD	Backlit LCD
Alternate testing site	Yes	Yes	Yes	Yes	Yes

Accepted manuscript

ACCEPTED MANUSCRIPT

Table 3

Table 1: Summary of LifeScan current main blood glucose meters, adapted from Lifescan, (2014), US Food and Drug Administration, (2014), LifeScan, (2011), LifeScan, (2009), LifeScan, (2009) and LifeScan, (2008)

Blood Glucose Meter	 OneTouch Ping	 OneTouch Ultra2	 OneTouch UltraMini	 OneTouch Verio IQ	 OneTouch VerioSync	 OneTouch UltraLink
Test Range (mmol/l)	1.1-33.3	1.1-33.3	1.1-33.3	1.1-33.3	1.1–33.3	1.1-33.3
Test Time (sec)	5	5	5	5	5	5
Blood Sample	Capillary	Capillary	Capillary	Capillary	Capillary	Capillary
Blood Volume (µl)	1	1	1	0.4	0.4	1
Memory (tests)	20000	500	500	750	500	500
Working Temperature (°C)	6-44	6-44	6-44	6-44	10-44	6-44
Working Humidity (%)	10-90	10-90	10-90	10-90	10-90	10-90
Assay Method	GOx	GOx	GOx	GDH-FAD	GDH-FAD	GOx
Dimensions LxWxH (cm)	9.7x 6.2 x2.8	7.9x5.7 x 2.3	10.8 x 3.2 x1.7	8.8 x 4.7x 1.2	9.9 x 4.1 x 1.3	8.9 x 6.1 x 2.5

Accepted manuscript

ACCEPTED MANUSCRIPT

Weight with batteries (g)	110	42.5	40	47	48	85
Battery Life (tests)		1095	1095	Rechargeable	Rechargeable	240
Calibration	One Code	One Code	One Code	Automatic	Automatic	One Code
Strips	Ultra	Ultra	Ultra	Verio	Verio	Ultra
Digital	Yes	Yes	Yes	Yes	Yes	Yes
Data Port	Micro USB	Micro USB	Micro USB	Mini USB	Bluetooth/ Micro USB	Bluetooth
Screen	Backlit LCD	Colour	Colour	Colour	Backlit LCD	LCD
Alternate testing site	Yes	Yes	Yes	Yes	No	No
Test-port light	No	No	No	Yes	Yes	No

Accepted manuscript

ACCEPTED MANUSCRIPT

Table 4

Table 1: Summary of Abbotts' current main blood glucose meters, adapted from (Abbott Diabetes Care Inc., 2009, Abbott Diabetes Care Inc., 2012 and Abbott Diabetes Care Inc., 2010)

Blood Glucose Meter	 FreeStyle InsulinX	 FreeStyle Lite	 FreeStyle Freedom Lite	 Precision Xtra	 Precision Xceed Pro
Test Range (mmol/l)	1.1-27.8	1.1-27.8	1.1-27.8	1.1-27.8	1.1-27.8
Test Time (sec)	5	5	5	5	20, 10
Blood Sample	Capillary	Capillary	Capillary	Capillary	Capillary
Blood Volume (µl)	0.3	0.3	0.3	0.6	0.6, 1.5
Memory (tests)	990	400	400	450	2500
Working Temperature (°C)	4-40	4-40	4-40	10-50	15-40
Working Humidity (%)	5-90	5-90	5-90	10-90	10-90
Assay Method	FAD-GDH	FAD-GDH	FAD-GDH	NAD-GDH	NAD-GDH

Accepted manuscript

ACCEPTED MANUSCRIPT

Dimensions LxWxH (cm)	6 x 9.5 x 1.5	5.1 x 8.4 x 1.6	5 x 8.4 x 1.6	5.3 x 7.5 x 1.6	19.7 x 7.5 x 5.3
Weight with batteries (g)	59.4	45.4	42.3	41.9	256
Battery Life (tests)	3000	500	500	1000	540
Calibration	None	None	None	None	Bar Code
Strips	InsulinX	FreeStyle Lite	FreeStyle Lite	Precision Xtra	Precision Xceed Pro blood glucose/β-Ketone, Precision PCx Plus,
Digital	Yes	Yes	Yes	Yes	Yes
Data Port	Micro USB	Headphone jack	Micro USB	Micro USB	Wireless/Micro USB
Screen	Backlit LCD, touch	Backlit LCD	LCD	LCD	LCD

Accepted manuscript

ACCEPTED MANUSCRIPT

Table 5

Table 1: Summary of Abbotts' current main blood glucose meters, adapted from (Abbott Diabetes Care Inc., 2009, Abbott Diabetes Care Inc., 2012 and Abbott Diabetes Care Inc., 2010)

Blood Glucose Meter	 FreeStyle InsulinX	 FreeStyle Lite	 FreeStyle Freedom Lite	 Precision Xtra	 Precision Xceed Pro
Test Range (mmol/l)	1.1-27.8	1.1-27.8	1.1-27.8	1.1-27.8	1.1-27.8
Test Time (sec)	5	5	5	5	20, 10
Blood Sample	Capillary	Capillary	Capillary	Capillary	Capillary
Blood Volume (µl)	0.3	0.3	0.3	0.6	0.6, 1.5
Memory (tests)	990	400	400	450	2500
Working Temperature (°C)	4-40	4-40	4-40	10-50	15-40
Working Humidity (%)	5-90	5-90	5-90	10-90	10-90
Assay Method	FAD-GDH	FAD-GDH	FAD-GDH	NAD-GDH	NAD-GDH

Accepted manuscript

ACCEPTED MANUSCRIPT

Dimensions LxWxH (cm)	6 x 9.5 x 1.5	5.1 x 8.4 x 1.6	5 x 8.4 x 1.6	5.3 x 7.5 x 1.6	19.7 x 7.5 x 5.3
Weight with batteries (g)	59.4	45.4	42.3	41.9	256
Battery Life (tests)	3000	500	500	1000	540
Calibration	None	None	None	None	Bar Code
Strips	InsulinX	FreeStyle Lite	FreeStyle Lite	Precision Xtra	Precision Xceed Pro blood glucose/β-Ketone, Precision PCx Plus,
Digital	Yes	Yes	Yes	Yes	Yes
Data Port	Micro USB	Headphone jack	Micro USB	Micro USB	Wireless/Micro USB
Screen	Backlit LCD, touch	Backlit LCD	LCD	LCD	LCD

Accepted manuscript

ACCEPTED MANUSCRIPT

Table 6

Table 1: Summary of Beijing Yicheng current main blood glucose meters, adapted from (Beijing Yicheng, 2014). There is no additional information available on the public domain in English language. Repeated approaches to this company for additional information in English language produced no results.

Blood Glucose Meter	JPS-5	JPS-6	JPS-7	5D-1	5D-2	5D-3	5D-6	5D-7	5DT-4
Test Range (mmol/l)	1.7-27.8	1.7-27.8	1.7-33.3	1.1-33.3	1.1-33.3	1.1-33.3	1.1-33.3	1.1-33.3	1.1-33.3
Test Time (sec)	20	20	20	5	5	5	5	5	5
Blood Sample	Peripheral	Peripheral	Peripheral	Peripheral	Peripheral	Peripheral	Peripheral	Peripheral	Peripheral
Blood Volume (µl)	1.5	1.5	1.5	≤ 0.5	≤ 0.5	≤ 0.5	≤ 0.5	≤ 0.5	≤ 0.5
Memory (tests)	10	256	256	256	300	256	256	256	256
Working Temperature (°C)	5-40	5-40	5-40	5-40	5-40	5-40	5-40	5-40	5-40
Working Humidity (%)	<85	<85	<85	<85	<85	<85	<85	<85	<85
Assay Method	GOx	GOx	GOx	GOx	GOx	GOx	GOx	GOx	GOx
Dimensions LxWxH (cm)	9.7×5.1×1.6	10×5×1.5	10.4×6×1.6	9.5×5×1.5	9.5×5×1.5	10.4×6×1.6	9.7×5.1×1.6	10.4×6×1.6	10.5×5.1×1

Accepted manuscript

ACCEPTED MANUSCRIPT

Weight with batteries (g)	50	50	70	50	50	70	55	70	60

Accepted manuscript

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Highlights

1. State of the art and pipeline devices for diabetes and glucose sensing
2. Future research direction in the field of glucose sensing for diabetes
3. Emphasis on the user friendly home blood glucose testing market
4. Technological advancement such as incorporation of the internet of things
5. Future technologies supporting closed loop systems

Accepted manuscript

ACCEPTED MANUSCRIPT

Table 1: Defining events and evolution blood glucose biosensor development, adapted from Clarke & Foster (2012), Niazi (2009), Newman & Setford (2006) and Newman & Turner (2005).

Date	Event
1916	Immobilisation of proteins report: adsorption of invertase on activated charcoal
1922	Glass pH electrode
1956	**Invention of the oxygen electrode (Clark)**
1957	Clinistix reagent strip utilising glucose oxidase reaction by Ames
1962	Description of a biosensor: amperometric enzyme electrode for glucose (Clark and Lyons)
1964	Dextrostix modified reagent strip for blood glucose by Ames
1967	**Practical enzyme electrode (Updike and Hicks)**
1970	Reflectance photometry with Dextrostix Ames Reflectance Meter Ames
1973	Eyetone mains-powered and single analogue scale by Ames
1973–5	**Commercial biosensor: Yellow Springs Instruments for glucose**
1975	Immunosensor: ovalbumin on a platinum wire Invention of the pO2/pCO2 optode (fluorescence signal & gas permeable membrane usage)
1976	Miles Biostator: first bedside artificial pancreas
1980	Digital display, whole blood standard Dextrometer Ames
1980	Glucochek/Glucoscan Lifescan Automatic timing
1981	Improved countdown timer with audio alarm Glucometer I Ames
1981	Stored calibration, low/high result alarms Glucometer I Ames
1982	First fibre optic-based biosensor for glucose (Schultz)
1984	Mediated amperometric glucose biosensor using ferrocene+glucose oxidase (Cass et al.)
1986	Data storage of results Glucometer M Ames
1987	OneTouch Lifescan test strip: Non-wipe, automatic timing, 45-▒seconds
1987	**Launch MediSense ExacTech blood glucose biosensor™**
1991	HemoCue capillary-fill (5▒µL) sampling
1992	i-STAT hand-held blood analyser launch
1996	Glucocard launch
1996	Abbott acquires MediSense for $867 million
1997	Glucometer Esprit Bayer-uploading results to personal computers
1998	Roche and Boehringer Mannheim merge to form Roche Diagnostics
1999	Third generation glucose biosensors: Medtronic
2000	GlucoWatch: Wearable non-invasive glucose meter
2001	LifeScan acquires Inverness Medical for $1.3 billion
2002	**Medtronic 'MiniMed' first implantable continuous glucose monitoring device**
2002	AccuChek Voicemate Roche for visually impaired
2003	i-STAT acquired by Abbott for $392 million
2003	Freestyle Freedom Abbott coulometry biosensor with alternative site testing
2003	Ascensia Breeze Bayer Autodisc of 10 strips

Accepted manuscript

ACCEPTED MANUSCRIPT

2004 Abbott purchases TheraSense for $1.2 billion

2005 AccuCheck Compact Roche 17-test strip barrel

2006 Continuous blood glucose meters from Abbot, Medtronic, DexCom, Menarini, Orsense

2008 Talking blood glucose meter SensoCard Plus BBI

2009 Transition from PQQ to FAD due to maltose interference

2009 Contour Didget DS games console compatability blood glucose meter

2010 USB attached BGM Contour USB Bayer

2012 Improved carbon nanotubes: ultilayered graphene petal nanosheets

2013 **Smartphone integration into self-monitoring blood glucose devices**

Accepted manuscript