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REVIEW ARTICLE

# Emerging Diabetes Technologies: Continuous Glucose Monitors/Artificial Pancreases

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**Abstract** | Over the past decade there have been many advances in diabetes technologies, such as continuous glucose monitors (CGMs), insulin-delivery devices, and hybrid closed loop systems. Now most CGMs (Medtronic-Guardian, Dexcom-G6, and Abbott-Libre-2) have MARD values of < 10%, in contrast to two decades ago when the MARD used to be > 20%. In addition, the majority of the new CGMs do not require calibrations, and the latest CGMs last for 10–14 days. An implantable 6-months CGM by Eversense-3 is now approved in the USA and Europe. Recently, the FDA approved Libre 3 which provides real-time glucose values every minute. Even though it is approved as an iCGM it is not interoperable with automatic-insulin-delivery (AID) systems. The newer CGMs that are likely to be launched in the next few months in the USA include the 10–11 days Dexcom G7 (60% smaller than the existing G6), and the 7-days Medtronic Guardian 4. Most of the newer CGM have several features like automatic initialization, easy insertion, predictive alarms, and alerts. It has also been noticed that an arm insertion site might have better accuracy than abdomen or other sites, like the buttock for kids. Lag time between YSI and different sensors have been reported differently, sometimes it is down to 2–3 min; however, in many instances, it is still 15–20 min, especially when the rate of change of glucose is > 2 mg/min. We believe that in the next decade there will be a significant increase in the number of people who use CGM for their day-to-day diabetes care.

**Keywords:** *CGM, HCL, TIR, TAR, HbA1c, Hypoglycemia*

**CGM:** A device that measures glucose values in the subcutaneous space via a sensor and is transmitted to a receiver/smartphone.

**Hybrid Closed Loop (HCL) Systems:** An insulin pump able to deliver variable insulin dosages based on CGM values using an algorithm.

## 1 Introduction

The global prevalence of diabetes has continued to increase in the past several decades. Over 530 million people are currently living with diabetes worldwide[1]. Unfortunately, there has been a disproportional increase in diabetes prevalence in emerging economies; such as India, China, Middle East, and Southeast Asia[2]. Diabetes is also more prevalent amongst minorities and socio-economically disadvantaged individuals, such as, Black Americans, Native Americans, Asian Americans, and Latinx in the United States of America (USA)[3–6].

It is known that socio-economically disadvantaged and minorities do not receive similar diabetes care[7–10]. For example, many times minorities are not even presented with new technologies as an option to facilitate their diabetes care. Both type 1 diabetes (T1D) and type 2 diabetes (T2D) are increasing globally at a rate of about 4% per year[1,11,12]. In the USA, 35–40 million people have diabetes[13]; of which, between 1.5 and 3 million have T1D[14]. The increasing prevalence, as reported by IDF, has been in part due to a lack of registries in many parts of the world and availability of inadequate data[1].

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Due to increasing prevalence of diabetes, the healthcare cost related to diabetes management has significantly increased in the past decade. For example, the total healthcare cost has increased to $4USD trillion per year. In the USA, the lifetime cost for managing a person with T1D is about $1.5USD million with a total cost of about $1.5USD trillion[15,16]. On an average, about 8% of the total healthcare expenditure is spent every year for diabetes management in the USA, which amounts to about $327USD billion annually[16]. About $1USD billion is spent on acute diabetes complications (diabetes ketoacidosis (DKA) and severe hypoglycemia (SH)). It is also been reported that about $800 billion USD is spent globally annually for type 2 diabetes management[17].

Recently, there has been a significant change in delivering diabetes care due to the COVID-19 pandemic since March of 2020. The development and rapid adoption of telehealth and virtual diabetes care has increased not only in the USA but throughout the world. It is expected that digital health expenditure in the next few years will outpace investments in other facets of diabetes care. The majority of this was facilitated by the availability of remote data through continuous glucose monitors (CGM), continuous subcutaneous insulin infusion (CSII or insulin pump), and hybrid closed-loop systems (HCL). In part, this was facilitated by the US Federal government's Food and Drug Administration (FDA) authorizing the availability of data from these emerging technologies to the patients and providers (temporarily, even across different States in the USA). It appears that telehealth is here to stay especially for ongoing diabetes management. As we have learned through the pandemic, one can deliver effective virtual care while initiating new technologies like CGM, insulin pumps, and HCL remotely.

**Insulin Pump:** A device that delivers insulin doses (basal and bolus).

It appears that about 150 million people require insulin therapy globally for their day-to-day diabetes management[18, 19]. About 30 million people have T1D globally and another 15–20% of people with T2D are misdiagnosed as they have positive antibodies (GAD, IAA, ICA, and ZnTr8), indicating beta-cell autoimmunity with slower onset of insulin dependence (T1D)[20]. In addition, 10–15% of patients with T2D will exhaust their beta-cell function during their lifetimes, as T2D diagnosis is occurring at an earlier age. Insulin-requiring patients will need close monitoring of their glucose levels so that their insulin dose can be manipulated safely. The CGM use, insulin pump therapy or a HCL, improves overall glucose control, especially reducing overnight hypoglycemia. However, less than 20–30% of T1D and less than 1% of T2D of insulin-requiring patients in the USA are on some sort of pump therapy[21]. Limited use is due to several barriers: cost, lack of knowledge, availability, and implementation challenges[22].

In the past three decades, there has been significant development of new technologies, newer non-insulin medications for T2D, and insulins for improving diabetes outcomes[23]. Due to all these advances, most people with T1D and T2D are living longer. It is not uncommon to see people with T1D living into their 8th or 9th decade of their lives[15,24]. In contrast, 40 years ago we were taught that the majority of T1D patients would not live beyond 30–40 years of age and most women were not allowed to conceive because of challenges in diabetes management and complications associated with pregnancy.

Despite advances in technologies and therapeutics, life expectancy is still reduced by 10–15 years in patients with T1D and T2D[25,26]. Generally, long-term diabetes complications have significantly decreased. However, the total number has risen due to an overall increase in prevalence. Recent data from the T1D Exchange in the US, Diabetes Registry in Germany (DPP), and SWEET Registry between US and Europe have shown that overall glucose control in patients with T1D is suboptimal despite an increase in the use of CGMs and insulin pumps[27]. Only about 1 out of 4 patients reach the American Diabetes Association (ADA) and the European Association of Study for Diabetes (EASD) target of glucose control (< 7%) as measured by A1c.

## 2 Glucose Monitoring

### 2.1 Urine Monitoring and Self-Monitoring of Blood Glucose (SMBG)

More than 40 years ago, patients diagnosed with diabetes could only monitor their blood glucose levels indirectly by checking the amount of glucose present in their urine (glucosuria)[28]. About 35 years ago, SMBG became first available where patients would acquire blood from a fingerstick, which then could be placed on a test strip to get the glucose values[28]. Nearly four decades ago, many physicians were questioning the usability of SMBG in clinical practice. It was not uncommon to hear ***"Who?" "When?" and "Why?"*** from providers and patients. However, SMBG was first used successfully in a large clinical trial sponsored by the National Institutes of Health (NIH, Bethesda, MD); Diabetes Control

and Complications Trial (DCCT)[29]. Since then, SMBG has been widely utilized for insulin-requiring patients to adjust their insulin dose and infrequently for patients with T2D not requiring insulin[30].

### 2.2 Continuous Glucose Monitoring (CGM)

In recent years, experts in diabetes have stressed the importance of CGM use, for improved glycemic outcomes[31–47]. What was commonly said about SMBG 35 years ago, was repeated two decades ago about CGM ***(Who? Why? When?)***[28]. However, there are now > 7 million CGM users worldwide, with a market cap of about $7USD billion at the time of this writing[48]. We believe that CGM will become the choice for glucose monitoring (replace SMBG) in clinical practice over the next 5–10 years in insulin-requiring patients with diabetes, assuming it is cost effective.

The first professional CGM was iPro, developed by MiniMed (now Medtronic Diabetes, Northridge, CA) in 1999[49]. The iPro collected continuous glucose data and after 3 days, the provider was able to download the data and adjust the patient's treatment accordingly. The earliest adjunctive real-time CGM (rtCGM) approved by the FDA was the GlucoWatch (GW) Biographer, developed about 24 years ago (Cygnus, Redwood City, CA)[31]. GW had a warm up period of 2 h and used reverse-iontophoresis to extract a small amount of interstitial fluid and measure glucose concentrations[32]. This data was displayed as a glucose value every 20 min on the GW for 12 h. When released, GW had a very high MARD (22%)[31,50]; whereas, most current CGMs have MARD values in the single digits (between 8 and 10%). Over the years several advancements in personal CGM devices included: better accuracy, increased duration of use, non-adjunctive, standalone, and decreased size.

The majority of CGMs measure glucose in the interstitial fluid every 1–5 min depending on the type of sensor[51]. These systems are considered personal (unmasked), where patients can access their glucose data in real-time. Or they can be professional (masked), where glucose values are downloaded and retrospectively reviewed in a clinic/research setting. Currently, patients with diabetes primarily utilize personal CGMs, and professional (retrospective) CGMs are rarely used; but are still utilized for research purposes.

A CGM can be worn on the skin or implanted subcutaneously[52,53]. Sensors can be real-time (rtCGM), where glucose values are transmitted to a receiver/smartphone continuously. Intermittently scanned CGMs (isCGM) require patients to scan with a receiver/smartphone. It is known that there is a lag period of 3–15 min between interstitial and blood glucose values depending on the device. Early CGMs required SMBG confirmation before user intervention (adjunctive)[31–44]. Newer CGMs data are used to make treatment decisions as standalone devices. Currently there are four major CGMs that are available and approved by the FDA in the USA: Medtronic, Dexcom (San Diego, CA), FreeStyle Libre (Alameda, CA), and Eversense (Senseonics, Baltimore, MD).

Medtronic introduced their Guardian CGM series in early 2000. Their first CGM was the Guardian REAL-Time system which provided glucose values every 5 min. Guardian 3 was an integrated CGM, that was only compatible with MiniMed insulin pumps[54,55]. Last year the Guardian 4 sensor was approved as a non-adjunctive CGM in Europe that can link to the 780G pump and the smart/memory insulin pen (Inpen)[56]. The Guardian 4 is currently not approved as an iCGM because of paracetamol interference and a MARD > 10%[57] (Fig. 1). The manufacturer has also been working on a new non-adjunctive 7-days CGM (Simplera formally known as Synergy) that combines both sensor and transmitter into one device like the Dexcom G7 and Libre 2 and 3[58]. Presently, Simplera has not been approved in the USA or Europe.

Dexcom has had many versions of CGMs. Initially, the Dexcom short-term sensor (STS) was approved in 2006 by the FDA as a 3-days adjunctive CGM. STS had higher MARD values, 16–25% when compared with SMBG and YSI[35]. A year later, the Dexcom SEVEN system was introduced which included 7 days of continuous wear and offered more convenience[59]. Subsequently, the introduction of the G4 PLATINUM in 2012 featured improved overall accuracy, especially in detection of hypoglycemia. The G4 expanded its' capabilities in 2015 by including a SHARE feature[60]. SHARE gave patients the ability to share their glucose data with up to five users. This feature allowed caretakers to remotely monitor glucose levels and offer treatment support. The same year, the G5 sensor was released, which incorporated wireless rapid data downloads on a smart phone and/or receiver[61]. The G6 was approved in 2018 as the first iCGM that allowed integration with different insulin pumps, such as Tandem and Omnipod 5[62,63]. In addition, iCGM doubled its' SHARE capabilities and increased wear time to 10 days[64,65]. The G7 iCGM is not yet approved

| Model | Guardian Real Time | iPro 2 | Enlite | Guardian 3 | Guardian 4 |
|---|---|---|---|---|---|
| |  |  |  |  |  |
| **Year of FDA Approval** | 2005 | 2011 | 2016 | 2018 | Not approved by FDA |
| **MARD** | 17.2% | 13.6% in adult 15% in pediatric | 18.3% | 8.7-9.14% in arm 9.6-10.5% in abdomen | 10.6% |
| **Wear Length Time** | 3 days | 6 days | 6 days | 7 days | |
| **Warm Up Time** | 2 hours | 1 hour | 2 hours | | |
| **Repeated Calibrations Needed** | Every 12 hours | 3-4 times a day | First day, every 6 hours. Afterwards, every 12 hours | Every 12 hours | No (Once the 1st day) |
| **Measures Glucose** | Every 5 minutes | | | | |
| **Wireless Data Sharing** | N/A | N/A | N/A | 5 people | |
| **Alerts** | N/A | N/A | N/A | Yes | |
| **Transmitter Duration** | 12 months | | | | |
| **Interference With** | Acetaminophen | Acetaminophen | None | Acetaminophen | Unknown |
| **Pump Integration** | N/A | N/A | Veo, MiniMed 530G,630G, & 670G | MiniMed 670G & 770G | MiniMed780G |

Figure 1: Development of Medtronic's Guardian CGMs. Features of Guardian sensors over the years. The figure gives details of MARD, wear length time, warm-up time, calibrations needed, transmitter duration, wireless data sharing, and different drug interferences. Images taken at the Barbara Davis Center for Diabetes.

by the FDA but is available in Europe (EMA). The G7 is 60% smaller, lasts 10.5 days, and has a warm-up period of less than 30 min. G7 has the sensor and transmitter as one piece[66] (Fig. 2).

Abbott originally developed their Navigator 5-days adjunctive CGM[67]. Many years later a smaller, factory-calibrated version, called the FreeStyle Libre (isCGM) was launched initially in Europe and then in the USA[68]. When released, the Libre had a 1-h warm-up period. The Libre and Libre 2 are approved as a 14-days isCGM, that need to be scanned every 8 h. Libre 2 also includes alarms to notify the user of hypo- and hyperglycemic events[69, 70]. The Libre 3 has a 70% thinner profile (size of a penny) and is an rtCGM that was recently FDA approved in the USA (though not available freely in the USA); it relays glucose values every minute[71]. In Europe, the Libre 3 has been approved and used by investigators with an automatic insulin delivery (AID) system. Although the Libre 3 is approved as an iCGM in the USA, it is not allowed for AID use due to interference with aspirin and Vitamin C. The MARD reported at Advanced Technology and Therapeutics in Diabetes (ATTD) 2022 in Barcelona was 7.9%, though no data is available in published literature (Fig. 3).

There have been attempts for a longer-term implantable sensor. The first attempt at an implantable sensor was developed by Dexcom more than 24 years ago. It was the size of a AA battery that was implanted in the abdomen (subcutaneously). Only 15 patients were enrolled in a small pilot study[34]. The sensor had a high MARD value of 25% and did not last the intended 6 months. In addition, the sensor moved in the subcutaneous space, especially in obese individuals. As a result, the studies were terminated early, and the data was never submitted for FDA or EMA for approval.

It was not until 2018 that an implantable sensor was approved by both the FDA and EMA. Senseonics (Baltimore, MD) developed a smaller sensor, the Eversense® for 90-day wear[72]. The sensor insertion requires a surgical intervention under local anesthesia. The sensor is implanted in the upper arm and requires a transmitter to be replaced every 24 h that relays glucose values to a smart phone/receiver. This sensor is capable of vibratory alerts through the transmitter. Sensor duration up to 180 days with the Eversense XL was approved only in Europe. Eversense 3 (E3)

| Model | Short Term Sensor (STS) | Dexcom SEVEN PLUS | Dexcom G4 | Dexcom G5 | Dexcom G6 | Dexcom G6 Pro | Dexcom G7 |
|---|---|---|---|---|---|---|---|
| |  |  |  |  |  |  |  |
| **Year of FDA Approval** | 2006 | 2007 | 2012 | 2015 | 2019 | 2019 | Not Approved |
| **MARD** | 26% | 16% | 13% | 9% | 9% | 9% | 8.1% in arm 9.1% in abdomen |
| **Wear Length Time** | 3 days | 7days | | | 10 days | | 10.5 days |
| **Warm Up Time** | 2 hours | | | | | | 27 minutes |
| **Repeated Calibrations Needed** | Every 6 hours | | | | No | | |
| **Measures Glucose** | Every 5 minutes | | | | | | |
| **Wireless Data Sharing** | N/A | | 5 people | | 10 people | N/A | 10 people |
| **Alerts** | Only for hypoglycemia | Yes | | | | | |
| **Transmitter Duration** | 6 months | | | 3 months | | 1 month | 10 days |
| **Interference With** | Aspirin Vitamin C | Acetaminophen | Acetaminophen Hydroxyurea | | Hydroxyurea | Ascorbic Acid Salicylic Acid | Unknown |
| **Pump Integration** | N/A | | Tandem | | Tandem Omnipod 5 | N/A | Unknown |

Figure 2: Development of Dexcom's CGMs. Features of Dexcom sensors over the years. The figure gives details of MARD, wear length time, warm-up time, calibrations needed, transmitter duration, wireless data sharing, and different drug interferences. Images taken at the Barbara Davis Center for Diabetes.

| Model | FreeStyle Libre Pro | FreeStyle Libre | FreeStyle Libre 2 | FreeStyle Libre 3 |
|---|---|---|---|---|
| |  |  |  |  |
| **Year of FDA Approval** | 2016 | 2017 | 2018 | 2022 |
| **MARD** | 12.3% | 12% | 9.5% | 7.9% |
| **Wear Length Time** | 14 days | | | |
| **Warm Up Time** | 1 hour | | | |
| **Repeated Calibrations Needed** | None | | | |
| **Measures Glucose** | Every 15 minutes | Every 1 minute | | |
| **Wireless Data Sharing** | N/A | 20 people | | |
| **Alerts** | N/A | | Yes; when scanned | Yes |
| **Transmitter Duration** | 14 days | | | |
| **Interference With** | Hydroxyurea | Vitamin C Aspirin | | |
| **Pump Integration** | N/A | | | |

Figure 3: Development of Abbot's FreeStyle Libre CGMs. Features of Freestyle Libre sensors over the years. The figure gives details of MARD, wear length time, warm-up time, calibrations needed, transmitter duration, wireless data sharing, and different drug interferences. Images taken at the Barbara Davis Center for Diabetes.

| Model | Dexcom Implantable Sensor  | Eversense  | Eversense XL  | Eversense (E3)  |
|---|---|---|---|---|
| Year of FDA Approval | Not approved by FDA | 2018 | Not approved by FDA | 2022 |
| MARD | 16-25% | 11.2% | 11.6% | 8.5% |
| Wear Length Time | 3 months | 90 days | 180 days | 180 days |
| Warm Up Time | N/A | 24 hours | | |
| Repeated Calibrations Needed | Every 12 hours | | | 2 calibrations per day, for the first 21 days of wear. Then, every 24 hours. |
| Measures Glucose | Every 5 minutes | | | |
| Wireless Data Sharing | N/A | 5 people | | |
| Alerts | Yes | | | |
| Transmitter Duration | 51-58 days | 3 months | 6 months | |
| Interference With | N/A | Tetracycline Mannitol | | |
| Pump Integration | N/A | | | |

Figure 4: Implantable CGMs. Features of implantable sensors over the years. The figure gives details of MARD, wear length time, warm-up time, calibrations needed, transmitter duration, wireless data sharing, and different drug interferences. Images taken at the Barbara Davis Center for Diabetes.

was approved by the FDA for 6-months use in adults in 2022[53]. E3 had already been approved as non-adjunctive by the EMA > 2 years ago. The E3 has sacrificial boronic acid which increased the life expectancy of the sensor. In preliminary studies, the E3 lasted the full 6 months in 90% of patients. The new E3 has improved accuracy with a MARD of 8.5%[53]. No AID studies have been conducted in the USA with the E3. The manufacturer is developing a 1-year implantable sensor (Fig. 4).

With improved accuracy, connectivity to insulin pumps, and improved insurance coverage, CGMs are increasingly adopted in clinical practice. At the time of enrollment the T1D Exchange Study (2010–2012) conducted in the USA, 7% of 25,833 patients were using a CGM[73]. The 5-year follow-up study reported that about 30% of those patients were now using a CGM[74]. The number of users is expected to increase exponentially in the next 5 years to about 15–20 million users.

The continued progression of CGMs have allowed for pump integration and compatibility between different manufactures. The FDA introduced a new category that allows expedited approval, called integrated/interoperable CGM (iCGM)[62]. CGM accuracy is assessed is by calculating the mean absolute relative difference (MARD) between paired glucose values from the CGM versus BG values from the Yellow Spring Instrument 2300 (YSI, CITY, OH). Lower MARD indicates better accuracy. iCGM approval requires CGM values to be within ± 15 mg/dL or ± 15%, 20/20%, 30/30%, and 40/40% of the YSI value[75]. For example, CGM values need to be within 15 mg/dL if BG is < 70 mg/dL, or within 15% if BG > 70 mg/dL, and so on. iCGM designation also requires no interference with paracetamol and/or vitamin C.

There are many limitations of A1c measurements (Table 1). It is still the gold standard for assessing long-term (1–3 months) diabetes control. Many international organizations like ADA, AACE, EASD, and ATTD now strongly recommend CGM use in patients with TID and those with T2D on multiple daily injections (MDI). CGM use in patients with diabetes have consistently shown improved time-in-range (TIR)[76], quality of life[77], glucose control (A1c)[78–85], decrease in DKA and hypoglycemia (Level 1 and Level 2). No DCCT like trials have been performed with CGMs, however, retrospective, and cross-sectional analysis have shown close correlation of TIR with micro- and macro vascular complications[76].

While the benefits of CGM use in T1D are well known, they are underutilized in patients with T2D on MDI. In a DIAMOND study of 148 patients with T2D on MDI, patients were randomized to a CGM or continued to use SMBG measurements. The CGM group improved their A1c by 0.3%, in comparison to the SMBG group[86]. Similar conclusions were made in the MOBILE study with 175 patients with T2D on basal insulin. Along with reduced hypoglycemia events, there was an overall reduction of A1c

Table 1: Limitations of A1C. Limitations of using A1c values in a medical setting.

| |
|---|
| 1. Does not detect hypoglycemia, hyperglycemia, and variability |
| 2. Cannot be used for acute glycemic management plan |
| 3. Does not reflect rapid changes of blood glucose |
| 4. False high and low values of A1C in certain situations: |
| a. Hematologic conditions |
| • Anemia |
| • Accelerate erythrocyte turnover |
| • Thalassemia |
| • Sickle cell disease |
| • Reticulocytotic |
| • Hemolysis |
| b. Disease States |
| • HIV infection |
| • Uremia |
| • Hyperbilirubinemia |
| • Dyslipidemia |
| • Cirrhosis |
| • Hypothyroidism |
| c. Physiologic states |
| • Aging |
| • Pregnancy |
| d. Medical therapies |
| • Blood transfusion |
| • Hemodialysis |
| e. Drugs/medications |
| • Iron |
| • Erythropoietin |
| • Dapsone |
| • Trimethoprim |
| f. Miscellaneous |
| • Alcoholism |
| • Chronic kidney disease |

by 0.4%[87]. CGM use has also been proven to be advantageous in patients with T2D that are using oral anti-hyperglycemic agents to manage their diabetes. However, CGM use in patients with T2D not requiring MDI is limited. This may be in part due to cost and insurance reimbursement challenges[88–93].

The CGM is used to assess glucose control and has built-in adjustable and predictive alarms/alerts for hyper- and hypo-glycemia. Different metrics include: TIR is 70–180 mg/dL, time-below-range (TBR) is < 70 mg/dL, time-above-range (TAR) is > 180 mg/dL, and time-in-tight-range (TITR) is 70–140 mg/dL (there is no consensus on TITR yet) (Table 2)[94]. 70% TIR usually represents an A1c of ~ 7%. Depending on the level of glucose control, a 5–10% change in TIR, may represent a 0.5% to 1% change in A1c[95]. The TIR goals may need to be modified for elderly, during pregnancy, toddlers, and high-risk individuals with diabetes (Fig. 5).

Additionally, these devices can be useful in managing diabetes in high-risk populations such as, toddlers, pregnant patients, the elderly, and patients with other comorbidities[97]. It is well known that elderly individuals with diabetes are at a higher risk of hypoglycemia[98]. CGM use can decrease occurrence of these events, which

Table 2: Commonly used glucose metrics.

| Keywords | Definitions | Interpretation |
|---|---|---|
| Standard Deviation (SD) | A measure of glucose excursions from the mean | Reflects fluctuations (high/low) from their mean glucose level<br><SD = More glucose excursions<br>>SD = Less glucose excursions |
| Coefficient of variation (CV) | Divide the SD by the mean glucose and multiply by 100. Used to correct and calculate glycemic variability (GV), or fluctuations in glucose levels over time | Reflects how stable a patient's glucose levels are. Larger variability correlates with increased risk of hypoglycemia<br><CV = Poor glycemic control<br>>CV = Good glycemic control<br>CV<33% = Stable glucose levels |
| Mean Absolute Relative Difference (MARD: either ≥100 mg/dL glucose or all levels) | The mean absolute relative difference between all CGM numbers and matched reference values | Used to calculate the accuracy of a CGM sensor |
| Mean Absolute Deviation) (MAD: <100 mg/dL glucose) | The mean absolute deviation between each data value and the mean of a data set | Calculates the accuracy of a CGM within the hypoglycemia range |
| HbA1c | Reflects the mean glucose levels for the previous three months. Used for testing for and managing diabetes | Normal: Below 5.7%<br>Prediabetes: 5.7–6.4%<br>Diabetes: 6.5% or above<br>Diabetes management goal: 7% or less |
| Time In Range (TIR) | The percentage of time that glucose levels are within the target range (generally 70-180 mg/dL)<br>Can be calculated for patients utilizing a CGM or fingerstick BGs (if <4x/day) | It is used in conjunction with SD/CV variability to assess glycemic control<br>Ideal TIR= 70% |
| Time Above Range (TAR)<br>Level 1 Hyperglycemia<br>Level 2 Hyperglycemia | The percentage of time glucose levels are above the target range, or hyperglycemia<br>- Blood glucose > 180mg/dL<br>- Blood glucose > 250mg/dL | - High glucose levels; needs monitoring<br>- Very high glucose levels; requires immediate management |
| Time Below Range (TBR)<br>Level 1 Hypoglycemia<br>Level 2 Hypoglycemia | The time the percentage of blood glucose is below the target range, hypoglycemia<br>- Blood glucose <70mg/dL<br>- Blood glucose < 54mg/dL | - Mild hypoglycemia; needs monitoring<br>- Moderate hypoglycemia; requires immediate management |
| Low blood glucose index (LBGI) | An established metric of hypoglycemia risk (<70 mg/dL) | Assess hypoglycemic risk |
| High blood glucose index (HBGI) | An established metric of hyperglycemia risk (<180 mg/dL) | Assess hyperglycemic risk |

may improve diabetes outcomes as measured by A1c, GV as measured by SD or CV, and quality of life. Furthermore, CGM use has been shown to be particularly useful in pregnant patients with diabetes. For example, CONCEPTT was an international multi-center RCT that studied CGM efficacy in pregnant patients with T1D. The CONCEPTT study showed a significant reduction of patient hyperglycemia and, in turn, improved neonatal outcomes[99]. Lastly, even people with prediabetes can benefit from CGM use. Patients with prediabetes have elevated postprandial glucose levels and CGM use may induce behavioral change, thus possibly delaying the onset of diabetes[100,101] (Fig. 5).

Since the COVID-19 pandemic, CGM has been used in hospitalized patients. CGM devices have allowed health care professionals to remotely monitor glucose levels. This is particularly important in ICU patients where frequent glucose measurements are recommended[102]. On the other hand, in certain circumstances such as in whole body cryotherapy, it is required to do SMBG measurements to avoid sensor inaccuracies, due to associated hypoxia[103,104].

In summary, CGM has come a long way in the past 25 years. CGM's accuracy has increased over time. Most have single-digit MARD values and can be used as non-adjunctive devices without requiring any SMBG calibrations. These devices

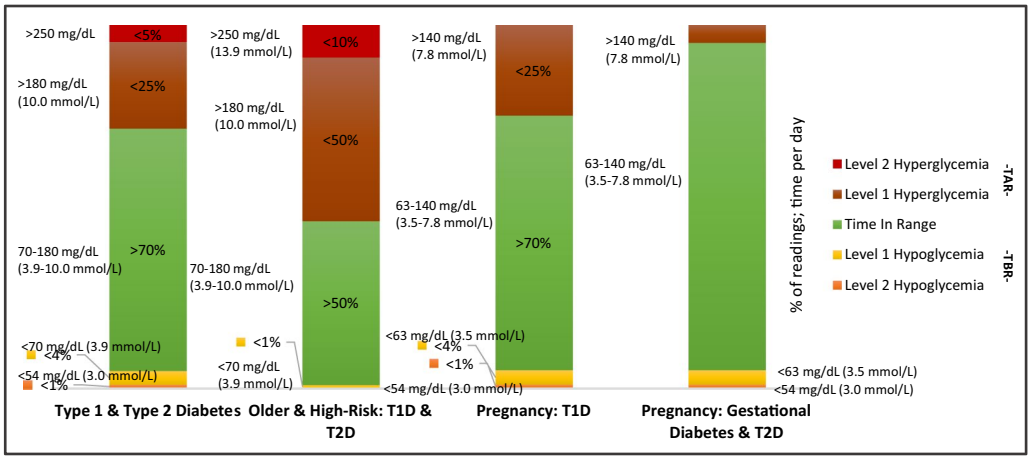


Figure 5: Blood glucose targets for different diabetes populations. Variable blood glucose targets specific to diabetes population. Data from: Kweon[96].

have also become more convenient due to their reduced sized and simple insertion devices. Users can share their data with family member and providers to guide therapeutic decisions. Overall, CGM use helps with early detection of T1D/T2D[97,100,101], improves glucose control, facilitates in-patient diabetes care, and enhances remote diabetes care through telehealth[102,105–107].

### 2.3 Insulin Pumps

In healthy individuals without diabetes, beta-cells of the pancreas, secrete insulin every minute in response to a rise in glucose values. Insulin is released directly into the liver for optimized glucose utilization. Physiologically, insulin is continuously secreted in small amounts to keep euglycemia, commonly referred to as basal insulin (long-acting). A burst of rapid-acting insulin is delivered based on food intake or to correct for high BG (bolus) after meals. Therapeutic goal in patients with diabetes has been to imitate normal insulin secretion[108].

Over the last three decades many rapid-acting insulin analogs (Lispro (Humalog), Aspart (Novolog, Fiasp), Glulisine (Apidra), Lispro-aabc (Lyumjev) have been made available that differ in pharmacokinetics and pharmacodynamics for insulin pump use[108]. Currently, human regular insulin is not approved for use in insulin pumps due to the risk of catheter occlusions, and as a result, higher risk of DKA[109].

As mentioned earlier, the DCCT compared intensive therapy, insulin pumps or MDI (3 or more daily injections), along with SMBG measurements vs. standard treatment (2 or less daily injections)[110]. The trial was terminated early due to the results being significantly positive in the intensively treated group. The DCCT established that maintaining glucose values within a specified range was key to reducing complications related to diabetes[110]. There was a significant reduction of all micro-vascular complications (diabetic kidney disease and diabetic retinopathy). Since the conclusion of the DCCT in 1993, intensive therapy has been the standard of care for management of T1D. Intensive therapy has shown similar benefits in non-insulin requiring patients with T2D. The United Kingdom Prospective Diabetes Study (UKPDS) studied 5102 patients with T2D and demonstrated that intensive therapy reduces overall diabetic-complications[111].

The first insulin pump was a large portable backpack developed by Kadish in 1963[112]. This prototype was an advanced closed-loop system that delivered insulin intravenously based on continuous blood glucose measurements. Unfortunately, it was impractical for day-to-day patient use. In 1974, Miles Laboratory (Elkhart, Indiana; USA) developed the first commercial inpatient pump, the Biostator[113]. However, outpatient use of this pump was not feasible due to its complexity and size. Two years later, Kamon engineered the first portable autosyringe insulin pump, known as the "Big Blue Brick"[112]. Due to its intricacy and bulkiness, they were only offered to patients awaiting pancreas transplants. These early CSII systems paved the way for the development of smaller and more sophisticated models.

Pacesetter Systems, now Medtronic MiniMed Inc., introduced the first miniaturized version of an insulin pump, the MiniMed 502[114,115]. This commercial pump allowed subcutaneous

continuous delivery of small amounts of insulin. Depending on food intake, patients could administer a bolus of an insulin analog. Three years later, the smaller 504 model was released, but with the same software as the 502. However, the launch of the MiniMed 506 in 1992 included significant advancements that incorporated daily insulin totals and bolus insulin memory. These new features centered on glucose trend tracking which helped users understand what contributed to a certain correction[116].

Despite many improvements, patients expressed the desire to temporarily detach from their pump at the insertion site. Thus in 1996, the MiniMed 507 included a quick release. The 507 model also increased the programmable basal rate from 6 to 12. The 507C model released three years later, again upgraded these rates, from 12 to 48. Later that same year, the MiniMed 508 included a vibration alerts, child-lock, specific programmable delivery patterns, and a remote-control feature.

With every version, the physical features of MiniMed pumps were modified. In 2001, Medtronic acquired MiniMed and combined their advanced algorithm software with these pumps for improved diabetes care. A year later, the MiniMed Paradigm 511 system consisted of an insulin pump and a CGM data display. Glucose values could be transferred from a SMBG meter to the Paradigm 511 insulin pump. This allowed patients to easily record, track, and share their glucose data. When Medtronic released the MiniMed Paradigm 512 in 2003, it included these same features but with wireless glucose data transmission. Although the Paradigm system was able to receive glucose data and suggest corrections, it could not automatically deliver insulin.

Tandem Diabetes Care (San Diego, CA, USA) released their first insulin delivery system in 2012, the t:slim[117]. It was the first touch-screen insulin pump in the USA[118]. Tandem received FDA approval in 2015 to integrate Dexcom G4 data using Bluetooth technology.

A tubeless insulin pump was released by Insulet (Bedford, MA, USA) in 2015, called the Omnipod[119]. The original Omnipod system consisted of a Personal Diabetes Manger (PDM) and a disposable pump (Pod) that contained an insulin reservoir that lasted 3 days. When first released, the PDM was a handheld analysis device that could wirelessly deliver insulin. Three more versions with minor improvements of the Omnipod system were made. The Omnipod Dash in 2019 included smartphone connectivity via Bluetooth, the Omnipod DISPLAY. The Dash also included Omnipod VIEW, which gave parents and caregivers remote and real-time access to glucose data, and insulin history from their smartphone. Wireless communication between an insulin pump and CGM, became the expectation when developing these devices.

Other manufacturers of insulin pumps available for a limited time in the USA included: (a) Deltec Cozmo in 2002 (Smiths Medical, London, UK), but suspended its operation in 2009 due to financial reasons[120]. (b) The Animas Corporation (West Chester, PA, USA) manufactured two pumps, the Animas Vibe and the OneTouch Ping, but stopped production in 2017 due to the competitive insulin pump market and financial infeasibility[121]. (c) In 2003, Roche Diabetes Care, Inc. (Indianapolis, IN) acquired Disetronic and marketed a newly designed Accu-Chek Spirit 3 years later. Subsequently, the Accu-Chek Combo was released and consisted of an insulin pump and a Bluetooth connected SMBG meter. This gave the user full remote control over insulin delivery. It was made available in the USA in 2012, but discontinued production in 2017 due to lack of traction in the USA. Accu-Chek pump is still available in Europe, primarily in UK.[122] The new Accu-Chek Solo is a tubeless insulin pump (like Omnipod) that features no screen and wireless connectivity and is only available in some parts of Europe.

Several other insulin pumps have also been manufactured worldwide, with limited patient use. The Kaleido, manufactured by ViCentra (Utrecht, Netherlands), is the smallest commercially available insulin pump, but it is only offered in Europe[123]. It comes with two rechargeable and interchangeable patch pumps that permits insulin delivery via a Bluetooth enabled PDM (like Omnipod). Notably, the Kaleido is a combination pump; it has a patch pump, but it also has tubing for flexibility in pump location when wearing specific clothes- the user wears two separate adhesives to their skin. SOOIL Development Co., Ltd. (Seoul, Korea) produces the DANA insulin pumps, which allow for remote control insulin dosing through a users' smart phone[124]. The DANA system is currently only available for patients in Europe and Asia. In 2020, Ypsomed (Burgdorf, Sweden) announced a partnership with Eli Lilly and Company (Indianapolis, IN) to develop a closed loop system[125]. Presently, it is only available in Europe.

Most of the pumps used in the USA are made by: Medtronic MiniMed Inc., Tandem Diabetes Care Inc., and Insulet Corporation.

### 2.4 Hybrid Closed-Loop Systems (HCL)

Unfortunately, at present there are no fully automated closed-loop systems available. Currently only HCL systems are approved for patients with diabetes. HCL is considered a hybrid system because it requires a patient to bolus insulin for carbohydrate (CHO) intake. An HCL system consist of an integrated insulin pump, CGM, and algorithm, to help sustain users at a desired glucose target. Many integrated HCL systems are now available. However, patients do not have the ability to customize and pair different insulin pumps, CGMs, and algorithms together. A fully automated closed-loop, or "bionic pancreas", might consist of a dual or triple hormone system (insulin, glucagon, and/or pramlintide)[126–128]. These new systems might include artificial intelligence to facilitate the algorithm that will automatically adjust to individual patient needs over time.

The MiniMed Paradigm REAL-Time system 515, released in 2006, was the first diabetes management system that combined insulin pump therapy with real-time updated glucose values every 5 min[129,130]. Due to differing regulations, the advanced MiniMed Veo which featured low-glucose suspend (LGS), was made available only in Europe in 2009[131]. This was the first LGS system, that suspended insulin delivery when glucose values reached a preset low value (40–110 mg/dL). Medtronic developed one more reiteration of the Paradigm system in the USA, the MiniMed Paradigm REAL-Time Revel 523. This combined system included CGM predictive alerts up to 30 min before hypoglycemia.

The MiniMed Veo was known as the 530G (MiniMed) in the USA in 2013. The 530G pump was integrated with a CGM that suspended insulin delivery using a preset modifiable low glucose range (60–90 mg/dL). When low glucose values were detected by the Enlite glucose (Medtronic, Northridge, CA) sensor, the 530G (also known as Threshold Suspend- TS) suspended insulin delivery for up to 2 h[132]. TS has been shown to significantly reduce hypoglycemic events. The ASPIRE in-clinic crossover study, where patients were randomized into LGS "on and off" (with a washout phase), supported this approval in the USA[133]. Patients spent significantly less time after exercise induced hypoglycemia in the in-clinic setting. Due to the cross-over design with this study, there was a spillover effect of hypoglycemia, commonly referred to as "hypoglycemia begets hypoglycemia". This was one of the most unethical studies because patients, although under close observation, had to stay in a hypoglycemic state for 4 h to verify that the TS feature worked effectively. During extended periods of insulin suspend for 4 h, counterregulatory hormones compensate and gluconeogenesis may raise the BG, which can lead to DKA (not observed in the ASPIRE in-clinic study)[134]. This study observation resulted in most future HCL studies avoiding a cross-over design.

A 3-months RCT, ASPIRE at home study was conducted to study 247 T1D adult patients with documented nocturnal hypoglycemia. This study evaluated the effects of changes in A1C and nocturnal hypoglycemia events when TS "on" or "off". Use of the TS system showed a 37% decrease in nocturnal hypoglycemia, in comparison to those using a sensor-augmented therapy without TS[135,136].

The launch of the 620G in 2014 was the first integrated insulin pump with a CGM launched in Japan. The continued evidence in support of TS systems lead to the release of the 630G in the USA, with the same algorithm as the 530G but with waterproofing, remote blousing, and the insulin on board (IOB) displayed on the screen. A year before, in 2015, the MiniMed 640G was made available outside the USA. The MiniMed 640G included "predictive low-glucose suspend" (PLGS) which predicted hypoglycemia (within 20 mg/dL) using a preset, and then stopped insulin delivery[137,138]. Although, never approved by the FDA, the 640G's PLGS system was useful in getting a HCL system (670G).

The first HCL system was the 670G, which included insulin suspension during hypoglycemia and automatic insulin delivery based on hyperglycemia[139–142]. This system allowed for personalized and automated basal insulin delivery[143]. It adjusted basal insulin based on a Proportional Integral Derivative (PID) algorithm system[144]. This algorithm changed the rate of insulin delivery based on how far from the glucose target is, and how much it has changed. This enabled the background insulin delivery needed to maintain a stable blood glucose value. To test this device, a single arm study was designed, as allowed by the FDA for faster approval processes because it only tested for safety. It was shown to significantly reduce hypoglycemia in patients with T1D[141,145]. The 670G was originally well-accepted by patients, however, due to repeated need for calibrations and multiple alarms, many patients discontinued device use[146].

In 2020, the MiniMed 770G was released using the same SmartGuard algorithm as the 670G but with added smartphone connectivity with possibility of shared data and increased user availability (age 2 and above). The MiniMed HCL

| Model | Medtronic 670G/ 770G | Medtronic 780G | Tandem t:slim X2 Basal-IQ | Tandem t:slim X2 Control-IQ | Omnipod 5 |
|---|---|---|---|---|---|
| |  |  |  |  |  |
| **FDA Approval** | 2017/2020 | Not yet approved | 2018 | 2020 | 2022 |
| **CGM Used** | Guardian 3 | Guardian 3 or 4 | G6 | | |
| **Auto-Mode** | After 48 hours | | Immediately | | |
| **Basal adjusted** | Every 2-6 days | | Based on previous basal program | | With each pad change |
| **Target Range (mg/dL)** | 120 | 100, 110 or 120 | N/A | 112.5-160 | 110, 120, 130, 140, or 150 |
| **Correction Target (mg/dL)** | Fixed at 150 | Fixed at 120 | N/A | Fixed at 110 | Flexible |
| **Modified Parameters** | ICR DIA | ICR DIA | ICR ISF Basal Rate | | ICR ISF DIA |
| **Fixed Parameters** | Basal Rate ICF | Basal Rate ICF | DIA is 5 Hours | DIA is 5 Hours Correction Target | Basal rate |
| **Exercise Mode (mg/dL)** | Temporary Target (150) | Exercise Mode (150) | N/A | Exercise Mode (140-160) | Activity Mode (150) |
| **Sleep mode (mg/dL)** | N/A | N/A | N/A | Sleep Mode (112.5-120) | N/A |
| **Additional Features (mg/dL)** | Recommended Bolus | Auto-Bolus | N/A | Extended Bolus Insulin Delivery | N/A |
| **Upload program** | CareLink | | t: Connect | | Glooko |
| **Insulin Carb Ratio (ICR), Duration Insulin Action (DIA), Insulin Sensitivity Factor (ISF)** | | | | | |

Figure 6: Commonly used HCL systems (FDA and/or EMA Approved). Comparison of commonly used HCL systems. Images from the PANTHER Program and through the Barbara Davis Center for Diabetes.

system began auto-mode after 48 h, so that it can program its own basal insulin rates, updating every 2–6 days. Within the same year, 780G was released with an advanced SmartGuard algorithm which included the ability for correction boluses every 5 min[147]. It featured auto-bolus capabilities, flexible target ranges 100, 110 or 120 mg/dL, and an improved exercise mode[148]. Initial registration studies showed improved TIR and a decrease of hypoglycemic events, especially nocturnal[149]. Real-world studies supported these findings[150, 151]. Although offered internationally, the 780G is currently not approved by the FDA in the United States at the time of this writing[150] (Fig. 6).

The tandem X2 pump can be used with two systems, Basal or Control-IQ[152,153]. Both systems were capable of suspending insulin delivery if sensor glucose is < 70 mg/dL[154]. The algorithm used is Model Predictive Control (MPC) which analyzes CGM data to reduce the risk of hypoglycemia. It automatically stopped insulin delivery if glucose was predicted to be < 80 mg/dL within 30 min[154]. The user can also choose to upgrade their X2 pump from Basal-IQ to Control IQ through an online software update. The control-IQ system has an added feature that adjusts basal insulin rates based on preprogrammed settings. Unlike MiniMed, Tandem allows users to set their body weight and basal insulin settings, allowing immediate access to "Control-IQ" (Fig. 6).

Control-IQ has a feature that can correct for predicted hyperglycemia (> 180 mg/dL) by automatically delivering 60% of the insulin sensitivity factor (ISF) as a correction bolus every hour to maintain a glucose target (112–160 mg/dl)[155]. Like the 780G, the Control-IQ system has an "exercise" feature which decreased the basal rate to allow for a higher target. Control-IQ has additional features like sleep mode and extended

bolus insulin delivery especially when high fat and protein meals are consumed[156].

A RCT using Control-IQ system showed increased TIR (>70%) in T1D patients, in both adult and pediatric age groups[155, 157–159]. The Control-IQ system was the first HCL that did not require finger calibrations to stay in an control-IQ; this made it easier for patients and clinicians. The 780G and the Control-IQ system are very similar, and many studies have compared the two[157,158,160]. However, the 780G was shown to be more effective in treating hyperglycemia; this may be since the 780G system adjusts insulin delivery every 5 min while Control-IQ adjusts every hour. In contrast, Control-IQ was shown to be more effective in hypoglycemia than 780G[160].

The Omnipod system includes a tubeless pump, a disposable pod, and a handheld Personal Diabetes Manager (PDM). The Pod contains an insulin reservoir that can hold up to 200 units of insulin and needs to be changed every 3 days. The Omnipod DASH was released in 2019 where CGM data was displayed on a PDM. The Omnipod system uses an MPC algorithm embedded in the Pod which communicates directly with a Dexcom CGM. A multicenter, inpatient feasibility study, showed that the Omnipod system was safe to use in adult, adolescent, and pediatric patients with T1D[161,162]. Although, the DASH permitted 12 different basal settings as well as a temp basal setting, it was not a HCL.

Omnipod 5 HCL was approved in 2022. Omnipod 5 is currently the only tubeless, AID system approved by the FDA. Like Tandem, Omnipod has an "automated mode feature that can be used without calibration. It adjusts insulin delivery based on data analytics for the last 72 h.[163] Omnipod and Tandem utilize the same MPC algorithm to adjust insulin delivery, every 5 min[164]. In contrast to MiniMed, Omnipod users can modify correction factors. The Omnipod system allows for up to 8 different glucose targets (110–150 mg/dL) in a day and allows small increments (10 mg/dL). The exercise mode is like other HCL systems. In a single arm study in pediatric patients, use of this AID system was safe and showed improved glycemic outcomes, increased TIR, and reduced hypoglycemia[163,165].The Omnipod is currently approved for patients with T1D above 2 years old[166]. All HCL systems revert to manual mode based on different safety parameters (Fig. 6).

There are many HCL algorithms currently not approved by the FDA. DBLG1 is a medical device company that customizes HCL systems with a self-learning algorithm between Dexcom and different insulin pumps (such as Roche Accu-Chek, ViCentra, Kaleido, SOOIL, and Cellnovo). It adjusts basal insulin delivery and corrects high glucose every 5 min. It also has Zen Mode for temporary targets. It requires weight, TDD, meal ratio, and basal rates to be entered. Entering the meal size instead of carb counting is a unique parameter. It was approved in Europe based on studies that showed improved glycemic control, increased TIR, and decreased hypoglycemia[167]. However, the DBLG1 system is currently not approved by the FDA.

CamAPS FX is an Android app that manages glucose levels in patients with T1D. The app is compatible with the YpsoPump, DANA Diabecare RS, and the DANA-I insulin pump. It uses the Cambridge control algorithm to automatically adjust insulin delivery every 12 min, based on Dexcom's G6 CGM readings[168]. This glucose data is uploaded to a universal diabetes management platform, Diasend or Glooko. A multicenter RCT study conducted on 86 T1D patients for 12 weeks documented improved glycemic control and decreased hypoglycemia for ages 6 years and older[169]. Although only approved in Europe, there is limited patient use in the USA.

At times, a system can be customized and built specifically for each unique user. These Do-It-Yourself (DIY) "artificial pancreas" systems (APS) are self-driven. Like commercial systems, they automatically adjust and control insulin dosing. Some examples of these systems include Open Artificial program system (OpenAPS) and the AndroidAPS; both utilize CGM readings (i.e. Dexcom or Medtronic Enlite) and a pump (Dana-RS) to make this possible. The community helps each other build their individualized system through these DIYAPS. Although these DIYAPS do not have any regulatory approvals, individuals are not prevented from using them[170–174].

The HCL systems approved by the FDA have all shown increased TIR with overall reduction of hypoglycemic events[175–179]. These systems also include higher glucose thresholds, allowing patients the ability to exercise without large fluctuations in glucose levels[140, 141, 148, 158]. Although none of these HCL systems are approved for use in patients with T1D associated with pregnancy, off-label use has shown improvement in glycemic control with improved maternal and fetal outcomes[99, 178, 180].

### 2.5 Smart Insulin Pen

**Smart Insulin Pens:** A reusable smart insulin injector that suggests and tracks dosing information via an app.

Due to the high cost of insulin pumps, most patients cannot afford them. As a result, many

have turned to smart pens (Memory/connected pens). Smart pens are more affordable and have proven to be beneficial for patients on MDI therapy. These pens use CGM data to help users guide their diabetes management, determine recommended insulin bolus, insulin dose reminders, and track the insulin dose. Smart pens utilize a mobile app that can be downloaded by the provider or patient. Currently, only one smart pen has been approved by the FDA, the InPen (Medtronic, Northridge, CA)[181–183]. The Inpen connects to the Guardian 4 and the Dexcom G5/G6 and was recently approved in Europe (EMA). Many trials have shown improvement in A1c, increase in TIR, and patient satisfaction and adherence to treatment while using these pens[184, 185].

Many smart pens are currently in development: NovoPen 6, NovoPen Echo Plus (Novo Nordisk; Bagsværd, Denmark), Esyta (Emperra GmbH E-Health Technologies; Potsdam, Germany), Pendiq 2.0 (Pendiq GmbH; Moers, Germany), YpsoMate SmartPilot (YpsoMed Holding HG; Burgdorf, Switzerland), Vigipen (Diabnext; Switzerland), KiCoPen (Cambridge Consultants Ltd; Cambridge, UK), and the Eli Lilly tempo pen (Indianapolis, IN)[19, 186]. Some of these smart pens are already available in Europe. There is an attempt to standardize the reporting of smart pens, CGM data, and HCL systems so that the report appears like an EKG[187–189]. There are many platforms that are available to download these reports such as, Care Link, Glooko, Clarity, and Libre view.

An insulin pen cap is a lid that can be attached to all disposable insulin pens (basal and bolus insulin pens) and is able to transmit dosing data to an app[19]. Along with this, information from a CGM is used to recommend correction doses. In 2021 the FDA approved the Bigfoot Unity Diabetes Management System (Bigfoot Biomedical; Milpitas, CA) insulin pen cap for use with the Libre 2 CGM (for patients > 12 years of age)[190]. Other smart caps such as the Insulclock (Insulcloud, Spain) and Go Cap (Common sensing company) are approved by the FDA but have limited patient use[186]. These Insulin pen caps have shown early promise in better diabetes control in T1D and T2M[19, 185, 186].

### 2.6 Exercise, hypoglycemia in T1D

Exercise continues to pose a significant risk of hypoglycemia in insulin-requiring patients with diabetes; whether they are using insulin pumps or MDI with/without CGM[191]. It has been shown that a mini-dose of glucagon can reduce events of exercise-induced hypoglycemia, even without carbohydrate counting[127, 192–195]. Investigators from UMASS have been developing a dual-hormone (insulin and glucagon) pump system bionic pancreas, iLet (Beta Bionics; Concord, MA) where the second hormone is glucagon to help reduce this[196]. It is important to keep in mind that there is no glucagon preparation that has been approved for pump use in the USA or Europe. Recent development of a stable injectable glucagon molecule called zegalogue (dasiglucagon) by Zealand Pharmaceuticals (Copenhagen, Denmark) has been authorized for evaluation in a bionic pancreas system by Beta Bionics[197]. This September, Zealand Pharmaceuticals entered a global license and development agreement with Novo Nordisk to help salvage to launch of zegalogue. These dual-hormone systems are in early stages and currently not available for commercial use.

As mentioned above, Beta Bionics (iLet bionic pancreas, Concord, MA) has been doing several studies in developing a bionic pancreas which replicates a healthy pancreas insulin and glucagon delivery. A small pilot study published in NEJM about 8 years ago showed promising results of using insulin and glucagon delivery in a hybrid closed-loop system[198]. Just like many other HCL systems the TIR and TBR were significantly lower with two hormones delivered through two separate pumps based on the algorithm. It's important to note that no glucagon preparations have been approved by the FDA for continuous pump use. Long term effects of continuous glucagon use are also unknown. As expected beyond the complexity and increase in cost, in dual hormone models the amount of insulin needed was significantly higher than a single hormone (insulin alone) in the HCL system[199].

At the time of this writing, Beta Bionics have successfully completed several insulin-only configurations of their bionic pancreas (BP) in adults and pediatric patients with type 1 diabetes. The 13-weeks trial, conducted at 16 clinical sites across the United States, enrolled 326 participants ages 6–79 years who had T1D and had been using insulin for at least 1 year[200]. This randomized trial was sponsored by the National Institutes of Health (Bethesda, MD). Participants were randomly assigned to either a treatment group using the BP device or a standard-of-care control group using their personal pre-study insulin delivery method. All participants in the control group were provided with a continuous glucose monitor, and nearly one-third of the control group

were using commercially available artificial pancreas technology during the study. This system is not approved in the USA (FDA) or in Europe (EMA). Their system does not require carbohydrate counting however patients are asked to enter the size of a meal to deliver the bolus of insulin for the meal[200]. There are five manuscripts that were recently published with BP system in randomized control trials[200–204]. The BP with insulin Aspart or insulin Lispro was shown to significantly improve A1c, TIR, and hyperglycemic metrics without increasing CGM measured hypoglycemia when compared with standard of care in adults and youth (ages 6–17 years) with T1D[202]. It is important to note that most of the studies with a BP system were short-term (13 weeks). The control arm included 32% of patients on MDI, 27% used a non-automated insulin pump, 5% used a pump with PLGS, and about 36% were using an approved HCL system before the study[201]. In addition, there was one study that reported results on using a faster-acting insulin Aspart (FIASP) within a BP in adults with T1D. They concluded that the use of Fiasp was no better than the reductions in A1c, TIR etc. observed with the BP using Aspart or Lispro[203]. Another study reported a 13-week extension of subjects who were randomized in the control arm who were allowed to use BP. The results concluded that the improvement in this extension study of BP was of similar magnitude to that observed in the RCT[204].

Hyperglycemic excursions especially after meals, even in HCL systems, continues to be a problem. One of the ways to mitigate hyperglycemia after meals is to use pramlintide to reduce these excursions[205, 206]. A study from researchers at Yale University proved that the use of pramlintide is possible in significantly reducing post-meal hyperglycemic excursions[207]. The biggest risk of using pramlintide in patients with T1D has been the risk of severe hypoglycemia[208,209]. This will need to be properly evaluated before it can be made available for clinical use. One day we could see a triple-hormone pump system that includes: insulin, glucagon, and pramlintide in an HCL system.

### 2.7 Inhaled (Afrezza) Insulin

Pulmonary delivery of insulin allows rapid onset of action with human regular insulin which is comparable to normal insulin action profile seen in healthy volunteers[210–212]. The first inhaled insulin, Exubera by Pfizer, was approved by the FDA in 2006[213]. Due to challenges in dose calculations and long-term unknown association of higher risk on lung cancer, its uptake was not good in the USA and was discontinued a year later[214]. The only pulmonary insulin available in the USA is Technosphere Insulin (TI), marketed as Afrezza (Mannkind Corporation, Westlake Village, CA, USA). TI has been shown to have a faster onset of action, but a shorter duration profile when compared to traditional rapid-action insulin analogs (Aspart, Lispro, or Glulisine)[215–217]. Many registration and other studies have shown its efficacy, lower hypoglycemia rates with tendency towards weight loss[218,219]. Due to the rapid onset of action but shorter duration of TI, studies have suggested higher insulin dose requirements[215, 216]. In many instances, second dose of inhaled insulin 1 or 2 h after meals may improve glycemic outcomes[215]. Some investigators in the USA have proposed correction boluses with inhaled insulin in patients using insulin pump or HCL users for rapidly correcting post-meal glucose excursions (off-label use)[220]. However, inhaled insulin dose is not accounted for in the total daily insulin dose for pump or HCL users.

### 2.8 Adjunctive Therapies

There has been recent interest in using SGLT1 and SGLT2-inhibitors in insulin-requiring patients with T1D. Some SGLT2-inhibitors have been approved in Europe for T1D; however, none of them have been approved in the USA because of DKA risks[221,222]. Regardless, their use in T2D has shown remarkable improvement in diabetic kidney disease and cardiovascular disease associated with diabetes[223–226]. Unless we have continuous ketone measurements (CKM) available (many companies are working adding CKM to CGMs)[227], it is hard to imagine that regulators especially in the USA will approve the use of SGLT2-inhibitors in T1D.

## 3 Conclusion

The technological and therapeutic advances in the field of diabetes over the last three decades has allowed patients to live longer and healthier lives[228, 229]. Quality and longevity of life has improved in patients with T1D/T2D, while simultaneously reducing overall diabetes burden. Implementation of CGMs, insulin pumps, and HCL systems, independently or in combination, have shown improved glucose control as measured by A1c and TIR[230,231]. Use of these technologies has shown significant reduction of long-term micro- and macrovascular complications and

hypoglycemic excursions and facilitated remote virtual care for patients with diabetes.

## Abbreviations

AID: Automated insulin delivery; A1C: Glycated hemoglobin.; APS: Artificial program system; ASPIRE: Automation to stimulate pancreatic insulin response; BGL: Blood glucose level; BP: Bionic pancreas; CGM: Continuous glucose monitors; CSII or insulin pump: Continuous subcutaneous insulin infusion; DCCT: Diabetes Control and Complications Trial; DPI: Derivative proportional integral; DKA: Diabetic ketoacidosis; FDA: U.S. Food and Drug Administration; FGM: Flash Glucose Monitoring; FIASP: Faster-acting insulin Aspart; GLP1: Glucagon like peptide 1 analog; GMI: Glucose management indicator.; GV: Glucose variability; GW: GlucoWatch; HCL: Hybrid closed-loop system; HBGI: High Blood Glucose Index; iCGM: Interoperable continuous glucose monitor; isCGM: Intermittently scanned continuous glucose monitoring; LBGI: Low Blood Glucose Index; LGS: Low glucose suspend; MAD: Mean absolute deviation; MARD: Mean absolute relative difference; MDI: Multiple daily injections; MPC: Model predictive control; PID: Proportional integral derivative; PDM: Personal diabetes management; PLGS: Predictive low glucose suspend; RCT: Randomized Controlled Trial; RT-CGM: Real-time CGM; R-CGM: Retrospective CGM; SBA: Sacrificial boronic acid; SD: Standard deviation; SGLTi: Sodium-glucose linked transporter inhibitor; SH: Severe hypoglycemia; SMBS: Self-monitoring blood sugar; STS: Short term sensor; TI: Technosphere insulin; T1D: Type 1 Diabetes; T2D: Type 2 diabetes; TAR: Time above range; TBR: Time below range; TIR: Time in range; TDD: Total daily dose; UKPDS: United Kingdom prospective diabetes study; YSI: Yellow Spring Instrument.

## Publisher's Note



## Declarations

## Conflict of interest

Related to this manuscript, there are no conflicts of interest for all three authors.

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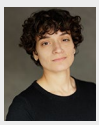

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