# Technology in the management of type 1 diabetes mellitus — current status and future prospects

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Abstract | Type 1 diabetes mellitus (T1DM) represents 5–10% of diabetes cases worldwide. The incidence of T1DM is increasing, and there is no immediate prospect of a cure. As such, lifelong management is required, the burden of which is being eased by novel treatment modalities, particularly from the field of diabetes technologies. Continuous glucose monitoring has become the standard of care and includes factory-calibrated subcutaneous glucose monitoring and long-term implantable glucose sensing. In addition, considerable progress has been made in technology-enabled glucose-responsive insulin delivery. The first hybrid insulin-only closed-loop system has been commercialized, and other closed-loop systems are under development, including dual-hormone glucose control systems. This Review focuses on well-established diabetes technologies, including glucose sensing, pen-based insulin delivery, data management and data analytics. We also cover insulin pump therapy, threshold-based suspend, predictive low-glucose suspend and single-hormone and dual-hormone closed-loop systems. Clinical practice recommendations for insulin pump therapy and continuous glucose monitoring are presented, and ongoing research and future prospects are highlighted. We conclude that the management of T1DM is improved by diabetes technology for the benefit of the majority of people with T1DM, their caregivers and guardians and health-care professionals treating patients with T1DM.

Worldwide, 5–10% of diabetes cases are type 1 diabetes mellitus (T1DM)[1]. Despite intensive research, T1DM is presently incurable. Over the past three decades, diabetes management has increasingly benefited from innovations in technologies aimed at diabetes care. The present era is witnessing the emergence, at an unprecedented scale, of innovative diabetes technologies aimed at improving outcomes and easing the burden of diabetes management. Glucose monitoring has evolved from inaccurate bulky devices to factory-calibrated continuous glucose-sensing devices that are connected to smartphones. Advances in insulin formulations and insulin delivery, including insulin pump therapy and glucose-responsive insulin delivery, have led to more effective insulin dosing than was available previously. Furthermore, software tools are now available that systematically track and manage complex glucose and insulin delivery data.

This Review covers established and novel diabetes technologies used in the management of patients with T1DM. We describe currently available technologies and their effect on health outcomes, including recommendations on their clinical use. We also provide insights into diabetes technologies that are not yet widely adopted or that are under development.

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## Widely adopted diabetes technologies

In this section, we review diabetes technologies used routinely in daily clinical practice. Four areas are covered: insulin delivery, glucose-sensing technologies, glucose-responsive insulin delivery systems and tools for data management (FIG. 1). An overview of diabetes technologies and evidence supporting their use is provided in TABLE 1 and TABLE 2 using the levels of evidence following the American Diabetes Association (ADA) guidelines (BOX 1).

### *Insulin delivery*

Over a considerable time period, conventional insulin therapy comprised one or two daily injections of insulin with daily urine or capillary blood glucose measurements. Following the publication of the Diabetes Control and Complications Trial in 1993 (REF.[2]), the treatment paradigm for T1DM shifted towards intensive insulin therapy based on frequent blood glucose monitoring and

**Key points**

- Innovations in technologies have greatly benefited diabetes management.
- Flexible ways of delivering insulin, such as insulin pump therapy, are increasingly popular.
- Minimally invasive real-time continuous glucose monitoring is progressing towards accurate, insulin-dosing approved, factory-calibrated systems and has become part of standard care for people with type 1 diabetes mellitus in many countries.
- Automated glucose-responsive insulin delivery systems, including threshold-based suspend, predictive low glucose management insulin pump therapy and hybrid closed-loop systems, offer means for further improvements in glycaemic control while reducing hypoglycaemia exposure.
- Data management tools and applications for diabetes self-management are helping people with type 1 diabetes mellitus and health-care professionals to manage intricate, extensive data created by diabetes technologies.
- Advances in bihormonal closed-loop technology, bioartificial pancreas systems and smart insulin might further improve the care and management of people with type 1 diabetes mellitus in the future.

flexible multiple daily administrations of insulin using an insulin pen or an insulin pump.

***Insulin pens.*** Insulin pens contain insulin in a cartridge and incorporate a fine replaceable needle. Introduced in 1981 as convenient, easy-to-use injection devices[3], pens are widely used as a part of multiple daily injection (MDI) therapy and are continuously evolving. Pens with memory functions (for example, HumaPen Memoir, Eli Lilly, and NovoPen Echo, Novo Nordisk) or pen caps that track past doses (such as Timesulin, Patients Pending, and GoCap, Common Sensing) are available. Within the past 2 years, pens with built-in Bluetooth connectivity have received regulatory approval in the USA (for instance, InPen, Companion Medical, and Esysta pen, Emperra Digital Diabetes Care). These smart pens enable users to track doses and automatically transfer data via Bluetooth to diabetes management apps on smartphones, with automatic cloud upload for sharing data with health-care professionals. However, no studies regarding the superiority of smart pens over conventional pens have been reported.

***Insulin pumps.*** Insulin pumps date back to the 1970s[4], but it took another 20 years for insulin pump therapy to become widely available. The increasing utilization of insulin pump therapy over the past 20 years has resulted from improvements in and increased reliability of pump technology, documented health benefits (which are still imperfect) and availability of rapid-acting insulin analogues. Utilization of pumps was further amplified by coverage by private insurance and public health-care systems. Uptake and availability of insulin pump therapy vary considerably between and within countries[5]; data from large diabetes registries show that in Western countries (which are most adept at pump use), pump users represent 40–60% of the population of patients with T1DM[6,7].

***Types of insulin pumps.*** Insulin pumps deliver short-acting or rapid-acting insulin into the subcutaneous tissue at preprogrammed rates, normally half-hourly to hourly (this rate is adjustable), with user-activated boosts (also called boluses) at mealtimes via self-inserted Teflon or steel catheters. In conventional or tethered pumps, the insulin reservoir of the pump and the transcutaneously placed cannula are connected via tubing that is 18–42 inches long. Patch pumps comprise a very short insulin infusion set that is typically embedded inside the pump housing or within the base part of pumps with a modular design[8]. Whereas tethered pumps are usually tucked into pockets or carried in pump pouches, patch pumps are attached directly to the user's skin. A retrospective observational study, published in 2017, did not demonstrate any differences in $HbA_{1c}$ levels when patients using patch pumps were compared with those using traditional tethered pumps[9].

***Adjunctive technologies.*** Modern insulin pumps usually come with adjunctive features, such as bolus calculators to facilitate the calculation of meal and correction boluses, bolus profiles that include immediate and/or extended delivery of a calculated bolus dose to meet postprandial insulin requirements, and temporary basal rates to accommodate physical activity that results in acutely reduced insulin needs or stress or illness that results in acutely increased insulin needs. Use of these advanced features might improve glycaemic outcomes, including $HbA_{1c}$ levels[10] and postprandial glycaemic excursions[11,12].

***Efficacy of insulin pump therapy.*** In adults with T1DM, the use of an insulin pump is associated with a modest 0.3–0.6% reduction in $HbA_{1c}$ levels compared with the use of MDI therapy[13–17], with those most poorly controlled on MDI experiencing the greatest and often a substantial and clinically valuable improvement in $HbA_{1c}$ levels when switching to pump therapy[13]. The risk of severe hypoglycaemia is similar with the two methods or slightly lower in those using pumps, while quality of life is higher in pump users than in those using MDI[13–17] (TABLE 1). Despite the high appeal of pumps for children and adolescents due to their increased flexibility and the subtly customizable insulin delivery, which is essential to paediatric needs, meta-analyses and systematic reviews of randomized controlled trials (RCTs) that include paediatric populations[13–16,18] are not as conclusive as those in adults. Similar to the findings in adults, slightly lower $HbA_{1c}$ levels and apparently no difference in the risk of severe hypoglycaemia were reported in meta-analyses of paediatric pump users compared with those using MDI therapy. Insulin requirements are usually lower when using a pump[15,18], while rates of diabetic ketoacidosis (DKA) do not differ between pump and MDI therapy[19]. In children and adolescents using pumps (and their parents), quality of life and treatment satisfaction are similar to higher than they are in those using MDI[14] (TABLE 2).

With respect to severe hypoglycaemia, however, these meta-analyses should be interpreted with caution owing to several issues; the duration of clinical trials was too short for severe hypoglycaemia to occur, or participation was limited intentionally or unintentionally to those with a very low baseline rate of hypoglycaemia. In addition, severe hypoglycaemia or hypoglycaemia unawareness might have been listed as specific exclusion

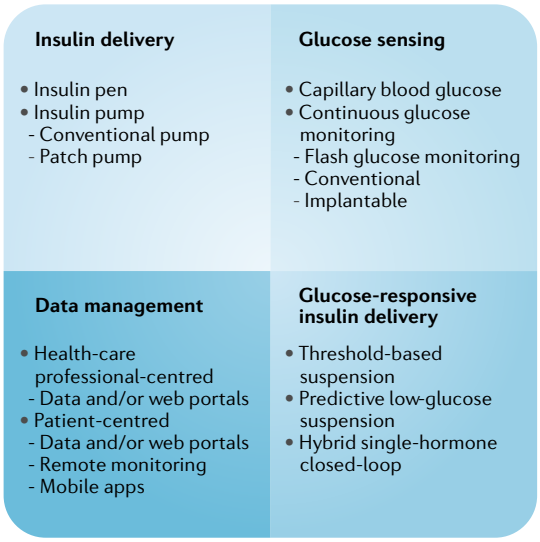


Fig. 1 | **Currently available diabetes technologies in type 1 diabetes mellitus.** Diabetes technologies are divided into four areas: insulin delivery, glucose sensing, glucose-responsive insulin delivery systems and data management tools.

criteria in these trials, or early-generation pumps and pump insulins might have been used with less favourable impact on glycaemic control. In a meta-regression analysis, it was demonstrated that there is a significant reduction in hypoglycaemia in children and adolescents using pump therapy compared with those using MDI therapy; however, this reduction is not as large as that seen in adults[13]. The greatest reductions in the incidence of severe hypoglycaemia during insulin pump therapy occurred in those with the highest baseline levels of hypoglycaemia and in elderly individuals.

While on the whole the above-mentioned meta-analyses of RCTs in paediatric and adult patients with T1DM cautiously favour insulin pump therapy over MDI therapy, observational studies published within the past 5 years more optimistically documented sustained benefit over long periods of pump use across different populations, including reductions in DKA and severe hypoglycaemia[20–25]. This finding might reflect the fact that white middle-income and high-income patients more frequently adopt insulin pump therapy than those from ethnic minorities or low-income backgrounds[7,26], factors associated with poorer glycaemic control per se[27].

### Glucose monitoring

***Capillary blood glucose measurements.*** The most widely used method of glucose monitoring is measuring capillary blood glucose levels using hand-held portable metres in combination with glucose test strips and a lancet. Capillary testing should be performed at a frequency necessary to optimize diabetes control, usually six to ten times a day, though the actual number should be individualized[28,29]. More frequent capillary blood tests correlate with improved $HbA_{1c}$ levels and reduced rates of acute dysglycaemia[30,31]. Similar to bolus calculators on insulin pumps, expert metres comprise integrated bolus advisers to calculate insulin dosages. RCTs within the past 10 years have shown a significant increase in the number of people achieving $HbA_{1c}$ targets[32–34] and a reduction in hypoglycaemia in those using a bolus calculator compared with control individuals[33,34].

Capillary blood glucose monitoring has its drawbacks as blood is sampled intermittently, providing only snapshots of glucose concentrations even if performed frequently. Episodes of hyperglycaemia and hypoglycaemia might therefore be missed and not factored into treatment decisions.

***Continuous glucose monitoring.*** The emergence of continuous glucose monitoring (CGM) has been an important step for the glucose-monitoring field. Currently available CGM devices measure interstitial glucose concentrations subcutaneously at 1–5-minute intervals using enzyme-tipped electrodes or fluorescence technology. Readers, either stand-alone devices or integrated into insulin pumps or mobile phones, display transmitted interstitial glucose readings either in real-time (real-time CGM) or on demand when scanning (flash glucose monitoring) or simply collect data for retrospective readout and analysis (professional, masked or blinded CGM).

Real-time CGM systems automatically display glucose readings at regular intervals and utilize real-time alarms when sensor glucose levels reach predefined thresholds regarding hypoglycaemia and hyperglycaemia, as well as rate-of-change alarms for rapid glycaemic excursion. Flash glucose monitoring systems (FreeStyle Libre, Abbott Diabetes Care), which were introduced in 2014, report glucose levels only when the user scans the sensor by holding a reader or a smartphone close to the sensor. Blinded CGMs are applied intermittently over a short period of time to provide more information about glycaemic excursions and patterns to the health-care professional to facilitate changes in therapy and could serve as educational tools. Blinded CGM and flash glucose monitoring systems do not provide alarms.

While most CGMs still require calibration using capillary blood glucose readings, the Libre flash glucose monitoring system is factory calibrated and does not require recalibration by the user[35]. Most CGM systems are minimally invasive and have a lifetime of 6–14 days. An implantable sensor that lasts up to 6 months (Eversense, Senseonics Inc) is available in Europe[36]. Sensor implantation and removal require a minor surgical procedure by a trained health-care professional, unlike for short-term CGM systems, which are self-inserted by the user.

***Continuous glucose monitoring uptake and use.*** A niche product in the past 10 years, CGM has now become the standard of care for people with T1DM[37]. Data presented in 2017 from the German/Austrian Diabetes Patienten Verlaufsdokumentation (DPV) registry and the T1D Exchange registry in the USA suggest that overall CGM use for all registry participants (DPV: $n = 20{,}938$; T1D Exchange: $n = 8{,}186$) is 18.4% (DPV) and 21.7%

Table 1 | **Evidence supporting the clinical use of different therapies in adults with T1DM**

| Therapy | Findings (level of evidence[a]) | Highest level of evidence | Refs |
|---|---|---|---|
| ***Insulin pump therapy*** | | | |
| | • Reduction in $HbA_{1c}$ compared with multiple daily injection therapy (A)<br>• Similar to reduced risk of severe hypoglycaemia compared with multiple daily injection therapy (A)<br>• Reduced insulin requirements (A)<br>• Improved quality of life and treatment satisfaction (A)<br>• Reduced cardiovascular mortality (B) | Systematic reviews and meta-analyses of RCTs | 13–17 |
| ***Continuous glucose monitoring*** | | | |
| Flash glucose monitoring | • Reduction in non-severe hypoglycaemia (A and C)<br>• Improvement in time in target glucose range (A)<br>• Improvement in glucose variability (A)<br>• Reduction in $HbA_{1c}$ levels (A and C)<br>• Improved quality of life and user satisfaction (C) | One RCT | 63,65–67 |
| Real-time continuous glucose monitoring | • Reduction in $HbA_{1c}$ levels (A)<br>• Reduction in moderate to severe hypoglycaemia (A)<br>• Reduction in time spent in hyperglycaemia (A)<br>• Improvement in quality of life (A)<br>• Benefits of continuous glucose monitoring are seen irrespective of insulin delivery method (pump or pen) but are conditioned on high regular sensor usage (A) | Systematic reviews and meta-analyses of RCTs | 14,48–50,52,54,55,58 |
| ***Glucose-responsive insulin delivery*** | | | |
| Threshold-based suspension | • Reduced risk of hypoglycaemia in patients who are prone to hypoglycaemia, particularly overnight (A)<br>• No apparent loss in overall glucose control (A) | RCTs | 70–72,74 |
| Predictive low-glucose suspension | Further reduction in number and duration of diurnal and nocturnal hypoglycaemic events (A) | RCTs | 76 |
| Hybrid single-hormone closed-loop | • Safe use in outpatient settings (A)<br>• Increased time in target glucose range (A)<br>• Reduced time in hypoglycaemia (A)<br>• Reduced time in hyperglycaemia (A)<br>• Modest reduction in $HbA_{1c}$ levels (A) | Systematic review and meta-analysis | 85–88 |

RCT, randomized controlled trial; T1DM, type 1 diabetes mellitus. [a]Based on the American Diabetes Association (ADA) evidence-grading system for clinical recommendations[28]. For details of the grading system, see BOX 1.

(T1D Exchange)[38]. Overall accuracy of the latest sensor generations measured as the mean relative absolute difference (MARD) versus a given laboratory standard is between 8% and 14%[35,36,39–41]; however, accuracy is lower when measuring in the hypoglycaemic range and when glucose levels are changing rapidly[42,43]. The technology has reached the proposed mark (MARD <10%) sufficient to allow patient self-adjustment of insulin dosage without confirmatory capillary blood glucose measurements[44,45]. CGM systems have been approved for non-adjunctive use in the USA (Dexcom G5 Mobile and Libre flash glucose monitor, Abbott Diabetes Care) and in the European Union (G5 Mobile, Dexcom, and Libre flash glucose monitor and FreeStyle Navigator II, Abbott Diabetes Care). Confirmatory capillary glucose measurement is suggested at hypoglycaemia with Libre or when clinical symptoms do not match Libre sensor readings.

Data provided by CGM devices allow the limitations of traditional glucose metrics such as $HbA_{1c}$ (for example, no information regarding hypoglycaemia or hyperglycaemia frequency and patterns) and capillary glucose measurements (for example, blood is sampled intermittently only, thus providing only snapshots of glucose levels) to be overcome. Indeed, a consensus report published in 2017 defined measures of glycaemic control based on CGM and highlighted the importance of CGM technology in modern diabetes care[46,47].

***Efficacy of continuous glucose monitoring.*** RCTs and meta-analyses using early-generation devices were cautious with respect to the overall benefit of CGM systems, particularly in children and young people with T1DM[14,48–53]. By contrast, data published in the past 10 years more consistently report that the use of CGM is

Table 2 | **Evidence supporting the use of therapies in children and adolescents with T1DM**

| Therapy | Findings (level of evidence[a]) | Highest level of evidence | Refs |
|---|---|---|---|
| ***Insulin pump therapy*** | | | |
| | • Similar to lower $HbA_{1c}$ compared with multiple daily injection therapy; inconclusive benefit in younger children (A)<br>• Inconclusive effect on severe hypoglycaemia<br>• Improved quality of life and treatment satisfaction (A)<br>• Similar risk of diabetic ketoacidosis to daily injections (A)<br>• Lower insulin requirements than with multiple daily injection therapy (A) | Systematic reviews and meta-analyses of RCTs | 13–16,18 |
| ***Continuous glucose monitoring*** | | | |
| Flash glucose monitoring | • Similar accuracy to real-time continuous glucose monitoring requiring capillary glucose calibrations (C)<br>• No data on clinical effectiveness are available | Non-controlled observational study | 64 |
| Real-time continuous glucose monitoring | Inconclusive effect on $HbA_{1c}$ and hypoglycaemia; benefit conditioned on high regular use (A) | Systematic reviews and meta-analyses | 14,50,51,53,55,57 |
| ***Glucose-responsive insulin delivery*** | | | |
| Threshold-based suspension | • Reduced risk of hypoglycaemia, particularly overnight (A)<br>• No apparent loss in overall glucose control (A) | RCTs | 70,71,73 |
| Predictive low-glucose suspension | Further reduction in number and duration of diurnal and nocturnal hypoglycaemic events (A) | RCTs | 76–78 |
| Hybrid single-hormone closed-loop | • Safe use in outpatient settings (A)<br>• Increased time in target glucose range (A)<br>• Reduced time in hypoglycaemia (A)<br>• Reduced time in hyperglycaemia (A) | Systematic review and meta-analysis | 41,85,86 |

RCTs, randomized controlled trials; T1DM, type 1 diabetes mellitus. [a]Based on the American Diabetes Association (ADA) evidence-grading system for clinical recommendations[28]. For details of the grading system, see BOX 1.

associated with an improvement in $HbA_{1c}$ levels, reduction in the incidence of mild to moderate hypoglycaemia and reduced variability in glucose levels[54–59]. While early analyses and guidelines favoured using CGM in combination with pump therapy[14,29,50,60], emerging evidence supports the use of CGM as part of MDI therapy[59,61–63]. As the technology is evolving fast, the older RTCs and meta-analyses have limited validity.

***Flash glucose monitoring.*** With a 2-week sensor life, factory calibration, satisfactory accuracy with an overall MARD of 11–14%, a small size and light weight, the Libre flash glucose monitoring system introduced in 2014 is particularly appealing and convenient for assessing glucose levels[63,64]. However, evidence on its effectiveness is limited[63,65–67]. An RCT showed that flash glucose monitoring in adults with well-controlled T1DM reduced time spent in hypoglycaemia, reduced glucose variability and improved time in target range compared with self-monitoring of capillary blood levels of glucose with a median 15 scans per day[63]. The benefits of using the Libre system were identical for users of insulin pump therapy and MDI therapy. However, in a head-to-head comparison of flash glucose monitoring and conventional CGM in adults with T1DM and impaired awareness of hypoglycaemia, CGM more effectively reduced time spent in hypoglycaemia than did flash glucose monitoring[68]. In the paediatric population, no evidence is currently available regarding the effectiveness of flash glucose monitoring[64]. Observational data link frequent scanning with the flash glucose monitoring device to improved outcomes[69]. Despite limited evidence from RCTs, flash glucose monitoring, a more affordable option of CGM, could certainly be regarded as an advance in the management of diabetes.

### *Glucose-responsive insulin delivery*

Automated suspension of insulin delivery at low glucose levels or when low glucose levels are predicted represents the early embodiment of technology-enabled glucose responsive regulation of insulin delivery to address the issue of hypoglycaemia. Closed-loop approaches are more complex and address both the issues of hypoglycaemia and hyperglycaemia.

***Threshold-based insulin suspend.*** Released in 2009, the Medtronic Paradigm Veo (Medtronic Diabetes) uses threshold-based insulin suspend. A revised version was approved in the USA in 2013 (MiniMed 530G). Threshold-based insulin suspend systems interrupt

Box 1 | **ADA evidence-grading system for clinical practice recommendations**[28]

**Level of evidence – A**

- Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including the following:
  - Evidence from a well-conducted multicentre trial
  - Evidence from a meta-analysis that incorporated quality ratings in the analysis
- Compelling nonexperimental evidence, that is, the all-or-none rule developed by the Centre for Evidence-Based Medicine at the University of Oxford, UK
- Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including the following:
  - Evidence from a well-conducted trial at one or more institutions
  - Evidence from a meta-analysis that incorporated quality ratings in the analysis

**Level of evidence – B**

- Supportive evidence from well-conducted cohort studies
  - Evidence from a well-conducted prospective cohort study or registry
  - Evidence from a well-conducted meta-analysis of cohort studies
- Supportive evidence from a well-conducted case–control study

**Level of evidence – C**

- Supportive evidence from poorly controlled or uncontrolled studies
  - Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results
  - Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls)
  - Evidence from case series or case reports
- Conflicting evidence with the weight of evidence supporting the recommendation

**Level of evidence – E**

- Expert consensus or clinical experience

insulin delivery when sensor glucose reaches a predefined low sensor threshold.

Multicentre randomized controlled[70–72] and nonrandomized studies[73–75] (including in children and adolescents[70,71,73]) in real-life settings have demonstrated that automated insulin suspension is safe and reduces the frequency and duration of overall and nocturnal hypoglycaemic episodes compared with insulin pump therapy alone[70] or sensor-augmented pump therapy[71,73] (TABLES 1,2). In addition, threshold-based suspend reduces the overall risk of severe and moderate hypoglycaemia in those with the highest risk, impaired hypoglycaemia awareness and the highest frequency of severe hypoglycaemia[70,74].

***Predictive low-glucose insulin suspend.*** Pumps using predictive low-glucose insulin suspend technology discontinue insulin delivery when hypoglycaemia is predicted by an algorithm. This feature was introduced in Europe and Australia in 2015 (MiniMed 640G pump, Medtronic Diabetes). A revised version of this pump was approved in the USA for those aged 16 years and older (MiniMed 630G pump).

In RCTs including adults[76], children and adolescents[76–78], the use of predictive low-glucose suspend technology reduces the exposure to nocturnal[76–78] and overall hypoglycaemia[78], including reduced frequency of nocturnal and diurnal episodes and a reduction in the incidence of lengthy nocturnal events. These benefits were achieved at the expense of mildly elevated levels of glucose overnight and in the morning[76,77] or increased time in moderate hyperglycaemia[78].

***Closed-loop insulin delivery.*** Closed-loop systems (also called the artificial pancreas or automated insulin delivery systems) are more elaborate through the use of a control algorithm that automatically and continually modulates insulin delivery below and above the pre-set rate based on sensor glucose levels.

Control algorithms used in academic and commercial closed-loop systems include a proportional–integral–derivative (PID) controller[79,80], a model predictive controller (MPC)[81], a controller based on fuzzy logic[82], or a combination of MPC and PID for insulin and glucagon co-delivery[83]. Dual-hormone or bihormonal systems deliver both insulin and glucagon or another hormone[84]. Most systems adopt the hybrid approach characterized by manual administration of prandial boluses to mitigate absorption delay of subcutaneously administered rapid-acting insulin.

According to two meta-analyses of RCTs comparing artificial pancreas systems with control therapy (either conventional pump therapy or sensor-augmented pump therapy) in outpatient settings[85], closed-loop therapy is associated with an increased percentage of time during which the sensor-reported level of glucose is within the near normoglycaemic range and reduced hyperglycaemia and hypoglycaemia while modestly reducing $HbA_{1c}$ levels[86,87]. Results of these findings support the progression of this technology from research to mainstream clinical practice.

With the approval of the first hybrid closed-loop system (MiniMed 670G pump, Medtronic) by the FDA in September 2016 based on a safety study[41,88] and its market introduction in the USA in early 2017, single-hormone closed-loop systems have entered mainstream clinical practice. Further tuning and refinements of the first generation of artificial pancreas systems are expected. Ultra-rapid insulin analogues, such as faster insulin aspart, adjunctive therapies using, for example, pramlintide, a sodium/glucose cotransporter 1 (SGLT1; also known as SLC5A1) or a combined SGLT1 and SGLT2 inhibitor[89], and inhaled insulin or ancillary technologies, such as site-warming of the infusion site, might help to address issues of exercise-induced hypoglycaemia and postprandial hyperglycaemia.

The interest in the artificial pancreas approach is underpinned by do-it-yourself artificial pancreas systems developed and utilized by a small but vocal community of people believing strongly in the potential of the closed-loop approach (OpenAPS[90,91] or Loop).

### *Data management*

Alongside the developments in insulin delivery and glucose monitoring that have been termed proximal technologies, advances have been made in the field of distal technologies that comprise devices and technologies used for communication, education, intervention and remote provision of services. Distal diabetes technologies, including telehealth, mobile health applications, game-based support, social platforms and patient portals, have been reviewed elsewhere[92]. In the context of this Review, we focus on cloud-upload technologies and applications that help people with T1DM

and health-care professionals to manage intricate data created by proximal technologies.

***Data download.*** Downloading data from devices such as pumps and CGM monitors to computers and ultimately the cloud enables the user to review summary statistics and to visualize patterns in glucose levels, including the ambulatory glucose profile[93]. Data are used to assist health-care professionals, people with T1DM and caregivers to optimize therapy regimens, to help users to understand their individual patterns and to support self-management. Routinely downloading and reviewing glycaemic data are associated with statistically significantly reduced levels of $HbA_{1c}$ (REF.[94]). However, only a small percentage of people with T1DM and/or caregivers routinely download and review their data[94,95]. Barriers to downloading have not been systematically evaluated but might include inconvenience, difficulties with the software and hardware and lack of training to interpret the data.

Software tools for downloading devices and data review can be operated by the health-care professional or the patient. Features typically include summary tables, charts such as repeating patterns, trends in blood levels of glucose, an ambulatory glucose report[93] and reviews of pump and CGM settings. Diabetes device companies offer proprietary tools (for example, Medtronic Carelink, Dexcom CLARITY, Abbott CoPilot, Roche Accu-Chek 360 and LifeScan OneTouch), but data aggregator portals exist, such as Glooko (now merged with Diasend). Many platforms enable users to link their personal accounts to a health-care provider's professional accounts for sharing and remote reviewing of the data, which enables more frequent dosing adjustments and faster clinical interventions than if the patient and their health-care provider rely on face-to-face appointments.

***Remote monitoring.*** CGM devices can send data continuously to the cloud, for instance, the Dexcom G5 mobile app, the LibreLink app and MiniMed Connect. If enabled, third parties, such as partners and caregivers, can view users' CGM traces and receive low glucose or other alerts on their own smartphone. The benefits of remote monitoring in daily living, apart from increased convenience, are yet to be formally evaluated in an RCT. Of note, the development of remote monitoring features was preceded and stimulated by the collaborative parent-led Nightscout Project[96,97].

***Mobile diabetes applications.*** The use of mobile health apps, including diabetes apps, is increasingly popular. There are over 165,000 general health-related apps and over 1,100 diabetes-specific apps[98]. Diabetes apps might improve diabetes self-management, as they offer a wide spectrum of features and activities ranging from simple logs and dosing reminders[99,100] to bolus calculators and carbohydrate counting and provide incentives to use boluses and peer support[101]. Apps such as Bant[102], Glooko, mySugr, One Drop and Tidepool[103] enable users to keep a detailed log of parameters related to their diabetes on their phones. Although meta-analyses and systematic reviews published in the past 3 years suggest that mobile apps and app-based interventions to support diabetes self-management improve $HbA_{1c}$ levels in patients with type 2 diabetes mellitus, evidence in patients with T1DM is limited[104,105]. Hence, providing evidence-based recommendations on app use is difficult.

### *Clinical practice recommendations*

The ADA[28], the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/CE)[106,107], the Endocrine Society (ES)[108,109], the International Society of Pediatric and Adolescent Diabetes (ISPAD)[29,110] and the National Institute for Health and Care Excellence (NICE)[111–114] provide recommendations and regular updates regarding clinical indications for use of insulin pump therapy and CGM. TABLE 3 summarizes these guidelines. The latest developments, including flash glucose monitoring, predictive low-glucose suspension and hybrid closed-loop systems, as well as the use of mobile apps and non-adjunctive use of CGM, have yet to be included in guidelines; however, position statements and practical guidelines on their use are under development[115–119].

## Ongoing work and future developments

### *Decision support systems*

Traditionally, insulin delivery settings, such as insulin:carbohydrate ratios, correction factors and long-acting insulin doses or basal insulin rates, were adjusted by health-care professionals at follow-up clinic visits on the basis of reviews of blood glucose diaries, glucose metre logs and insulin pump downloads. Currently, insulin dose self-adjustment is an essential part of intensified insulin therapy and a core element of structured education programmes for people with T1DM. However, tuning of insulin-dosing parameters beyond the simple arithmetic of calculating insulin dosing for meals can be challenging. Multiple groups are developing automated decision support systems by algorithmically optimizing dosing recommendations[120–122]. Preliminary results look promising, and while most systems are still predominantly being used in the research setting, regulatory approval is expected soon for insulin-dosing decision support systems in T1DM and type 2 diabetes mellitus[123].

### *Intraperitoneal insulin delivery*

From a physiological standpoint, intraperitoneal insulin delivery is attractive owing to a faster insulin absorption and action than the subcutaneous route of insulin delivery and first-pass hepatic insulin extraction restoring a metabolically more favourable positive portal to systemic insulin gradient. Although implantable pump therapy has been available for over three decades and a potential amelioration of metabolic and endocrine dysregulation in T1DM has been documented with this system, its use is limited[124]. Limitations of intraperitoneal insulin delivery include the risk of complications, higher costs and limited clinical evidence from prospective RCTs. In a closed-loop setting, a proof-of-concept nonrandomized pilot trial compared fully automated closed-loop delivering intraperitoneal insulin via DiaPort (Roche Diagnostics) with that of subcutaneous insulin delivery[125]. Results demonstrated higher time in

Table 3 | **Professional society guidelines[a] for the use of insulin pump therapy and CGM in T1DM**

| Indication or criterion | Children and adolescents | | Adults | |
|---|---|---|---|---|
| | Insulin pump therapy | CGM | Insulin pump therapy | CGM |
| $HbA_{1c}$ | • Recommended if $HbA_{1c}$ is persistently above the individual goal (ISPAD)<br>• Recommended if $HbA_{1c}$ levels are elevated on injection therapy (AACE/ACE) | • In children and adolescents who have $HbA_{1c}$ levels <7.0% (53 mmol/mol), as it will assist in maintaining target $HbA_{1c}$ levels while limiting the risk of hypoglycaemia<br>• In children and adolescents with $HbA_{1c}$ ≥7.0% (53 mmol/mol) and who are able to use the devices on a nearly daily basis (ES) | • Patients with T1DM who do not reach glycaemic goals despite adherence to maximum MDI (AACE/ACE)<br>• $HbA_{1c}$ levels have remained high (>8.5% (69 mmol/mol) or above) on MDI (NICE) | • Patients with $HbA_{1c}$ levels above and below target (ES)<br>• Hyperglycaemia ($HbA_{1c}$ level of 75 mmol/mol (9%) or higher) that persists despite testing at least ten times a day (NICE)<br>• Continue real-time CGM only if $HbA_{1c}$ can be sustained at or below 7% (53 mmol/mol) and/or there has been a decrease in $HbA_{1c}$ of 2.5% (27 mmol/mol) or more (NICE) |
| Hypoglycaemia | • If hypoglycaemia is a major problem (ISPAD)<br>• Frequent and severe hypoglycaemia (AACE/ACE) | • CGM recommended for patients with impaired awareness of hypoglycaemia (AACE, ADA, ES, ISPAD and NICE)<br>• History of severe hypoglycaemia (AACE)<br>• Frequent severe hypoglycaemia (NICE)<br>• Frequent hypoglycaemia (ADA) and nocturnal hypoglycaemia (ES)<br>• Inability to recognize or communicate about symptoms of hypoglycaemia (for example, because of cognitive or neurological disabilities) (NICE) | • Attempts to achieve target $HbA_{1c}$ levels with MDI result in the person experiencing disabling hypoglycaemia (NICE)<br>• Frequent severe hypoglycaemia and/or hypoglycaemia unawareness (AACE/ACE) | • Hypoglycaemia unawareness (ADA and NICE)<br>• Frequent hypoglycaemic episodes (ADA)<br>• Frequent (more than two episodes a week) asymptomatic hypoglycaemia that is causing problems with daily activities (NICE)<br>• More than one episode a year of severe hypoglycaemia with no obviously preventable precipitating cause (NICE)<br>• Extreme fear of hypoglycaemia (NICE) |
| Hyperglycaemia, ketonaemia and glucose variability | • Patients with pronounced dawn phenomenon (AACE/ACE)<br>• Patients prone to ketosis (AACE/ACE)<br>• Widely fluctuating glucose levels (AACE/ACE) | Intermittent use in children and young people who continue to have hyperglycaemia despite insulin adjustment and additional support | • Patients who have very labile diabetes (erratic glucose control including recurrent DKA) (AACE/ACE)<br>• Significant dawn phenomenon (AACE/ACE) | NA |
| Quality of life and psychosocial aspects | • If quality of life needs to be improved (ISPAD)<br>• If current treatment regimen compromises lifestyle (AACE/ACE)<br>• Children with pronounced needle phobia (AACE/ACE)<br>• Treatment option for children younger than 12 years provided that MDI therapy is considered to be impractical or inappropriate (NICE) | NA | Fear of hypoglycaemia (NICE) | NA |
| Education, training, adherence and follow-up | Ideal paediatric candidates are those with motivated families who are committed to monitoring blood glucose ≥4 times per day and have a working understanding of basic diabetes management (AACE/ACE) | • In patients who are able to use the devices on a nearly daily basis (ES)<br>• Robust diabetes education, training and support are required for optimal CGM implementation and ongoing use (ADA)<br>• CGM users must know the basics of sensor insertion, calibration and real-time data interpretation (AACE/ACE) | • Currently performing ≥4 insulin injections and ≥4 self-monitored blood glucose measurements daily (AACE/ACE)<br>• Motivated to achieve optimal blood glucose control (AACE/ACE)<br>• Regular follow-up with specialist team (AACE/ACE) | • When prescribing CGM, robust diabetes education, training and support are required for optimal CGM implementation and ongoing use (ADA)<br>• In patients who are willing and able to use these devices on a nearly daily basis (ES)<br>• CGM to be considered in adults who are willing to commit to using it at least 70% of the time and to calibrate it as needed (NICE) |

Table 3 (cont.) | **Professional society guidelines[a] for the use of insulin pump therapy and CGM in T1DM**

| Indication or criterion | Children and adolescents | | Adults | |
|---|---|---|---|---|
| | Insulin pump therapy | CGM | Insulin pump therapy | CGM |
| Special populations | • For patients with microvascular complications and/or risk factors for macrovascular complications (AACE/ACE)<br>• Very young children (AACE/ACE)<br>• Athletes (AACE/ACE)<br>• Adolescents with eating disorders (AACE/ACE)<br>• Pregnant teenagers (AACE/ACE) | • CGM to be considered in neonates, infants and pre-school children (NICE)<br>• CGM to be considered in children and young people who have comorbidities or who are receiving treatments that can make blood glucose control difficult (NICE)<br>• CGM to be considered in children and young people who undertake high levels of physical activity (NICE)<br>• No recommendations about the use of CGM in children less than 8 years of age (ES) | • Preconception (AACE/ACE)<br>• Pregnancy (AACE/ACE)<br>• Competitive athletes (AACE/ACE)<br>• Patients with extreme insulin sensitivity (AACE/ACE) | NA |

CGM, continuous glucose monitoring; DKA, diabetic ketoacidosis; MDI, multiple daily injection; NA, not available; T1DM, type 1 diabetes mellitus; [a]American Diabetes Association (ADA)[28], American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE)[106,107], Endocrine Society (ES)[108,109], International Society of Pediatric and Adolescent Diabetes (ISPAD)[29,110] and National Institute for Health and Care Excellence (NICE)[111–114].

range (80 mg/dl to 140 mg/dl and 70 mg/dl to 180 mg/dl), lower mean glucose and no difference with respect to percent time spent <70 mg/dl when insulin was delivered with the intraperitoneal route[125]. However, given the aforementioned limitations and the rapid development of subcutaneous insulin-based therapies (that is, ultra-fast-acting analogues) and non-insulin adjunctive therapies (for example, glucagon-like peptide 1 (GLP1) agonist), the use of intraperitoneal delivery seems to be limited to people with life-limiting issues related to subcutaneous insulin delivery.

### *Single-port platform*

Feasibility studies have demonstrated that glucose sensing at the site of insulin delivery is possible[126]. Single-port devices are being developed that combine sensor glucose measurements with an insulin infusion cannula into a single subcutaneous insulin infusion set intended to simplify device insertion and site management[127,128]. This kind of device would be of particular benefit to children as they have a limited amount of skin areas for placement of sensors or insulin cannulas. However, discordance in insertion patterns (the cannula is replaced every 2–3 days, whereas the sensor is replaced every 7–14 days) and reduced sensor accuracy during the first day after insertion remain limiting factors.

### *Bihormonal artificial pancreas*

Bihormonal or dual-hormone closed-loop systems deliver glucagon (or another hormone) in addition to insulin[84,129]. Glucagon delivery is triggered when hypoglycaemia is impending or predicted. Two approaches have been adopted in terms of the underlying insulin delivery[84,129]. One approach tunes insulin delivery in a similar way to that of a single-hormone closed-loop system, adding glucagon to reduce the residual risk of hypoglycaemia[130]. The other approach delivers insulin aggressively and counteracts insulin over delivery with glucagon[131].

Short-term studies published to date have confirmed a reduction in hypoglycaemia risk with the use of glucagon[85]. However, such systems have increased complexity and an intricate developmental pathway. Efforts are underway to develop dual-chamber pumps and glucagon that is stable at room temperature for use in bihormonal closed-loop systems[132]. Long-term data are needed to assess the safety and tolerability of chronic subcutaneous delivery of glucagon.

Apart from glucagon, other adjunctive therapies, including pramlintide and GLP1, to suppress postprandial hyperglucagonaemia and associated hyperglycaemia have been evaluated in combination with close-loop insulin delivery in people with T1DM in research facility settings[133–135]. Data collected so far suggest that co-delivery of subcutaneously administered pramlintide or GLP1 is beneficial to reduce postprandial glucose excursions compared with closed-loop delivery alone[133–135].

### *Bioartificial pancreas*

In addition to algorithm-driven glucose-responsive insulin delivery, biological approaches have been explored. These approaches include encapsulated islets[136], glucose-responsive polymer encapsulation of insulin and molecular modification of insulin[137].

Islets, with their inherent ability to release insulin in response to glucose, are the main focus of research regarding the bioartificial pancreas. To circumvent the need for immunosuppression, islets can be encapsulated within a biocompatible semipermeable matrix that enables the passage of small molecules, such as glucose, insulin and oxygen, but prevents the entry of immune cells and antibodies[136]. Intravascular devices contain artificial capillaries and are connected to the host systemic circulation via vascular anastomoses, such as the deep femoral artery or a venous fragment of an arteriovenous anastomosis in the forearm, creating an intravascular shunt. Extravascular devices, subclassified

into microcapsular and macrocapsular devices, do not require the creation of intravascular shunts and could be transplanted into different sites, such as the peritoneum, subcutaneous adipose tissue or renal capsule[136]. Limited data from human trials utilizing encapsulated islet xenografts or allografts show a transient reduction in total daily insulin requirements, including anecdotal reports of transient insulin independence[138–140]. With the rise of pancreatic endocrine cells derived from human embryonic stem cells, the use of pig islets and xenotransplantation has become less favourable[136].

In polymer-based smart insulin systems, insulin is encapsulated within glucose-responsive polymeric matrix-based vesicles or hydrogels embedded in large implants, transdermal patches, microparticles or nanoparticles[137]. Such matrices are compact during hypoglycaemia or normoglycaemia. Insulin is released in response to rising glucose levels, and consecutive structural transformations of the matrices promote the release of sequestered insulin. Candidate systems at advanced development stages have demonstrated their potential in preclinical in vitro studies and animal trials[137]. No human data are available. Other approaches focus on molecular modification of insulin, which involves the introduction of a glucose-sensitive motif to the insulin molecule or its formulation, thus promoting an intrinsic glucose-responsive activity[137]. Current candidate technologies rely on sequestration of active insulin hormone within the subcutaneous space or within the bloodstream (as inactive complexes), with enhanced release or activation only during hyperglycaemia. At present, such strategies remain in the early stages of development.

## Conclusions

Diabetes technology is enhancing care and management of people with T1DM. Innovations in glucose sensing and insulin delivery have reduced the burden of self-care and facilitated improved outcomes. A notable milestone has been achieved with the translation of research into clinical use of algorithm-driven glucose-responsive insulin delivery in the form of a hybrid artificial pancreas system. In the coming decade, advanced closed-loop systems with add-on data management features will become the standard of care for people with T1DM across all age groups, while the bioartificial pancreas and 'smart' insulin strategies will take considerably longer to demonstrate safety and efficacy in humans.

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**Author contributions**
Both authors contributed to all aspects of the article.

**Competing interests**
R.H. has received speaker honoraria from Eli Lilly, Novo Nordisk and Astra Zeneca, has served on the advisory panel for Eli Lilly and Novo Nordisk, has received licence fees from B. Braun and Medtronic, has served as a consultant to B. Braun and has patents and patent applications related to closed-loop systems. M.T. has received speaker honoraria from Medtronic and Novo Nordisk.

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**Review criteria**
The narrative is based on results from clinical studies and meta-analyses known to the authors. Relevant studies were identified by searching PubMed and Web of Science for articles on each of the technologies up to November 2017, as well as using cited literature in retrieved articles. Information relevant to children, adolescents and adults with type 1 diabetes mellitus was considered; studies in pregnancy complicated by diabetes were excluded. Priority was given to meta-analyses and systematic reviews.