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Continuous glucose monitoring systems - Current status and future perspectives of the flagship technologies in biosensor research -

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ABSTRACT

Diabetes mellitus is a chronic illness in the United States affecting nearly 120 million adults, as well as increasing in children under the age of 18. Diabetes was also the 7th leading cause of death in the United States with 270 K deaths in 2017. Diabetes is best managed by tight glycemic control, as achieving near-normal glucose levels is key to reduce the risk of microvascular complications. Currently, continuous glucose monitoring (CGM) systems have been recognized as the ideal monitoring systems for glycemic control of diabetic patients. Briefly, a CGM system measures blood glucose levels in subcutaneous tissue by attaching a CGM sensor to the skin, allowing the users to make appropriate modifications to their medical interventions according to experience or empirically derived algorithms. The principles of the glucose sensing employed in the current commercially available CGM systems are mainly electrochemical, and employ the gold standard enzyme, glucose oxidase, as the glucose sensing molecule with the combination of hydrogen peroxide monitoring or with the combination of redox mediator harboring hydrogel. Recently, by employing an abiotic synthetic receptor harboring a fluorescent probe combined with a fluorescent detection system, a chronic CGM was commercialized. In addition, the development of less or non-invasive monitoring sensors targeting glucose in tears, sweat, saliva and urine have become of great interest although their clinical relevancy is still controversial. This review article introduces current and future technological aspects of CGM systems, the flagship technology in biosensor research, which was initiated, matured and is still growing in North America.

1. Introduction

Diabetes is a chronic illness in the United States affecting nearly 120 million adults, as well as increasing in children under the age of 18 (CDC 2020 Report; https://www.cdc.gov/diabetes/library/features/diabetes-stat-report.html). Segmenting the types of diabetes leads to a better understanding of the epidemic. Of the 120 million patients, approximately 32.5 million have type II diabetes, 1.71 million have type I diabetes, and remaining 88 million have prediabetes, or impaired glucose tolerance (IGT) (CDC 2020 Report; https://www.cdc.gov/diabetes/library/features/diabetes-stat-report.html) (Fig. 1). Diabetes was also the 7th leading cause of death in the United States with 270 K deaths in 2017 (Diabetes org report; https://www.diabetes.org/resources/statistics/statistics-about-diabetes). The burden of diabetes in 2017 reached $327 billion dollars, split mostly between $237 billion in direct medical costs and $90 billion attributed to loss of productivity.

Diabetes mellitus is best managed by tight glycemic control, as achieving near-normal glucose levels is key to reduce the risk of microvascular complications. Currently, continuous glucose monitoring (CGM) systems have been recognized as the ideal monitoring systems for glycemic control of diabetic patients. According to National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases (NIH-NIDKK) (https://www.niddk.nih.gov/health-information/diabetes/overview/managing-diabetes/continuous-glucose-monitoring), CGM systems and their features are defined as follows. CGM systems are the sensors which automatically monitor blood glucose levels throughout the day and night, by measuring glucose concentration in interstitial fluid (ISF), and then are converted to blood glucose values. Current CGM systems generally employ a small flex sensor inserted or implanted under the skin, measuring ISF glucose concentration every few minutes. Sensor readout will send the data wirelessly to a monitor, thereby providing how glucose level changeover hours to days (Fig. 2A). These sensors used for current CGM systems are all

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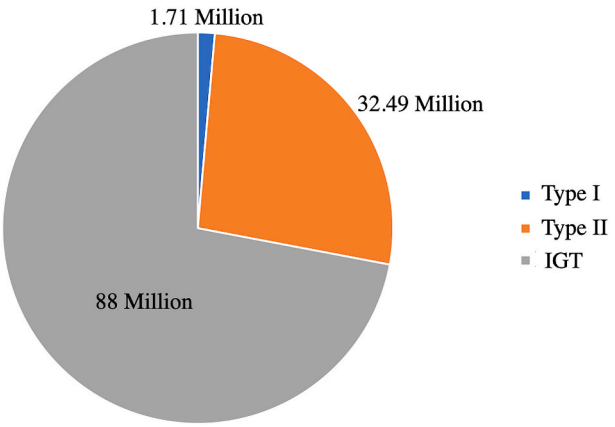

Fig. 1. Population breakdown of the 3 types of diabetes within the United States.
Type I; number of patients with Type I diabetes, Type II; number of patients with Type II diabetes, IGT; number of prediabetes patients with Impaired Glucose Tolerance (IGT). All numbers are in millions.

categorized as minimally invasive sensors (Keenan et al., 2009), as the term "minimally invasive" refers to inserting a needle into the skin to measure glucose concentration in ISF, but not drawing blood (Fig. 2). In contrary, the word "invasive" refers to drawing blood from a blood vessel puncture and not to how deeply the sensor is placed.

There have been varieties of challenges reported to develop glucose sensors suitable for CGM use. In addition, the development of less or non-invasive monitoring sensors targeting glucose in tears, sweat, saliva and urine have become of great interest although their clinical relevancy is still controversial. The principles of the glucose sensing employed in the current commercially available CGM systems are mainly electrochemical, which employ the gold standard enzyme, glucose oxidase, as the glucose sensing molecule with the combination of hydrogen peroxide monitoring or with the combination of redox mediator harboring hydrogel. Recently, by employing an abiotic synthetic receptor harboring a fluorescent probe combined with a fluorescent detection system, a chronic CGM was commercialized.

CGM system monitor glucose levels in real time, which can help diabetic patients and physicians make informed medical decisions. Most of the CGM systems have connectivity with variety of devices including personal smart devices or upload data to cloud data base. The most remarkable feature of CGM system is alarming systems for hyper- and hypo-glycemic level. This means, current CGM system is capable of monitoring glucose, in vivo, in situ, continuously, not only real-time, but

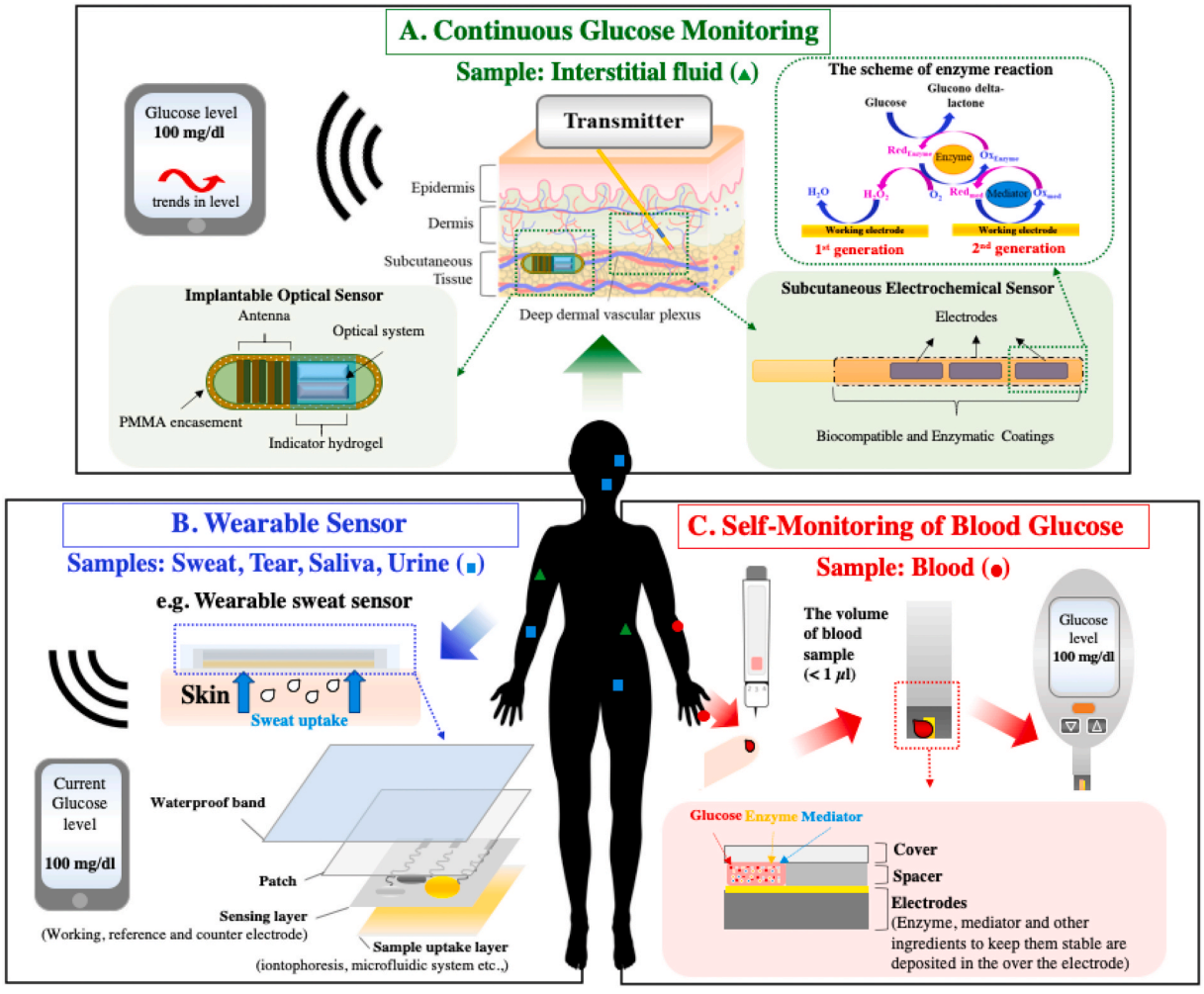

Fig. 2. Schemes for the sensors and systems for A; CGM, B; wearable sensor, and C; self-monitoring of blood glucose (SMBG), including location of sampling, and system components.
A: General layout of a subcutaneously implanted, minimally invasive glucose sensors for continuous glucose monitoring, which are currently on the market. B: Example of a wearable sensor targeting glucose monitoring in the sweat using sampling patch. C: Representative sensor and monitor for SMBG.

is also capable of predicting glucose concentrations in the future.

With the increasing the accuracy of glucose monitoring, some CGM models are now approved for treatment decisions, meaning patients can make changes to the diabetes care plan based on CGM results alone. In 2016, the U.S. Food and Drug Administration (FDA) approved a medical device for insulin infusion for Type I diabetic patients, called a hybrid closed-loop system. This system measured glucose levels every 5 min by a glucose sensor inserted under the skin monitoring glucose concentration in ISF, and automatically informs the patients about the right amount of basal insulin, a short-acting insulin, through a separate insulin pump (https://www.fda.gov/news-events/press-announcements/fda-approves-first-automated-insulin-delivery-device-type-1-diabetes).

This is the first stand-alone medical system in the human history which administrates medication based on the biochemical monitoring by medical device alone. In other words, this is the first biosensor, the glucose sensor, which is integrated into a medical device to provide the necessary information for the medical treatment.

Needless to say, the current achievement of CGM is the future feature of biosensors; in vivo or in situ, continuous, real time monitoring, and being able to predict future target concentration.

Besides, in 2016, FDA also approved the use of some CGM devices to allow for replacement of fingerstick blood glucose (sugar) testing for diabetes treatment decisions (https://www.fda.gov/news-events/press-announcements/fda-expands-indication-continuous-glucose-monitoring-system-first-replace-fingerstick-testing).

This review article introduces current and future technological aspects of CGM systems, the flagship technology in biosensor research, which was initiated, matured and is still growing in North America. First, a brief historical view of glucose sensors, glucose sensors for self-monitoring of blood glucose (SMBG) (Fig. 2C) and CGM are introduced. Secondly, current commercially available CGM systems in North America are reviewed by introducing principles, devices, and performances. Then recent most advanced biosensor researches relating CGM systems are introduced. This section includes sensor technologies in the "wearable sensors", which monitor glucose concentration in sweat, tears, saliva and urine, non-invasively (Fig. 2B). Finally, the prospects of CGM system will be addressed.

2. History and basic principle of CGM systems

2.1. From the dawning of glucose sensor to direct electron transfer based glucose sensor

Late Professor Leland C. Clark Jr, University of Alabama Medical College (Heineman and Jensen, 2006), invented the Clark oxygen electrode (Clark 1956), and then proposed the principle enzyme sensors (Clark and Lyons, 1962; Clark 1965). In the first academic article described by Clark & Lyons, two principles were introduced (quote) "The determination of glucose, using a Cuprophane-glucose oxidase Cuprophane membrane and a pH electrode, illustrates one use of this system. Glucose diffusing through such a membrane is converted to gluconic acid, which then diffuses both toward the pH sensitive glass and back into the donor solution. This causes a drop in pH, the magnitude of which is largely determined by the concentration of the glucose" and "By using a hydrophobic (eg., polyethylene) membrane, a dialysis membrane, glucose oxidase, and a pO_2 electrode, a system can be arranged that is sensitive to glucose by virtue of the fact that oxygen is consumed from the flowing glucose solution in proportion to its glucose content". The former description is about the potentiometric glucose enzyme principle. The latter case is about the amperometric glucose enzyme sensor principle, which we currently recognized as the 1st generation glucose enzyme sensor, which was claimed in his patent filed in 1965 (Clark 1965). Updike and Hicks then reported glucose sensor by combining oxygen electrode and glucose oxidase (GOx) (Updike and Hicks, 1967). These are the beginning of the history of biosensors and glucose sensors. Since then, thousands of biosensor principles were reported by the combination of biological components and transducers. The first electrochemical glucose sensor was commercialized based on his invented principle, but by monitoring hydrogen peroxide liberated by the reduction of oxygen as the electron acceptors.

In parallel to the bench top size glucose sensors, glucose test strip equipped with GOx, peroxidase and color-developing reagents with the combination of reflectometry monitor realized the first personal glucose monitoring system, or SMBG (Fig. 2C), which were developed in accordance with increasing demand for personal glycemic level monitoring for diabetic patient care. The principle, using GOx and oxygen as an electron acceptor for glucose oxidation, has been recognized as 1st generation of glucose sensor (Fig. 3A) which was proposed by Clark and Lyons (1962), as described above. Development of a hand-held 1st generation type glucose sensing system made SMBG available for millions of diabetes patients to control their glycemic level, thereby established a stably growing commercial and now commoditized market (Yamada 2011). The next development was 2nd generation glucose sensor principle using artificial electron acceptors, or mediators, for the oxidative half reaction in the oxidation of glucose by GOx or by glucose dehydrogenases (GDHs) (Fig. 4).Unlike the 1st generation based reflectometric principle based glucose monitoring systems, that were equipped with relatively large size monitors to detect color changes on glucose test strips, and large volume of blood sample (approximately 30 μl), the 2nd generation glucose sensor systems were mainly based on the electrochemical principle, which employ disposable electrode sensor strips enabling the miniaturization of monitoring device (meter) with tiny volume of blood sample, which is usually less than 1 μl. Employing disposable enzyme electrodes and hand-held electrochemical monitors, which provided the results within several seconds require less than 1 μl whole blood sample. This miniaturization reduced the cost of sensors and simultaneously realized the less painful blood sampling process by alternate site testing. The employment of the 2nd generation sensor principle (Fig. 3B) enabled the use of several types of GDHs, nicotinamide adenine dinucleotide (NAD) dependent GDH, pyrroloquinoline quinone (PQQ) dependent GDH and flavin adenine dinucleotide dependent (FAD) GDHs (Ferri et al., 2011). Currently the most popular enzymes for SMBG sensors are fungi derived FADGDHs, considering their oxygen insensitivity and superior substrate specificity (Okuda-Shimazaki et al., 2020). However, GOx has still been used since the first glucose sensor considering its reliable stability and substrate specificity, keeping as the gold standard enzyme in glucose sensors. These 1st and 2nd principle based glucose sensors are based on amperometric detection by monitoring electrochemical oxidation of hydrogen peroxide or reduction of oxygen for 1st generation principle based sensors, or electrochemical oxidation of reduced mediators in the 2nd generation principle based sensors. There have been extensive studies on potentiometric enzyme glucose sensor focusing on the pH change by the formation of gluconic acid, as was reported by Clark and Lyons (1962), using pH sensitive electrodes or field-effect transistors (FETs). However, due to the cost of sensor materials, industries selected amperometric glucose sensing technology for SMBG sensors, considering cost effective disposable electrodes.

The majority of commercially available CGM systems are equipped with the electrochemical glucose sensors, employing 1st or 2nd generation principles and they all utilize GOx as the enzyme. However, there are no commercially available GDH based CGM system in the market. To the best of our knowledge, there are no reports nor statement about why GDH based CGM was not available. However, based on our empirical information, the lack in the compatibilities with current available 2nd generation technologies (e.g. redox hydrogel-polymer for GDH immobilization to electrode) and/or the instability of current available fungi derived FADGDH compared with GOx, would be the reason. In addition, GDH should be used in the 2nd generation principle, which requires toxic mediators. The limitation of availability of mediator and/or mediator containing redox polymers to be used in 2nd generation CGM system suitable for the clinical application, would be also the reason

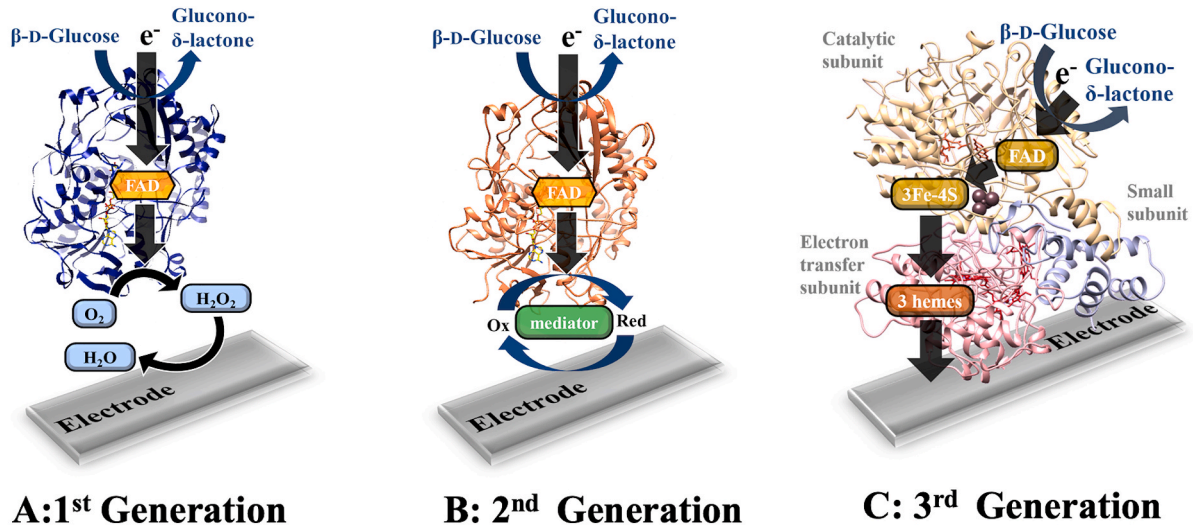

Fig. 3. Three generations of electrochemical glucose sensing principles.
(A) First generation; sensors utilize oxygen as an electron acceptor, (B) Second generation; sensors utilize artificial electron acceptors or mediators, (C) Third generation; sensors which do not utilize neither oxygen nor mediators, but enzyme can transfer electron directly to the electrode.

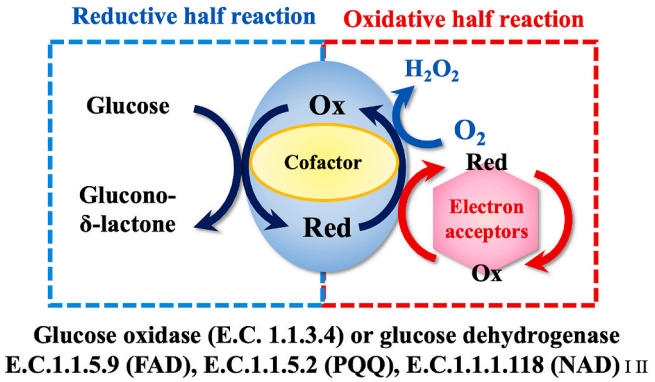

Fig. 4. Glucose oxidase and glucose dehydrogenase.
Glucose oxidase oxidizes glucose using oxygen as a primary electron acceptor, whereas glucose dehydrogenase oxidizes glucose using varieties of electron acceptors but not oxygen.

why GDH has not yet been utilized for the sensor of CGM system. The first CGM system, Medtronic Minimed Gold, was approved by FDA in 1999, and was a wired-type glucose electrochemical needle type sensor inserted under the skin. The glucose sensors employed 1st generation principle and measured hydrogen peroxide. Current Medtronic CGM systems are all equipped with wireless transmission. Dexcom Inc. lunched their first CGM system in 2006, which also employed 1st generation principle, and was equipped with wireless transmission. Abbott lunched the first 2nd generation type CGM system in 2008, by employing their iconic technology redox-polymer hydrogel, that contains osmium complex as electron mediator, with the combination of GOx.

3rd generation principle, which is the use of glucose oxidizing enzyme capable of direct electron transfer (DET) (Yamashita et al., 2018) with the electrode (Fig. 3C), is recognized as the ideal principle for the CGM. A CGM sensor employing the DET-type glucose oxidizing enzyme has various advantages compared to the predecessors (Lee et al., 2018). First, sufficient electrochemical signals can be generated by the enzyme itself without the use of electron mediators or oxygen, reducing the number of essential reactions for glucose detection. Second, electrochemical signals can be generated at a lower potential. The potential window of a glucose sensor depends on the redox potential of the enzyme's cofactor. The redox potential of DET-type glucose oxidizing enzyme is far lower than the oxidation potential of an artificial mediator or hydrogen peroxide oxidation. The low redox potential will reduce the oxidation of interfering substances at the electrode, and thus simplify electrode surface treatments required to reduce interference. Together, the sensor fabrication steps and surface chemistry can be greatly simplified.

The first 3rd generation type CGM sensor was reported with the principle of open circuit potential (OCP) measurement with the combination of DET type flavin adenine dinucleotide (FAD) glucose dehydrogenase (FADGDH) and wireless transmission system (Kakehi et al., 2007). The DET type FADGDH used in the study consists of 3 subunits; a catalytic subunit, a small subunit, and an electron transfer subunit (Sode et al., 1996; Yamazaki et al., 1999; Inose et al., 2003; Yamaoka et al., 2004; Tsuya et al., 2006). Glucose is oxidized by the catalytic subunit of this enzyme, and electrons generated by the oxidation of glucose are transferred to the electron transfer subunit via intramolecular electron transfer (FAD, 3Fe–4S cluster and hemes) (Shiota et al., 2016; Yamashita et al., 2018). The 3D structure of the complex for catalytic subunit and small subunit was already elucidated (Yoshida et al., 2019). Finally, the electron is transferred to the electrode by the heme of the electron transfer subunit. The first amperometric DET type sensor using this enzyme was reported by Yamazaki et al. (2008) followed by the recent achievement of an amperometric glucose sensor combining a self-assembled monolayer (SAM) (Lee et al., 2018). The self-powered glucose sensing systems were also reported based on 3rd generation principle with the combination of the concept of "Biocapacitor" (Hanashi et al., 2009, 2011, 2012, 2014; Sode et al., 2016; Lee et al., 2017a). Recently, OCP based CGM sensor was reported using 3rd generation principle, showing long term operational stabilities, with high reproducibility of measurement and sensor preparation, waved from the impact of the presence of electrochemically active ingredients, such as acetaminophen and ascorbic acid (Lee et al., 2019). However, commercial CGM product based on 3rd generation glucose sensing has been yet to be done.

2.2. From stand-alone CGM to linking with insulin pump to realize artificial pancreas

The early developed CGM systems were stand-alone glucose monitoring system, but not real-time, and were for professional use only. The professional CGM systems have been used by healthcare providers to

obtain and monitor glycemic level of diabetic patients during typical everyday life. Improvement of glucose sensor accuracy and establishment of calibration methods for CGM systems using blood glucose monitoring systems, enabled the combination of insulin pump technology with CGM's for continuous subcutaneous insulin infusion (CSII) therapy. The most remarkable achievement was the realization of sensor augmented insulin pumps, which are operated solely based on the results of CGM system. Throughout the strategic gradual stages; low glucose suspended insulin pump operation, Threshold Suspend Device System (https://www.fda.gov/medical-devices/artificial-pancreas-device-system/types-artificial-pancreas-device-systems), pump suspending automatically before a low glucose is predicted, and the most recent technology so called "Hybrid Closed Loop" system, the CGM system is progressing to realize the artificial pancreas system (https://www.fda.gov/news-events/press-announcements/fda-approves-first-automated-insulin-delivery-device-type-1-diabetes). The current available technologies to realize Hybrid Closed Loop system are reviewed in a later section.

2.3. CGM replacement of SMBG

Initially the stand-alone CGM systems were provided for professional use, now these products are focusing on replacing the role of SMBG, to realize personal real-time CGM. In 2016 (quote; https://www.fda.gov/news-events/press-announcements/fda-expands-indication-continuous-glucose-monitoring-system-first-replace-fingerstick-testing), FDA expanded the approved use of Dexcom's G5 Mobile Continuous Glucose Monitoring System to allow for replacement of fingerstick blood glucose testing for diabetes treatment decisions in people 2 years of age and older with diabetes. This was the first FDA-approved CGM system that can be used to make diabetes treatment decisions without confirmation with a traditional fingerstick test. The system was previously approved to complement, not replace, fingerstick testing for diabetes treatment decisions. Abbott Freestyle Libre, a CGM system employing 2nd generation glucose sensing principle, was then approved as the sensor intended to replace blood glucose testing with a fingerstick for diabetes treatment decisions.

2.4. Abiotic based glucose sensing principle and its application for CGM system

In addition to electrochemical based glucose monitoring, optical glucose sensors have been vigorously studied and developed into successful CGM systems. Instead of glucose oxidizing enzymes, optical sensors employed glucose binding molecules, such as glucose/galactose binding protein (GGBP), concanavalin A (ConA), hexokinase (HK) (without using its catalytic reaction) and abiotic synthetic molecules represented as diboronic acid derivatives. Optical continuous glucose sensing systems are mostly based on fluorescence monitoring, detecting the change of fluorescence properties of fluorescence probe modified on the glucose binding molecules (Pickup et al., 2005). Biological molecules, such as GGBP, ConA and HK, have been extensively studied, to realize optical fluorescence CGM systems, and human trial has been also reported (Judge et al., 2011). Despite their superior properties, simplicity in the electrochemical devices for CGM systems was superior to fluorescence systems, therefore, these have not been finally commercialized. Abiotic based glucose sensing systems have been superior in their stability compared to enzymatic based glucose monitoring, suitable for fully implantable long term continuous monitoring system. Among varieties of glucose sensing abiotic synthetic receptors, diboronic acid derivatives have been considered as the most reliable, selective, and sensitive for in vivo continuous glucose sensing. The history of the development of synthetic glucose receptors was well summarized in a review article by Sun and James (2015). Shinkai and his group has been engaged in the development of abiotic glucose sensing ligands, and they are the pioneer of diboronic acid derivatives for glucose sensing. They have found that two-point interrogation by a diboronic acid is the most expeditious approach towards the selective detection of saccharides (Kondo et al., 1992). They found that the spatial disposition of the two boronic acid moieties determines which saccharide is bound preferentially and elucidated that two appropriately positioned boronic acids could modulate selectivity by two-point binding interactions with glucose. Based on their findings, they have reported the first photoinduced electron transfer (PET) glucose sensing molecule (James et al., 1994; Kawanishi et al., 2004). Further extensive studies (Heo et al., 2011; Mortellaro and DeHennis, 2014) developed the first commercially available fully implanted CGM system employing abiotic glucose sensing molecule based on fluorescence detection principle. Eversense by Senseonics, is a subcutaneously implantable sensor that uses a fluorescent, diboronic acid based glucose indicating hydrogel and a miniaturized optical detection system, which was approved by FDA in 2019. The Eversense Continuous Glucose Monitoring System (quote; https://www.fda.gov/medical-devices/recently-approved-devices/eversense-continuous-glucose-monitoring-system-p160048s006) is a prescription device that provides real-time glucose monitoring every 5 min for up to 90 days at a time for people with diabetes (in USA). The system consists of an implantable fluorescence-based sensor, a smart transmitter, and a mobile app for displaying glucose values, trends, and alerts on the patient's compatible mobile device (smart phone, tablet, etc.). Sensor implantation under the skin is done by a physician, in either an outpatient center or clinic. The implanted fluorescence probe modified by diboronbic acid, is excited by light source equipped in the implanted device, and fluorescence is detected by a miniaturized implanted photodetector, which is powered by near field communication. The sensor signal is obtained wirelessly every 5 min to a compatible mobile device (smart phone, tablet, etc.) for display to a user. Currently, the system is applied for an approval for the extended the wearable period from 90 days to 180 days, which was already approved by CE in EU.

3. Currently commercially available CGMs and their technologies

With the increasing number of diabetic patients (Diabetes Atlas, 2019; https://www.diabetesatlas.org/en/), technology development of glucose sensors and related technologies have also continuously proceeded. Consequently, to improve the care and outcomes, technologies, and pharmaceuticals have been developed such as novel insulin analogues, to various continuous glucose monitors now available on the market. Continuous glucose monitors have had tremendous research and success in the market for both type I and type II patients (Gorst et al., 2015; Carlson et al., 2017). The CGM has become the gold standard for type I diabetes requiring intensive insulin therapy, especially when introduced early in diagnoses (Ruedy et al., 2017; Prahalad et al., 2020). The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group has shown improvement of HbA1C outcomes (The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group 2008; 2009; 2010). The DIAMOND study showed an improved change in A1C of −1% vs −0.4% when comparing the use of a CGM vs SMBG (>4 test/day) over a 24-week period (Beck et al., 2017a). The use of CGM's have also increased in both type II and prediabetics, as a similar DIAMOND study showed that within a cohort of 158 patients with type II diabetes, they recorded an average improvement of HbA1c of about −0.3% when compared to nominal therapy (Beck et al., 2017b). Chakarova et al. (2019) performed a small study with 32 prediabetic patients, showing that those with prediabetes have higher glucose variability, then non pre diabetic (Chakarova et al., 2019), suggesting that earlier application of glucose monitoring through CGM's may prove appropriate. Different use cases for the CGM have also expanded the technology. Abbott, created the "Flash" glucose monitor, coined "FGM" which is calibration free, and allows the user to transmit data at their own need (FreeStyle Libre | Flash Glucose Monitoring | FGM). Recently

the term "intermittently scanned CGM (isCGM)", is generally used for FGM, to discriminate from the conventional CGM, which is now called as "real-time CGM (rtCGM)" (Edelman et al., 2018).

These findings have been laying the pathway for CGM use among new, and vastly different populations. In this section, sensor configurations of currently commercially available CGM systems are introduced based on each specific sensor domain, following the 4 commercially available CGM systems together with their sensor performance specs. Then, current sources of error in glucose sensors, algorithms, calibration, and filtering aspects of continuous glucose monitoring systems are introduced.

3.1. Sensor domains

3.1.1. Electrode domain

The first domain of focus for the CGM is the working electrode surface which transducers electrons from the specific electron acceptors (oxygen or synthetic electron acceptors, e.g. osmium complex) to the internal hardware for measurement. Key to this domain is the functional surface area available for electron transfer, which will impact the current density measured based on the equation below:

$$nFA\left(\frac{dglu}{dt}\right) = i \tag{1}$$

Where F is faradays constant, A is functional surface area, n molar coefficient, $\frac{dglu}{dt}$ is the flux of glucose or flux of electron caring electron acceptor (O_2 in 1st generation sensors) with the units of concentration/time. (Bard and Faulkner, 2000). Clearly by increasing the surface area, the current will also increase proportionally. Many researchers have developed very novel methods to optimize the useable surface area, using nanoporous gold, or carbon nanotubes, maximizing the current measured (Huang et al., 2019; Liu et al., 2008; Hoss and Budiman, 2017). This works very well when using a clean sample, but in practice can pose many draw backs. Increasing the surface area may also increase interference, and baseline noise compared to the change due to glucose influx. Further, with the advent of "Factory Calibration" the ability to produce repeatable current density outweighs the need for maximum current density. The counter electrode must also be capable of balancing the electron transfer reactions occurring at the working electrode. For every peroxide molecule oxidized at the surface for the working electrode, a subsequent reduction reaction must occur at the counter electrode. As surface area of the working electrode increases, the electrode area for the counter must increase even higher to ensure that the reduction reaction is never the rate limiting step.

The final electrode is the reference electrode, used to hold a potential against during the sensor's entire lifetime. All current products use Ag/AgCl (silver-silver/chloride) as the reference electrode due to ease in manufacturing, well understood biocompatibility and known potential. For 3-electrode configurations, the reference electrode is used independent of the surface reactions as a stand-alone known potential. Where in 2 electrode systems, the reference will also act as the counter, both reducing molecules and acting as the stable potential. Medtronic and Abbott both use a 3-electrode system, having current flow through the working to counter, independent of the reference electrode. Dexcom, uses only 2 electrodes, shorting the counter and reference. This is another factor impacting the working electrode surface area, and current measured. In a 2-electrode set up, if the current gets too high (greater than 1 nA), the reference electrode may fail, or become damaged (Bard and Faulkner, 2000). Dexcom most likely uses a large reference/counter electrode relative to working electrode to ensure the reference potential is not disrupted during function. These electrodes are manufactured using some patterning process, generally either roll-to-roll, or photolithography as the patterning, and plating, sputtering, and etching as the deposition processes.

3.1.2. Enzyme domain

The next key domain is the enzyme layer which is responsible for driving the oxidation of glucose and reduction of oxygen or the electron mediator. Principles of reactions, and diffusion apply to this layer, where at low enzyme loading, the substrate can penetrate through the enzyme domain, having a homogenous reaction. While at high loading, and dense enzyme layers, the reaction will occur in a more heterogenous state, as the substrate is almost entirely reacted near the surface of this domain. Ideally all the sensors developed by Abbott, Medtronic, or Dexcom are in heterogenous reaction schemes and are diffusion limited. This entails that the limiting rate is the diffusion of substrate to the sensor, not the reaction of the substrate and catalyst. To ensure this, most companies load much high quantities of enzyme than needed. This is in part due to the modes of enzyme inactivation which can occur. Generally, the enzyme is inactivated through hydrogen peroxide mediated deactivation, or spontaneous inactivation due to the structural instability over time. In the homogenous scheme, there is high probability of the enzyme layer inactivating since the substrate is reacting with the entire domain (Gough and Bremer, 2000). In the heterogenous scheme, only the surface of the enzyme domain is actively reacting with the substrate (until the enzyme begins to inactivate, and substrate slowly penetrates lower into this layer). Ensuring diffusion limited is then accomplished by both the loading of the enzyme and limiting the amount of glucose that reaches the enzyme layer (discussed in the following section). This layer is also crosslinked using a polymer like cross-linked glutaraldehyde, and a blocker to ensure enzyme does not leach from the sensor over time, as well as better stabilizes the enzyme for 7-14-day use (Gough and Bremer, 2000; Solomon et al., 1977; Rodrigues et al., 2013). This also may affect calibration aspects of the sensor, if not enough enzyme is deposited, the dependence on glucose may shift to dependence on enzyme concentration. Requiring frequent calibrations to ensure accurate glucose concentration to current response.

3.1.3. Glucose limiting membrane domain

The next domain found on all commercialized CGM's is a glucose limiting layer. This layer serves several purposes for function of sensors. As mentioned previously, CGM's function in the diffusion limited regime, meaning that the current measured is limited by the rate at which glucose arrives to the enzyme domain. This applies to both the substrate (glucose) and co-substrate (oxygen) if needed for function. Both Medtronic and Dexcom's CGM relies on oxygen reduction to hydrogen peroxide to measure glucose. This is a challenge in vivo as glucose exist at a much greater concentration than oxygen in ISF. The glucose limiting membrane is used to overcome this challenge, restricting the amount of glucose that reaches the enzyme domain, while being permeable to oxygen. The glucose limiting membrane also increases the linear response region of sensors. By altering the limiting membranes thickness, diffusion coefficient, and permeability to glucose, commercialized sensors can ensure that the current measured is due strictly to the dependence of glucose diffusion. Gough has greatly elucidated an empirical relationship between the enzyme stability, and glucose limiting membrane properties to indicate whether a sensor will perform under diffusion limited regime, or kinetically limited regime (Gough and Bremer, 2000).

$$\sigma_{glu} = \left(\frac{K_{cat} * Conc_{GOX} * X^2}{D_{glu} * K_m}\right)^{\frac{1}{2}} \tag{2}$$

Equation (2) is a unitless parameter that relates the enzyme catalytic activity (K_{cat}) the enzyme concentration ($Conc_{GOX}$), enzyme/diffusion membrane thickness (X), membranes glucose diffusivity coefficient (D_{glu}), and the Michaelis Menten constant for the enzyme (K_m). When σ_{glu} is greater then 1, the sensor will behave in a diffusion limited regime, while when σ_{glu} is below 1, the sensor will be kinetically limited. Based off this equation, one would try and minimize the diffusion coefficient of

glucose, maximize the membrane thickness and enzyme concentration. As the catalytic properties are very challenging to control during manufacturing, these are generally considered constants. The tradeoff of having to low of diffusion, or too thick of the membrane layer is the time lag between an environmental change in glucose, and the change occurring at the enzyme domain surface. The relationship between time to diffuse a distance if the square of the distance multiplied diffusion coefficient over 2 (Bard and Faulkner, 2000).

$$\frac{\left(x^2 * D_{glu}\right)}{2} = t \tag{3}$$

Where x^2 is distance, D_{glu} is diffusivity to glucose, and t is the time is takes for a molecule to diffuse the distance x. This can become a serious issue for type I diabetics during episode of hypoglycemia, where "real time" data becomes essential for good outcomes. Based on these tradeoffs, most sensors try to optimize the combination of being diffusion limited through the entire sensor lifetime and being able to measure rapid changes in glucose real time (Gough and Bremer, 2000; Gough and Armour, 1995; Bard and Faulkner, 2000).

3.1.4. Interference rejection domain

The last domain is about the membranes to prevent the impact of the presence of interferants on sensor signals. Certain molecules may interfere with the acquired signal during in vivo glucose monitoring. This interference is caused by the spontaneous reduction or oxidation of small molecules against the electrode domain. Ascorbic acid for example will be oxidized between 0.26 and 0.29 V as shown in cyclic voltammetry using platinum as the substrate while hydrogen peroxide (the common electrode reactant for 1st generation glucose sensors) may absorb and oxidize around 0.6 V and higher (Ernst and Knoll, 2001; Katsounaros et al., 2012). Due to this challenge, many sensors (especially those functioning at high potentials) may suffer from inadvertent oxidation, corrupting the signal. One approach to overcome this adversity by using interference rejection polymers. These polymers may use methods such as size exclusion or be semi permeable to allow only specific types of molecules through. These membranes include material like Nafion, cellulose acetate, and poly-l-lysine (Heller and Feldman, 2008; Teymourian et al., 2020; Kim et al., 2019a).

Kim et al. (2019a) developed a cellulose/β-cyclodextrin nanofiber with immobilized glucose oxidase to both transduce the signal form glucose to the electrode, but also to mitigate interference from Acetaminophen, and Uric Acid (Kim et al., 2019a). Arakawa et al. (2020) demonstrated similar performance of interference rejection using cellulose acetate to prevent both acetaminophen, and uric acid from impacting the signal (Arakawa et al., 2020). Ribet et al. (2018) developed an ultra-micro glucose sensor using wafer fabrication. To mitigate interference from acetaminophen, and uric acid, Nafion was employed. Nafion helps exclude anion species which may be electroactive towards the electrode domain (Ribet et al., 2018). These membranes are starting to become a needed layer to meet the high accuracy, and precision needed requirements for modern use.

3.2. Commercially available CGM systems in US

3.2.1. Dexcom

The Dexcom glucose sensor is a wire-based sensor, using a first-generation electrochemical process to measure glucose. The sensor uses 2 electrodes, a working electrode which is platinum, or platinum iridium, and a reference/counter electrode composed of silver/silver chloride (Ag/AgCl). The working electrode facilitates the oxidation of hydrogen peroxide. The sensor is designed starting with a platinum or platinum iridium wire, which is then serially coated and patterned with insulating polymers, using methods such as photolithography, grit blasting, etching or laser ablation (Simpson et al., 2015). These polymers may be polyimide, polyurethane, or perylene all of which provide insulation for the working and reference/counter electrode (Simpson et al., 2015). This also allows for selective exposed openings of the underlying working electrode. The reference/counter electrode is added via dip coating, screen printing, or jet printing process, where the thickness, and location of Ag/AgCl layer is controlled (Tapsak et al., 2002).

Dexcom's sensor chemistry is added after the electrode layers, through similar processes such as photolithography, dip coating, etc. The chemistry layers added can be broken into various "domains" each with a specific role within the sensor. The enzyme domain contains the active enzyme being used in the electrochemical reaction. Also for Dexcom, this enzyme is GOx (Broock and Rixman, 2009). The layer will also consist of some crosslinking polymer such as perfluorocarbons, or a silicon impregnated with polyethylene glycol ensuring the enzyme does not leach out of the sensor and that sufficient oxygen is present to interact with. The next domain is a glucose diffusion barrier layer which both ensures the sensor functions in the diffusion limiting regime, and that there is sufficient oxygen to glucose concentrations within the enzyme layer. The diffusion membrane is designed to be semi-permeable polymer, made up of an oxygen soluble material such as silicone, while having elements added to reduce the solubility and permeability to glucose (Broock and Rixman, 2009).

3.2.2. Medtronic

Medtronic's glucose sensor has similar function to Dexcom's, being wire based, and using first generation process to measure glucose. Unlike Dexcom's sensor, Medtronic has 3 distinct electrodes, a working electrode, a counter electrode, and a reference electrode. The working and counter electrodes are platinum based, using an electroplating process to create a targeted roughness factor. The reference electrode is Ag/AgCl, also being electroplated onto the surface (Shah and Gottlieb, 2005; Van Antwerp and Mastrototaro, 1999; Cheney and Van Antwerp, 1994). The electrode roles are like those used via Dexcom, except for the counter and reference electrode being separate. Medtronic reference electrode only serves as a stable potential to measure and apply voltage against, while the counter electrode balances the current flow through reducing molecules such as oxygen. Sensor design begins with a carrier substrate which is coated with some insulator such as polyimide to be used as the base of the electrode. This layer is then built upon in a layer by layer fashion using methods such as photolithography, wet and dry etch, and deposition methods to selectively pattern the 3 electrodes (Van Antwerp and Mastrototaro, 1999).

Medtronic's glucose sensor chemistry is applied after the substrate layers. These domains include an enzymatic domain harboring GOx, and glucose diffusion domain. The enzyme domain is deposited via deposition techniques such as dipping, spraying, or others. Following this, an adhesion domain such as glutaraldehyde is added as a crosslinker to prevent enzyme leaching of minimize delamination occurring from the base substrate. The glucose limiting domain uses materials such as polyamines, and siloxanes such as polyoxypropylene-diamine, and polydimethylsiloxane respectively to create a glucose semi permeable membrane. Where polyoxypropylene-diamine is glucose permeable, and the siloxane group is impermeable (Shah and Gottlieb, 2005). Using different ratios of these to polymers to control the diffusion rate of glucose through the limiting domain. The glucose limiting domain is used to prevent early saturation of the enzyme, as well as ensure that oxygen is present in surplus (Van Antwerp 1995).

3.2.3. Abbott

Abbott's glucose sensor relies on electrochemical reactions like Medtronic. The main difference is that Abbott uses a 2nd generation principle. Using osmium complex as an electron mediator between GOx and the carbon electrode surface. Otherwise, Abbott's sensor design is like Medtronic's, having 3 distinct electrodes, working, counter and reference. The reference electrode is made up of Ag/AgCl which allows for a reliable potential to apply the overpotential against.

Using osmium complex as the electron mediator, enables the sensor to be oxygen free, and independent to fluctuations in local tissue oxygen. One key advantage of using osmium complex is that oxidation potential is lower than hydrogen peroxides. This enables Abbott to apply a smaller overpotential across the working electrode mitigating certain interference (Heller and Feldman, 2008; Say et al., 1998). Abbott's sensor is developed quite differently, using a roll-to-roll process which leverages a continuous film having various components added in series, ideally in a single line. Starting with a base substrate roll, an initial heating, or treatment step may be done to enable deformation of the base substrate. The substrate then is fed through a series of embossing rollers which apply conductive ink, insulation layer, and specific chemistry to the areas of interest (Feldman et al., 2004). The final stacked substrate can then be removed from the film using laser cutting or stamping methods (Feldman et al., 2003).

Like both Dexcom, and Medtronic, Abbott leverages a glucose limiting membrane to ensure the sensor is diffusion limited through the duration of the device. Unlike the previous two companies, Abbott uses polymeric membranes, such as poly-pyridine or poly-imidazole to control the flux of glucose towards the enzyme layer.

3.2.4. Senseonics

Senseonics stands out from the rest by using fluorescent based detection, derived from the interaction of a fluorophore linked divalent boronic acid, and glucose instead of electrochemical methods. When glucose concentrations are low, the unbound boronic acid quenches the fluorescence through photoinduced electron transfer (PET), while at higher glucose concentrations PET is disrupted due to glucose interactions, increasing the fluorescent signal. The mechanism for this event due to the formation of boron-nitrogen bonds which prevent PET from occurring from the amine.

Different from enzyme-based sensors, the binding with glucose and boronic acid does not produce any product, merely a bond related to glucose concentration (Mortellaro and DeHennis, 2014). The molecular recognition element layer is coated with poly(methyl methacrylate) (PMMA) for glucose flux control and biocompatibility. Dexamethasone (DEX) silicone ring which releases the DEX at controlled rates to improve the lifespan of the sensor by mitigating local inflammation response.

3.2.5. Sensor performance specifications

The Dexcom glucose sensor currently can be worn for 10 days requiring no calibration by the user. The sensor is worn on the abdomen and can transmit data to either the patients personal cell phone using an app, or a secondary device. The MARD published by Dexcom is approximately 9.9% over the 10 days although may be better or lower based on the patient use. Recently Tandem has begun using Dexcom's sensor in a "closed loop" based system with the Tslim ×2 insulin pump. The Dexcom G6 data specs is included in Table 1 below.

Medtronic's glucose sensor life is 7 days and requires 2 calibrations each day to ensure the accuracy of the device. The MARD of the sensor ranges from 8.7 to 10.5% although this includes data requiring 4 calibrations a day which is very impractical for a patient. The 670G insulin pump communicates real time with the glucose sensor allowing patients to have real time changing basal, targeting a preset glucose range. Recently Medtronic took this further with the 780G pump, getting CE marked which allows for more aggressive auto bolus corrections to prevent hyperglycemia, while still minimizing the risk of hypoglycemia through basal control. These two requirements help increase Medtronic sensor linear range and allow for less reliance on oxygen fluctuations occurring locally around the sensor.

Abbott's Libre Pro sensor is worn for 14 days and requires no user calibration. Abbott's published MARD is 9.4% over the 14-day use period. Currently Abbott's continuous glucose sensor cannot be paired with any insulin pump on the market. This may change, as recently Abbott teamed with Tandem to begin integrating the 2 systems.

Senseonics implantable sensor is useable for 90 days in the US, and 180 days in Europe. In addition, the company is currently working on a clinical study to enable 1-year use (365 days). Their published MARD is 8.8%, the lowest of all the sensors on the market, but requires 2 calibrations each day. Up to date Senseonics is not integrated with any insulin pump system, being a stand-alone device.

As CGM technology advances, leading to better patient control of A1C and glycemic variability, certain drawback remains apparent. Interference of foreign substances is a key challenge many sensors still face. Various molecules such as acetaminophen, and ascorbic acid can interfere with the oxidative signal acquired over the working electrode. This issue is further exemplified due to the Corona Virus outbreak. The FDA has now allowed various companies to administer CGM's in hospital settings vastly increasing the number of possible interference that companies have never tested against (Freeman 2020). This poses a new risk to patients not previously understood or quantified by sensor developers. Issues further stem out of longevity, calibration, and accuracy. All three electrochemical sensor's (Medtronic, Dexcom and Abbott) last no more than 14 days at most, while Medtronic still requires frequent calibrations (twice a day). These are challenging that impact patient adoption, outcomes, and experience with the devices. Several companies are working on better adhesives for patients, intending on extending the life of the sensor. While others (Medtronic) are developing new technology to enable minimal calibrations, and improved lifetime either through improved performance of the device, or as Abbott, improved manufacturing methods (Hoss and Budiman, 2017).

The manufacturing capability, enzyme specificity, limiting membranes ability to control diffusion, while mitigate interference, as well as other variables all impact the "accuracy" of the sensor. Further this is a changing variable over time, as the enzyme breaks down, or membrane breaks down the ability to confidently measure glucose may also decline. As the sensors are used more aggressively in closed loop systems, and remove the burden form the patient, this accuracy becomes more vital to the systems function (Hughes et al., 2017).

Distribution of CGM's is another key challenge persisting for patients. Generally driven by cost, and coverage, many patients, type II,

Table 1
The features of commercially available CGM sensors.

Metric/Device	Dexcom G6	Libre Pro	Guardian Sensor 3	Eversense
Company	Dexcom	Abbott	Medtronic	Senseonics
MARD	9.9%	9.4%	8.7–10.5%	8.8%
Calibration with SMBG is required	No	No	twice to 4 times/day	twice/day
Sampling Rate	5 min	5 min	5 min	5 min
Lifetime	10 days	14 days	7 days	90 days
Sensing Molecules	Glucose Oxidase	Glucose Oxidase	Glucose Oxidase	Boronic Acid
Transduction Method	Amperometry Detection	Amperometry Detection	Amperometry Detection	PET Fluorescence
Detection Principle	Electrochemical 1st generation	Electrochemical 2nd generation	Electrochemical 1st generation	Optical (Fluorometry)
Warm Up time	2 h	12 h	2 h	24 h
Insulin Pump Integration	T:slim ×2 (Tandem)	N/A (in progress with Tandem)	MiniMed 670G	N/A

and pre-diabetic, underutilize this technology. Those in poverty also lack the access to this technology to better improve outcomes. Abbott Libre has begun to overcome this challenge with their system priced from $75-$150 per month (Kompala and Neinstein, 2019), compared to traditional systems costing between $250-$400 per month. Other patient focus changes are still underway, such as lowering the pain due to insertion, the size of the wearable component, and interaction with the patient/health provided through easy to use app.

Recently due to the Corona Virus outbreak the FDA has allowed various companies to administer CGM's in hospital settings vastly increasing the number of possible interference that companies have never tested against. This poses a new risk to patients not previously understood or quantified by sensor developers (Freeman 2020).

3.3. Current sources of error in glucose sensors

There have been large amounts of research involved with classifying error regarding CGM's performance. There are many factors that may affect a reading output by either the point of care sensors or CGM. Sensors are rated according to their precision and accuracy. Precision being the reproducibility of the sensor, or manufacturing process, and the accuracy being how close anyone reading is with respect to the reference measurement. The current gold standard for depicting both accuracy and precision is by plotting the measured value in the y-axis, against the reference value in the x-axis. This graph can be presented in either the Clark Error Grid, or the Surveillance Error Grid. In the Clark Error Grid, majority of the data points should ideally fall within zone A, which shows that the measured points are within 20% error of the reference methods. The Surveillance Error Grid is a more visual version of Clark Error Grid developed recently by Klonoff (Klonoff et al., 2014). It converts the error into risk levels and present them in a color-coded manner.

The difference between the measured values and reference values are known as error. While there are multiple ways to express errors, such as the coefficient of variance or standard deviation, MARD (mean absolute relative deviation) has gain popularity as it can summarize the accuracy of a CGM over time in a single value (Ginsberg 2009; Reiterer et al., 2017). It is typically obtained using data from clinical trials by computing the difference between the CGM measurements and the values that are simultaneously measured by a reference system. These error values are heavily valued by FDA and the International Standards Organization (ISO) to develop the standards for blood glucose meters. Following this in 2013 ISO worked with a plethora of health providers, and government agencies to develop the ISO 15197–2013 which stated the following (ISO standard):

- 99% of results must fall within zones A + B of the Consensus Error Grid (CEG) for T1
- 95% of results >5.5 mmol/L must fall within 15% of the reference method
- 95% of results <5.5 mmol/L must fall within 0.83 mmol/L of the reference method

Various other groups have advised tightening these controls including the American Diabetes Association (ADA) suggesting that 95% of glucose readings be within 5% of the reference value. There are a multitude of factors which affect the error of these devices. Strip to strip error can occur through the size variation of the well shape, as well as variance within the amount of enzyme applied.

CGM's have various error sources which affect the accuracy of the readouts. Coming from variables that may be altered or lack control during manufacturing. Each domain discussed in the earlier section (electrode, enzyme, and limiting membrane) all are variable sources where erroneous data can manifest from. Each step in manufacturing these sensors represents a distribution of physical parameters, such as electrode surface area, enzyme thickness and activity, glucose limiting membrane permeability, diffusivity to glucose or oxygen and thickness. As these distributions build up on one another the error will also incrementally increase (Ginsberg 2009; Reiterer et al., 2017; Panteleon et al., 2003). Other general errors can occur from motion artifact, enzyme deactivation over time, and changes to the electrode surface.

3.4. Continuous glucose sensing algorithms, calibration, and filtering aspects

There have been many review articles on the design of glucose sensors, ranging from chemistry to the transduction method, as well as various clinical studies of their efficacy. One characteristic that receives much less attention are the calibration algorithms, and methods of filtering the raw signal coming from the device. These algorithms are used for various reasons, such as predictive modeling for hypo/hyperglycemia alarms, lag time between the signal glucose and current levels, as well as filtering the raw signal into a manageable curve (Bequette 2010). Typically, a linear regression calibration curve is applied for the detection of glucose:

$$y = mx + b \tag{4}$$

Where y represents the current signal and x the corresponding glucose pair. This equation must then be calibrated to find a relation to the blood glucose from the interstitial glucose levels which is essentially the slope (m) of the curve. This then takes the form:

$$m = \frac{y - b}{x} \tag{5}$$

Using a linear regression method as the one described above assumes that the independent variable is known, and that the dependent variable is uncertain. Past studies, such as those from Panteleon, and Ginsberg (Ginsberg 2009; Panteleon et al., 2003) have shown that using the glucose signal as the independent variable improves the signal. This then flips the equation to be as follows:

$$x = my + b + e \tag{6}$$

Where e represents source error, and variance from the calibrated reading to the predicted reading. Once given a calibration, the system then will use a technique of minimizing the sum of the squares (or similar method) to attempt and eliminate the difference in reference value to the calculated values. This takes the equation of:

$$\min_{m,b} \sum_{i=1}^{N} e^2 = \min_{m,b} \sum_{i=1}^{N} (x_i - x_{cal})^2 \tag{7}$$

Where i is the specific data point, N is the total number of previous points, with the goal of minimizing error (e) while controlling the slope and y-intercept (b) (Bequette 2010). One other major challenge with calibration is the time in which a patient calibrates his/her sensor. A group called DirecNet Study characterized various noises introduced to the calibration method leveraging Medtronic CGM's, finding that accuracy quickly degraded when the sensors are calibrated during a rapid change in glucose (about 1.5 mg/dl/min or more). This suggest that for optimal calibrated, a steady state current, or glucose value would be beneficial as the best correlation between ISF and blood glucose occurs during steady state periods.

The next aspect is filtering the data being input, which various common filters being used. These are finite impulse response filters, infinite impulse response filters, Kalman filter, and wiener filter. Medtronic has patented a weiner filter where the parameters of a finite impulse response filter are found by minimizing the sum of the squares error between the signal and the reference value applied. The next important filter is the Kalman filter which is considered superior to the weiner filters shown in a few studies (Bequette 2010; Facchinetti et al., 2010; Knobbe and Buckingham, 2005). The Kalman model switches

between the prediction value based on statistical certainty based on time-varying events (Bequette 2010). Depending on the strength of the model, the Kalman filter can achieve stronger glucose relationships for ISF to blood, as well as strong predictive analytics. Boiroux et al. (2016) performed a comparison of various Kalman filter methods such as least squares estimation, Huber regression, and Gaussian maximum likelihood (Boiroux et al., 2016). The results of this study showed that the Gaussian maximum likelihood method achieved best results, as well as enabled the ability to include uncertainties from various errors, or from population-based models. The strong drawback was that this method did require the most time to compute the outcome of an event.

Another concept which has been applied to Dexcom was the use of a "Smart CGM Sensor". This idea was to modularize the individual components which are used to improve the sensor signal, using a cascading approach. The basic architecture is as follows:

1. Denoising Module: The raw glucose signal is ran through an adaptive filter, which mitigates noise and error from the raw signal.
2. Enhancement Module: The newly denoised data is then enhanced by application of calibration algorithms accounting for drift, or time lag. Or by correcting for signal bias which may occur over time. This enhancing module may also receive its input through manufacturing controls and measurements like factory calibration.
3. Prediction Module: By using the derivative of the curve, one may predict the acute glucose concentration. If this prediction for either hyperglycemia, or hypoglycemia, is beyond a threshold, then a patient alarm may signal, notifying the user to intervene.

The "Smart CGM Sensor" idea was used and demonstrated by Dexcom, improving there MARD nearly 4% without the need of any substantial hardware manipulations (Facchinetti 2016).

Current CGM's are becoming "factory calibrated" which eliminate the need for patients to prick their finger and calibrate the sensor. Abbott was the first to develop such a sensor based on relating in vitro response to in vivo response. Abbott performed a pilot study in 2010, looking at factory calibration of the FreeStyle Navigator. The variables used during the study where sensor to sensor reproducibility within a single lot, shelf life of sensors was characterized over 24 months in an unrefrigerated condition, inter, and intra subject variance of sensor response and 5-day sensor stability was also analyzed using a clinical study (Hoss et al., 2010). More recently a study showing that their sensors sensitivity to glucose had minimal change over their 14 day use case while analyzing similar variables (Hoss and Budiman, 2017). The ability to "Factory Calibrate" is tied mostly to manufacturing variability as was shown in both studies. Being able to develop an in vivo/vitro model for glucose response based upon measured process variance. Factors mentioned above, including enzyme layer thickness, glucose limiting membrane thickness, electrode surface area, are all examples of factors that may be monitored to predict the sensors response to glucose fluctuations. As well as the stability of the sensor signal over the entire lifetime of the device (Hoss and Budiman, 2017).

4. Recent new biosensing technologies for CGM systems

Technology has expanded in the last 20 years. Innovations have not only been limited to the sensing principles, but the sample location, device use case, and interaction with patient. Clinically, samples for glucose detection are mostly taken from blood serum, ISF, and urine. Academically, sample locations have expanded to every possible location, inducing saliva, sweat, and tears, each with their own unique challenges and benefits (Heikenfeld et al., 2019; Kim et al., 2019b). Glucose detection using these non-traditional methods demonstrates challenges regarding sampling, reproducibility, and usability for patients.

For the CGM system, there are a lot of varieties on target sample types, sensor elements and detection principles and these differences have provided new and various technologies for CGM systems until the present. In contrast with blood and ISF, urine, sweat, saliva and tear are currently sorted to clinically non-relevant sample. Among them, although sweat and saliva still needs further investigation regarding correlation between glucose level in those samples and plasma glucose level, it is expected that these 2 samples can provide relatively reliable plasma glucose level (Moyer et al., 2012; Satish et al., 2014).

In this section, we summarized new technologies in CGM system from research side based upon differences of sample type, sensor element and detection principle (Table 2). In this section, most recent research achievements and some pre-commercial products on the measurement of glucose from blood, ISF, urine, sweat, saliva and tear are introduced. This includes sensor technologies in the "wearable sensors", which monitor glucose concentration, non-invasively (Fig. 2).

The sample for glucose detection will be mainly divided into 2 types which are clinically relevant sample and clinically non-relevant sample. In this part, we summarized recent reports using different sample types for glucose detection. Blood and ISF are clinically relevant sample, and the sensor which target to those samples is already commercially available.

4.1. Blood

Blood is one of the most clinically relevant sample for glucose. However, since it is challenging to take a sample for continuous glucose monitoring, blood sample have been usually used as a sample for self-monitoring blood glucose meter. Nevertheless, some of attempts which used blood sample for continuous glucose monitoring have been reported. Zhang et al. (2018) have developed self-powered and implantable skin-like glucose meter for blood glucose level detection in real time (Zhang et al., 2018). The skin-like glucose meter was fabricated by modifying GOx onto the ZnO nanowire surface. Since the outputting piezoelectric voltage of sensor can provide electricity power as well as glucose level information, this sensor does not require any external electricity power. Based on the piezoelectric signal change containing glucose level information, the sensor was able to measure glucose concentration from 0.024 to 0.119 g/L and the limit of detection was 0.019 g/L in vitro. The sensor was finally implanted in the mouse's abdomen, and they were able to successfully measure blood glucose level by self-powered. While the blood sample have some advantages, such as providing accurate glucose levels compared with other samples, there is a challenge that the sensor must be surgically implanted to contact blood sample (Brockway et al., 2015; Yu et al., 2016). There has also been reports of blood glucose sensor which measure glucose directly from the blood without the need of surgery. Rachim and Chung (2019) reported a wearable-band type blood glucose sensor combining visible-near infrared spectroscopy (Rachim and Chung, 2019). The sensor was consisted of four output channels which have different optical wavelength (950, 850, 660 and 530 nm) and the reflected optical signal was collected by visible-near infrared spectroscopy. The sensor was in contact with skin tissue and noninvasively traced blood glucose level changes for a full day. Such kinds of optical principles have been employed frequently to realize non-invasive blood glucose monitoring (Li et al., 2019). They demonstrated a new approach to measure blood glucose level based on bioimpedance changes considering blood volume pulsation. They were able to confirm that the normalized bioimpedance difference was decreased from 1 Ω to 0.930 Ω when the glucose concentration was increased from 0 mmol/L to 200 mmol/L in vitro experiment, and confirmed the similar trend even in vivo experiment. Chen et al. (2017) reported non-invasive skin like biosensor for blood glucose monitoring and they focused on the development of a new method for taking a sample non-invasively (Chen et al., 2017). The authors designed specific electrochemical twin channels which can drive out blood glucose from the vessel to ISF and transport it to the skin surface and integrated amperometric GOx glucose sensor. The sensitivity of this sensor was 130.4 mA/mM, and the results from this

Table 2
Summary of novel CGM technologies based on sample types, detection principles, sensor elements, and sensor types.

Table 2-1 Blood glucose monitoring

Sample type	Detection principle	Sensor element	Sensor type	Detection range of glucose	Reference
Blood	Electrochemical principle (Piezoelectric)	Glucose oxidase	Implantable	0.024–0.119 g/L	Zhang et al. (2018)
	Electrochemical principle (Current)	Glucose oxidase	Implantable	20–850 mg/dl	Brockway et al. (2015)
	Magnetic induction principle	Glucose sensitive hydrogel	Implantable	0.2–0.6 mM	Yu et al. (2016)
	Optical principle (Visible-near infrared spectroscopy)	Optical source (wave lengths: 950, 850, 660, 530 nm)	Wearable	N.A.	Rachim and Chung (2019)
	Optical principle (Raman Spectroscopy)	Raman scattering photons	Non-invasive	N.A.	Li et al. (2019)
	Bioimpedance principle	Polygraph system (Electrode)	Non-invasive	0–200 mM	Li et al. (2018)
	Electrochemical principle (Current)	Glucose oxidase	Wearable	50–100 μM	Chen et al. (2017)

Table 2-2 ISF glucose monitoring

Sample type	Detection principle	Sensor element	Sensor type	Detection range of glucose	Reference
Interstitial fluid	Electrochemical principle (Current)	Glucose oxidase	Implantable	0–30 mM	Xiao et al. (2015)
	Electrochemical principle (Current)	Glucose oxidase	Implantable	0–570 mg/dl	Pu et al. (2018)
	Optical principle (A quantum cascade laser)	A quantum cascade laser (wavenumber ranges: 900–1200 cm^{-1} and 1500–1750 cm^{-1})	Implantable	N.A.	Isensee et al. (2018)
	Electrochemical principle (Current)	Glucose oxidase	Minimally implantable	0–20 mM	Chen et al. (2015)
	Electrochemical principle (Current)	Glucose oxidase	Implantable	N.A.	Vallejo-Heligon et al. (2016)
	Electrochemical principle (Current)	Glucose oxidase	Minimally implantable	0–30 mM	Sharma et al. (2016)
	Electrochemical principle (Current)	Glucose oxidase	Minimally implantable	0–200 mg/dl	Ribet et al. (2018)
	Electrochemical principle (Current)	FAD dependent glucose dehydrogenase	Minimally implantable	0.1–10 mM	Bollella et al. (2019)
	Electrochemical principle (Current)	Glucose oxidase	Minimally implantable	0.05–20 mM	Kim et al. (2019c)
	Electrochemical principle (Current)	Glucose oxidase	Minimally implantable	1.7–10.4 mM	Zhao et al. (2020)
	Electrochemical principle (Current)	Glucose oxidase	Wearable	N.A.	Lipani et al. (2018)
	Electrochemical principle (Current)	Glucose oxidase	Wearable	0–160 μM	Kim et al. (2018a)
	Microwave	Two separated split-ring resonators	Wearable	N.A.	Choi et al. (2015)
	Microwave	Split ring microwave resonators	Wearable	2–25 mM	Baghelani et al. (2020)

Table 2-3 Urine glucose monitoring

Sample type	Detection principle	Sensor element	Sensor type	Detection range of glucose	Reference
Urine	Optical principle	Hydrogel containing phenylboronic acid	Non-invasive	0–10 mM	Yan et al. (2016)
	Optical principle (Colorimetry)	Glucose oxidase and horseradish peroxidase	Non-invasive	0–30 μM	Zhang et al. (2017)
	Optical principle (Colorimetry)	Peroxidase-mimic Nanozyme, Glucose oxidase and 3,3′,5,5′-tetramethylbenzidine	Non-invasive	0.1–2 mM	Karim et al. (2018)
	Optical principle (Colorimetry)	Peroxidase mimic-nanocomposite which is prepared from FeOOH and N-doped carbon nanosheets, Glucose oxidase and 3,3′,5,5′-tetramethylbenzidine	Non-invasive	8–800 μM	Tran et al. (2018)
	Electrochemical principle	Glucose oxidase	Non-invasive	N.A.	Mohammadifar et al. (2019)
	Electrochemical principle (Current)	Glucose oxidase	Non-invasive	0.002–10 mM	Hossain and Park (2016)
	Optical principle	Midinfrared spectroscopy	Non-invasive	N.A.	Yamamoto et al. (2018)

(*continued on next page*)

Table 2 (*continued*)

Table 2-4 Sweat glucose monitoring

Sample type	Detection principle	Sensor element	Sensor type	Detection range of glucose	Reference
Sweat	Electrochemical principle (Current)	Glucose oxidase	Wearable	N.A.	Zhao et al. (2019a)
	Electrochemical principle (Current)	Glucose oxidase	Wearable	25–300 μM	He et al. (2019)
	Electrochemical principle (Open circuit potential)	Glucose oxidase	Wearable	40–200 μM	Yu et al. (2020)
	Electrochemical principle (Current)	Glucose oxidase	Wearable	0–400 μM	Bandodkar et al. (2019)
	Optical principle (Colorimetry)	Glucose oxidase and Chromogenic reagent	Wearable	N.A.	Koh et al. (2016)
	Optical principle (Colorimetry)	Glucose oxidase and dye (Glucose colorimetric assay kit)	Wearable	N.A.	Choi et al. (2019)
	Electrochemical principle (Current)	Glucose oxidase and Prussian blue	Wearable	0–1 mM	Lee et al. (2017b)
	Electrochemical principle (Current)	Nanoporous gold	Wearable	0.01–1 mM	Bae et al. (2019)
	Electrochemical principle (Current)	Nanohybrid fibers made of reduced graphene oxide−polyurethane with gold nanowrinkles	Wearable	0–1.71 mM	Toi et al. (2019)
	Electrochemical principle (Current)	Glucose oxidase and Prussian blue	Wearable	0–500 μM	Zhao et al. (2019b)
	Electrochemical principle (Current)	Glucose oxidase	Wearable	0–100 μM	Emaminejad et al. (2017)
	Optical principle (Colorimetry)	Glucose oxidase Colorimetric chemical reagent	Wearable	N.A.	Choi et al. (2018)

Table 2-5 Saliva glucose monitoring

Sample type	Detection principle	Sensor element	Sensor type	Detection range of glucose	Reference
Saliva	Electrochemical principle (Current)	Glucose oxidase	Wearable	1.75–10000 μM	Arakawa et al. (2020)
	Optical principle (Colorimetry)	Glucose oxidase, N,N′-diethyl-p-phenylenediamine, 4-chloro-1-naphthol, and horseradish peroxidase	Wearable	1–10 mg/dl	Jung et al. (2017)
	Optical principle (Colorimetry)	Glucose oxidase, horseradish peroxidase and chromogenic reagent	Wearable	0–2 mM	de Castro et al. (2019)
	Quartz crystal microbalance	Glucose sensitive hydrogel covalently bonded with rigid phenylboronic acid	Wearable	0–36 mg/L	Zhang et al. (2020)
	Electrochemical principle (Current)	Glucose oxidase	Non-invasive	17–810 μM	Zhang et al. (2015)
	Electrochemical principle (Current)	Glucose oxidase, horseradish peroxidase and osmium complex	Non-invasive	0.05–1.5 mM	Liu et al. (2016)

Table 2-6 Tear glucose monitoring

Sample type	Detection principle	Sensor element	Sensor type	Detection range of glucose	Reference
Tear	Electrochemical principle (Current)	Glucose oxidase	Wearable	0–0.9 mM	Park et al. (2018)
	Optical principle	Hydrogel containing phenylboronic acid	Wearable	0−50 mM	Elsherif et al. (2018)
	Optical principle	Hydrogel containing phenylboronic acid	Wearable	0–20 mM	Lin et al. (2018)
	Electrochemical principle (Current)	Glucose oxidase	Wearable	N.A.	Sempionatto et al. (2019)
	Optical principle (Colorimetry)	Glucose oxidase, horseradish peroxidase and 3,3′,5,5′-tetramethylbenzydine	Non-invasive	0.1–1 mM	Gabriel et al. (2017)
	Optical principle (Colorimetry)	Glucose-sensitive photonic crystal material based on monolayered colloidal crystals which is coated by a 4-borono-benzaldehyde-functionalized poly(vinyl alcohol) hydrogel	Non-invasive	0.1–0.6 mM	Chen et al. (2018)
	Quantitative scanning for determining cleavage ratio of DNAzyme	Glucose oxidase and pistol-like DNAzyme	Non-invasive	100 nM-10 mM	Liu et al. (2015)

noninvasive sensor was correlated with clinically measured blood glucose levels.

4.2. ISF

ISF is one of sample which is the most corresponded with blood sample. Although there are reports that a ~5 min physiological time lag on glucose concentration between blood and ISF exit (Kulcu et al., 2003), it can be compensated through filtering process (Keenan et al., 2009). Since ISF has been used as a sample which provides a reliable blood glucose level and be easily accessed compared with blood sample, there are many reports using ISF as a sample for continuous glucose monitoring. Xiao et al. (2015) have developed an implantable RFID sensor tag containing GOx based working electrode for targeting a long-term glucose sensor. The sensor was able to measure glucose concentration from 0 mM to 30 mM based on current with a sensitivity of 0.74 nA/mM. They also demonstrated continuous in vivo detection using rats, and the sensor result matched the result from blood glucose

level measured by a commercial glucometer as a reference. Pu et al. (2018) have reported a cylindrical flexible enzyme (GOx) electrode sensor. The sensor was fabricated by rotated inkjet printing and the sensor was able to measure current change depending on glucose concentration from 0 mg/dl to 570 mg/dl. The fully implanted glucose sensor was successfully able to measure glucose concentration and provide similar result with a commercial glucometer. The Clarke error gird was obtained to evaluate the prediction accuracy. As a result, 65% of the predicted values filled in the A zone and 35% of the predicted values filled in the B zone. Since 99% of the values from glucose meter must fall within A zone and B zone for regulatory clearance, this sensor was comparable with commercially available CGM sensor. A quantum cascade laser-based glucose sensor was also reported as fully implantable for a long-term glucose monitoring (Isensee et al., 2018). A miniaturized optofluidic interface was utilized for measuring the characteristic mid-infrared absorption properties of glucose. The sensor was able to trace changes in glucose concentrations rapidly and was stable for 42 days in vitro experiment. They also evaluated the prediction accuracy by Parkes error grid. 100% of predicted values fell in the A zone, therefore this sensor have higher predicted accuracy that is required with commercially available CGM sensor. As such, the ISF has been being used as an ideal sample for fully implanted chronical sensor (Chen et al., 2015; Vallejo-Heligon et al., 2016), Sharma et al. (2016) have reported microneedle array glucose sensor which is minimally invasive glucose sensor. The GOx functionalized microneedle array-based sensor was able to detect glucose from 0 mM to 30 mM and showed high correlation with self-monitoring blood glucose meter in vivo experiment. In addition, there are more reports to target ISF as a sample using microneedle-based glucose sensor (Ribet et al., 2018; Bollella et al., 2019; Kim et al., 2019c; Zhao et al., 2020), and those reports employed enzyme-based glucose sensor and measured glucose level electrochemically. ISF has been used not only in invasive glucose sensors but also non-invasive glucose sensors. Lipani et al. (2018) developed non-invasive glucose monitoring with a graphene-based platform. The glucose monitoring system extracted glucose from ISF by employing the reverse iontophoresis extraction circuit and detected hydrogen peroxide biproduct from the catalytic reaction of GOx. They demonstrated that the sensing system was able to track blood glucose level by monitoring extracted glucose from ISF. Kim et al. (2018a) reported a single wearable tattoo based biosensor platform which can monitor sweat alcohol and ISF glucose simultaneously (Kim et al., 2018a). For the glucose detection, the authors fabricated GOx immobilized tattoo sensor, and glucose was also sampled from ISF by iontophoretic extraction. The linear detection range of glucose was 0–160 μM in vitro, and the measured readings of sweat alcohol and ISF glucose showed similar trends with results from commercial glucometers in vivo. Choi et al. (2015) reported non-invasive glucose sensor with microwave (Choi et al., 2015). The sensor is composed of two separated split-ring resonators and reflects dielectric characterization on sensor signal. As a result, they were able to confirm that the change of sensor response is dominated by change of glucose level, and the interference effects are negligible. Baghelani et al. (2020) also reported a chipless printable sensor based on split ring microwave resonators, and they successfully detected 2–25 mM of glucose concentration in synthetic ISF (Baghelani et al., 2020).

4.3. Urine

For glucose detection in urine, optical based glucose sensors have been reported in large volume. Yan et al. (2016) have reported 2D photonic crystal hydrogel-based glucose sensor (Yan et al., 2016). The sensor was fabricated by embedding 2D polystyrene crystalline colloidal array in 3-acrylamidophenylboronic acid-functionalized hydrogel. When the glucose binds to boronic acid, the volume of hydrogel will change depending on glucose concentration. The sensor can detect glucose level by monitoring the change of diffracted light due to the volume change of hydrogel. The senser was able to measure glucose concentrations ranging from 0 to 10 mM. Zhang et al. (2017) also reported an optical urine glucose sensor employing enzymatic-like reaction mediating the etching of gold nanorods (Zhang et al., 2017). With MoO_4^{2-}, the gold nanorods were etched by hydrogen peroxide, which is produced as a biproduct in the catalytic reaction of GOx. Since the etching of gold nanorods lead to a blue shift of longitudinal localized surface plasmon resonance of gold nanorods, the color change can be observed from blue to red. The sensor was able to detect glucose concentrations from 0 to 30 μM. Karim et al. (2018) used catalytically active Ag nanoparticle embedded cotton fabric with peroxidase-mimic nanozyme, GOx and 3,3′,5,5′-tetramethylbenzidine (Karim et al., 2018). The sensor detected glucose concentrations from 0.1 to 2 mM by oxidation of 3,3′,5,5′-tetramethylbenzidine. Tran et al. (2018) also reported a peroxidase mimic-nanocomposite which is prepared from FeOOH and N-doped carbon nanosheets. The sensor was able detect from 8 to 800 μM of glucose by monitoring color change due to oxidation of 3,3′,5,5′-tetramethylbenzidine. Electrochemical based urine glucose sensors have also been reported. Mohammadifar et al. (2019) reported a disposable paper-based glucose sensing strip integrated with discrete optical readout circuit (Mohammadifar et al., 2019). A GOx based biofuel cell is placed onto a paper glucose sensor and is connected to an optical readout circuit that powers a light-emitting diode (LED), and LED will emit on when a predefined glucose concentration is reached. The authors were able to confirm five different glucose level (1, 2, 3, 4 and higher than 4 mM) visually. Hossain and Park (2016) also reported an electrochemical based urine glucose sensor which is made up of glucose-treated reduced graphene oxide-activated carbon composites, platinum nanoparticles, chitosan-GOx composites and Nafion (Hossain and Park, 2016). The sensor showed an increase in current from 0.002 mM to 10 mM glucose and a sensitivity of 61.06 μA/mMcm^2. Yamamoto et al. (2018) developed an ultrasonic liquid cell for mid-infrared spectroscopy integrated in smart toilets (Yamamoto et al., 2018). In the ultrasonic liquid cell, a reflection plane is generated inside the sample by ultrasonic standing wave. The authors demonstrated glucose detection based the absorption peak of glucose using internal reflected light and confirmed correlation between the measured result and the reference glucose concentration in urine (50, 100, and 200 mg/dL).

4.4. Sweat

Sweat based sensors are published in high volumes, in part due to the promise of wearable sensors improving the daily lives of patients, and ease of integration into daily activities. Certain challenges still exist regarding the use of sweat for sampling, the first being its clinical relevancy. Interpreting the blood glucose based on sweat poses obstacles, sweat rates for instance affect this relationship, as well as may dilute, or alter the sensor algorithm being used (Moyer et al., 2012). Challenges also arise from “old” or previous sweat samples remaining on the active sensor mixing and convoluting the most recent data being measured. Glucose levels in sweat may also be nearly 100 times diluted relative to ISF counterparts, vastly increasing the resolution requirements for such a sensor (Kim et al., 2018b). pH changes may also affect the measured glucose adding further complexity to the sensor requirements, and algorithm requirements (Lee et al., 2017b). For sweat based sensors to find footing as a reliable, and useable sampling source, a reproducible, and stable sweat acquisition system must be developed. Clinical reliability/use of the sample must also forgo examination and clinicals to show efficacy of sweat glucose control for patient outcomes.

The sweat sample have been mostly utilized as a sample for wearable glucose sensor. Zhao et al. (2019a) built a self-powered smartwatch including Zn–MnO_2 batteries as an energy storage device, amperometric GOx based glucose sensor, signal processing and display (Zhao et al., 2019a). The smart watch displayed “low”, “medium” and “high” according to the concentration range of glucose instead of the exact

glucose level. The reliability was confirmed using a gold standard reference. He et al. (2019) and Yu et al. (2020) also reported a patch type sweat sensor for multiplex sweat analysis (He et al., 2019; Yu et al., 2020). He et al. (2019) demonstrated simultaneous detection of glucose, lactate, ascorbic acid, uric acid, Na+ and K+ using their sweat analysis patch, and Yu et al. (2020) was also able to successfully detect NH_4+, urea, glucose and pH using their self-powered electric skin sweat sensor with biofuel cell. Both groups fabricated GOx based glucose sensor, and measured glucose level electrochemically. The linear glucose detection range was 25–300 μM (He et al., 2019) and 40–200 μM (Yu et al., 2020), respectively. Rogers group reported a wearable device employing electrochemical GOx based glucose sensor (Bandodkar et al., 2019) and GOx based colorimetric glucose sensor (Koh et al., 2016; Choi et al., 2019), and they successfully measured glucose level in sweat employing both detection principles. Moreover, Lee et al. (2017b) demonstrated integrated multiple sensor device including glucose, humidity, pH, and temperature sensor with multistage transdermal drug delivery module (Lee et al., 2017b). For the transdermal drug delivery module, the phase change materials (PCM) covered microneedle is consists of hyaluronic acid hydrogel, drug-loaded phase change nanoparticles (PCN) were fabricated. The integrated heater dissolves both the PCM and PCN coatings and the completely dissolved microneedle can release the drug. The authors were able to confirm blood glucose level decreasing after treatment with microneedle based transdermal drug delivery module in vivo. In addition, there are many reports to improve mechanical properties of patches, such as stretchability (Bae et al., 2019; Toi et al., 2019; Zhao et al., 2019b) and efficiency of sweat sampling (Emaminejad et al., 2017; Choi et al., 2018).

4.5. Saliva

Saliva has become a strong area of interest for many academics, in part being due to the large sample collection, and relative lack of interfering molecules when compared to blood plasma. With this comes many practical challenges, such as needing to fast, or "clean" the sample for reliable measurements (Zhang et al., 2015). There are also irregularities in sample distribution, analyte partitioning, and relevance to blood concentrations. Ergonomics of a continuous saliva-based sensor is also a major obstacle being less convenient for long term wear as mouthguards and retainers are impracticable, and uncomfortable. Calibration may also be challenging when sample rates can be irregular, and non-reliable relative to blood or ISF. Some of these challenges are unique only to continuous detection where point of care sensors may pose benefit. GBS Inc. for instance is developing point of care test strips for saliva-based glucose monitoring using organic thin film transistor, which has Nafion-GOx ink printed directly onto the iridium tin oxide which acts as the source and drain component (https://gbs.inc/saliva-glucose/; Elkington et al., 2014). Being point of care, this system eliminates challenges such as drift over time, patient discomfort, and any irregularities in salvation due to physiological processes which may vary with time. Overcoming the finger pricking with current SMBG sensors is a strong user upgrade for diabetic patients, especially those who may not require a CGM (https://gbs.inc/diabetes/). Arakawa et al. (2020) have reported the development of mouthguard biosensor for continuous glucose monitoring in saliva (Arakawa et al., 2020). The mouthguard is consisting of amperometric GOx based glucose sensor and wireless transmitter. Since the sensor was able to detect from 1.75 μM to 10000 μM of glucose, it was indicated that the mouthguard was able to sufficiently measure a glucose level range in saliva (20 μM–200 μM). The optical based saliva glucose monitoring sensor was also reported (Jung et al., 2017). The saliva containing hydrogen peroxide which is produced by catalytic reaction of GOx was mixed with N, N′-diethyl-p-phenylenediamine (DEPDA), 4-chloro-1-naphthol (4CN), and horseradish peroxidase (HRP) to colorize the saliva. It was confirmed that the absorbance at 630 nm was increased depending on glucose concentration (1–10 mg/dl). de Castro et al. (2019) have also reported paper microfluidic device based on colorimetric detection employing GOx and HRP, and the sensor provided linear detection range from 0 to 2.0 mM of glucose and limit of detection of 27 μM (de Castro et al., 2019). Zhang et al. (2020) have reported a quartz crystal microbalance (QCM) sensor which is coated by a glucose sensitive hydrogel covalently bonded with rigid phenylboronic acid containing graphene oxide (Zhang et al., 2020). The linear glucose detection range was 0–36 mg/L and lower limit of detection which is 1 mg/L. Zhang et al. (2015) and Liu et al. (2016) both reported disposable saliva glucose sensor for use of continuous measurement (Zhang et al., 2015; Liu et al., 2016). Zhang et al. (2015) attempted to modify multilayer films containing GOx, single-walled carbon nanotubes and gold nano particles, and the sensor exhibited linear detection range over 17 μM–810 μM and limit of detection of 5.6 μM. Liu et al. (2016) fabricated electrochemical saliva glucose sensor composed of dual enzymes which are GOx and HRP, carbon nanotubes and osmium complex. The sensor showed linear detection range from 0.05 mM to 1.5 mM of glucose and limit of detection of 0.003 mM. The sensor was able to provide stable current signal in 1 mM glucose over 2 h.

4.6. Tear

Tear based glucose sensors gained popularity due to the cleanliness of sample, and like ISF, the sample volume, and glucose concentrations are well maintained and stable. Currently no tear-based glucose sensor exists on the market and remains in low maturity. Partly due to low correlative studies for tear glucose compared to blood glucose, let alone dynamic studies looking at time lags, or rapid changes. Aihara et al. (2018) showed a loose correlation between blood glucose and tears during a dynamic period but had several sporadic points (Aihara et al., 2018). Aihara et al. (2020) performed a more recent study comparing the tear glucose to blood glucose of 30 subjects, 10 non-diabetic, and 20 diabetics, showing some correlation across the glucose range of interest but still had various outliers (Aihara et al., 2020). One interesting start up Noviosense has developed a three-electrode coil wrapped with the antenna and uses electrochemical based glucose sensor for continuous detection in tears (Kownacka et al., 2018). This system conforms to the lower eyelid, for comfort and ease of insertion. The electrodes are developed with platinum iridium and are coated with a soft hydrophilic polysaccharide doped with glucose oxidase.

Contact lens-based glucose sensor is a representative sensor type which uses tear as a sample for continuous glucose monitoring. Park et al. (2018) reported a soft and smart contact lens composed of GOx based glucose sensor, wireless power transfer circuit and display pixels. Those components are fully integrated with stretchable nanostructures and the display pixel can visualize sensing signals in real time. The fully integrated contact lens type glucose sensor showed limit of detection of 12.57 μM, and linear detection range from 0 to 0.9 mM of glucose. Elsherif et al. (2018) and Lin et al. (2018) have also reported contact lens type glucose sensor, and both groups utilized the phenomenon that hydrogel containing phenylboronic acid is swelled when glucose bound to phenylboronic acid (Elsherif et al., 2018; Lin et al., 2018). The former group demonstrated the glucose measurement by detecting a change in diffraction efficiency due to swelling of the hydrogel, and the latter group attempted to detect changes in the red light which reflects the change of hydrogel thickness. Glucose detection was also demonstrated by using eyeglasses-based tear biosensing system (Sempionatto et al., 2019). The authors gathered a tear sample from a microfluidic detector on a nose-bridge pad of eyeglasses and demonstrated glucose detection electrochemically. The GOx based glucose sensor was able to monitor glucose level effectively through their tear concentration. Gabriel et al. (2017) demonstrated glucose detection in human tear samples using their paper-based colorimetric biosensor. The proposed colorimetric biosensor utilized catalytic reaction of GOx and HRP, and they were able to detect color change of 3,3′,5,5′-tetramethylbenzydine in a range of glucose from 0.1 to 1 mM. Chen et al. (2018) also developed a

glucose-sensitive photonic crystal material based on monolayered colloidal crystals which is coated by a 4-boronobenzaldehyde-functionalized poly(vinyl alcohol) hydrogel (Chen et al., 2018). During the glucose detection, glucose binds to borate and will shift the Bragg diffraction of gelated monolayered colloidal crystal by changing the hydrogel volume. As a result, 0.1–0.6 mM of glucose was able to be detected based on the color change of gelated monolayered colloidal crystal. Liu et al. (2015) reported GOx coupled pistol-like DNAzyme that is an oxidative DNA-cleaving DNAzyme sensor for glucose detection in tears and saliva (Liu et al., 2015). The sensor measured hydrogen peroxide produced by the catalytic reaction of GOx. The produced peroxide was recognized by the DNAzyme as a secondary signal and performed self-cleavage reaction. The sensor had a linear range from 100 nM to 10 mM by monitoring the cleavage rate of pistol-like DNAzyme.

5. Future prospective

CGM systems are expected to increase in use for both Type I and Type II patients due to their ease of use and improve comfort when compared to SMBG type sensors. Although the accuracy of CGM systems is increasing, BGM sensors still show superior results in terms of accuracy, to those of CGM systems (Campos-Náñez and Breton, 2017; Heinemann 2018; Freckmann et al., 2018, 2019). In addition, to see an increase in use of CGM systems by Type II diabetic patients, the current economic aspects of CGM must be addressed and improved. Ideally a CGM system would perform without the need for insertion. Two decades ago, an innovative CGM system with an enzyme glucose sensor equipped with non-invasive sampling system was developed and commercialized, Glucowatch by Cignas Inc., followed by Animas Inc. The system employed reverse iontophoresis, thereby measuring glucose extracted from the ISF. The electrode attached to the skin using an adhesive lasting 3 days of continuous monitoring. However, the system was discontinued in 2007 after complaints about its accuracy and that it caused skin irritation in some users. Recently, Nemaura Medical launched a CGM system, SugarBEAT (https://nemauramedical.com/), commercialized in UK, which employed non-invasive glucose sampling system similar to Glucowatch, but with improved properties with reduced period of usage, replacing sensor patch daily, which resulted in no skin-irritation. Currently, even though sweat, tear, saliva and urine are useful sample for non-invasive continuous glucose, those samples are still not recognized for their clinical relevancy. One of the reasons is time lag between blood glucose and each sample. It has been reported that sweat and saliva have time lag for tens of minutes and ones to tens of minutes (Heikenfeld et al., 2019) respectively, and the time lag of tear glucose have also reported fives to tens of minutes (Badugu et al., 2005; Zhang et al., 2011). Furthermore, sweat, saliva and tear have over 1000 times lower concentration than blood glucose concentration, and it is lower even than ISF which have up to 10 times lower concentration than blood glucose concentration (Heikenfeld et al., 2019). These uncleared correlations with blood glucose make those sample locations difficult to be used in a clinical setting. Although sweat, tear and saliva require further and detailed investigations for revealing clear correlation with blood glucose, we believe that those samples can be used as the sample for continuous glucose monitoring and they will follow same steps like as ISF in the future. On the other hand, urine not only has time lag with blood glucose but also has a threshold of around 180 mg/dl which is normal renal threshold. However, the value of renal max threshold is variable from 54 to 300 mg/dl in diabetes patients, therefore the variation in renal max threshold causes misreading when compared to actual blood glucose level (Walker et al., 1990). This means that a diabetic patient with blood glucose of 150 mg/dl may read 54 mg/dl if their renal threshold is altered. From the issues which urine has, it is regarded as being difficult to use urine as reliable sample for continuous glucose monitoring. Moreover, the current popular medication for type-2 diabetes, sodium-glucose cotransporter-2 inhibitors, or known as SGLT2 inhibitors, which lower blood sugar by causing the kidneys to remove sugar from the body through the urine, makes it difficult to use urine glucose concentration as the indicator of glycemic level. Considering that glucose concentration from non-invasively available samples, are still not recognized for their clinical relevancy, the revival of reversed iontophoresis system for glucose sensing indicates the future possibility of the development of novel and effective non-invasive ISF sampling systems in near future.

The success and impact of Eversense Continuous Glucose Monitoring System (Senseonics) prompted the researchers and industries to focus on fully implantable chronic CGM systems, which will last for months and even years of continuous in vivo operation. Considering the operation period of the sensors which inserted under the skin and operated with the controller mounted on the skin, is currently limited not by the sensor/enzyme molecules but the availability of non-allergic adhesive material. Which can cause skin irritation over the 2 weeks period of attachment, including hygienic issues (Englert et al., 2014; Gisin et al., 2018; Messer et al., 2018). Eversense Continuous Glucose Monitoring System, instead employed a fully implanted sensor with its controller devices. The sensor is powered by near field communication (NFC) technologies; therefore, sensor implantation should be done by micro-surgery by the trained physician. Patients should visit physician to start and to replace the sensor/device every 3 months. This mandatory requirement for the relatively frequent visit to the physician triggered the temporally suspension of commercial sales of its Eversense CGM in the United States, due to the COVID-19, which caused the difficulty in the access to the physicians. But research on fully implantable electrochemical sensors have been also reported, acknowledging cutting edge microelectronics together with the low-power wireless transmission systems. An example of this is the Glysens glucose sensor developed by Gough, which measured the reduction of oxygen like the first Clarke glucose sensor. The Glysens system was tested in vivo using dogs for over 1 year, using catalase, a secondary enzyme to help mitigate GOx deactivation from hydrogen peroxide (Armour et al., 1990; Gough et al., 1982, 2010). Currently Glysens is funded to work on a 2-year clinical study for the fully implantable system termed the “Eclipse 3 ICGM System” (http://glysens.com/?page_id=102).

Therefore, the new technological breakthrough to realize continuous long-term chronic CGM system are expected, not only in the sensor principle/sensing molecule development, but the method of sensor implantation and removal without professional surgical processes, and the development of non-allergic or minimally allergic and antibacterial materials for long-term sensor and controlled adhesion on the skin.

The success in the realization of sensor augmented insulin pumps, which are operated based on the results of CGM system, have driven researchers to develop the next stage of biomedical devices for Type I diabetic patients, the fully automated artificial pancreas system. Currently available closed-loop systems monitor glucose levels and automatically infuse the required amount of insulin. Recently, the bihormonal system which uses both insulin and glucagon infusions, has been developed. These systems include sophisticated algorithms that compute the optimal insulin dose to infuse, and then instruct an insulin pump to deliver it. Current challenges are now shifting toward the sensing non-glucose information to tightly control glycemic revel in the patient, especially physiological variables.

The complexity of glucose homeostasis presents a challenge for tight control of the blood glucose concentration. A patient’s metabolic and physical activities have significant effects on glucose and insulin dynamics. Therefore, the monitoring of energy expenditure can be used as an indicator of physical activity. Physiologic stress also affects patient glycemic level, consequently physical activity can increase the risk of hypoglycemia. Therefore, physiologic stress needs to be considered to control closed-loop studies. There has been proven relationship between stress and galvanic skin response (GSR), therefore, GSR can be used as an indicator for stress which will be combined with closed-loop system control. In addition, continuous monitoring of insulin concentration will

be also improving the tight control of glycemic level, avoiding the risk of hypoglycemia. Therefore, the extensive studies are now progressing to combine CGM systems with varieties of wearable physical activity and physiological parameter monitoring (Turksoy et al., 2018a, 2018b). Namely, the future of CGM systems will be strongly dependent on the combinations and availabilities of both non-invasively monitoring physical activity sensors, together with other minimally invasively continuous monitoring physiological biomarkers biosensors, to realize fully automated artificial pancreas system.

Finally, the future of CGM systems is also not the exceptional of the Green innovation, reducing carbon footprint in the future technology development. Diabetes Technology Society (DTS) is a nonprofit organization committed to promoting development and use of technology in the fight against diabetes, where the pioneering CGM systems have been introduced and taking the leadership in the accelerate the development artificial pancreas system. Recently DTS announced the Green Diabetes Initiative (Klonoff et al., 2020), to conserve natural resources and waste management processes to promote environmental sustainability in the used disposable diabetes devices intended for one-time use in the home create a large amount of waste. These devices include injection needles, syringes, lancets, blood glucose monitoring strips, blood glucose monitors, continuous glucose sensors, insulin bottles, pens, infusion tubing, and disposable pumps, as well as device batteries and packaging. They call for (1) reducing, (2) reusing, (3) recycling, (4) redesigning, and (5) re-educating in diabetes device waste. These five "R" strategies are intended to support extraction of the maximum practical benefits from disposable diabetes. Upon this initiative, the manufactures of CGM systems are intensively responded to downsizing their products, as well as the packaging of their product to meet the Green Diabetes Initiative. Future developments of CGM systems and their sensors, should meet this initiative, not only by reducing their size, but changing/developing materials/design and increasing their operational stability and availability of reuse/recycling of sensors/transducers/devices and chemicals/biosensing molecules, to reduce carbon footprint.

6. Conclusion

Diabetes is a chronic illness in the United States affecting nearly 120 million adults, as well as increasing in children under the age of 18. Diabetes was also the 7th leading cause of death in the United States with 270 K deaths in 2017. Diabetes mellitus is best managed by tight glycemic control, as achieving near-normal glucose levels is key to reduce the risk of microvascular complications. Currently, continuous glucose monitoring (CGM) systems have been recognized as the ideal monitoring systems for glycemic control of diabetic patients. The first principle of glucose sensor, the first commercially available glucose sensing system for personal use, and the first CGM system are all reported in US.

There have been varieties of challenges reported to develop glucose sensors suitable for CGM use. The principles of the glucose sensing employed in the current commercially available CGM systems are mainly electrochemical (Medtronic, Dexcom, Abbott), which employs the gold standard enzyme, glucose oxidase, as the glucose sensing molecule with the combination of hydrogen peroxide monitoring or with the combination of redox mediator harboring hydrogel. Recently, by employing abiotic synthetic receptor harboring fluorescent probe with the combination of fluorescent detection system, a chronic CGM was commercialized (Senseonics).

The most remarkable feature of CGM system is alarming systems for hyper- and hypo-glycemic level. This means, current CGM system is capable of monitoring glucose, in vivo, in situ, continuously, not only real-time, but is capable to predict glucose concentration in the future by analyzing the rate of glucose over time. With the increasing the accuracy of glucose monitoring, some CGM models are now approved for treatment decisions, meaning patients can make changes to the diabetes care plan based on CGM results alone, realizing a medical device for insulin infusion for Type I diabetic patients, called a hybrid closed-loop system.

Currently, the development of less or non-invasive monitoring sensors targeting glucose in tear, sweat, saliva and urine have become of great interest. These sensors are categorized as "wearable biosensors" which are the current hottest research topics in biosensor research. Not only various target sample types, but also by developing innovative microsystems including micro-needle arrays, transducers including flexible electrode based sensing platforms, data transmission systems including the ones which can be wireless and self-powered operated, varieties of wearable glucose sensors have been reported which are awaiting for the approval the clinical relevancy of glucose in tear, sweat, saliva and urine.

Future prospective of CGM systems is summarized in the following 4 categories; 1) CGM systems being the replacement of BG system to be used for Type II diabetic patients, which should be highly accurate, less invasive and economical, 2) fully implantable chronic CGM system which will be based on the method of sensor implantation and removal without professional surgical processes, and also the development of non-allergic or minimally allergic and antibacterial materials for long-term sensor and controlled adhesion on the skin, 3) as the component of multimodal sensing to realize fully automated artificial pancreas system with the combination of both non-invasively monitoring physical activity sensors and other minimally invasively continuous monitoring physiological biomarkers biosensors, and 4) CGM systems meeting "Green innovation", not only by reducing their size, but changing/developing materials/design and increasing their operational stability and availability of reuse/recycling of sensors/transducers/devices and chemicals/biosensing molecules, to reduce carbon footprint.

Author contributions

Inyoung Lee (IL), David Probst (DP), David Klonoff (DK) and Koji Sode (KS) planned, prepared and wrote the article. IL and DP analyzed the current available data resources. KS and DK reviewed and analyzed the description prepared in this review article. KS prepared section 1,2 and 5. IL and DP prepared section 3 and 4.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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