Received: 1 July 2018 | Accepted: 10 July 2018

DOI: 10.1111/pedi.12731

WILEY ISPAD

ISPAD CLINICAL PRACTICE CONSENSUS GUIDELINES

ISPAD Clinical Practice Consensus Guidelines 2018: Diabetes technologies

Jennifer L. Sherr[1] | Martin Tauschmann[2,3] | Tadej Battelino[4,5] | Martin de Bock[6] | Gregory Forlenza[7] | Rossana Roman[8] | Korey K. Hood[9] | David M. Maahs[10]

[1]Department of Pediatrics, Yale School of Medicine, Yale University, New Haven, Connecticut

[2]Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge, Cambridge, UK

[3]Department of Paediatrics, University of Cambridge, Cambridge, UK

[4]UMC-University Children's Hospital, Ljubljana, Slovenia

[5]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

[6]Department of Paediatrics, University of Otago, Christchurch, New Zealand

[7]University of Colorado Denver, Barbara Davis Center, Aurora, Colorado

[8]Medical Sciences Department, University of Antofagasta and Antofagasta Regional Hospital, Antofagasta, Chile

[9]Department of Psychiatry & Behavioral Sciences, Stanford University School of Medicine, Palo Alto, California

[10]Department of Pediatrics, Stanford University School of Medicine, Palo Alto, California

Correspondence
Jennifer Sherr, One Long Wharf Drive, Suite 503, New Haven, CT 06511.
Email: jennifer.sherr@yale.edu

1 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

- Continuous subcutaneous insulin infusion (CSII) pump therapy can be used safely and effectively in youth with type 1 diabetes (T1D) to assist with achieving targeted glycemic control (B).
- Insulin pump therapy can assist with reducing episodes of hypoglycemia (B).
- Insulin pumps reduce chronic complications of T1D in youth, even when compared to those with similar hemoglobin A1c (HbA1c) levels on multiple daily injection (MDI) therapy (B).
- Insulin pump therapy is appropriate for youth with diabetes, regardless of age (B).
- Infusion set failures are common and must be recognized early so as to avoid episodes of diabetic ketoacidosis (DKA) (B).
- Real-time continuous glucose monitors (CGM) can be used effectively for lowering HbA1c, reaching target HbA1c, reducing glucose variability (both for insulin pumps and MDIs), and increasing time in range (TIR) in the pediatric population with T1D (A).
- Assessing clinically meaningful outcomes beyond HbA1c is possible through the use of CGM technologies to determine both glycemic variability and TIR, which encompasses time in target (often defined as 70-180 mg/dL [3.9-10.0 mmol/L]), as well as time spent hypoglycemic (level 1: <70-54 mg/dL [<3.9-3.0 mmol/L] and level 2: <54 mg/dL [<3.0 mmol/L]) and time spent with hyperglycemia (levels 1: >180 mg/dL [>10 mmol/L] and level 2: >250 mg/dL [>13.9 mmol/L]) (E).
- Real-time CGM can be used effectively for reducing mild to moderate hypoglycemia and shortening the time spent in hypoglycemia in the pediatric population with T1D (B)
- The effectiveness of CGM in children and adolescents with T1D is significantly related to the amount of sensor use (A).
- Intermittent, retrospective or real-time CGM use may be useful for diagnostic purposes and in evaluating the effects of major changes in treatment regimens (C).
- Use of intermittently scanned/viewed CGM (isCGM), also known as flash glucose monitoring, in the pediatric population is safe (C).
- Sensor augmented pump (SAP) therapy is superior in children and adolescents over MDI with self-monitoring of blood glucose (SMBG) in reduction of HbA1c without an increase in hypoglycemia or severe hypoglycemia (A). However, this benefit is mediated by adherence to sensor therapy, with at least 60% use being associated with these findings.
- Low glucose suspend (LGS) systems reduce the severity and duration of hypoglycemia while not leading to deterioration of glycemic control, as measured by HbA1c (A).

- Predictive low glucose suspend (PLGS) systems can prevent episodes of hypoglycemia and have been shown to reduce hypoglycemia exposure (B).
- Automated insulin delivery (closed loop) systems improve TIR, including minimizing hypoglycemia and hyperglycemia (A). Commercial availability of automated insulin delivery systems is currently limited, but patient access to these systems is anticipated to improve in the near future.
- Automated insulin delivery systems have proven to be especially beneficial in attaining targeted control in the overnight period (A).
- There exists a wide spectrum of cell phone apps to aid patients with diabetes. Use of evidence-based apps has shown glycemic benefit for adult patients with type 2, but not T1D (A).
- Bolus calculators, either on insulin pumps or as phone apps for MDI users, aid patients with diabetes in determining carbohydrate and correction dosing. Their use is associated with improved glycemic control in patients with T1D and should be encouraged for all patients (B).
- Automated algorithmic adjustment of open-loop pump settings and insulin dosing parameters is an emerging area of research and clinical care in diabetes technology (E). The first system for automated dosing adjustment with health care provider approval has just received regulatory approval.
- Routine downloading of diabetes devices (blood glucose monitors, pumps, or CGM) is associated with better glycemic control, though overall rates of patients downloading their devices are extremely low (C).
- Telemedicine, whereby patients or providers, receive care from a specialist remotely through video conferencing may assist with improving glycemic control and increase the frequency of visits for patients with diabetes living in remote or rural locations (C).
- Setting realistic expectations for the integration of diabetes technologies is paramount to the success of patients as they adopt new technologies (B).
- Identification and counseling of potential barriers to adoption of new technologies or continued use of devices is critical (B).

2 | INTRODUCTION

Numerous milestones mark the advance of diabetes care since the discovery of insulin in 1921. Glucose monitoring has progressed from urine to blood to interstitial fluid measurements every 5 to 15 minutes with continuous glucose monitors (CGM). Similarly, advances in insulin formulations and their delivery include rapid acting and basal insulins as well as insulin pumps to more effectively dose insulin.

While progress has been made in glycemic control, most youth with type 1 diabetes (T1D) do not meet ISPAD targets for hemoglobin A1c (HbA1c) based on data from international diabetes registries.[1–5] Additionally, hypoglycemia and severe hypoglycemia continue to plague youth with T1D and prevent optimal glycemic control.[2,6–8] Early advances in diabetes treatment may have inadvertently increased the burden of diabetes care, which for some people may impair quality of life and psychosocial health.[9–12] Thus, a body of research has explored how the burdens of these technologies can be offset by the benefits they may provide, determining how to set realistic expectations for what assistance new therapies may provide, and informing the development of the next generation of technologies to minimize the burden they may cause. Therefore, diabetes technology presents an opportunity to improve glycemic control by lowering HbA1c, reducing hypoglycemia, and lowering the burden of care for T1D on children, adolescents, young adults, and their families.[13]

Since the 2014 ISPAD guidelines, numerous advances have been made in diabetes technology. The purpose of this new chapter is to review evidence on diabetes technology in children, adolescents, and young adults and to provide practical advice and approaches on their use. Topics include: insulin pumps, CGM, sensor augmented pumps (SAP), closed loop systems, diabetes apps and automated decision support systems, downloading technologies, telehealth, quality of life issues related to diabetes technology, and a consideration of how to use these technologies in resource-limited situations.

3 | INSULIN PUMPS

3.1 | The dawn of technology use in diabetes care

The first application of technology to improve the care of those living with T1D can arguably be traced to the dawn of insulin pump therapy in the late 1970s.[14–16] However, integration of continuous subcutaneous insulin infusion (CSII) pump therapy into the care of youth with T1D remained minimal until the turn of the century. Since then, a very consistent picture has emerged in the literature supporting the use of pump therapy for youth with T1D, namely mean HbA1c decreased 0.2% to 1.1%,[17–30] clinically important hypoglycemia was reduced,[17–22,25–31] and no significant increase in body mass index (BMI) z-score was recorded.[17,19–30] These data held true regardless of whether the multiple daily injection (MDI) comparator group used Neutral Protamine Hagedorn (NPH)[17–26,29,32] or glargine insulin.[33–36] Randomized controlled trials (RCTs) assessing the use of insulin pumps have yielded conflicting results, with some showing improvement of glycemic control with use of the technology.[33,34] Yet, the RCT studies that have not shown a lowering of HbA1c have highlighted the endorsement of pump therapy as patients randomized to the technology continued its use by the end of the study,[37–39] had higher reports of treatment satisfaction,[40] and reported decreased diabetes-related worry.[41] Interestingly, prospective examination of nearly 1000 patients either on pump or MDI therapy found that despite similar HbA1c levels attained, lower rates of retinopathy and peripheral nerve abnormality were noted in the insulin pump treated group.[42] Furthermore, data from meta-analyses conducted by various groups have depicted similar findings with pump therapy. Namely, this mode of insulin delivery is associated with reductions in the mean HbA1c,[43–45] lowering of the total daily insulin dose,[43,44] and decreased rates of severe hypoglycemia.[45] A meta-analysis by Yeh et al found no difference between insulin pump therapy and MDI in regards to glycemic control attained or rates of severe hypoglycemia.[46] As these metanalyses are based on clinical trial data obtained prior to 2008, the pumps utilized are at least 10-years older than current technology available;

thus, lacking some more advanced features now available in the newer generation pumps. Additionally, integration of pump therapy into clinical practice may have had implicit issues, as clinicians' comfort in training patients and titrating doses with this "new" technology may have been limited.

With the wealth of participants included and the long-term follow-up they afford, registries provide means to assess real-world use of these technologies. Data from the US-based type 1 diabetes exchange (T1DX) registry focusing on children <6 years demonstrated lower HbA1c levels for those on pumps, with a tendency for lower HbA1c levels prior to pump initiation, suggesting selection of an ideal population for pump use may have occurred.[47] The SWEET (better control in Pediatric and Adolescent Diabete**S: W**orking to create C**E**n-**T**ers of Reference) centers found that almost half of the 16 000 registry participants used pumps, and this technology was associated with lower HbA1c and daily insulin dose as compared to MDI.[48] In a cross-sectional comparison of three large, transatlantic registries, which included the US-based T1DX, the German/Austrian Prospective Diabetes Follow-up Registry (DPV), and the English/Welsh National Pediatric Diabetes Audit (NPDA), a pooled analysis of nearly 55 000 pediatric participants, pump use was associated with lower mean HbA1c (pump 8.0% ± 1.2% vs injection: 8.5% ± 1.7%, $P < 0.001$).[49] DPV database analysis of almost 10 000 participants on pump therapy matched to those on injections therapy showed lower rates of severe hypoglycemia (pump: 9.55 vs injection: 13.97 per patient-years) and reduced frequency of diabetic ketoacidosis (DKA) (pump 3.64 vs 4.26 per 100patient-years), favoring pump use.[7] While HbA1c levels were lower in the pump treated group (pump: 8.04% [95% confidence interval, CI]: 8.00-8.07) vs injection: 8.22% (95% CI 8.18 to 8.25), the clinical significance of this difference in glycemic control is unclear.[7] Additionally, in an observational study of data on those with T1D in Nordic countries, using an insulin pump was associated with a decreased rate of severe hypoglycemia.[50] Thus, the benefits of pump use have now been echoed in various registry assessments.

3.2 | Advanced pump settings

More advanced features of pump therapy include the ability to set temporary basal rates and alter the pattern of bolus insulin delivery. Temporary basal rates allow for adjustments to the usually programmed basal rate: decreasing the delivery in the case of physical activity or increasing doses for situations like inter-current illness, which may be further exacerbated by steroid therapy as would be used for an asthma exacerbation.[51] Similarly, different preprogrammed basal patterns can be utilized when days of differing insulin sensitivity are predictable, for example, during menstruation in women. Bolus doses of insulin can be delivered: (1) immediately, known as a standard or normal bolus, (2) slowly over a certain duration of time, deemed an extended or square bolus, or (3) a combination of the two, that is, a combo or dual wave bolus.[51] Foods that are higher in fat may lead to the need for an extended or combo bolus as the rise in glucose following the meal will be delayed by the high fat content. Pumps reduce bolus insulin delivery based on the proportion of insulin that is still deemed "active" from the last bolus, which may be a reason lower rates of severe hypoglycemia are appreciated for those on pump therapy.

TABLE 1 Indications for use of insulin pumps in Pediatrics—adapted from Reference (52)

Conditions under which insulin pumps should be considered
• Recurrent severe hypoglycemia
• Wide fluctuations in blood glucose levels regardless of A1c
• Suboptimal diabetes control (ie, A1c exceeds target range for age)
• Microvascular complications and/or risk factors for macrovascular complications
• Good metabolic control but insulin regimen that compromises lifestyle
Circumstances in which insulin pumps may be beneficial
• Young children and especially infants and neonates
• Children and adolescents with pronounced dawn phenomenon
• Children with needle phobia
• Pregnant adolescents, ideally preconception
• Ketosis prone individuals
• Competitive athletes

3.3 | Spanning childhood: Incorporation of pump therapy regardless of age or disease duration

Consensus guidelines have been developed for use of pump therapy in youth with T1D, which, based on the indications, likely apply to every youngster living with T1D (Table 1).[52] Recently, an ISPAD Clinical Practice Consensus Guideline has been released entitled "Managing Diabetes in Preschool Children," which states pump therapy is the recommended mode of insulin delivery for those under the age of 7 years.[53] In order to overcome the mechanical barrier dictated by the lowest basal and bolus delivery doses feasible with pump therapy, application of diluted insulin to the youngest population has offered the opportunity to more finely tune insulin delivery.[54–57] While concern is sometimes expressed over how paid care providers will adopt this technology, a study by Weinzimer et al highlighted that children whose parents work outside of home tended to see the largest improvement in glycemic control with transition to pump therapy.[30]

Immediate incorporation of pump therapy at the time of diagnosis has been shown to be successful in terms of glycemic control achieved.[58–60] While a theory exists that achieving more targeted control shortly after diagnosis may help to preserve beta cell function, this finding has not been corroborated by these trials.[60,61]

The long-term benefits of pump therapy have been depicted in some of the initial studies of this insulin delivery modality[31,62] and more recently, continued improvement in glycemic control was seen over 7-years of treatment.[63] Furthermore, those with suboptimal control (HbA1c >8.5%) at pump initiation, were found to have persistent benefits even after 4 years of treatment and those on MDI therapy had higher rates of severe hypoglycemia and DKA.[63]

3.4 | Barriers to adoption of pump therapy and predictors of success

Despite the literature supporting the benefits of pump therapy in the pediatric population, universal adoption of this technology has not occurred. A T1DX study reported pump use varied widely between centers and concluded health care provider preferences influence the proportion of patients using pumps in a given center, similar to a

Pediatric Diabetes Consortium (PDC) study reporting 18% to 59% use within the first year after diagnosis.[47,64] In the PDC study, pump therapy was more common in those with private health insurance, non-Hispanic white race, annual family income over $100 000, and a parent with a college education.[64] A more recent analysis has echoed these findings showing sociodemographic factors, namely, income and parental education, increased frequency of blood glucose monitoring, and CGM use were predictive of pump use.[65] The authors also highlight potential barriers to uptake of the technology, which include concerns regarding the physical footprint and interference of the device, therapeutic effectiveness of the technology, and to a lesser extent, financial burdens this mode of insulin delivery may cause.[65] In some countries, non-coverage of pump therapy by the health care/insurance system likely influences the low adoption rates of this technology.[49]

Distinguishing what makes integration of pump therapy more successful could help guide clinical centers in assuring a smooth transition for patients. Having more preprogrammed basal rates has been found to correlate with more targeted control.[66] Others have determined that the total number of boluses delivered daily correlates with HbA1c achieved, more frequent bolusing being associated with more targeted control, and that basal insulin delivery <50% was also important.[67] In the adolescent population, increasing basal rates at the expected time of meals has been used to account for missed meal boluses; yet, if someone does not eat at one of these prespecified time periods they are at increased risk for hypoglycemia, which could be further exacerbated in the setting of an intercurrent illness.

3.5 | Frequency and causes of discontinuation of pump therapy

Generally, discontinuation of pump therapy is uncommon. The DPV registry over the period of 1995 to 2009 found attrition from this technology to be, in general, very low at 4%.[68] Adolescents aged 10 to 15 years had the highest rate of pump discontinuation, and those who discontinued were more likely to be female[68] with similar results from the T1DX registry.[69] Reasons for discontinuing pump therapy cited by participants included problems with wearability (57%), disliking the pump or feeling anxious (44%), and problems with glycemic control (30%).[69] Higher depressive symptoms, as captured by the Children's Depression Inventory, has also been reported in those who cease pump therapy.[70] From these findings, it appears targeting support to those who are in suboptimal control and/or exhibiting alterations in psychological well-being would be warranted.[69]

3.6 | Complications of pump therapy: Infusion sets and hypertrophy

Data regarding adverse events, including pump malfunctions, infusion set failures, alarms, and other problems, associated with insulin pump use demonstrate that these issues are not uncommon-with reported frequencies of 40% to 68% of pump users experiencing such events.[71,72] One of the major complications of pump therapy remains issues with infusions sets.[71,73–75] Questions remain regarding whether steel cannulas or flexible Teflon are ideal and whether certain infusions sets are better based on the age of the patient using the pump. The major concern is occlusion, whether it be full or partial, or dislodgement of the site thereby interrupting the rapid-acting analog being delivered subcutaneously and putting the patient at risk for developing ketoacidosis. Some have explored the use of a small dose of basal insulin, like glargine, to help minimize this complication.[76] Widespread adoption of this has not occurred, and many groups continue to explore how to develop improved infusion sets[77] or fault detection algorithms to advise a user of when insulin delivery may be interrupted.[78,79]

Some studies have documented between a 2- and a 5-fold higher risk of DKA in those on pump therapy.[80,81] Yet, a cornerstone to avoiding such increased rates of DKA is adequate education on the risk of DKA and how to manage persistent hyperglycemia in pump-treated patients. For those on pump therapy, the most common cause of DKA, per ISPAD Clinical Practice Consensus Guidelines on Diabetic Ketoacidosis and hyperglycemia hyperosmolar state, is failure to inject insulin, with either a syringe or pen, when hyperglycemia and hyperketonemia/ketonuria occur.[82]

Lipohypertrophy, or local fat accumulation, at the site of insulin administration, is another issue that is frequently encountered with pump therapy.[83] Fat loss at the site of prior insulin infusion sites, lipoatrophy, is less common and has been seen more frequently in those with multiple autoimmune diseases.[84] Both of these findings are categorized as lipodystrophy and earlier studies have shown a greater risk of these issues in those with higher insulin autoantibodies.[85] Lipodystrophy can impact how insulin is absorbed and thus lead to deterioration in glycemic control. Interestingly, use of lipohypertrophied tissues for placement of a CGM was found to not impact the sensor accuracy.[86] Thus, while resting the impacted tissue from continued insulin infusion, the hypertrophied space for diabetes-related devices may still be utilized for sensor placement.

3.7 | Practical considerations

When preparing to transition patients from MDI to insulin pump therapy, one of the first steps is to have the patient select the pump model they would like to utilize, if insurance coverage does not dictate the decision. To accomplish this, charts and literature describing the differences among the models is helpful, with the annual consumer guide published by Diabetes Forecast being an easily accessible, useful online reference (http://www.diabetesforecast.org). The selection of a pump should be based on features desired by the patient and their family with guidance provided by the multidisciplinary team members.

In determining initial pump settings, oftentimes the total daily insulin dose is used for initial calculations. Table 2 provides some suggestions to determine initial pump settings. Critical to success with the adoption of pump therapy is advising patients on risks of infusion set failure, which if unrecognized can lead to metabolic decompensation and potentially DKA.[87] A useful framework to review these issues and optimize the transition are presented by Diess et al.[88] As steel cannulas are less likely to kink or dislodge they may be the ideal infusion set for the youngest patients adopting pump therapy.

Introducing patients to advanced pump features should be done over time as they show proficiency with the basic skills for success with

TABLE 2 Basic guidelines for starting insulin pump therapy

Total daily dose (TDD) prior to pump initiation
- May be used to determine initial pump settings
- Consider reducing total daily dose in those at targeted glycemic control or patients with frequent or severe hypoglycemia.

Proportion basal vs bolus insulin delivery
- In older children and adolescents expect a 50/50 split
- In children <7 years, basal insulin delivery may make up ~30% to 35% of the TDD[51]

Determination of basal rates
- Take the amount to be delivered as basal (ie, 50% of the TDD) and divide by 24 for the number of hours in a day (if basal insulin per day will be 20 units then hourly rate would be set at 0.8 units/h)
- Increases in basal rates in early morning hours are often needed in adolescents who experience the dawn phenomenon[311,312]
- Pre-school aged children may have higher basal insulin requirements between 9 PM and 12 AM and then lower basal rates during early morning hours[312]

Determination of correction factors/insulin sensitivity factors
- If using a correction factor prior to transition to the pump, start with the usual factor.
- Otherwise, a correction factor can be determined by dividing 1800 by the TDD if glucose readings are in mg/dL (or dividing 100 by the TDD if glucose readings are in mmol/L). Depending on insulin sensitivity, the 1800 rule can be adjusted upward (2000/TDD) for those who are insulin sensitive or downward (1500/TDD) for those who are more insulin resistant.

Determination of insulin to carbohydrate ratios
- If using a carbohydrate ratio prior to transition to the pump, start with the usual factor.
- Otherwise, carbohydrate ratio can be determined by dividing 500 by the TDD
- Young children may need more aggressive meal coverage[313,314] and a 350 rule may be employed

Close monitoring following initiation
- Consider frequent blood glucose checks prior to and 2-hours postmeals to help inform insulin dose titrations
- Consider overnight checks at midnight and 3 AM to assess overnight basal rates
- CGM readings may be used in place of SMBG

Abbreviations: CGM, continuous glucose monitor; SMBG, self-monitoring of blood glucose.

the pump: changing the site every 3 days, bolusing for all carbohydrate intake prior to eating, and correction of hyperglycemia. Temporary basal rates, including complete suspension of basal insulin delivery, have been tested and shown to help mitigate hypoglycemia associated with exercise.[89] Incorporation of advanced boluses includes the use of an extended/square wave bolus, which administers insulin slowly over a certain duration of time or a combination/dual wave bolus, which administers some of the insulin immediately with another portion of that bolus extended over time and may be of benefit when consuming a high fat food. For the extended bolus, the user sets the duration of the extension; whereas, for combo boluses they not only choose the duration to extend but also the amount to be delivered upfront (eg, 40% of the bolus immediately and the remaining 60% over 4 hours-time).

By uploading pump data, clinic visits become more nuanced in regards to the alterations in the medical regimen that can be prescribed and the data download provides a portal by which clinicians can initiate a conversation on behavioral factors, including frequency of infusion set changes and timing of meal boluses.

4 | CONTINUOUS GLUCOSE MONITORS

Self-monitoring of capillary blood glucose (SMBG) is an essential tool in the optimal management of diabetes in children and adolescents with T1D as established by the landmark Diabetes Control and Complications Trial (DCCT).[90] Early methods of measurement for SMBG relied upon reflectance assays coupled with oxidation of glucose allowing for a colorimetric readout; whereas more recent glucometers utilize a electrochemical assay that couples glucose oxidation to the generation of a current that is proportional to the glucose concentration. Prior to the advent of SMBG, patients with diabetes relied upon urinary glucose measurements, thus the ability to conduct a rapid, capillary assessment afforded by SMBG has been instrumental in achievement of target control. In fact, it has been well documented the frequency of SMBG correlates with improved HBA1c levels and reduced acute complications.[91–93] SMBG should be prescribed at a frequency to optimize each child's diabetes control, usually six to ten times a day, though the actual number should be individualized.[94] However, SMBG has limitations: it only provides single snapshots of glucose concentrations. Consequently, episodes of hyper- and hypoglycemia, in particular nocturnal and asymptomatic episodes, as well as dynamics in blood glucose concentrations may be missed and not factored into treatment decisions.

CGM devices provide patients, caregivers, and health care professionals a broad spectrum of information on real-time glucose trends. Currently available CGM devices measure interstitial glucose concentrations subcutaneously at 5 to 15 minute intervals utilizing enzyme-tipped electrodes or fluorescence technology. When interpreting historic data on CGM use, it is critical to take the results in context of the older technology utilized, especially when considering the pediatric age group. Recent advances in these systems have led to improved system performance, accuracy, and user experience; thus, limiting extrapolation of studies conducted with first generation technologies.

4.1 | Categories of sensors

CGM can be divided into three categories: blinded/retrospective CGM, real time CGM, and intermittently scanned/viewed CGM (isCGM).

Blinded CGM is usually applied intermittently over a short period of time providing health care professionals with sufficient information on glucose excursions and patterns to aid with diagnosis, facilitate changes in therapy, and might serve as an educational tool to improve glycemic control.

Real-time CGMs utilize real-time alarms for thresholds and predictions of hypo- and hyperglycemia, as well as rate of change alarms for rapid glycemic excursion. In addition, new technological developments now enable some CGM sensors to transmit signals to the "cloud," and allow for digital remote monitoring, through which caregivers are able to view a patient's CGM tracing and receive alerts on their own devices, including smartphones, tablets, and smart watches.[95]

Recently, introduced isCGM systems, also known as flash glucose monitoring (FreeStyle Libre, Abbott Diabetes Care, Alameda, California), do not automatically display glucose readings at regular intervals, but report glucose levels only when the user scans the sensor by holding a reader, or a cell phone, close to the sensor. Real-time interstitial glucose levels and glucose trend arrows as well as a graph of current and stored glucose readings are provided on demand. However, these systems do not alarm. While current CGMs for blinded and real-time

use still require calibration using fingerstick blood glucose monitoring results, isCGM systems are factory calibrated, thus eliminating the need for recalibration and increase ease of use and economic feasibility.[96]

Most sensors are self-inserted transcutaneously, and have a lifetime of 6 to 14 days. A new type of long-term implantable sensor for real-time use (Eversense, Senseonics Inc, Germantown, Maryland) is available as an alternative for transcutaneous CGM, with approval in Europe for up to 6-months use while in the United States up to 3-months of use has been approved.

4.2 | CGM use and uptake

The concept of interstitial continuous glucose monitoring has existed since the 1990s with the first system being released by Medtronic in 1999 (CGMS Gold; Medtronic, Inc., Northridge, California). A niche product in the past, CGM use has now become standard of care in many countries. Along with substantial advancement of CGM technology over the past 5 years, CGM uptake has increased as supported by data from big western diabetes registries. In 2012, an analysis from the prospective DPV diabetes documentation and quality management system from Germany and Austria showed that CGM was used in 4.8% of all patients and in 2.3% of all pediatric patients.[97] In 2014, the T1DX registry in the United States reported CGM was used by 6% of children <13 years, 4% of adolescents, and 6% of young adults aged 18 to 25 years.[98] Recent data from both registries suggests that overall CGM use is growing exponentially with usage in pediatric age groups reported at 18.4% (DPV) and 21.7% (T1D), respectively, with highest use among preschool-aged and early school-aged children (28.2% DPV; 44.5% T1DX).[99] Higher use in younger children might be due to better hypoglycemia detection even in children who are unable to express symptoms of hypoglycemia. Furthermore, these youngsters may benefit from reduced number of painful fingersticks and remote monitoring features of the latest system. Apart from technological advances and higher patient satisfaction, greater overall uptake might reflect changes in insurance coverage, provider beliefs, and CGM training practices.

4.3 | Efficacy of CGM

4.3.1 | Impact on metabolic control

Following its market launch, CGM was widely advocated as a great advance, despite limited accuracy, limited duration of use, and limited usability of early generation systems. However, early clinical studies and meta-analysis have demonstrated mixed results demonstrating only limited overall benefit of CGM, particularly in pediatric age groups with use of these early-generation systems.[46,100–102] The Juvenile Diabetes Research Foundation (JDRF) landmark trial, performed in 2008, and its follow-up studies evaluated the benefit of third-generation CGM compared with SMBG for T1D management.[103–106] In adults, CGM use for 26 weeks significantly reduced HbA1c by 0.5% without any increase in hypoglycemia. However, in the younger age groups (8-14 years and 14-25 years) there was no benefit in overall glycemic control associated with CGM use, likely related to <50% adherence in these groups. A secondary analysis of the JDRF cohort demonstrated a benefit across all age groups when the sensor was used ≥6 days/week.[105] Furthermore, when restricting the analysis to those already in optimal glycemic control (HbA1c <7.0%), the same group showed that CGM is of benefit, in terms of sustaining HbA1c and reduction in hypoglycemia.[104]

Studies and analyses conducted since 2010, utilizing fourth and fifth generation CGM systems, have more consistently shown that use of real-time CGM improves glycemic control in both children and adults with T1D in terms of improved HbA1c levels and reduced glucose variability.[98,100,106–113] Clearly, the benefit of CGM is seen primarily in those patients with near daily use.[100,106,111,114] However, evidence regarding positive impact of CGM on glycemic control in younger children is still limited. Although data from small observational studies suggest that CGM can be used successfully in patients <8 years,[115,116] an RCT in children aged 4 to 9 years did not demonstrate improvements in glycemic control even over extended CGM use.[117] In toddlers <4 years, there was no difference in HbA1c after 6 months of use; however, there was a high degree of parental satisfaction and sustained use of the devices.[118]

While earlier analysis and guidelines were favoring CGM use in combination with pump therapy,[46,94,101,119] there is now emerging evidence that improvement in glycemic control is equivalent in users of insulin pump therapy and MDI therapy.[112,120–122]

4.3.2 | Impact on hypoglycemia

RCTs evaluating the benefit of CGM mainly focused on HbA1c as the primary outcome. Apart from the SWITCH study showing a significant effect of adding CGM to insulin pump therapy on time spent in hypoglycemia,[111] most studies failed to demonstrate a significant, or relevant reduction, in mild hypoglycemia.[103,107,117,123–127] Notably, RCTs primarily aimed at hypoglycemia prevention did demonstrate a significant reduction in mild hypoglycemia in terms of reducing the time spent in hypoglycemia by approximately 40%, and reducing the number of mild hypoglycemic events per day.[104,110] Clear evidence on the positive impact of CGM on severe hypoglycemia is missing. Only one RCT reported a significant increase in severe hypoglycemic events using CGM as compared with SMBG.[124] Notably, one RCT in pediatric patients reported a significant decrease in severe hypoglycemia using CGM.[128] However, data from meta-analysis published in 2011 and 2012 suggest that there is no significant difference in incidence rates of severe hypoglycemia between CGM and SMBG; yet, this likely represented what was capable with older generation CGM systems.[100,101] In adult patients with T1D and impaired hypoglycemia awareness, data from a recent RCT[129] and from an observational study[130] suggest reduced severe hypoglycemia using CGM compared with SMBG; thus, supporting the concept of using CGM in this high-risk population.

4.3.3 | Intermittent use of real-time and retrospective CGM

Although intermittent application of retrospective or real time CGM may be of use in children and adolescents with T1D to detect postprandial hyperglycemia, the dawn phenomenon, asymptomatic and nocturnal hypoglycemia, and in evaluating the effect of major changes

in treatment regimens,[131–133] there are no data that support long-lasting clinical benefits of short-term applications of CGM.[134]

4.4 | Accuracy of CGM

The accuracy and precision of first generation CGM systems were notably inferior to those of capillary blood glucose monitors. Over the past 5 years, however, there has been continuing improvement in the accuracy of CGM sensors. Overall accuracy of the latest sensor generations measured as the mean absolute relative difference (MARD) vs a given laboratory standard is in the 8% to 14% range,[96,135–138] with some sensors reaching the proposed mark sufficient to permit self-adjustment of insulin dosage without confirmatory capillary blood glucose measurements (MARD, <10%).[139] Sensor accuracy depends on the glucose level and rate of change, with lower accuracy in the hypoglycemic range and at rapidly changing blood glucose (BG) concentrations.[140,141] In the REPLACE BG study, Aleppo et al recently demonstrated that non-adjunctive use of CGM (ie, adjustment of insulin dosage without confirmatory capillary glucose measurement) is as safe and effective as using CGM and confirmatory blood glucose readings in adults with T1D.[142]

4.5 | Non-adjuvant use

Real-time CGM systems were originally approved for adjunctive use, meaning the sensor glucose results needed to be verified by capillary SMBG before taking action. The latest generation of Dexcom sensors (G5 and G6 Mobile CGM, Dexcom, San Diego, California) has received Food and Drug Administration (FDA) and CE approval for non-adjunct use in persons aged 2 years and older.[143] Outside the United States, FreeStyle Navigator II (Abbott Diabetes Care, Alameda, California) is approved for diabetes management including insulin dosing when glucose is not changing rapidly. The Abbott Libre Flash Glucose Monitor (Abbott Diabetes Care) is approved for treatment decisions if the person is not hypoglycemic, if glucose is not changing rapidly, and if symptoms are concordant with the system readings. Some have called into question whether this approval for non-adjunctive use of sensors was based on patient testimonials and not clinical evidence. It is noted that nearly 40 000 instances of device inaccuracy have been reported, with some leading to deleterious consequences including loss of consciousness, seizures, motor vehicle accidents, hospitalizations, intensive care unit stays, and deaths.[144] Yet, the presumption here is that the accuracy of blood glucose meters exceeds what is achieved by sensor therapy.[145] Ekhlaspour et al recently assessed 17 commercially available glucometers and found MARD to be quite variable, ranging from 5.6% to 20.8%.[146] Indeed, only one-third of the meters assessed met the latest International Organization for Standardization standard (IWO 15197-2013).[146] Furthermore, the T1DX REPLACE BG study provided evidence of the safety and effectiveness of non-adjunctive sensor use and registry data indicates only 26% of participants using CGM always verified the sensor glucose by performing SMBG .[142] Practical guidelines for non-adjunctive use are being developed.[147–154] However, research and clinical experience on non-adjunctive use of CGM systems are limited in pediatric populations.[155]

4.6 | Intermittently scanned/viewed CGM

Recently introduced isCGM systems are factory calibrated, small in size, light weight, have good user acceptance and satisfactory accuracy with an overall MARD of 11% to 14%.[122,156,157] Outside of the United States, the device is approved for 2-week wear, as compared to the 10-day approval granted by the FDA. Results of a large multicenter RCT, known as IMPACT, demonstrated that use of a isCGM system statistically reduced the time adults with well controlled T1D spent in hypoglycemia, reduced glucose variability, and improved time in range (TIR) (3.9-10.0 mmol/L, 70 to 180 mg/dL) when compared to self-monitoring of blood glucose with capillary strips.[122,158] Benefits were identical for users of MDI and insulin pump therapy. This is supported by a range of non-controlled observational studies highlighting the potential of isCGM technology to improve clinical outcomes including HbA1c in adults with diabetes.[158–160] Limited evidence in terms of effectiveness of isCGM systems is available in the pediatric population. As of February 2018, this system is CE marked for use by adults and by children (age 4-17 years). The FDA has approved the device in those aged 18 and over, but has required a longer start-up time (12 vs 1 hour) and a shorter duration of use per sensor (10 vs 14 days). Differences in Consensus error grid accuracy have been noted on the first day as compared to other days of wear (zone A day 1 = 72.0% vs day 2 = 88.4%), which may have led to the decision for the longer duration prior to availability of sensor glucose data for the device in the United States.[96]

4.7 | Implantable sensors

A new type of long-term implantable sensor (Eversense, Senseonics Inc, Germantown, Maryland) is available as an alternative for transcutaneous CGM. In Europe, this sensor has been approved for up to 6-months of wear, while in the United States it has been approved for up to 3-month duration. Safety and accuracy (MARD = 11.1%) of this implantable system was demonstrated in a prospective multicenter pivotal trial,[138] with a subsequent study demonstrating improved accuracy with a MARD of 8.8%.[161] Implantable sensors may provide additional ease of use over standard transcutaneous CGM systems, since frequent sensor insertions through the skin are not needed. However, the need for implantation and removal through a minor in-clinic procedure by a trained health care professional is a significant limitation of the system, particularly in regards to its potential application in the pediatric population where there is no data available yet.

4.8 | Practical considerations

Success with CGM requires detailed education and training in diabetes management coupled with extensive training in the use of CGM and high level of contact during the first months of wear.[151,155,162] Table 3 provides some components that should be considered as sensor therapy is initiated.

Educational materials should also be provided to teachers at school.[163] Written individualized health care plans should be provided and agreed upon between parents, school nurses, professional caregivers, teachers, and the child, when appropriate.[164] Decreased

TABLE 3 Basic guidelines for starting sensor therapy

Insertion and adherence
- Time spent at initiation of sensor therapy to ensure adequate insertion technique will allow for easier incorporation of the device.
- Use of supplementary adhesive products may be required. These include:
  - Wipes: skin tac IV prep, skin prep
  - Dressings and barriers: tegaderm, IV-3000, hypafix
  - External Wraps: Coban, PreWrap
- Adhesive removers may be required to help remove the sensor. These may include specialized adhesive removers like unisolve or detachol, or products one may have at home, like baby oil.

Calibration
- For those sensors requiring calibrations, discussion of frequency of calibrations and ideal times to calibrate should be held.
  - Consider preemptive calibration schedule. If calibrations are required every 12 hours, encourage patients to calibrate three times a day (eg, prior to breakfast, dinner and bedtime)
  - Discuss calibrating when glucose is relatively stable (no arrows present, no rapid change on sensor glucose graph)

Alerts and alarms
- Consider leaving alerts off as patients initiate sensor therapy. This may help prevent alarm fatigue.
- When incorporating alerts, personalize them and use wide thresholds at first (ie, 70-250 mg/dL [3.9-13.9 mmol/L]). These can be adjusted over time.
  - For those with recurrent hypoglycaemia, set low alert first.
  - For those with sub-optimal control, set high alert first.
- In the beginning, do not employ rate of change or predictive alerts. Consider how these additional alerts may be actionable moments prior to incorporating them. This will help prevent alarm fatigue.

Retrospective review
- Encourage downloading, if this is required to review data.
- Encourage retrospective review of data to help inform insulin dose titrations.

Real-time data
- As appropriate discuss, non-adjunctive use of sensor data
- Consider recommendations on adjustments of insulin doses based on sensor glucose values. This may be based off of an individual's correction factor to guide alterations in insulin dosing[155]

supervision during school days could be overcome by recently available remote monitoring capabilities of CGM systems and collaborative intensive diabetes management by parents and daytime care-collaborative givers.[165] Additional discussion of the psychosocial elements of CGM sharing are reviewed later, in this chapter.

CGM systems allow a wide variety of alert settings. Many people with diabetes are willing to accept the burden of alarms. However, many also experience alarm fatigue. Hence, when setting up alerts, it may be inappropriate to enable all of the alert types at once. Hirsch et al suggest initial threshold values of 70 and 250 mg/dL (3.9 and 13.9 mmol/L) and further suggest a stepwise introduction of alarms.[166,167]

Barriers to long-term use of CGM sensors include sensor adhesiveness and skin irritation, particularly in young children where body surface is limited. Supplementary adhesive products (eg, liquid adhesives, adhesive wipes) and external wraps are recommended to help secure the sensor to the skin.[168] The number of reports about (severe) skin reactions to the sensor adhesives is quite limited, but might be under-reported.[169] Skin issues might become more prevalent due to longtime use of sensors and availability of devices with longer wear time. Transparent dressings, special tapes, and barriers could be used in case of allergic reaction to the sensor adhesive or skin irritation from the plastic or metal components of the sensor/transmitter unit. Additionally, regular site rotation to prevent rashes and dry skin due to frequent application, and removal of sensor adhesives are recommended.[168] Adhesive remover could be used to make the sensor removal less traumatic for both the patient and the skin.[168]

5 | SENSOR-AUGMENTED PUMP THERAPY

SAP therapy, defined as combination of the technologies described above (insulin pumps and CGM), represents the first step on the path toward an artificial pancreas.

5.1 | A single platform: The beginnings of SAP therapy

The first RCT comparing SAP to insulin pump therapy in those with T1D showed similar reductions in HbA1c after 6-months, but, this was associated with significantly increased hypoglycemia exposure in the insulin pump with SMBG group.[124] Reduction in HbA1c was recorded in those who had at least 60% sensor utilization.[124]

The **S**ensor-Augmented Pump **T**herapy for **A**1c **R**eduction (STAR) 3 study randomized participants to either SAP or maintained them on MDI therapy with conventional SMBG checks for a 1-year study period and reported a greater reduction in HbA1c was associated with an increased frequency of sensor use. Children, defined as those ages 7 to 12, had a ×1.5 higher use of sensors as compared to the adolescent cohort, who were 13 to 18 years old.[170] Those using SAP were more likely to attain the 2010 American Diabetes Association (ADA) age adjusted HbA1c targets, have decreased hyperglycemic exposure, and decreased glycemic variability.[107,170] While rates of severe hypoglycemia and DKA did not differ among the treatment groups, frequency of these events was relatively low in the entire study cohort.

Glycemic variability, measured as sensor glucose SD and coefficient of variation (CV) in the STAR3 group was assessed.[171] Those with HbA1c <8% in the SAP group were found to have lower sensor glucose SD and CV than those in the control group, suggesting that glycemic excursions may be reduced with use of this technology in an HbA1c independent manner.[171] At the end of the year-long STAR3 trial, a 6-month continuation phase demonstrated that those participants (including children) initially randomized to SAP-maintained improvements in HbA1c levels at the 18-month mark and those who were in the control arm and crossed over to SAP also achieved significantly decreased HbA1c.[109,171]

5.2 | Low glucose suspend systems: Reducing the severity and duration of hypoglycemia

With integration of CGM data and insulin pump delivery into one device, the next logical step is to alter insulin delivery based on sensor glucose readings. As fear of hypoglycemia may preclude patients and providers to attain targeted control and knowing that suspension of insulin is less "risky" than automating insulin delivery, investigation into low glucose suspend (LGS) systems began. Feasibility data on the efficacy and safety of LGS from early closed-loop studies demonstrated the ability of insulin suspension to mitigate the risk of hypoglycemia .[172,173]

Current LGS systems interrupt insulin delivery for 2 hours when sensor glucose reaches a predefined low sensor threshold and automatically resumes insulin delivery regardless of current sensor glucose levels. The **A**utomation to **S**imulate **P**ancreatic **I**nsulin **Re**sponse (ASPIRE) in-clinic study demonstrated that the mean duration of hypoglycemia was shorter with LGS-On and the nadir glucose was slightly higher.[174]

Next, the ASPIRE in home study reported a 37.5% reduction in the primary end-point—area under the curve (AUC) <3.9 mmol/L (<70 mg/dL) for nocturnal hypoglycemia—in the SAP with LGS vs SAP.[174,175] More importantly, percentages of sensor readings <3.9 mmol/L (<70 mg/dL), <3.3 mmol/L (<60 mg/dL), and <2.8 mmol/L (<50 mg/dL) were all significantly reduced in the SAP with LGS as compared to SAP alone; yet, despite this reduction in hypoglycemia there was no deterioration in glycemic control as measured by HbA1c.[175] After 2-hours of nocturnal insulin suspensions, sensor glucose was 92.6 ± 40.7 mg/dL (5.1 ± 2.6 mmol/L) and 168.8 ± 64.6 mg/dL (9.4 ± 3.6 mmol/L) at 4 hours post-initiation of the suspension.[175]

The benefits of a LGS system in those with proven impaired hypoglycemia awareness were shown by a reduction in combined severe (seizures/coma) and moderate hypoglycemia favoring the LGS vs pump with SMGB group.[176] There were 0 severe hypoglycemic events in the LGS arm vs 6 events in the pump with SMBG (P = 0.02) and significantly less percentage of time was spent in hypoglycemia, particularly during the night.[176]

Observational studies have corroborated the results from the two RCTs described above. A pediatric observational study included 21 children and compared a 2-week run-in period where low sensor glucose alerts were set to sound at 75 mg/dL (4.2 mmol/L) to 6-weeks with the LGS feature on.[177] A full 2-hour suspend most often occurred during the night and AUC <70 mg/dL (<3.9 mmol/L) was significantly smaller during LGS-On vs LGS-Off.[177] Finally, an analysis of uploaded data from 935 patients providing 49 867 patient-days (with LGS used for 82%) was performed,[178] only 11% of the suspensions lasted for >115 minutes, with the mean sensor glucose during these episodes being 59 ± 12 mg/dL (3.3 ± 0.7 mmol/L) at LGS activation, 102 ± 53 mg/dL (5.7 ± 2.9 mmol/L) by the end of the LGS episode, and 150 ± 69 mg/dL (8.3 ± 3.8 mmol/L) 2 hours after insulin delivery resumed.[177,178] This delayed rise in glucose despite resumption of insulin 2 hours prior represents the pharmacodynamic profile of current rapid acting insulin analogs, as peak insulin action is 1 to 3 hours after administration.[179]

To address concerns of what could happen if insulin suspension occurred based off the readings of an inaccurate CGM, random 2-hour preprogrammed insulin suspensions were conducted overnight in a cohort of participants in their home setting as long as pre-bed blood glucose was <300 mg/dL (16.7 mmol/L) and blood beta-hydroxybutyrate (BHB) levels were <0.5 mmol/L.[180] A total of 118 suspend nights were compared to 131 non-suspend nights and showed the morning after suspensions, blood glucose was ~50 mg/dL (2.7 mmol/L) higher but there was no clinically meaningful difference in BHB levels.[180]

5.3 | Mitigating hypoglycemia: The benefits of predictive low glucose suspend

Furthering the automation process, predictive low glucose suspend (PLGS) systems suspend insulin delivery in hopes of preventing hypoglycemia. In 45 participants between the ages of 15 and 45 years, the system reduced hypoglycemia exposure by 81% and time spent <60 mg/dL (<3.3mmo/L) by 70%.[181] The same system assessed in a pediatric cohort reduced median time <70 mg/dL (3.9 mmol/L), while not leading to a difference in BHB levels in the morning.[182] The system was found equally efficacious in all groups.[183]

The MiniMed 640G and 670G system (Medtronic, Northridge, California) provide the PLGS feature in clinical practice, which interrupts insulin delivery if the sensor glucose is predicted to reach 20 mg/dL (1.1 mmol/L) above the preset low glucose limit within 30-minutes and automatically resumes basal insulin delivery after recovery from hypoglycemia. An in-clinic assessment utilized basal rate increases to induce hypoglycemia with the system set at 65 mg/dL (3.6 mmol/L); hypoglycemia was avoided in 60% of the 69 experiments.[184] A RCT conducted in 100 children and adolescents with T1D demonstrated that use of the PLGS feature reduced the number of hypoglycemic events.[185] However, the authors note that use of the PLGS feature led to a concomitant rise in the time spent in the hyperglycemic range.[185] More recently, a 6-month multicenter RCT demonstrated the ability of this feature to reduce time spent with sensor glucose <63 mg/dL (<3.5 mmol/L), with no change in HbA1c level at the end of the study.[186] In a real-world assessment, initiation of the PLGS system while at camp was shown to be possible and there was persistence of sensor use, with 74% of the cohort at 3-months and 66% of the cohort achieving sensor wear at least 70% of the time.[181,187] It was proposed that this continuation of sensor use was due both to adequate education at initiation of therapy as well as the benefits of PLGS feature.[187] More recently, Tandem received FDA approval of its PLGS system, the t:slimX2 insulin pump with Basal IQ Technology (Tandem, San Diego, California), which uses the Dexcom sensor. Supporting approval of this system, a RCT of 102 participants found that the PLGS system led to a 31% relative reduction overall in sensor time <70 mg/dL (<3.9 mmol/L) by 31%.[188]

Highlighting the safety of a PLGS system, BHB levels were assessed on 1954 mornings, half of which occurred after an intervention night.[189] Frequency of BHB >0.6 mmol/L was not different between the two study conditions supporting the recommendation that assessing for ketones should not be different regardless of whether a patient is using a PLGS system.[189]

5.4 | Practical considerations

Success with SAP, in many ways, hinges on integration and understanding of the system components, namely the CGM and pump. Scaramuzza et al have provided a framework by which to initiate PLGS in children.[190] Topics that should be considered when initiating these therapies may include expected frequency of sensor use, and how treatment may vary when breaks from sensor therapy may occur. This may be especially important in those utilizing systems that

suspend insulin delivery as behavioral changes may be needed to mitigate the risk of hypoglycemia when the system is not actively being use.

Discussion should be held regarding whether alarms should be set for when suspensions occur. Furthermore, patients are usually encouraged to allow LGS systems to work overnight, but should an alert occur while the patient is awake, they can consume carbohydrates. With a PLGS system, should a hypoglycemic event occur despite insulin suspension carbohydrate intake may need to be decreased as compared to usual treatment strategies to prevent rebound hyperglycemia. Analysis of downloads can assist decisions regarding frequency of suspending insulin and whether changes in insulin doses and treatment for low blood glucose values is required.

6 | CLOSED LOOP SYSTEMS

Automated insulin delivery systems consist of three components: an insulin pump, a continuous glucose sensor, and an algorithm that determines insulin delivery. These systems not only suspend insulin delivery, like the LGS and PLGS system discussed above, but also can increase insulin delivery based on sensor glucose values. Single hormone (insulin) and dual hormone systems, which consist of insulin and another hormone like glucagon or pramlintide, have been tested. Several automated insulin delivery platforms exist utilizing various combinations of insulin pumps, CGMs and algorithms. There are three core algorithm constructs: (1) proportional integrative derivative (PID),[191] (2) model predictive control (MPC)[192] and (3) fuzzy logic.[193]

6.1 | Adopting a hybrid approach

Early, fully closed loop studies found significant postprandial glycemic excursions compared to a premeal bolus[194] due to the delay of insulin absorption and the delayed onset of action of currently available rapid acting insulin analogs. Now, the majority of automated insulin delivery systems use a "hybrid" approach, where background (or basal) insulin is controlled by the algorithm, but the user needs to manually announce meals with carbohydrate estimation combined with capillary glucose level and deliver an insulin bolus. Nevertheless, the technical evolution in automated insulin delivery systems has been rapid, from proof of concept experiments published in 2006[195] to the first commercial release of a single hormone hybrid system (Minimed Medtronic 670G, approved in the United States only, for those aged 14 years and over in 2016, and by 2018 it has received CE mark and FDA clearance for those 7 years and older), taking just over a decade to see this technology available in clinical care.

6.2 | Controlled studies: From the clinic to transitional settings of camps and hotels

Early studies focused on demonstrating feasibility of automated insulin delivery in carefully controlled in-clinic studies, and were conducted in a range of patients including children,[196,197] adolescents,[196–204] adults,[197,199,201,203–211] and in pregnant women.[212] These included single hormone,[196,197,200–202,206,207] dual hormone systems,[198,199,205,208,209] and the incorporation of insulin absorption adjuncts.[203,204,210,211] In-clinic studies that simulated hypothetical real world challenges including exercise,[209,213–215] alcohol,[206] high fat meals,[206] and inaccurate continuous glucose sensors[213] followed, and demonstrated that the automated insulin delivery systems remained safe and effective. Accordingly, closely supervised outpatient studies at diabetes camps for children and adolescents,[55,216–222] and hotel studies for adults[223–226] were conducted. All studies consistently showed safety and a 10% to 20% improved time spent in target glucose sensor range of 70 to 180 mg/dL (3.9-10 mmol/L) with a concomitant reduction in time spent hypoglycemic, in comparison to either conventional insulin pump therapy, or SAP therapy.

6.3 | Free living assessments of automated insulin delivery

"Free-living" outpatient studies, despite heterogeneous design and a range of different automated insulin delivery systems, have invariably demonstrated safety and efficacy. Very young children,[227] adolescents,[228–237] adolescents with sub-optimal control,[238] and adults[79,228–230,232–234,236,237,239–245] all demonstrated a 10% to 20% improvement in TIR compared to insulin pumps, SAP or SAP + LGS, and less time spent with hypoglycemia. Some studies used automated insulin delivery overnight only,[228,230–234,236,237,239,243,245] while others applied automated insulin delivery for 24 hours a day.[79,227,229,235,237–240,242,244] In the 24-hour use studies, the improvement in overall time spent in range is mainly due to improved overnight glucose levels. In a meta-analysis that included free living, camp and hotel studies, time in target range of 70 to 180 mg/dL (3.9-10 mmol/L) improved by 12.59% using automated insulin delivery compared to insulin pumps or SAP.[246] There have been no reports of severe hypoglycemia or DKA during the use of automated insulin delivery.

The longest outpatient RCT published to date by Thabit et al compared a model-predictive-control automated insulin delivery device to SAP for 12 weeks.[237] There were two sub studies included; (1) a cohort of 33 adult participants who used the system 24 hours per day, and (2) a child and adolescent study (n = 25) who used the system only overnight. Adults improved time in target range (3.9-10 mmol/L) by 11%, and the children and adolescents improved overnight glucose time in target range 70 to 145 mg/dL (3.9-8 mmol/L) by 24.7%.[237] A 3 month non-controlled trial using the only commercially available automated insulin delivery system (Minimed Medtronic 670G) (n = 124) demonstrated safety,[247] and improved HbA1c in adults (7.3% $\pm$ 0.9% to 6.8% $\pm$ 0.6%) and adolescents (7.7% $\pm$ 0.8% to 7.1% $\pm$ 0.6%).[137] Recently, data on the use of the same system in 105 participants aged 7 to 13 years demonstrated a reduction in HbA1c (7.9%-7.5%, P < 0.001) and an increase in time in target range by ~9%.[248] The system has now obtained CE Mark and FDA approval for patients aged 7 and up.

Use of automated insulin delivery systems have been shown to reduce nocturnal hypoglycemia following physical activity occurring in the afternoon[215] and increase TIR as compared to open-loop therapy.[222,249] Yet, the ability to mitigate hypoglycemia during exercise

has remained elusive leading to the development of different system announcements, incorporation of heart rate data, dual hormone approaches, and intake of carbohydrates being applied to overcome this obstacle.[214,250–253]

High user acceptability and improved measures of treatment satisfaction have been shown.[254–257] However, it should be noted that device alerts and alarms and technical difficulties can negatively affect the overall experience using automated insulin delivery.[256]

6.4 | Practical considerations

As the first commercially available hybrid closed loop system penetrates the market, clinicians will need to be prepared to assist their patients in adopting this technology. Furthermore, it is expected that in the coming years a number of other companies and academic groups will see regulatory approval of their first-generation systems as their pivotal trials are planned. To ensure success with adoption of this technology, it will be important for clinicians to have a framework to integrate this technology. Use of the acronym CARE, has been suggested as a strategy to help clinicians conceptualize the differences between automated insulin delivery systems.[258] This acronym can assist clinicians in answering four fundamental questions related to the patient and device, and include:

- **C**alculate: How does the system CALCULATE insulin delivery?
- **A**djust: How to ADJUST insulin doses—immediately and long term?
- **R**evert: When to stop automated insulin delivery and REVERT to pump settings; also, when the system automatically REVERTS to pump mode?
- **E**ducate: Where does the user/provider find EDUCATION resources?

It will also be important to reinforce with patients the tasks that will be necessary to utilize automated insulin delivery, which at least will include having a functional CGM and use of a pump, as well as bolusing for carbohydrate intake when using a hybrid closed loop system. Indeed, for many patients currently struggling with diabetes management, education on these foundational skills will be critical to ensure they are afforded equal access to these systems while setting the stage for success. Finally, reviewing with patients how to treat both hyper and hypoglycemia will be important. Carbohydrate intake required for hypoglycemia may need to be reduced with prolonged basal insulin suspension. Conversely, patients will need to be reminded about the risk of infusion set failures that may lead to persistent hyperglycemia and the potential for ketosis. While automated insulin delivery holds the promise of reducing glycemic variability, it will be critical to discuss realistic expectations as patients adopt these technologies to help mitigate the frustration they may feel as early systems will likely require user input and not be a set and forget device. Moreover, how best to expand access to these systems is a top priority that will require exploration of both the economic as well as educational challenges that remain.

7 | DIABETES APPS, AUTOMATED DECISION SUPPORT, AND BOLUS CALCULATORS

7.1 | Diabetes applications

Patients with T1D who are on MDI therapy may seek to obtain some of the benefits of the calculators and bolus wizards of an insulin pump via use of a cell phone based mobile application “app” on their smart phone. In addition, patients on pumps and/or CGM may seek to gather all of their data in one place and receive advice on bolusing, carbohydrate amounts, or device tuning. Apps cover a broad spectrum of self-management activities from simple blood glucose logs and dosing reminders,[259,260] to carbohydrate counting and bolus calculators[261]; also reaching into the realm of providing incentives to bolus and peer support.[262] The challenge for many patients, however, is that there are over 165 000 general health-related apps which may aid in assessment of diet and physical activity, and over 1100 diabetes-specific apps from which to choose.[263] With this wide variety and rapidly changing landscape, little guidance is available to patients on what app may be right for them. Similarly, physicians and educators may find it difficult to be aware of the spectrum of options for their patients. Most available apps are not evidence based,[264] and one study concluded that few are informed by either users or professionals during their development.[265] A recent cross-sectional survey by Trawley et al investigated demographic, clinical, and psychological variables associated with app use.[263] They found that in Australia, 21% of adolescents reported using an app for diabetes management with 89% of those using it for carbohydrate counting assistance.[263] App usage was associated with shorter duration of T1D, higher socioeconomic status, and more frequent blood sugar testing. Barriers to app use were identified as lack of awareness of suitable products and the belief that the app would not provide benefit.[263]

Providing evidence-based recommendations on diabetes apps has been similarly difficult. In 2016, Hou et al conducted a review and meta-analysis of 14 randomized trials on apps and their impact on HbA1c identifying 1360 participants in 14 studies.[266] They found that for patients with type 2 diabetes (T2D), there was a significant overall improvement in HbA1c of −0.49 (−0.68, −0.30)% in the app-use groups compared to the control groups.[266] For patients with T1D, however, there was no significant improvement in HbA1c −0.36 (−0.87, 0.14)%.[266] Another review from 2017 by Wu et al attempted to identify functions of apps associated with glycemic efficacy.[267] They identified 974 participants across 12 trials, with some trial overlap with the Hou review. They similarly identified significant HbA1c improvement in patients with T2D with HbA1c reduction of −0.52 (−0.85, −0.18), without significant improvement in patients with T1D.[267] App characteristics associated with greater HbA1c improvement included having a complication prevention module and having a structured display. They did not find having a clinical decision-making function to be associated with HbA1c reduction.[267]

Table 4 provides a good starting point for app recommendation as of this writing in 2018. Some apps such as Calorie King and My Fitness Pal are general health apps that provide information beneficial to patients with T1D. These apps may assist patients with carbohydrate

TABLE 4 Diabetes apps, automated decision support, bolus calculators, and downloading software

App	Category	Website	Phones Supported	Cost	BG Meter Integration	Pump and/or CGM Integration	Decision Support	Evidence Based Research
Bant	Diabetes	www.bantapp.com	iPhone and Android	Free	None	None	No	Yes
Calorie King	General health	www.calorieking.com	iPhone and Android	Free	N/A	N/A	N/A	No
Glooko/Diasend	Diabetes	https://glooko.com	iPhone and Android	$$ Subscription	Over 60 BGM's digitally uploadable	Animas, Dexcom G4 or G5, Omnipod, Medtronic, Tandem	No	Yes, FDA cleared, HIPAA compliant
My Fitness Pal	General health	www.myfitnesspal.com	iPhone and Android	Free for Basic $$ for Pro	N/A	N/A	No	No
mySugr	Diabetes	https://mysugr.com	iPhone and Android	Free for Basic $$ for Pro	Any BGM via photo of number	FreeStyle Libre or Medtronic CGM	In Pro version (EU only)	Yes
One Drop	Diabetes	onedrop.today	iPhone and Android	$$ Subscription	Via One Drop BGM, other BGM via Apple Health	Dexcom integration via Apple Health	Via coaching subscription	Yes
Sugar.IQ	Diabetes	none	iPhone	Free for Medtronic users	Via Medtronic Pump	Medtronic pump and CGM	Yes	Yes, FDA Approved
Tidepool	Diabetes	https://tidepool.org	iPhone and Android	Free for user version	Bayer, Abbott, and OneTouch	Animas, Dexcom G4 or G5, Omnipod, Medtronic, Tandem	No	Yes

Abbreviation: BG, blood glucose; BGM, blood glucose meter; CGM, continuous glucose monitor; FDA; Food and Drug Administration; HIPPA , health insurance portability and accountability act; N/A is not applicable.

counting as well as exercise tracking. More diabetes-specific apps such as Bant, Glooko, mySugr, One Drop, and Tidepool enable patients to maintain a digital diabetes log on their phone, often interacting directly or indirectly with their BGM, some even assist with carbohydrate counting and insulin bolus calculations. Indeed, the Dreamed Advisor Pro, which analyzes the volumes of data that fill each patient's life including insulin dosing, blood glucose readings, and other factors such as carbohydrate intake and then suggests alterations in insulin dosing, has recently received regulatory approval in Europe and is currently under review by the FDA. Additionally, the Sugar.IQ diabetes assistant (Medtronic, Inc., Northridge, California) allows those wearing the Guardian 3 sensor to be alerted to patterns in their CGM tracings, which may lead to investigation of whether behavioral changes or insulin dose adjustments would be warranted. For patients on CGM or insulin pumps these apps may allow uploading of their device data to be reviewed by their diabetes health care team.

7.2 | Bolus calculators

Despite advances in other areas of technology, accurately counting carbohydrates and bolusing based on an insulin to carbohydrate (I:C) ratio prior to meals will remain a key to optimal diabetes therapy for the near future. The need to perform calculations for the I:C may also be complicated for some patients and is prone to simple human error. Insulin pumps have long offered bolus calculators which handle the I:C and correction factor calculations and account for active insulin on board (IOB), generally resulting in a positive impact on glycemic control.[268] Similar bolus calculators are now available on some commercial blood glucose meters or as cell phone apps.[269,270] The Automated Bolus Advisor Control and Usability Study (ABACUS) showed that significantly more patients using the bolus calculator achieved an HbA1c reduction of >0.5% compared to the control group (56% vs 34%; $P < 0.01$).[271] A recent study showed a significant increase in the number of patients achieving HbA1c targets and a reduction in hypoglycemia in the bolus calculator use group compared to the active control group.[272,273] In patients on insulin pump therapy, the rate of bolus calculator use has been correlated with improved glycemic control in both the adult and pediatric populations.[268,274,275] Overall, these studies show that for MDI and conventional insulin pump patients, use of a bolus calculator reduces burden, improves glycemic control, and improves quality of life.

7.3 | Automated decision support systems

Beyond the simple arithmetic of calculating insulin dosing for meals is the more complex tuning of insulin dosing parameters. To better aid patients with insulin dosing adjustments between visits, multiple groups are developing automated decision support systems that may be used to algorithmically optimize dosing recommendations. Such adjustments may be beneficial for patients on MDI therapy, conventional pump therapy, and may even help tune emerging artificial pancreas systems. Wang et al conducted a pilot study assessing a learning-type artificial pancreas, which showed significant improvement in the time spent in target range with use of this learning system

vs open loop control (P = 0.02).[276] Dassau et al conducted a randomized crossover trial where algorithmic adjustment of open-loop settings was conducted prior to artificial pancreas (AP) control and was compared to AP control without algorithmic adjustment, similar TIR was noted between the two groups.[277] Recently, DreaMed Diabetes obtained CE Mark clearance and FDA approval for its Advisor Pro (DreamMed Diabetes LTD, Petach Tikva, Israel) which is a decision support tool that aggregates and analyzes data from patient downloads and provides dose adjustment recommendations, which must be signed off by a health care provider prior to distribution. Further work in this area is ongoing with extension to the MDI population in several studies that are ongoing in 2018.

8 | DOWNLOADING TECHNOLOGIES

Insulin pumps, CGMs, and most blood glucose meters have the ability to be downloaded onto either the manufacturer's platform or a uniform secondary service. Downloading of device data enables patients and their caregivers to visualize graphics, see summary statistics and review trends in glycemic data. It also enables clinicians and diabetes educators to review such data remotely between visits and make more frequent dosing adjustments. Wong et al found that routinely downloading and reviewing glycemic data was associated with a significantly lower HbA1c (7.2% ± 1.0% vs 8.1% ± 1.6%; P = 0.03).[278] Despite this positive association, they showed that only 31% of adults and 56% of caregivers reported ever downloading data from devices, and even fewer routinely reviewed the downloaded data.[278] In a commentary to this article, Beck presented previously unpublished data from the T1DX showing that participants reported rarely or never downloading their devices for BGM (75%), CGM (51%), and insulin pumps (59%).[279] To date, there have been no published reports investigating barriers to device downloading, but anecdotal experience suggests that patients have difficulty with the downloading software, do not remember their log in information, do not have the necessary cables, and may not find the downloaded information to be directly beneficial to them. More patient centered platforms such as Glooko/Diasend, Tidepool, and One Drop seek to bridge this divide and empower patients to download and visualize their own data via improved connectivity and user interfaces. In addition, many device manufacturers are working towards perpetually connected devices which utilize cell phone and Wi-Fi connectivity to continually download data; thus, relieving the burden of periodic downloading placed on patients. These efforts may reduce or eliminate user burden associated with device downloads in the future, though review of the data by the patient, or their care provider, will still be necessary for optimal benefit to be seen.

9 | TELEHEALTH

As the vast majority of youth fail to meet glycemic targets, consideration needs to be given to alternative care models to help improve care. Telemedicine is a practice by which video conferencing is utilized to deliver health care to patients in their local region. Telemedicine has a particularly valuable role in allowing specialized tertiary centers to reach out to patients and health care professionals in rural or remote locations.[280,281] Typically, video tele-consultation is operated in real-time providing a virtual face-to-face meeting online with a specialized provider. The clinician has access to the patient medical record and provides oral and written advice to the patient. Various consultation models are used, including the patient situated in a primary care medical facility, with or without a trained health worker alongside them, or with consultations provided directly to the patient in his/her home.

9.1 | Telemedicine advantages and limitations

ISPAD guidelines recommend that all patients with T1D have their care reviewed every 3 months.[282] The greatest advantage of telemedicine is the ability to provide access to specialized care in remote locations. Reduction in traveling costs and saved working days for parents and school days for children may overcome some of the barriers to adhering to the frequency of follow-up recommended. One method that has been employed previously is having a clinician travel to more remote locations to see patients; yet, in assessing the efficiency of such satellite clinics one would need to consider the travel time and travel cost to the clinician. Thus, telemedicine has the benefit of delivering specialized care while reducing costs of travel to both patients and clinicians, and potentially increasing the likelihood of follow-up visits being completed.

However, telemedicine is limited by access to the required technology at the remote site. Additionally, concerns exist regarding reimbursement for the visits and whether one must hold a license in the location where they practice as well as the location where the patients are being seen. Further, the remote site (either the home, or primary care facility) must have the ability to download glucometers and insulin pumps, when applicable, in order for the specialized team to review clinical data that informs decisions. Body language might be more demonstrative than verbal language and these physical cues may be missed in a teleconference. Additionally, unless the visit is conducted in a medical facility it may not be possible to conduct some recommended components of these quarterly visits including anthropomorphic measures, pubertal staging, and assessment of general health. In a survey of health care providers, the biggest concerns reported in a qualitative assessment of telemedicine were problems with the technology components and a concern about the lack of physical contact with patients.[283] Finally, specifically with respect to adolescents with T1D, discussions regarding risk taking behavior and psychological aspects may be limited due to the challenge of creating a confidential consultation environment. Therefore, consideration should be given to conduct face to face consultations with a specialized service at least annually.

9.2 | Data on telemedicine application to those with diabetes

Data on the use of telehealth in patients with diabetes is encouraging. **T**elemedicine **T**o **R**each, **E**ducation, **A**ccess, and **T**reatment is a program that included adults with diabetes residing in rural communities,

which found participants were generally satisfied with this mode of care delivery, had improvement in HbA1c values, and a better understanding of diabetes.[284]

Assessment on the application of telemedicine in Denmark has been conducted over a 7-year period in those with both T2D and T1D.[285] The program has shown good results in diabetes treatment parameters and has been associated with improved cost-effectiveness and patient satisfaction.[285]

The telemedicine intervention of the **I**nformatics for **D**iabetes **E**ducation **a**nd **Tel**emedicine project, offered in-home telemedicine visits with a diabetes educator for elderly rural adults with diabetes. While some noted difficulties related to the use of the computer,[286] telemedicine resulted in net improvements in self-management, glycemic control, low density lipoprotein (LDL)-cholesterol and blood pressure levels over 1 year,[287] and over 5 years of follow-up in an ethnically diverse, elderly, rural population.[288]

A retrospective analysis of US Army soldiers with T1D who used telemedicine as their mode of care delivery documented clear success based on glycemic parameters with A1c levels trending to targeted control (baseline A1c 9.8%, 3-month 7.3% and end of study 6.9%)[289] Use of telemedicine over a 1-year period in a pediatric diabetes clinic has also been conducted at the Barbara Davis Center, which has a large catchment area including neighboring states. While telemedicine resulted in no alteration in HbA1c levels, frequency of annual visits was increased, the frequency of missed school/work was reduced and financial burdens were decreased.[290] As there is a tendency for deterioration of glycemic control during adolescence, likely secondary to the increased insulin resistance associated with puberty,[291] this lack of rise in HbA1c levels is quite compelling. Others have corroborated these findings through their use of telemedicine in rural areas.[292]

Telemedicine can also be applied in the school setting. A study run with children 5 to 14 years old showed the benefits of once a month telemedicine communication between the school nurse and the diabetes team in addition to the regular care. Children in the telemedicine group had lower HbA1c, improvements in the Pediatric Diabetes Quality of Life questionnaire, and fewer hospitalizations/emergency department visits.[293]

Building on the traditional telemedicine model, Project ECHO (**E**xtension for **C**ommunity **H**ealthcare **O**utcomes) employs primary care clinicians who receive "telementoring" from a specialist to guide the management of their own patients with complex medical conditions.[294] Ongoing assessment of this model is being conducted in those with diabetes, with the primary clinician working in consort with a multi-disciplinary team, with longitudinal assessment of this approach planned.[294]

9.3 | Adoption of telemedicine into clinical practice

Telemedicine has the potential to help reduce disparities in diabetes management especially in remote regions, by improving access to care and reducing health care costs as demonstrated in this study of older adults.[295] While a recent meta-analysis found a mean reduction in HbA1c of 0.18% with use of telemedicine, given the paucity of data available and heterogeneity of the studies included in the analysis, the findings are limited.[296] When impact of telemedicine was investigated by subpopulation, its use was noted to be successful in adolescents with a mean difference in HbA1c of −0.32% between groups.[296] Importantly, those studies with longer duration (>6 months) and those that recruited individuals with higher baseline HbA1c values (≥9%) demonstrated greater benefit.[296] Thus, a cautious optimism can be used when considering application of this technology in the future.

The immediate cost of implementing telemedicine can be high.[297] However, today, less costly smartphones, iPads, and laptop devices are widely available and there are other less well-defined economic benefits due to a positive impact on either the health care system and/or business productivity.

For pediatric patients, one must consider a few important factors in the integration of telemedicine into clinical care. First and foremost, at diabetes onset the initial management and education should be given in person by a multi-disciplinary diabetes team staffed by subspecialists. In regions with established telemedicine programs, the follow-up appointments could alternate between on-site and remote consultations, as body weight and pubertal staging are important factors to consider when adjusting insulin therapy and provides the opportunity to assess any deviations in normal growth and development.[298,299] Taking into account the few, encouraging available studies and the comfort level of both the adolescent age group and parents, there is hope that telemedicine could become an option, interspersed with face-to-face visits for children and adolescents from underserved locations.

9.4 | Limited resource settings

Provider availability is critical in improving health care accessibility.[281] In underserved, undeveloped regions, the first step is to train local health workers to improve diabetes diagnosis and early management. The second step is to encourage health policies, philanthropic organizations and industry to focus on increasing access to insulin, glucose test strips and diabetes education, since advice may be useless if patients do not have the basic supplies need to comply with medical advice. As a third step, telemedicine might be developed to deliver specialized advice in regions with limited access or care.[287,288,295,297] Nevertheless, electricity, internet and technological devices may not be available in some rural underdeveloped areas where remote consultation may be a challenging goal to achieve .[300]

10 | QUALITY OF LIFE/PATIENT SATISFACTION/BURDEN WITH USE OF TECHNOLOGIES

Uptake and use of diabetes devices and technologies are associated with psychosocial and family factors. Psychosocial factors are broadly defined as behavioral, emotional, and social variables that characterize an individual across both dimensions of promoting health (eg, resilience) and having negative effects on health (eg, depression). The focus on psychosocial factors in relation to diabetes device and technology use has grown out of the broader interest in understanding how these factors impact diabetes management and health outcomes. For example, it is well established that personal strength and resilience

factors, along with positive family communication, are associated with optimal management and outcomes.[301,302] Likewise, psychosocial factors such as diabetes distress and depression and family conflict are common in youth with diabetes and often lead to suboptimal management and outcomes.[303,304] Herein, the current understanding of the association between psychosocial factors and device and technology use will be highlighted.

Prior ISPAD guidelines on the psychosocial care of youth and the recently released American Diabetes Association guidelines for the psychosocial care of people with diabetes[10] highlight that attending to the psychosocial needs of all youth and their families is critical. Similarly, when considering whether diabetes devices and technologies should be recommended or encouraged, understanding the psychosocial aspects of the user and family will help optimize a good fit for the device. The most evidence is available for insulin pumps and CGM. Notably, youth on insulin pumps tend to experience a benefit in health-related quality of life,[221–223] but factors such as depression lead to discontinuation of insulin pump use.[70] As noted previously, CGM is linked to optimal glycemic outcomes and many users report greater treatment satisfaction.[225] However, there are reports of heightened worries[305] among adolescents and young adults and many discontinue CGM for a variety of reasons including cost, too many alarms, issues with accuracy, and discomfort wearing a device on one's body.[12] Thus, setting realistic expectations for potential users and their families and providing referrals for any psychosocial need that may serve as a barrier to optimal use, are indicated. In addition, the following recommendations are made when considering device and technology use in diabetes care practices:

- Portray the use of diabetes devices and technologies as an option that can be a good fit for many youth and families; provide education and encourage youth and families to review vetted websites and device informational materials.
- Encourage uptake and refrain from having youth and families "earn" the right to use devices (ie, achieve a certain hemoglobin HbA1c before considering starting a device). If payers/insurance companies require logging or other documentation prior to device approval, convey that directly instead of a requirement of the diabetes care practice.
- Conduct a brief assessment of barriers to uptake and use. Common barriers are cost (often noted by parents of youth), wearing multiple devices, sensation of wearing a device on changing and growing body, frequent alarms and maintenance of device.
- Problem solve with the youth and their family on ways to break down barriers. This may require referral to a psychological care provider to teach problem solving skills[10]
- If psychosocial needs are reported or identified, refer to psychological care provider.[10]

Beyond insulin pumps and CGM, two other areas with psychosocial components and considerations are automated insulin delivery/closed loop technologies and digital health applications. Given the rapidly advancing state of closed loop described earlier, there is a need to understand psychosocial factors leading to the uptake and use of these systems as well as whether they offer psychosocial benefits. As noted, to maximize benefit from closed loop systems, users will need to wear an insulin pump and CGM continuously. However, rates of uptake of these technologies are lagging. Thus, the above recommendations are relevant for each component of the closed loop system. In a recent report of 284 potential users of closed loop in the United States and United Kingdom,[306] three themes were identified as critical for uptake: developing trust in the system and degree of control of it; features of the closed loop systems; and concerns about the everyday barriers to adoption. Children and adolescents differed from parents in that youth primarily identified needs specific to their immediate contexts (eg, school and peers). Parents were most concerned about the accuracy and ensuring that systems stabilize glucose levels and reduce risk for long-term complications. Other reports emphasize these same ideas of setting realistic expectations[229,230] and potential benefits on quality of life and well-being are already being realized with closed loop systems.[226,228,231]

In addition to these developments over the past decade, there have been developments in the realm of mobile applications which can serve as adjunct strategies for improving diabetes management and outcomes. Several thousand diabetes-related applications are available in the Apple iTunes store and Android Play store.[307] Some apps target health behaviors such as physical activity, sleep, and nutrition, while others target blood glucose monitoring, provide diabetes education, and/or enable users to share their diabetes data with others. For example, applications such as "bant" (www.bantapp.com), which enables users to link their blood glucose meter directly to an application that synthesizes data, has been shown to increase rates of glucose checking in adolescents.[262] While promising and exciting, the documentation of the effectiveness of these applications to facilitate behavior change lags behind the pace that these applications hit the marketplace. Research has shown the utility of a mobile and web-based program called YourWay[308] to improve the management and glycemic outcomes of adolescents with T1D. Further, another study found that for adolescents with T1D, use of technology (eg, social networking, websites, pump/glucose meter software) was associated with better diabetes self-management behaviors.[309]

In sum, the current evidence base points to psychosocial and quality of life benefits from using insulin pumps, and growing evidence of benefits with CGM, closed loop, and digital health. Interventions to reduce barriers to technology use are actively being investigated.[12] However, more clinically translatable research, specifically conducted in the pediatric population is needed on the best ways to break down barriers to device and technology use and prevent discontinuation. This likely rests in setting realistic expectations, teaching effective problem-solving skills (general and technology specific), and viewing digital health applications as a scaffolding for youth to internalize the salience and routine of specific health behaviors.

11 | CONCLUSION

Just as our everyday lives have vastly changed with integration of new technologies including computers, smartphones, and the increased connectivity of devices, the management of diabetes is in the midst of a technological revolution. It is likely that the years ahead

will see significant growth in this realm of diabetes care with the hopes that these mechanical solutions may afford patients, and their families, the ability to achieve glycemic targets while reducing the burden of this chronic medical condition. Furthermore, as both diabetes care providers and patients now recognize the importance of not just relying on HbA1c to determine adequacy of control, a shift is occurring to define clinically meaningful outcomes such as TIR (defined as 70-180 mg/dL [3.9-10 mmol/L]), measures of hypoglycemia, and glycemic variability.[310] Through the use of CGM this data can be collected in both research and clinical settings, and the true test of new technologies will be to see how they can reduce glycemic variability by achieving a greater proportion of TIR. Paramount in the integration of technology into clinical care will be the need for a better understanding of the cost-benefit analysis that may help justify coverage of such innovations in the future. Indeed, as many of these technologies are quite expensive, further understanding of the health economics will provide valuable information for clinicians, their patients, as well as payors. This chapter has reviewed evidence on diabetes technology in children, adolescents, and young adults with the aim of providing practical advice and approaches on their use. Further updates are anticipated in this rapidly evolving area of research and practice.

Conflict of interest

J.L.S. reports having receiving speaker honoraria from Medtronic. J.L.S. also serves on advisory boards of Bigfoot Biomedical, Eli Lilly (Nasal Glucagon), and Insulet Corporation. J.L.S.'s institution received research grant support from JDRF, Medtronic and Insulet. M.T. reports having received speaker honoraria from Medtronic and Novo Nordisk. T.B. served on advisory boards of Novo Nordisk, Sanofi, Eli Lilly, Boehringer, Medtronic, DreaMed Diabetes and Bayer Health Care. T.B.'s Institution received research grant support, with receipt of travel and accommodation expenses in some cases, from Abbott, Medtronic, Novo Nordisk, GluSense, Sanofi, Sandoz and Diamyd. T.B. received honoraria for participating on the speaker's bureaux of Eli Lilly, Bayer, Novo Nordisk, Medtronic, Sanofi and Roche. T.B. owns stocks of DreamMed. M.D. has received honorarium from Medtronic. G.F. reports grants from NIH NIDDK; grants and personal fees from Medtronic, grants and personal fees from Tandem, grants and personal fees from Dexcom, grants from Insulet, grants and personal fees from Abbott, grants from Bigfoot, and grants from NovoNordisk. R.R. reports no conflicts of interest. K.H. serves as a consultant to J&J Diabetes Institute, Bigfoot Biomedical, Lilly Innovation Center, and Insulet. Receives research support for investigator-initiated study from Dexcom, Inc. D.M. has research support from the NIH, JDRF, NSF, and the Helmsley Charitable Trust and his institution has research support from Medtronic, Dexcom, Insulet, Bigfoot Biomedical, and Roche. D.M. has consulted for Abbott, the Helmsley Charitable Trust, Sanofi, and Eli Lilly and has served on an advisory board for Insulet.

ORCID

Jennifer L. Sherr http://orcid.org/0000-0001-9301-3043
Tadej Battelino http://orcid.org/0000-0002-0273-4732
Martin de Bock http://orcid.org/0000-0002-6998-7566
David M. Maahs http://orcid.org/0000-0002-4602-7909

REFERENCES

1. Miller KM, Foster NC, Beck RW, et al. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D exchange clinic registry. *Diabetes Care*. 2015;38(6):971-978.
2. Cengiz E, Xing D, Wong JC, et al. Severe hypoglycemia and diabetic ketoacidosis among youth with type 1 diabetes in the T1D exchange clinic registry. *Pediatr Diabetes*. 2013;14(6):447-454.
3. Wood JR, Miller KM, Maahs DM, et al. Most youth with type 1 diabetes in the T1D exchange clinic registry do not meet American Diabetes Association or International Society for Pediatric and Adolescent Diabetes clinical guidelines. *Diabetes Care*. 2013;36(7):2035-2037.
4. McKnight JA, Wild SH, Lamb MJ, et al. Glycaemic control of type 1 diabetes in clinical practice early in the 21st century: an international comparison. *Diabet Med*. 2015;32(8):1036-1050.
5. Witsch M, Kosteria I, Kordonouri O, et al. Possibilities and challenges of a large international benchmarking in pediatric diabetology-The SWEET experience. *Pediatr Diabetes*. 2016;17(suppl 23):7-15.
6. Haynes A, Hermann JM, Miller KM, et al. Severe hypoglycemia rates are not associated with HbA1c: a cross-sectional analysis of 3 contemporary pediatric diabetes registry databases. *Pediatr Diabetes*. 2017;18(7):643-650.
7. Karges B, Schwandt A, Heidtmann B, et al. Association of insulin pump therapy vs insulin injection therapy with severe hypoglycemia, ketoacidosis, and glycemic control among children, adolescents, and young adults with type 1 diabetes. *JAMA*. 2017;318(14):1358-1366.
8. O'Connell SM, Cooper MN, Bulsara MK, Davis EA, Jones TW. Reducing rates of severe hypoglycemia in a population-based cohort of children and adolescents with type 1 diabetes over the decade 2000-2009. *Diabetes Care*. 2011;34(11):2379-2380.
9. Whittemore R, Jaser S, Chao A, Jang M, Grey M. Psychological experience of parents of children with type 1 diabetes: a systematic mixed-studies review. *Diabetes Educ*. 2012;38(4):562-579.
10. Young-Hyman D, de Groot M, Hill-Briggs F, Gonzalez JS, Hood K, Peyrot M. Psychosocial care for people with diabetes: a position statement of the American Diabetes Association. *Diabetes Care*. 2016;39(12):2126-2140.
11. Naranjo D, Tanenbaum ML, Iturralde E, Hood KK. Diabetes technology: uptake, outcomes, barriers, and the intersection with distress. *J Diabetes Sci Technol*. 2016;10(4):852-858.
12. Tanenbaum ML, Hanes SJ, Miller KM, Naranjo D, Bensen R, Hood KK. Diabetes device use in adults with type 1 diabetes: barriers to uptake and potential intervention targets. *Diabetes Care*. 2017;40(2):181-187.
13. Prahalad P, Tanenbaum M, Hood K, Maahs DM. Diabetes technology: improving care, improving patient-reported outcomes and preventing complications in young people with Type 1 diabetes. *Diabet Med*. 2018;35(4):419-429.
14. Tamborlane WV, Sherwin RS, Genel M, Felig P. Reduction to normal of plasma glucose in juvenile diabetes by subcutaneous administration of insulin with a portable infusion pump. *N Engl J Med*. 1979;300(11):573-578.
15. Pickup JC, Keen H, Parsons JA, Alberti KG. Continuous subcutaneous insulin infusion: an approach to achieving normoglycaemia. *Br Med J*. 1978;1(6107):204-207.
16. Pickup JC, Keen H, Stevenson RW, et al. Insulin via continuous subcutaneous infusion. *Lancet*. 1978;2(8097):988-989.
17. Ahern JA, Boland EA, Doane R, et al. Insulin pump therapy in pediatrics: a therapeutic alternative to safely lower HbA1c levels across all age groups. *Pediatr Diabetes*. 2002;3(1):10-15.
18. Saha ME, Huuppone T, Mikael K, Juuti M, Komulainen J. Continuous subcutaneous insulin infusion in the treatment of children and adolescents with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab*. 2002;15(7):1005-1010.
19. Litton J, Rice A, Friedman N, Oden J, Lee MM, Freemark M. Insulin pump therapy in toddlers and preschool children with type 1 diabetes mellitus. *J Pediatr*. 2002;141(4):490-495.

20. Willi SM, Planton J, Egede L, Schwarz S. Benefits of continuous subcutaneous insulin infusion in children with type 1 diabetes. *J Pediatr*. 2003;143(6):796-801.
21. Sulli N, Shashaj B. Continuous subcutaneous insulin infusion in children and adolescents with diabetes mellitus: decreased HbA1c with low risk of hypoglycemia. *J Pediatr Endocrinol Metab*. 2003;16(3):393-399.
22. Plotnick LP, Clark LM, Brancati FL, Erlinger T. Safety and effectiveness of insulin pump therapy in children and adolescents with type 1 diabetes. *Diabetes Care*. 2003;26(4):1142-1146.
23. Hanas R, Adolfsson P. Insulin pumps in pediatric routine care improve long-term metabolic control without increasing the risk of hypoglycemia. *Pediatr Diabetes*. 2006;7(1):25-31.
24. Sulli N, Shashaj B. Long-term benefits of continuous subcutaneous insulin infusion in children with type 1 diabetes: a 4-year follow-up. *Diabet Med*. 2006;23(8):900-906.
25. Jeha GS, Karaviti LP, Anderson B, et al. Insulin pump therapy in preschool children with type 1 diabetes mellitus improves glycemic control and decreases glucose excursions and the risk of hypoglycemia. *Diabetes Technol Ther*. 2005;7(6):876-884.
26. Maniatis AK, Klingensmith GJ, Slover RH, Mowry CJ, Chase HP. Continuous subcutaneous insulin infusion therapy for children and adolescents: an option for routine diabetes care. *Pediatrics*. 2001;107(2):351-356.
27. Nimri R, Weintrob N, Benzaquen H, Ofan R, Fayman G, Phillip M. Insulin pump therapy in youth with type 1 diabetes: a retrospective paired study. *Pediatrics*. 2006;117(6):2126-2131.
28. Mack-Fogg JE, Orlowski CC, Jospe N. Continuous subcutaneous insulin infusion in toddlers and children with type 1 diabetes mellitus is safe and effective. *Pediatr Diabetes*. 2005;6(1):17-21.
29. Berhe T, Postellon D, Wilson B, Stone R. Feasibility and safety of insulin pump therapy in children aged 2 to 7 years with type 1 diabetes: a retrospective study. *Pediatrics*. 2006;117(6):2132-2137.
30. Weinzimer SA, Ahern JH, Doyle EA, et al. Persistence of benefits of continuous subcutaneous insulin infusion in very young children with type 1 diabetes: a follow-up report. *Pediatrics*. 2004;114(6):1601-1605.
31. Jakisch BI, Wagner VM, Heidtmann B, et al. Comparison of continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDI) in paediatric type 1 diabetes: a multicentre matched-pair cohort analysis over 3 years. *Diabet Med*. 2008;25(1):80-85.
32. Boland EA, Grey M, Oesterle A, Fredrickson L, Tamborlane WV. Continuous subcutaneous insulin infusion. A new way to lower risk of severe hypoglycemia, improve metabolic control, and enhance coping in adolescents with type 1 diabetes. *Diabetes Care*. 1999;22(11):1779-1784.
33. Doyle EA, Weinzimer SA, Steffen AT, Ahern JA, Vincent M, Tamborlane WV. A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. *Diabetes Care*. 2004;27(7):1554-1558.
34. Alemzadeh R, Ellis JN, Holzum MK, Parton EA, Wyatt DT. Beneficial effects of continuous subcutaneous insulin infusion and flexible multiple daily insulin regimen using insulin glargine in type 1 diabetes. *Pediatrics*. 2004;114(1):e91-e95.
35. Schiaffini R, Ciampalini P, Spera S, Cappa M, Crino A. An observational study comparing continuous subcutaneous insulin infusion (CSII) and insulin glargine in children with type 1 diabetes. *Diabetes Metab Res Rev*. 2005;21(4):347-352.
36. Schiaffini R, Patera PI, Bizzarri C, Ciampalini P, Cappa M. Basal insulin supplementation in type 1 diabetic children: a long-term comparative observational study between continuous subcutaneous insulin infusion and glargine insulin. *J Endocrinol Investig*. 2007;30(7):572-577.
37. DiMeglio LA, Pottorff TM, Boyd SR, France L, Fineberg N, Eugster EA. A randomized, controlled study of insulin pump therapy in diabetic preschoolers. *J Pediatr*. 2004;145(3):380-384.
38. Wilson DM, Buckingham BA, Kunselman EL, Sullivan MM, Paguntalan HU, Gitelman SE. A two-center randomized controlled feasibility trial of insulin pump therapy in young children with diabetes. *Diabetes Care*. 2005;28(1):15-19.
39. Fox LA, Buckloh LM, Smith SD, Wysocki T, Mauras N. A randomized controlled trial of insulin pump therapy in young children with type 1 diabetes. *Diabetes Care*. 2005;28(6):1277-1281.
40. Weintrob N, Benzaquen H, Galatzer A, et al. Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens in children with type 1 diabetes: a randomized open crossover trial. *Pediatrics*. 2003;112(3, pt 1):559-564.
41. Opipari-Arrigan L, Fredericks EM, Burkhart N, Dale L, Hodge M, Foster C. Continuous subcutaneous insulin infusion benefits quality of life in preschool-age children with type 1 diabetes mellitus. *Pediatr Diabetes*. 2007;8(6):377-383.
42. Zabeen B, Craig ME, Virk SA, et al. Insulin pump therapy is associated with lower rates of retinopathy and peripheral nerve abnormality. *PLoS One*. 2016;11(4):e0153033.
43. Jeitler K, Horvath K, Berghold A, et al. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. *Diabetologia*. 2008;51(6):941-951.
44. Pankowska E, Blazik M, Dziechciarz P, Szypowska A, Szajewska H. Continuous subcutaneous insulin infusion vs. multiple daily injections in children with type 1 diabetes: a systematic review and meta-analysis of randomized control trials. *Pediatr Diabetes*. 2009;10(1):52-58.
45. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. *Diabet Med*. 2008;25(7):765-774.
46. Yeh HC, Brown TT, Maruthur N, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. *Ann Intern Med*. 2012;157(5):336-347.
47. Blackman SM, Raghinaru D, Adi S, et al. Insulin pump use in young children in the T1D exchange clinic registry is associated with lower hemoglobin A1c levels than injection therapy. *Pediatr Diabetes*. 2014;15(8):564-572.
48. Szypowska A, Schwandt A, Svensson J, et al. Insulin pump therapy in children with type 1 diabetes: analysis of data from the SWEET registry. *Pediatr Diabetes*. 2016;17(suppl 23):38-45.
49. Sherr JL, Hermann JM, Campbell F, et al. Use of insulin pump therapy in children and adolescents with type 1 diabetes and its impact on metabolic control: comparison of results from three large, transatlantic paediatric registries. *Diabetologia*. 2016;59(1):87-91.
50. Birkebaek NH, Drivvoll AK, Aakeson K, et al. Incidence of severe hypoglycemia in children with type 1 diabetes in the Nordic countries in the period 2008-2012: association with hemoglobin A 1c and treatment modality. *BMJ Open Diabetes Res Care*. 2017;5(1):e000377.
51. Adolfsson P, Ziegler R, Hanas R. Continuous subcutaneous insulin infusion: special needs for children. *Pediatr Diabetes*. 2017;18(4):255-261.
52. Phillip M, Battelino T, Rodriguez H, et al. European Society for Paediatric Endocrinology; Lawson Wilkins Pediatric Endocrine Society; International Society for Pediatric and Adolescent Diabetes; American Diabetes Association; European Association for the Study of Diabetes. Use of insulin pump therapy in the pediatric age-group: consensus statement from the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes, endorsed by the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2007;30(6):1653-1662.
53. Sundberg F, Barnard K, Cato A, et al. Managing diabetes in preschool children. *Pediatr Diabetes*. 2017;18(7):499-517.
54. Elleri D, Allen JM, Tauschmann M, et al. Feasibility of overnight closed-loop therapy in young children with type 1 diabetes aged 3-6 years: comparison between diluted and standard insulin strength. *BMJ Open Diabetes Res Care*. 2014;2(1):e000040.
55. Del Favero S, Boscari F, Messori M, et al. Randomized summer camp crossover trial in 5- to 9-year-old children: outpatient wearable artificial pancreas is feasible and safe. *Diabetes Care*. 2016;39(7):1180-1185.

56. Ruan Y, Elleri D, Allen JM, et al. Pharmacokinetics of diluted (U20) insulin aspart compared with standard (U100) in children aged 3-6 years with type 1 diabetes during closed-loop insulin delivery: a randomised clinical trial. *Diabetologia*. 2015;58(4):687-690.
57. Mianowska B, Fendler W, Tomasik B, Mlynarski W, Szadkowska A. Effect of insulin dilution on lowering glycemic variability in pump-treated young children with inadequately controlled type 1 diabetes. *Diabetes Technol Ther*. 2015;17(9):605-610.
58. Ramchandani N, Ten S, Anhalt H, et al. Insulin pump therapy from the time of diagnosis of type 1 diabetes. *Diabetes Technol Ther*. 2006;8(6):663-670.
59. Berghaeuser MA, Kapellen T, Heidtmann B, et al. Continuous subcutaneous insulin infusion in toddlers starting at diagnosis of type 1 diabetes mellitus. A multicenter analysis of 104 patients from 63 centres in Germany and Austria. *Pediatr Diabetes*. 2008;9(6):590-595.
60. de Beaufort CE, Houtzagers CM, Bruining GJ, et al. Continuous subcutaneous insulin infusion (CSII) versus conventional injection therapy in newly diagnosed diabetic children: two-year follow-up of a randomized, prospective trial. *Diabet Med*. 1989;6(9):766-771.
61. Buckingham B, Beck RW, Ruedy KJ, et al. Effectiveness of early intensive therapy on beta-cell preservation in type 1 diabetes. *Diabetes Care*. 2013;36(12):4030-4035.
62. Scrimgeour L, Cobry E, McFann K, et al. Improved glycemic control after long-term insulin pump use in pediatric patients with type 1 diabetes. *Diabetes Technol Ther*. 2007;9(5):421-428.
63. Johnson SR, Cooper MN, Jones TW, Davis EA. Long-term outcome of insulin pump therapy in children with type 1 diabetes assessed in a large population-based case-control study. *Diabetologia*. 2013;56(11):2392-2400.
64. Lin MH, Connor CG, Ruedy KJ, et al. Race, socioeconomic status, and treatment center are associated with insulin pump therapy in youth in the first year following diagnosis of type 1 diabetes. *Diabetes Technol Ther*. 2013;15(11):929-934.
65. Commissariat PV, Boyle CT, Miller KM, et al. Insulin pump use in young children with type 1 diabetes: sociodemographic factors and parent-reported barriers. *Diabetes Technol Ther*. 2017;19(6):363-369.
66. Nabhan ZM, Rardin L, Meier J, Eugster EA, Dimeglio LA. Predictors of glycemic control on insulin pump therapy in children and adolescents with type I diabetes. *Diabetes Res Clin Pract*. 2006;74(3):217-221.
67. Danne T, Battelino T, Jarosz-Chobot P, et al. Establishing glycaemic control with continuous subcutaneous insulin infusion in children and adolescents with type 1 diabetes: experience of the PedPump Study in 17 countries. *Diabetologia*. 2008;51(9):1594-1601.
68. Hofer SE, Heidtmann B, Raile K, et al. Discontinuation of insulin pump treatment in children, adolescents, and young adults. A multicenter analysis based on the DPV database in Germany and Austria. *Pediatr Diabetes*. 2010;11(2):116-121.
69. Wong JC, Boyle C, DiMeglio LA, et al. Evaluation of pump discontinuation and associated factors in the t1d exchange clinic registry. *J Diabetes Sci Technol*. 2017;11(2):224-232.
70. Wong JC, Dolan LM, Yang TT, Hood KK. Insulin pump use and glycemic control in adolescents with type 1 diabetes: predictors of change in method of insulin delivery across two years. *Pediatr Diabetes*. 2015;16(8):592-599.
71. Wheeler BJ, Heels K, Donaghue KC, Reith DM, Ambler GR. Insulin pump-associated adverse events in children and adolescents--a prospective study. *Diabetes Technol Ther*. 2014;16(9):558-562.
72. Guenego A, Bouzille G, Breitel S, et al. Insulin pump failures: has there been an improvement? Update of a prospective observational study. *Diabetes Technol Ther*. 2016;18(12):820-824.
73. Heinemann L, Krinelke L. Insulin infusion set: the Achilles heel of continuous subcutaneous insulin infusion. *J Diabetes Sci Technol*. 2012;6(4):954-964.
74. Heinemann L, Walsh J, Roberts R. We need more research and better designs for insulin infusion sets. *J Diabetes Sci Technol*. 2014;8(2):199-202.
75. Heinemann L. Insulin infusion sets: a critical reappraisal. *Diabetes Technol Ther*. 2016;18(5):327-333.
76. Alemzadeh R, Parton EA, Holzum MK. Feasibility of continuous subcutaneous insulin infusion and daily supplemental insulin glargine injection in children with type 1 diabetes. *Diabetes Technol Ther*. 2009;11(8):481-486.
77. Gibney M, Xue Z, Swinney M, Bialonczyk D, Hirsch L. Reduced silent occlusions with a novel catheter infusion set (BD FlowSmart): results from two open-label comparative studies. *Diabetes Technol Ther*. 2016;18(3):136-143.
78. Cescon M, DeSalvo DJ, Ly TT, et al. Early detection of infusion set failure during insulin pump therapy in type 1 diabetes. *J Diabetes Sci Technol*. 2016;10(6):1268-1276.
79. Forlenza GP, Deshpande S, Ly TT, et al. Application of zone model predictive control artificial pancreas during extended use of infusion set and sensor: a randomized crossover-controlled home-use trial. *Diabetes Care*. 2017;40(8):1096-1102.
80. Hanas R, Lindgren F, Lindblad B. A 2-yr national population study of pediatric ketoacidosis in Sweden: predisposing conditions and insulin pump use. *Pediatr Diabetes*. 2009;10(1):33-37.
81. Brorsson AL, Viklund G, Ortqvist E, Lindholm OA. Does treatment with an insulin pump improve glycaemic control in children and adolescents with type 1 diabetes? A retrospective case-control study. *Pediatr Diabetes*. 2015;16(7):546-553.
82. Wolfsdorf JI, Nicol G, Michael A, et al. Diabetic ketoacidosis and hyperglycemic hyperosmolar state: a consensus statement from the international society for pediatric and adolescent diabetes. *Pediatr Diabetes*. 2018.
83. Kordonouri O, Lauterborn R, Deiss D. Lipohypertrophy in young patients with type 1 diabetes. *Diabetes Care*. 2002;25(3):634.
84. Kordonouri O, Biester T, Schnell K, et al. Lipoatrophy in children with type 1 diabetes: an increasing incidence? *J Diabetes Sci Technol*. 2015;9(2):206-208.
85. Raile K, Noelle V, Landgraf R, Schwarz HP. Insulin antibodies are associated with lipoatrophy but also with lipohypertrophy in children and adolescents with type 1 diabetes. *Exp Clin Endocrinol Diabetes*. 2001;109(8):393-396.
86. DeSalvo DJ, Maahs DM, Messer L, et al. Effect of lipohypertrophy on accuracy of continuous glucose monitoring in patients with type 1 diabetes. *Diabetes Care*. 2015;38(10):e166-e167.
87. Wolfsdorf JI, Allgrove J, Craig ME, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Pediatr Diabetes*. 2014;15(suppl 20):154-179.
88. Deiss D, Adolfsson P, Alkemade-van Zomeren M, et al. Insulin infusion set use: european perspectives and recommendations. *Diabetes Technol Ther*. 2016;18(9):517-524.
89. Tsalikian E, Kollman C, Tamborlane WB, et al. Prevention of hypoglycemia during exercise in children with type 1 diabetes by suspending basal insulin. *Diabetes Care*. 2006;29(10):2200-2204.
90. The Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329(14):977-986.
91. Haller MJ, Stalvey MS, Silverstein JH. Predictors of control of diabetes: monitoring may be the key. *J Pediatr*. 2004;144(5):660-661.
92. Ziegler R, Heidtmann B, Hilgard D, et al. Frequency of SMBG correlates with HbA1c and acute complications in children and adolescents with type 1 diabetes. *Pediatr Diabetes*. 2011;12(1):11-17.
93. Miller KM, Beck RW, Bergenstal RM, et al. Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A1c levels in T1D exchange clinic registry participants. *Diabetes Care*. 2013;36(7):2009-2014.
94. Rewers MJ, Pillay K, de Beaufort C, et al. ISPAD clinical practice consensus guidelines 2014. Assessment and monitoring of glycemic control in children and adolescents with diabetes. *Pediatr Diabetes*. 2014;15(suppl 20):102-114.
95. Cengiz E. Analysis of a remote system to closely monitor glycemia and insulin pump delivery--is this the beginning of a wireless transformation in diabetes management? *J Diabetes Sci Technol*. 2013;7(2):362-364.

96. Bailey T, Bode BW, Christiansen MP, Klaff LJ, Alva S. The performance and usability of a factory-calibrated flash glucose monitoring system. *Diabetes Technol Ther*. 2015;17(11):787-794.
97. Ludwig-Seibold CU, Holder M, Rami B, et al. Continuous glucose monitoring in children, adolescents, and adults with type 1 diabetes mellitus: analysis from the prospective DPV diabetes documentation and quality management system from Germany and Austria. *Pediatr Diabetes*. 2012;13(1):12-14.
98. Wong JC, Foster NC, Maahs DM, et al. Real-time continuous glucose monitoring among participants in the T1D Exchange clinic registry. *Diabetes Care*. 2014;37(10):2702-2709.
99. DeSalvo D, Miller K, Hermann J, Maahs D, Hofer S, Clements M, et al. Continuous glucose monitoring (cgm) and glycemic control among youth with type 1 diabetes (T1D): international comparison from the T1D exchange (T1DX) and the DPV initiative. 43rd Annual Conference of the International Society for Pediatric and Adolescent Diabetes; Innsbruck, Austria, 2017.
100. Pickup JC, Freeman SC, Sutton AJ. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. *BMJ*. 2011;343:d3805.
101. Langendam M, Luijf YM, Hooft L, Devries JH, Mudde AH, Scholten RJ. Continuous glucose monitoring systems for type 1 diabetes mellitus. *Cochrane Database Syst Rev*. 2012;1:CD008101.
102. Szypowska A, Ramotowska A, Dzygalo K, Golicki D. Beneficial effect of real-time continuous glucose monitoring system on glycemic control in type 1 diabetic patients: systematic review and meta-analysis of randomized trials. *Eur J Endocrinol*. 2012;166(4):567-574.
103. Tamborlane WV, Beck RW, Bode BW, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med*. 2008;359(14):1464-1476.
104. Beck RW, Hirsch IB, Laffel L, et al. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. *Diabetes Care*. 2009;32(8):1378-1383.
105. Beck RW, Buckingham B, Miller K, et al. Factors predictive of use and of benefit from continuous glucose monitoring in type 1 diabetes. *Diabetes Care*. 2009;32(11):1947-1953.
106. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Effectiveness of continuous glucose monitoring in a clinical care environment: evidence from the Juvenile Diabetes Research Foundation continuous glucose monitoring (JDRF-CGM) trial. *Diabetes Care*. 2010;33(1):17-22.
107. Bergenstal RM, Tamborlane WV, Ahmann A, et al. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *N Engl J Med*. 2010;363(4):311-320.
108. Hermanides J, Nørgaard K, Bruttomesso D, et al. Sensor-augmented pump therapy lowers HbA(1c) in suboptimally controlled type 1 diabetes; a randomized controlled trial. *Diabet Med*. 2011;28(10):1158-1167.
109. Bergenstal RM, Tamborlane WV, Ahmann A, et al. Sensor-augmented pump therapy for A1C reduction (STAR 3) study: results from the 6-month continuation phase. *Diabetes Care*. 2011;34(11):2403-2405.
110. Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. *Diabetes Care*. 2011;34(4):795-800.
111. Battelino T, Conget I, Olsen B, et al. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. *Diabetologia*. 2012;55(12):3155-3162.
112. Beck RW, Riddlesworth T, Ruedy K, et al. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. *JAMA*. 2017;317(4):371-378.
113. El-Laboudi AH, Godsland IF, Johnston DG, Oliver NS. Measures of glycemic variability in type 1 diabetes and the effect of real-time continuous glucose monitoring. *Diabetes Technol Ther*. 2016;18(12):806-812.
114. Chase HP, Beck RW, Xing D, et al. Continuous glucose monitoring in youth with type 1 diabetes: 12-month follow-up of the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized trial. *Diabetes Technol Ther*. 2010;12(7):507-515.
115. Jeha GS, Karaviti LP, Anderson B, et al. Continuous glucose monitoring and the reality of metabolic control in preschool children with type 1 diabetes. *Diabetes Care*. 2004;27(12):2881-2886.
116. Gandrud LM, Xing D, Kollman C, et al. The medtronic minimed gold continuous glucose monitoring system: an effective means to discover hypo- and hyperglycemia in children under 7 years of age. *Diabetes Technol Ther*. 2007;9(4):307-316.
117. Mauras N, Beck R, Xing D, et al. A randomized clinical trial to assess the efficacy and safety of real-time continuous glucose monitoring in the management of type 1 diabetes in young children aged 4 to <10 years. *Diabetes Care*. 2012;35(2):204-210.
118. Tsalikian E, Fox L, Weinzimer S, et al. Feasibility of prolonged continuous glucose monitoring in toddlers with type 1 diabetes. *Pediatr Diabetes*. 2012;13(4):301-307.
119. Fonseca VA, Grunberger G, Anhalt H, et al. Continuous glucose monitoring: a consensus conference of the american association of clinical endocrinologists and American College of Endocrinology. *Endocr Practice*. 2016;22(8):1008-1021.
120. Foster NC, Miller KM, Tamborlane WV, Bergenstal RM, Beck RW, Network TDEC. Continuous glucose monitoring in patients with type 1 diabetes using insulin injections. *Diabetes Care*. 2016;39(6):e81-e82.
121. Lind M, Polonsky W, Hirsch IB, et al. Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections: The GOLD randomized clinical trial. *JAMA*. 2017;317(4):379-387.
122. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kroger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. *Lancet*. 2016;388(10057):2254-2263.
123. Deiss D, Bolinder J, Riveline JP, et al. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. *Diabetes Care*. 2006;29(12):2730-2732.
124. Hirsch IB, Abelseth J, Bode BW, et al. Sensor-augmented insulin pump therapy: results of the first randomized treat-to-target study. *Diabetes Technol Ther*. 2008;10(5):377-383.
125. Raccah D, Sulmont V, Reznik Y, et al. Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: the RealTrend study. *Diabetes Care*. 2009;32(12):2245-2250.
126. O'Connell MA, Donath S, O'Neal DN, et al. Glycaemic impact of patient-led use of sensor-guided pump therapy in type 1 diabetes: a randomised controlled trial. *Diabetologia*. 2009;52(7):1250-1257.
127. Riveline JP, Schaepelynck P, Chaillous L, et al. Assessment of patient-led or physician-driven continuous glucose monitoring in patients with poorly controlled type 1 diabetes using basal-bolus insulin regimens: a 1-year multicenter study. *Diabetes Care*. 2012;35(5):965-971.
128. Kordonouri O, Pankowska E, Rami B, et al. Sensor-augmented pump therapy from the diagnosis of childhood type 1 diabetes: results of the Paediatric Onset Study (ONSET) after 12 months of treatment. *Diabetologia*. 2010;53(12):2487-2495.
129. van Beers CA, DeVries JH, Kleijer SJ, et al. Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycaemia (IN CONTROL): a randomised, open-label, crossover trial. *Lancet Diabetes Endocrinol*. 2016;4(11):893-902.
130. Choudhary P, Ramasamy S, Green L, et al. Real-time continuous glucose monitoring significantly reduces severe hypoglycemia in hypoglycemia-unaware patients with type 1 diabetes. *Diabetes Care*. 2013;36(12):4160-4162.
131. Chase HP, Roberts MD, Wightman C, et al. Use of the GlucoWatch biographer in children with type 1 diabetes. *Pediatrics*. 2003;111(4, pt 1):790-794.
132. Kaufman FR, Gibson LC, Halvorson M, Carpenter S, Fisher LK, Pitukcheewanont P. A pilot study of the continuous glucose monitoring system: clinical decisions and glycemic control after its use in pediatric type 1 diabetic subjects. *Diabetes Care*. 2001;24(12):2030-2034.
133. Ludvigsson J, Hanas R. Continuous subcutaneous glucose monitoring improved metabolic control in pediatric patients with type 1 diabetes: a controlled crossover study. *Pediatrics*. 2003;111(5, pt 1):933-938.

134. Golicki DT, Golicka D, Groele L, Pankowska E. Continuous glucose monitoring system in children with type 1 diabetes mellitus: a systematic review and meta-analysis. *Diabetologia*. 2008;51(2):233-240.
135. Bailey TS, Chang A, Christiansen M. Clinical accuracy of a continuous glucose monitoring system with an advanced algorithm. *J Diabetes Sci Technol*. 2015;9(2):209-214.
136. Laffel L. Improved accuracy of continuous glucose monitoring systems in pediatric patients with diabetes mellitus: results from two studies. *Diabetes Technol Ther*. 2016;18(suppl 2):S223-S233.
137. Garg SK, Weinzimer SA, Tamborlane WV, et al. Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. *Diabetes Technol Ther*. 2017;19(3):155-163.
138. Kropff J, Choudhary P, Neupane S, et al. Accuracy and longevity of an implantable continuous glucose sensor in the PRECISE Study: a 180-day, prospective, multicenter, Pivotal Trial. *Diabetes Care*. 2017;40(1):63-68.
139. Kovatchev BP, Patek SD, Ortiz EA, Breton MD. Assessing sensor accuracy for non-adjunct use of continuous glucose monitoring. *Diabetes Technol Ther*. 2015;17(3):177-186.
140. Kropff J, Bruttomesso D, Doll W, et al. Accuracy of two continuous glucose monitoring systems: a head-to-head comparison under clinical research centre and daily life conditions. *Diabetes Obes Metab*. 2015;17(4):343-349.
141. Pleus S, Schoemaker M, Morgenstern K, et al. Rate-of-change dependence of the performance of two cgm systems during induced glucose swings. *J Diabetes Sci Technol*. 2015;9(4):801-807.
142. Aleppo G, Ruedy KJ, Riddlesworth TD, et al. REPLACE-BG: a randomized trial comparing continuous glucose monitoring with and without routine blood glucose monitoring in adults with well-controlled type 1 diabetes. *Diabetes Care*. 2017;40(4):538-545.
143. FDA advisory panel votes to recommend non-adjunctive use of Dexcom G5 Mobile CGM. *Diabetes Technol Ther*. 2016;18(8):512-516.
144. Shapiro AR. FDA approval of nonadjunctive use of continuous glucose monitors for insulin dosing: a potentially risky decision. *JAMA*. 2017;318(16):1541-1542.
145. Beck RW. Continuous glucose monitors for insulin dosing. *JAMA*. 2018;319(13):1383.
146. Ekhlaspour L, Mondesir D, Lautsch N, et al. Comparative accuracy of 17 point-of-care glucose meters. *J Diabetes Sci Technol*. 2017;11(3):558-566.
147. Edelman SV. Regulation catches up to reality. *J Diabetes Sci Technol*. 2017;11(1):160-164.
148. Pettus J, Edelman SV. Recommendations for using real-time continuous glucose monitoring (rtCGM) data for insulin adjustments in type 1 diabetes. *J Diabetes Sci Technol*. 2017;11(1):138-147.
149. Castle JR, Jacobs PG. Nonadjunctive use of continuous glucose monitoring for diabetes treatment decisions. *J Diabetes Sci Technol*. 2016;10(5):1169-1173.
150. Forlenza GP, Argento NB, Laffel LM. Practical considerations on the use of continuous glucose monitoring in pediatrics and older adults and nonadjunctive use. *Diabetes Technol Ther*. 2017;19(S3):S13-S20.
151. Buckingham B, Xing D, Weinzimer S, et al. Use of the DirecNet Applied Treatment Algorithm (DATA) for diabetes management with a real-time continuous glucose monitor (the FreeStyle Navigator). *Pediatr Diabetes*. 2008;9(2):142-147.
152. Scheiner G. *Practical CGM: A Guide to Improving Outcomes Through Continous Glucose Monitoring*. Arlington: VA, American Diabetes Association, Inc.; 2015.
153. Klonoff DC, Kerr D. A simplified approach using rate of change arrows to adjust insulin with real-time continuous glucose monitoring. *J Diabetes Sci Technol*. 2017;11(6):1063-1069.
154. Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care*. 2017;40(12):1631-1640.
155. Laffel LM, Aleppo G, Buckingham BA, et al. A practical approach to using trend arrows on the Dexcom G5 CGM system to manage children and adolescents with diabetes. *J Endocr Soc*. 2017;1(12):1-16.
156. Edge J, Acerini C, Campbell F, et al. An alternative sensor-based method for glucose monitoring in children and young people with diabetes. *Arch Dis Child*. 2017;102(6):543-549.
157. Olafsdottir AF, Attvall S, Sandgren U, et al. A clinical trial of the accuracy and treatment experience of the flash glucose monitor FreeStyle Libre in adults with type 1 diabetes. *Diabetes Technol Ther*. 2017;19(3):164-172.
158. Dover AR, Stimson RH, Zammitt NN, Gibb FW. Flash glucose monitoring improves outcomes in a type 1 diabetes clinic. *J Diabetes Sci Technol*. 2017;11(2):442-443.
159. Ish-Shalom M, Wainstein J, Raz I, Mosenzon O. Improvement in glucose control in difficult-to-control patients with diabetes using a novel flash glucose monitoring device. *J Diabetes Sci Technol*. 2016;10(6):1412-1413.
160. McKnight JA, Gibb FW. Flash glucose monitoring is associated with improved glycaemic control but use is largely limited to more affluent people in a UK diabetes centre. *Diabet Med*. 2017;34(5):732.
161. Christiansen MP, Klaff LJ, Brazg R, et al. A prospective multicenter evaluation of the accuracy of a novel implanted continuous glucose sensor: PRECISE II. *Diabetes Technol Ther*. 2018;20(3):197-206.
162. Messer L, Ruedy K, Xing D, et al. Educating families on real time continuous glucose monitoring: the DirecNet navigator pilot study experience. *Diabetes Educ*. 2009;35(1):124-135.
163. Benassi K, Drobny J, Aye T. Real-time continuous glucose monitoring systems in the classroom/school environment. *Diabetes Technol Ther*. 2013;15(5):409-412.
164. Bratina N, Battelino T. Insulin pumps and continuous glucose monitoring (CGM) in preschool and school-age children: how schools can integrate technology. *Pediatr Endocrinol Rev*. 2010;7(suppl 3):417-421.
165. Erie C, Van Name MA, Weyman K, et al. Schooling diabetes: use of continuous glucose monitoring and remote monitors in the home and school settings. *Pediatr Diabetes*. 2018;19(1):92-97.
166. Hirsch IB, Armstrong D, Bergenstal RM, et al. Clinical application of emerging sensor technologies in diabetes management: consensus guidelines for continuous glucose monitoring (CGM). *Diabetes Technol Ther*. 2008;10(4):232-244. quiz 45-6.
167. Hirsch IB. Clinical review: realistic expectations and practical use of continuous glucose monitoring for the endocrinologist. *J Clin Endocrinol Metab*. 2009;94(7):2232-2238.
168. Englert K, Ruedy K, Coffey J, et al. Skin and adhesive issues with continuous glucose monitors: a sticky situation. *J Diabetes Sci Technol*. 2014;8(4):745-751.
169. Heinemann L, Kamann S. Adhesives used for diabetes medical devices: a neglected risk with serious consequences? *J Diabetes Sci Technol*. 2016;10(6):1211-1215.
170. Slover RH, Welsh JB, Criego A, et al. Effectiveness of sensor-augmented pump therapy in children and adolescents with type 1 diabetes in the STAR 3 study. *Pediatr Diabetes*. 2012;13(1):6-11.
171. Buse JB, Kudva YC, Battelino T, Davis SN, Shin J, Welsh JB. Effects of sensor-augmented pump therapy on glycemic variability in well-controlled type 1 diabetes in the STAR 3 study. *Diabetes Technol Ther*. 2012;14(7):644-647.
172. Elleri D, Allen JM, Nodale M, et al. Suspended insulin infusion during overnight closed-loop glucose control in children and adolescents with Type 1 diabetes. *Diabet Med*. 2010;27(4):480-484.
173. Cengiz E, Sherr JL, Weinzimer SA, Tamborlane WV. Clinical equipoise: an argument for expedited approval of the first small step toward an autonomous artificial pancreas. *Expert Rev Med Devices*. 2012;9(4):315-317.
174. Garg S, Brazg RL, Bailey TS, et al. Reduction in duration of hypoglycemia by automatic suspension of insulin delivery: the in-clinic ASPIRE study. *Diabetes Technol Ther*. 2012;14(3):205-209.
175. Bergenstal RM, Klonoff DC, Garg SK, et al. Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N Engl J Med*. 2013;369(3):224-232.
176. Ly TT, Nicholas JA, Retterath A, Lim EM, Davis EA, Jones TW. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. *JAMA*. 2013;310(12):1240-1247.

177. Danne T, Kordonouri O, Holder M, et al. Prevention of hypoglycemia by using low glucose suspend function in sensor-augmented pump therapy. *Diabetes Technol Ther*. 2011;13(11):1129-1134.
178. Agrawal P, Welsh JB, Kannard B, Askari S, Yang Q, Kaufman FR. Usage and effectiveness of the low glucose suspend feature of the Medtronic Paradigm Veo insulin pump. *J Diabetes Sci Technol*. 2011; 5(5):1137-1141.
179. Danne T, Bangstad HJ, Deeb L, et al. ISPAD Clinical Practice Consensus Guidelines 2014: Insulin treatment in children and adolescents with diabetes. *Pediatr Diabetes*. 2014;15(suppl 20):115-134.
180. Sherr JL, Collazo MP, Cengiz E, et al. Safety of nighttime 2-hour suspension of basal insulin in pump-treated type 1 diabetes even in the absence of low glucose. *Diabetes Care*. 2014;37(3):773-779.
181. Maahs DM, Calhoun P, Buckingham BA, et al. A randomized trial of a home system to reduce nocturnal hypoglycemia in type 1 diabetes. *Diabetes Care*. 2014;37(7):1885-1891.
182. Buckingham BA, Raghinaru D, Cameron F, et al. Predictive low-glucose insulin suspension reduces duration of nocturnal hypoglycemia in children without increasing ketosis. *Diabetes Care*. 2015; 38(7):1197-1204.
183. Calhoun PM, Buckingham BA, Maahs DM, et al. Efficacy of an overnight predictive low-glucose suspend system in relation to hypoglycemia risk factors in youth and adults with type 1 diabetes. *J Diabetes Sci Technol*. 2016;10(6):1216-1221.
184. Buckingham BA, Bailey TS, Christiansen M, et al. Evaluation of a predictive low-glucose management system in-clinic. *Diabetes Technol Ther*. 2017;19(5):288-292.
185. Battelino T, Nimri R, Dovc K, Phillip M, Bratina N. Prevention of hypoglycemia with predictive low glucose insulin suspension in children with type 1 diabetes: a randomized controlled trial. *Diabetes Care*. 2017;40(6):764-770.
186. Abraham MB, Nicholas JA, Smith GJ, et al. Reduction in hypoglycemia with the predictive low-glucose management system: a long-term randomized controlled trial in adolescents with type 1 diabetes. *Diabetes Care*. 2018;41(2):303-310.
187. Scaramuzza AE, Arnaldi C, Cherubini V, et al. Use of the predictive low glucose management (PLGM) algorithm in Italian adolescents with type 1 diabetes: CareLink data download in a real-world setting. *Acta Diabetol*. 2017;54(3):317-319.
188. Buckingham B, Pinsker J, Forlenza G, et al. PROLOG: a randomized clinical trial to assess the efficacy of predictive low glucose suspend versus sensor-augmented pump therapy in the management of type 1 diabetes. Advanced technologies and treatments of diabetes; Vienna, Austria. *Diabetes Technol Ther*. 2018;20(Supplement 1):A-12.
189. Beck RW, Raghinaru D, Wadwa RP, et al. Frequency of morning ketosis after overnight insulin suspension using an automated nocturnal predictive low glucose suspend system. *Diabetes Care*. 2014; 37(5):1224-1229.
190. Scaramuzza AE, Arnaldi C, Cherubini V, et al. Recommendations for the use of sensor-augmented pumps with predictive low-glucose suspend features in children: the importance of education. *Pediatr Diabetes*. 2017;18(8):883-889.
191. Steil G, Rebrin K, Mastrototaro JJ. Metabolic modelling and the closed-loop insulin delivery problem. *Diabetes Res Clin Pract*. 2006; 74:S183-S186.
192. Hovorka R, Canonico V, Chassin LJ, et al. Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. *Physiol Meas*. 2004;25(4):905.
193. Mauseth R, Wang Y, Dassau E, et al. Proposed clinical application for tuning fuzzy logic controller of artificial pancreas utilizing a personalization factor. *J Diabetes Sci Technol*. 2010;4(4):913-922.
194. Weinzimer SA, Steil GM, Swan KL, Dziura J, Kurtz N, Tamborlane WV. Fully automated closed-loop insulin delivery versus semiautomated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. *Diabetes Care*. 2008;31(5):934-939.
195. Steil GM, Rebrin K, Darwin C, Hariri F, Saad MF. Feasibility of automating insulin delivery for the treatment of type 1 diabetes. *Diabetes*. 2006;55(12):3344-3350.
196. Hovorka R, Allen JM, Elleri D, et al. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. *Lancet*. 2010;375(9716):743-751.
197. Nimri R, Danne T, Kordonouri O, et al. The "Glucositter" overnight automated closed loop system for type 1 diabetes: a randomized crossover trial. *Pediatr Diabetes*. 2013;14(3):159-167.
198. Castle JR, Engle JM, El Youssef J, et al. Novel use of glucagon in a closed-loop system for prevention of hypoglycemia in type 1 diabetes. *Diabetes Care*. 2010;33(6):1282-1287.
199. El-Khatib FH, Russell SJ, Magyar KL, et al. Autonomous and continuous adaptation of a bihormonal bionic pancreas in adults and adolescents with type 1 diabetes. *J Clin Endocrinol Metab*. 2014;99(5): 1701-1711.
200. O'Grady MJ, Retterath AJ, Keenan DB, et al. The use of an automated, portable glucose control system for overnight glucose control in adolescents and young adults with type 1 diabetes. *Diabetes Care*. 2012;35(11):2182-2187.
201. Nimri R, Atlas E, Ajzensztejn M, Miller S, Oron T, Phillip M. Feasibility study of automated overnight closed-loop glucose control under MD-logic artificial pancreas in patients with type 1 diabetes: the DREAM Project. *Diabetes Technol Ther*. 2012;14(8):728-735.
202. Ruiz JL, Sherr JL, Cengiz E, et al. Effect of insulin feedback on closed-loop glucose control: a crossover study. *J Diabetes Sci Technol*. 2012;6(5):1123-1130.
203. Sherr JL, Patel NS, Michaud CI, et al. Mitigating meal-related glycemic excursions in an insulin-sparing manner during closed-loop insulin delivery: the beneficial effects of adjunctive pramlintide and liraglutide. *Diabetes Care*. 2016;39(7):1127-1134.
204. Weinzimer SA, Sherr JL, Cengiz E, et al. Effect of pramlintide on prandial glycemic excursions during closed-loop control in adolescents and young adults with type 1 diabetes. *Diabetes Care*. 2012; 35(10):1994-1999.
205. Haidar A, Legault L, Dallaire M, et al. Glucose-responsive insulin and glucagon delivery (dual-hormone artificial pancreas) in adults with type 1 diabetes: a randomized crossover controlled trial. *Can Med Assoc J*. 2013;185(4):297-305.
206. Hovorka R, Kumareswaran K, Harris J, et al. Overnight closed loop insulin delivery (artificial pancreas) in adults with type 1 diabetes: crossover randomised controlled studies. *BMJ*. 2011;342:d1855.
207. Kovatchev B, Cobelli C, Renard E, et al. Multinational study of subcutaneous model-predictive closed-loop control in type 1 diabetes mellitus: summary of the results. *J Diabetes Sci Technol*. 2010;4(6): 1374-1381.
208. Russell SJ, El-Khatib FH, Nathan DM, Magyar KL, Jiang J, Damiano ER. Blood glucose control in type 1 diabetes with a bihormonal bionic endocrine pancreas. *Diabetes Care*. 2012;35(11): 2148-2155.
209. Van Bon AC, Jonker LD, Koebrugge R, Koops R, Hoekstra JB, DeVries JH. Feasibility of a bihormonal closed-loop system to control postexercise and postprandial glucose excursions. *J Diabetes Sci Technol*. 2012;6(5):1114-1122.
210. Renukuntla VS, Ramchandani N, Trast J, Cantwell M, Heptulla RA. Role of glucagon-like peptide-1 analogue versus amylin as an adjuvant therapy in type 1 diabetes in a closed loop setting with ePID algorithm. *J Diabetes Sci Technol*. 2014;8(5):1011-1017.
211. Zisser H, Dassau E, Lee JJ, Harvey RA, Bevier W, Doyle FJ III. Clinical results of an automated artificial pancreas using technosphere inhaled insulin to mimic first-phase insulin secretion. *J Diabetes Sci Technol*. 2015;9(3):564-572.
212. Murphy HR, Kumareswaran K, Elleri D, et al. Safety and efficacy of 24-h closed-loop insulin delivery in well-controlled pregnant women with type 1 diabetes: a randomized crossover case series. *Diabetes Care*. 2011;34(12):2527-2529.
213. de Bock M, Dart J, Roy A, et al. Exploration of the performance of a hybrid closed loop insulin delivery algorithm that includes insulin delivery limits designed to protect against hypoglycemia. *J Diabetes Sci Technol*. 2017;11(1):68-73.
214. Jacobs P, El Youssef J, Reddy R, et al. Randomized trial of a dual-hormone artificial pancreas with dosing adjustment during exercise compared with no adjustment and sensor-augmented pump therapy. *Diabetes Obes Metab*. 2016;18(11):1110-1119.
215. Sherr JL, Cengiz E, Palerm CC, et al. Reduced hypoglycemia and increased time in target using closed-loop insulin delivery during

nights with or without antecedent afternoon exercise in type 1 diabetes. *Diabetes Care*. 2013;36(10):2909-2914.
216. Ly TT, Breton MD, Keith-Hynes P, et al. Overnight glucose control with an automated, unified safety system in children and adolescents with type 1 diabetes at diabetes camp. *Diabetes Care*. 2014;37(8):2310-2316.
217. Ly TT, Buckingham BA, DeSalvo DJ, et al. Day-and-night closed-loop control using the unified safety system in adolescents with type 1 diabetes at camp. *Diabetes Care*. 2016;39(8):e106-e107.
218. Ly TT, Keenan DB, Roy A, et al. Automated overnight closed-loop control using a proportional-integral-derivative algorithm with insulin feedback in children and adolescents with type 1 diabetes at diabetes camp. *Diabetes Technol Ther*. 2016;18(6):377-384.
219. Ly TT, Roy A, Grosman B, et al. Day and night closed-loop control using the integrated Medtronic hybrid closed-loop system in type 1 diabetes at diabetes camp. *Diabetes Care*. 2015;38(7):1205-1211.
220. Phillip M, Battelino T, Atlas E, et al. Nocturnal glucose control with an artificial pancreas at a diabetes camp. *N Engl J Med*. 2013;368(9):824-833.
221. Russell SJ, Hillard MA, Balliro C, et al. Day and night glycaemic control with a bionic pancreas versus conventional insulin pump therapy in preadolescent children with type 1 diabetes: a randomised crossover trial. *Lancet Diabetes Endocrinol*. 2016;4(3):233-243.
222. Breton MD, Chernavvsky DR, Forlenza GP, et al. Closed-loop control during intense prolonged outdoor exercise in adolescents with type 1 diabetes: the Artificial Pancreas Ski Study. *Diabetes Care*. 2017;40(12):1644-1650.
223. Russell SJ, El-Khatib FH, Sinha M, et al. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. *N Engl J Med*. 2014;371(4):313-325.
224. Brown SA, Kovatchev BP, Breton MD, et al. Multinight "bedside" closed-loop control for patients with type 1 diabetes. *Diabetes Technol Ther*. 2015;17(3):203-209.
225. Kovatchev BP, Renard E, Cobelli C, et al. Safety of outpatient closed-loop control: first randomized crossover trials of a wearable artificial pancreas. *Diabetes Care*. 2014;37(7):1789-1796.
226. Kovatchev BP, Renard E, Cobelli C, et al. Feasibility of outpatient fully integrated closed-loop control first studies of wearable artificial pancreas. *Diabetes Care*. 2013;36(7):1851-1858.
227. DeBoer MD, Breton MD, Wakeman C, et al. Performance of an artificial pancreas system for young children with type 1 diabetes. *Diabetes Technol Ther*. 2017;19(5):293-298.
228. Sharifi A, De Bock MI, Jayawardene D, et al. Glycemia, treatment satisfaction, cognition, and sleep quality in adults and adolescents with type 1 diabetes when using a closed-loop system overnight versus sensor-augmented pump with low-glucose suspend function: a randomized crossover study. *Diabetes Technol Ther*. 2016;18(12):772-783.
229. de Bock MI, Roy A, Cooper MN, et al. Feasibility of outpatient 24-hour closed-loop insulin delivery. *Diabetes Care*. 2015;38(11):e186-e187.
230. Haidar A, Rabasa-Lhoret R, Legault L, et al. Single-and dual-hormone artificial pancreas for overnight glucose control in type 1 diabetes. *J Clin Endocrinol*. 2016;101(1):214-223.
231. Hovorka R, Elleri D, Thabit H, et al. Overnight closed-loop insulin delivery in young people with type 1 diabetes: a free-living, randomized clinical trial. *Diabetes Care*. 2014;37(5):1204-1211.
232. Nimri R, Muller I, Atlas E, et al. Night glucose control with MD-Logic artificial pancreas in home setting: a single blind, randomized crossover trial—interim analysis. *Pediatr Diabetes*. 2014;15(2):91-99.
233. Nimri R, Muller I, Atlas E, et al. MD-Logic overnight control for 6 weeks of home use in patients with type 1 diabetes: randomized crossover trial. *Diabetes Care*. 2014;37(11):3025-3032.
234. Spaic T, Driscoll M, Raghinaru D, et al. Predictive hyperglycemia and hypoglycemia minimization: in-home evaluation of safety, feasibility, and efficacy in overnight glucose control in type 1 diabetes. *Diabetes Care*. 2017;40(3):359-366.
235. Tauschmann M, Allen JM, Wilinska ME, et al. Day-and-night hybrid closed-loop insulin delivery in adolescents with type 1 diabetes: a free-living, randomized clinical trial. *Diabetes Care*. 2016;39(7):1168-1174.
236. Thabit H, Elleri D, Leelarathna L, et al. Unsupervised home use of an overnight closed-loop system over 3–4 weeks: a pooled analysis of randomized controlled studies in adults and adolescents with type 1 diabetes. *Diabetes Obes Metab*. 2015;17(5):452-458.
237. Thabit H, Tauschmann M, Allen JM, et al. Home use of an artificial beta cell in type 1 diabetes. *N Engl J Med*. 2015;373(22):2129-2140.
238. Tauschmann M, Allen JM, Wilinska ME, et al. Home use of day-and-night hybrid closed-loop insulin delivery in suboptimally controlled adolescents with type 1 diabetes: a 3-week, free-living, randomized crossover trial. *Diabetes Care*. 2016;39(11):2019-2025.
239. Anderson SM, Raghinaru D, Pinsker JE, et al. Multinational home use of closed-loop control is safe and effective. *Diabetes Care*. 2016;39(7):1143-1150.
240. Blauw H, van Bon A, Koops R, DeVries J. Performance and safety of an integrated bihormonal artificial pancreas for fully automated glucose control at home. *Diabetes Obes Metab*. 2016;18(7):671-677.
241. Del Favero S, Bruttomesso D, Di Palma F, et al. First use of model predictive control in outpatient wearable artificial pancreas. *Diabetes Care*. 2014;37(5):1212-1215.
242. El-Khatib FH, Balliro C, Hillard MA, et al. Home use of a bihormonal bionic pancreas versus insulin pump therapy in adults with type 1 diabetes: a multicentre randomised crossover trial. *Lancet*. 2017;389(10067):369-380.
243. Kropff J, Del Favero S, Place J, et al. 2 month evening and night closed-loop glucose control in patients with type 1 diabetes under free-living conditions: a randomised crossover trial. *Lancet Diabetes Endocrinol*. 2015;3(12):939-947.
244. Leelarathna L, Dellweg S, Mader JK, et al. Day and night home closed-loop insulin delivery in adults with type 1 diabetes: three-center randomized crossover study. *Diabetes Care*. 2014;37(7):1931-1937.
245. Thabit H, Lubina-Solomon A, Stadler M, et al. Home use of closed-loop insulin delivery for overnight glucose control in adults with type 1 diabetes: a 4-week, multicentre, randomised crossover study. *Lancet Diabetes Endocrinol*. 2014;2(9):701-709.
246. Weisman A, Bai J-W, Cardinez M, Kramer CK, Perkins BA. Effect of artificial pancreas systems on glycaemic control in patients with type 1 diabetes: a systematic review and meta-analysis of outpatient randomised controlled trials. *Lancet Diabetes Endocrinol*. 2017;5(7):501-512.
247. Bergenstal RM, Garg S, Weinzimer SA, et al. Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. *JAMA*. 2016;316(13):1407-1408.
248. Buckingham B, Shulman D, Folenza G, et al. Glycemic outcomes during Minimed 670G system use in children with T1D. Advanced Technologies & Treatments of Diabetes; Vienna, Austria. *Diabetes Technol Ther*: Mary Ann Liebert, Inc. 2018;20(Supplement 1):39.
249. Dovc K, Macedoni M, Bratina N, et al. Closed-loop glucose control in young people with type 1 diabetes during and after unannounced physical activity: a randomised controlled crossover trial. *Diabetologia*. 2017;60(11):2157-2167.
250. Castle J, El Youssef J, Wilson LM, et al. Randomized outpatient trial of single and dual-hormone closed-loop systems that adapt to exercise using wearable sensors. *Diabetes Care*. 2018;41(7):1471-1477.
251. Patel NS, Van Name MA, Cengiz E, et al. Mitigating reductions in glucose during exercise on closed-loop insulin delivery: The Ex-Snacks Study. *Diabetes Technol Ther*. 2016;18(12):794-799.
252. Forlenza GP, Cameron FM, Ly TT, et al. Fully closed-loop multiple model probabilistic predictive controller artificial pancreas performance in adolescents and adults in a supervised hotel setting. *Diabetes Technol Ther*. 2018;20(5):335-343.
253. DeBoer MD, Chernavvsky DR, Topchyan K, Kovatchev BP, Francis GL, Breton MD. Heart rate informed artificial pancreas system enhances glycemic control during exercise in adolescents with T1D. *Pediatr Diabetes*. 2017;18(7):540-546.
254. Troncone A, Bonfanti R, Iafusco D, et al. Evaluating the experience of children with type 1 diabetes and their parents taking part in an artificial pancreas clinical trial over multiple days in a diabetes camp setting. *Diabetes Care*. 2016;39(12):2158-2164.
255. Barnard KD, Wysocki T, Allen JM, et al. Closing the loop overnight at home setting: psychosocial impact for adolescents with type

1 diabetes and their parents. *BMJ Open Diabetes Res Care*. 2014;2(1): e000025.
256. Barnard KD, Wysocki T, Thabit H, et al. Psychosocial aspects of closed-and open-loop insulin delivery: closing the loop in adults with type 1 diabetes in the home setting. *Diabet Med*. 2015;32(5): 601-608.
257. Weissberg-Benchell J, Hessler D, Polonsky WH, Fisher L. Psychosocial impact of the bionic pancreas during summer camp. *J Diabetes Sci Technol*. 2016;10(4):840-844.
258. Messer LH, Forlenza GP, Wadwa RP, et al. The dawn of automated insulin delivery: a new clinical framework to conceptualize insulin administration. *Pediatr Diabetes*. 2017;19(1):14-17.
259. Froisland DH, Arsand E, Skarderud F. Improving diabetes care for young people with type 1 diabetes through visual learning on mobile phones: mixed-methods study. *J Med Internet Res*. 2012;14(4):e111.
260. Hanauer DA, Wentzell K, Laffel N, Laffel LM. Computerized Automated Reminder Diabetes System (CARDS): e-mail and SMS cell phone text messaging reminders to support diabetes management. *Diabetes Technol Ther*. 2009;11(2):99-106.
261. Forlenza GP. Relevance of Bolus calculators in current hybrid closed loop systems. *Diabetes Technol Ther*. 2017;19(7):400-401.
262. Cafazzo JA, Casselman M, Hamming N, Katzman DK, Palmert MR. Design of an mHealth app for the self-management of adolescent type 1 diabetes: a pilot study. *J Med Internet Res*. 2012;14(3):e70.
263. Trawley S, Browne JL, Hagger VL, et al. The use of mobile applications among adolescents with type 1 diabetes: results from diabetes MILES Youth-Australia. *Diabetes Technol Ther*. 2016;18(12):813-819.
264. Goyal S, Cafazzo JA. Mobile phone health apps for diabetes management: current evidence and future developments. *QJM*. 2013; 106(12):1067-1069.
265. Majeed-Ariss R, Baildam E, Campbell M, et al. Apps and adolescents: a systematic review of adolescents' use of mobile phone and tablet apps that support personal management of their chronic or long-term physical conditions. *J Med Internet Res*. 2015;17(12):e287.
266. Hou C, Carter B, Hewitt J, Francisa T, Mayor S. Do mobile phone applications improve glycemic control (HbA1c) in the self-management of diabetes? A systematic review, meta-analysis, and GRADE of 14 randomized trials. *Diabetes Care*. 2016;39(11): 2089-2095.
267. Wu Y, Yao X, Vespasiani G, et al. Mobile app-based interventions to support diabetes self-management: a systematic review of randomized controlled trials to identify functions associated with glycemic efficacy. *JMIR Mhealth Uhealth*. 2017;5(3):e35.
268. Ramotowska A, Golicki D, Dzygalo K, Szypowska A. The effect of using the insulin pump bolus calculator compared to standard insulin dosage calculations in patients with type 1 diabetes mellitus – systematic review. *Exp Clin Endocrinol Diabetes*. 2013;121(5):248-254.
269. Schmidt S, Meldgaard M, Serifovski N, et al. Use of an automated bolus calculator in MDI-treated type 1 diabetes: the BolusCal Study, a randomized controlled pilot study. *Diabetes Care*. 2012;35(5): 984-990.
270. Schmidt S, Norgaard K. Bolus calculators. *J Diabetes Sci Technol*. 2014;8(5):1035-1041.
271. Ziegler R, Cavan DA, Cranston I, et al. Use of an insulin bolus advisor improves glycemic control in multiple daily insulin injection (MDI) therapy patients with suboptimal glycemic control: first results from the ABACUS trial. *Diabetes Care*. 2013;36(11):3613-3619.
272. Vallejo Mora MR, Carreira M, Anarte MT, Linares F, Olveira G, Gonzalez RS. Bolus calculator reduces hypoglycemia in the short term and fear of hypoglycemia in the long term in subjects with type 1 diabetes (CBMDI STUDY). *Diabetes Technol Ther*. 2017;19(7): 402-409.
273. Vallejo-Mora MD, Carreira-Soler M, Linares-Parrado F, et al. The Calculating Boluses on Multiple Daily Injections (CBMDI) study: A randomized controlled trial on the effect on metabolic control of adding a bolus calculator to multiple daily injections in people with type 1 diabetes. *J Diabetes*. 2017;9(1):24-33.
274. Groat D, Grando MA, Soni H, et al. Self-management behaviors in adults on insulin pump therapy. *J Diabetes Sci Technol*. 2017;11(2): 233-239.
275. Patton SR, Driscoll KA, Clements MA. Adherence to insulin pump behaviors in young children with type 1 diabetes mellitus. *J Diabetes Sci Technol*. 2017;11(1):87-91.
276. Wang Y, Zhang J, Zeng F, et al. "Learning" can improve the blood glucose control performance for type 1 diabetes mellitus. *Diabetes Technol Ther*. 2017;19(1):41-48.
277. Dassau E, Brown SA, Basu A, et al. Adjustment of open-loop settings to improve closed-loop results in type 1 diabetes: a multicenter randomized trial. *J Clin Endocrinol Metab*. 2015;100(10):3878-3886.
278. Wong JC, Neinstein AB, Spindler M, Adi S. A minority of patients with type 1 diabetes routinely downloads and retrospectively reviews device data. *Diabetes Technol Ther*. 2015;17(8):555-562.
279. Beck RW. Downloading diabetes device data: empowering patients to download at home to achieve better outcomes. *Diabetes Technol Ther*. 2015;17(8):536-537.
280. Denham SA, Wood L, Remsberg K. Diabetes care: provider disparities in the US Appalachian region. *Rural Remote Health*. 2010;10(2): 1320.
281. Jin YZW, Yuan B, Meng Q. Impact of health workforce availability on health care seeking behavior of patients with diabetes mellitus in China. *Int J Equity Health*. 2017;16(1):80.
282. Pihoker C, Forsander G, Fantahun B, et al. ISPAD Clinical Practice Consensus Guidelines 2014. The delivery of ambulatory diabetes care to children and adolescents with diabetes. *Pediatr Diabetes*. 2014;15(suppl 20):86-101.
283. Sandberg JTP, Izquierdo R, Goland R, et al. A qualitative study of the experiences and satisfaction of direct telemedicine providers in diabetes case management. *Telemed J E Health*. 2009;15(8):742-750.
284. Griffith ML, Siminerio L, Payne T, Krall J. A shared decision-making approach to telemedicine: engaging rural patients in glycemic management. *J Clin Med*. 2016;5(11):1-7.
285. Levin K, Madsen JR, Petersen I, Wanscher CE, Hangaard J. Telemedicine diabetes consultations are cost-effective, and effects on essential diabetes treatment parameters are similar to conventional treatment: 7-year results from the Svendborg Telemedicine Diabetes Project. *J Diabetes Sci Technol*. 2013;7(3):587-595.
286. West SPLC, Trief PM, Izquierdo R, Weinstock RS. Goal setting using telemedicine in rural underserved older adults with diabetes: experiences from the informatics for diabetes education and telemedicine project. *Telemed J E Health*. 2010;16(4):405-416.
287. Shea SWR, Starren J, Teresi J, et al. A randomized trial comparing telemedicine case management with usual care in older, ethnically diverse, medically underserved patients with diabetes mellitus. *J Am Med Inform Assoc*. 2006;13(1):40-51.
288. Shea SWR, Teresi JA, Palmas W, et al. IDEATel Consortium. A randomized trial comparing telemedicine case management with usual care in older, ethnically diverse, medically underserved patients with diabetes mellitus: 5 year results of the IDEATel study. *J Am Med Inform Assoc*. 2009;16(4):446-456.
289. Choi YS, Cucura J, Jain R, Berry-Caban C. Telemedicine in US Army soldiers with type 1 diabetes. *J Telemed Telecare*. 2015;21(7): 392-395.
290. Wood CLCS, McFann K, Slover R, Thomas JF, Wadwa RP. Use of telemedicine to improve adherence to American Diabetes Association Standards in pediatric type 1 diabetes. *Diabetes Technol Ther*. 2016;18(1):7-14.
291. Caprio S, Plewe G, Diamond MP, et al. Increased insulin secretion in puberty: a compensatory response to reductions in insulin sensitivity. *J Pediatr*. 1989;114(6):963-967.
292. Guttmann-Bauman I, Kono J, Lin AL, Ramsey KL, Boston BA. Use of telehealth videoconferencing in pediatric type 1 diabetes in Oregon. *Telemed J E Health*. 2018;24(1):86-88.
293. Izquierdo RMP, Bratt K, Moreau Z, et al. School-centered telemedicine for children with type 1 diabetes mellitus. *J Pediatr*. 2009; 155(3):374-379.
294. Bouchonville MF, Paul MM, Billings J, Kirk JB, Arora S. Taking telemedicine to the next level in diabetes population management: a review of the Endo ECHO Model. *Curr Diab Rep*. 2016;16(10):96.
295. Weinstock RSTJ, Goland R, Izquierdo R, et al. IDEATel Consortium. Glycemic control and health disparities in older ethnically diverse underserved adults with diabetes: five-year results from the

Informatics for Diabetes Education and Telemedicine (IDEATel) study. *Diabetes Care*. 2011;34(2):274-279.
296. Lee SWHOL, Lai YK. Telemedicine for the management of Glycemic control and clinical outcomes of type 1 diabetes mellitus: A systematic review and meta-analysis of randomized controlled studies. *Front Pharmacol*. 2017;8:330.
297. Palmas W, Shea S, Starren J, et al. Medicare payments, healthcare service use, and telemedicine implementation costs in a randomized trial comparing telemedicine case management with usual care in medically underserved participants with diabetes mellitus (IDEATel). *J Am Med Inform Assoc*. 2010;17(2):196-202.
298. Chowdhury S. Puberty and type 1 diabetes. *Indian J Endocrinol Metab*. 2015;19(1):51-54.
299. Trast J. CE: Diabetes and puberty: a glycemic challenge. *Am J Nurs*. 2014;114(7):26-35.
300. Piloya-Were TSM, Ogle GD, Moran A. Childhood diabetes in Africa. *Curr Opin Endocrinol Diabetes Obes*. 2016;23(4):306-311.
301. Katz ML, Volkening LK, Butler DA, Anderson BJ, Laffel LM. Family-based psychoeducation and Care Ambassador intervention to improve glycemic control in youth with type 1 diabetes: a randomized trial. *Pediatr Diabetes*. 2014;15(2):142-150.
302. Hilliard ME, Iturralde E, Weissberg-Benchell J, Hood KK. The diabetes strengths and resilience measure for adolescents with type 1 diabetes (DSTAR-Teen): validation of a new, brief self-report measure. *J Pediatr Psychol*. 2017;42(9):995-1005.
303. Jaser SS, Patel N, Xu M, Tamborlane WV, Grey M. Stress and coping predicts adjustment and glycemic control in adolescents with type 1 diabetes. *Ann Behav Med*. 2017;51(1):30-38.
304. Hilliard ME, Lawrence JM, Modi AC, et al. Identification of minimal clinically important difference scores of the PedsQL in children, adolescents, and young adults with type 1 and type 2 diabetes. *Diabetes Care*. 2013;36(7):1891-1897.
305. Markowitz JT, Pratt K, Aggarwal J, Volkening LK, Laffel LM. Psychosocial correlates of continuous glucose monitoring use in youth and adults with type 1 diabetes and parents of youth. *Diabetes Technol Ther*. 2012;14(6):523-526.
306. Naranjo D, Suttiratana SC, Iturralde E, et al. What end users and stakeholders want from automated insulin delivery systems. *Diabetes Care*. 2017;40(11):1453-1461.
307. Hartz J, Yingling L, Powell-Wiley TM. Use of mobile health technology in the prevention and management of diabetes mellitus. *Curr Cardiol Rep*. 2016;18(12):130.
308. Mulvaney SA, Rothman RL, Wallston KA, Lybarger C, Dietrich MS. An internet-based program to improve self-management in adolescents with type 1 diabetes. *Diabetes Care*. 2010;33(3):602-604.
309. Vaala SE, Hood KK, Laffel L, Kumah-Crystal YA, Lybarger CK, Mulvaney SA. Use of commonly available technologies for diabetes information and self-management among adolescents with type 1 diabetes and their parents: a web-based survey study. *Interact J Med Res*. 2015;4(4):e24.
310. Agiostratidou G, Anhalt H, Ball D, et al. Standardizing clinically meaningful outcome measures beyond hba1c for type 1 diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. *Diabetes Care*. 2017;40(12):1622-1630.
311. Bode BW, Kaufman FR, Vint N. An expert opinion on advanced insulin pump use in youth with type 1 diabetes. *Diabetes Technol Ther*. 2017;19(3):145-154.
312. Danne T, Battelino T, Kordonouri O, et al. A cross-sectional international survey of continuous subcutaneous insulin infusion in 377 children and adolescents with type 1 diabetes mellitus from 10 countries. *Pediatr Diabetes*. 2005;6(4):193-198.
313. Alemzadeh R, Hoffmann RG, Dasgupta M, Parton E. Development of optimal kids insulin dosing system formulas for young children with type 1 diabetes mellitus. *Diabetes Technol Ther*. 2012;14(5):418-422.
314. Hanas R, Adolfsson P. Bolus calculator settings in well-controlled prepubertal children using insulin pumps are characterized by low insulin to carbohydrate ratios and short duration of insulin action time. *J Diabetes Sci Technol*. 2017;11(2):247-252.

How to cite this article: Sherr JL, Tauschmann M, Battelino T, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Diabetes technologies. *Pediatr Diabetes*. 2018;19 (Suppl. 27):302–325. https://doi.org/10.1111/pedi.12731