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AACE Guideline

American Association of Clinical Endocrinology Clinical Practice Guideline: The Use of Advanced Technology in the Management of Persons With Diabetes Mellitus

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ABSTRACT

Objective: To provide evidence-based recommendations regarding the use of advanced technology in the management of persons with diabetes mellitus to clinicians, diabetes-care teams, health care professionals, and other stakeholders.
Methods: The American Association of Clinical Endocrinology (AACE) conducted literature searches for relevant articles published from 2012 to 2021. A task force of medical experts developed evidence-based guideline recommendations based on a review of clinical evidence, expertise, and informal consensus, according to established AACE protocol for guideline development.
Main Outcome Measures: Primary outcomes of interest included hemoglobin A1C, rates and severity of hypoglycemia, time in range, time above range, and time below range.
Results: This guideline includes 37 evidence-based clinical practice recommendations for advanced diabetes technology and contains 357 citations that inform the evidence base.
Recommendations: Evidence-based recommendations were developed regarding the efficacy and safety of devices for the management of persons with diabetes mellitus, metrics used to aide with the assessment of advanced diabetes technology, and standards for the implementation of this technology.
Conclusions: Advanced diabetes technology can assist persons with diabetes to safely and effectively achieve glycemic targets, improve quality of life, add greater convenience, potentially reduce burden of

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care, and offer a personalized approach to self-management. Furthermore, diabetes technology can improve the efficiency and effectiveness of clinical decision-making. Successful integration of these technologies into care requires knowledge about the functionality of devices in this rapidly changing field. This information will allow health care professionals to provide necessary education and training to persons accessing these treatments and have the required expertise to interpret data and make appropriate treatment adjustments.

Lay Abstract

It has been 100 years since the discovery of insulin and over the past 50 years sophisticated tools have been developed that help persons with diabetes greatly improve the quality of their lives and more easily manage their condition. This guideline provides recommendations based on scientific evidence for health care professionals in the safe and effective use of advanced diabetes technology. While many persons with diabetes use self-monitoring of blood glucose and insulin injections or insulin pens, these tools are being replaced by more advanced technologies that provide more useful data and greater convenience. Advanced tools, such as continuous glucose monitors (CGMs), provide data in real time to help persons with diabetes avoid experiencing low and high blood sugar levels. As partners with their patients, doctors also use CGM to identify challenges, set goals, and find the best personalized treatment options for each individual. Persons with diabetes who are managed with multiple daily injections now may use connected insulin "smart" pens to optimize insulin dosing. Insulin pumps offer the ability to have adjustable basal rates and more fine-tuned insulin-bolus dosing through the use of bolus calculators that allow for the use of insulin-to-carbohydrate ratios and correction factors to be set by time of day and allow smaller dosing increments of insulin when compared with injected insulins. Newer tools combine CGM with continuous insulin infusion pumps that automate insulin dosing and delivery. Ideally, a knowledgeable health care team provides education and training to persons using these new treatments to manage their diabetes and understands the data that these tools can provide to allow them to make the best treatment decisions for each person. Diabetes technology is rapidly changing and improving and can be beneficial for all those living with diabetes.

Abbreviations

AACE, American Association of Clinical Endocrinology; A1C, hemoglobin A1c; AHCL, advanced hybrid closed loop; AID, automated insulin dosing; AGP, ambulatory glucose profile; BEL, best evidence level; CAN, cardiovascular autonomic neuropathy; CDCES, clinical diabetes care and education specialist; CGM, continuous glucose monitoring; COVID-19, coronavirus disease 2019; CSII, continuous subcutaneous insulin injection; CV, coefficient of variation; DCCT, Diabetes Control and Complications Trial; DIY, do-it-yourself; DKA, diabetic ketoacidosis; DSMES, diabetes self-management education and support; EL, evidence level; FDA, Food and Drug Administration; GDM, gestational diabetes mellitus; GMI, glucose management indicator; HCL, hybrid closed loop; ICER, incremental cost-effectiveness ratio; isCGM, intermittently scanned CGM; LGS, low-glucose suspend; MDI, multiple daily injection; NICU, neonatal intensive care unit; PLGS, predictive low-glucose suspend; Q, question; QALY, quality-adjusted life years; QoL, quality of life; R, recommendation; RCT, randomized controlled trial; rtCGM, real-time CGM; SAP, sensor-augmented pump; SD, standard deviation; SMBG, self-monitoring of blood glucose; TAR, time above range; TIR, time in range; TBR, time below range; T1D, type 1 diabetes; T2D, type 2 diabetes

Structure of Clinical Practice Guideline

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     - Insulin Delivery Technologies
       - Insulin Pumps
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   - Recommendation
   - Recommendation grade, strength of evidence grade, best evidence level (BEL)
   - Evidence Base: summary of clinical background and highlighted studies that best support the recommendation

Introduction

While insulin therapy has been available for a century, the past 50 years have seen advances in glucose monitoring and insulin delivery technologies, which have led to the development of sophisticated tools that enable persons with diabetes to significantly enhance their daily self-management and improve the quality of their lives. Innovations, such as continuous glucose monitoring (CGM), provide glucose data that allow persons with diabetes to achieve their overall glycemic targets as they avoid the acute complications of hypoglycemia and hyperglycemia. A retrospective analysis of CGM data enables clinicians and persons with diabetes to collaboratively work in identifying problem areas, set achievable goals, and determine appropriate therapies.

Intensive insulin therapy involves the use of either multiple daily injections (MDIs), defined as 3 or more injections per day, or the use of a continuous subcutaneous insulin infusion (CSII) pump. Persons with diabetes who choose to manage their diabetes with MDI therapy now have connected insulin pens with integrated bolus calculators that simplify insulin administration as well as simplify the accuracy of dosage calculation. The integration of CGM with CSII technologies has led to the development of sensor-augmented insulin pumps (SAPs) and laid the foundation for automated insulin dosing (AID) systems that combine automated basal insulin delivery,

with some systems now incorporating automatic correction boluses, based on real-time CGM (rtCGM) glucose values.

Importantly, these technologies have the potential to improve clinicians' effectiveness and efficiency by providing critical data in standardized formats, such as the ambulatory glucose profile (AGP), which facilitates more rapid, better informed decision-making. However, the integration and effective use of these technologies will require a multidisciplinary team of diabetes specialists who are thoroughly trained in the functionality of all current devices, are able to provide necessary education and training to persons utilizing these treatment options, and have the tools required to allow them to access reports as well as the expertise needed in interpreting the data and making appropriate treatment adjustments.

Purpose

While the majority of individuals whose diabetes requires the use of insulin continue to use self-monitoring of blood glucose (SMBG) and insulin injections or insulin pens, these tools are being augmented by more advanced technologies that provide more actionable data and greater convenience. As such, providing recommendations regarding the use of SMBG and insulin pens is beyond the scope of the clinical guidelines presented here. The safety and efficacy of advanced diabetes technologies have been demonstrated in large randomized controlled trials (RCTs) and real-world prospective and retrospective, observational studies. However, practical guidance in applying these tools in clinical settings has been sparse, and many clinicians lack clear direction for the integration of these tools in clinical settings.

Therefore, the American Association of Clinical Endocrinology (AACE) developed the following clinical practice guideline for the use of advanced diabetes technology in clinical settings. The recommendations presented are intended to address key topics and relevant questions for determining the evidence behind the efficacy and safety of devices, metrics used to aide with the assessment of diabetes technology, and standards for clinicians and other health care professionals to use advanced diabetes technology in the management of persons with diabetes. By understanding these cornerstones and recommendations for advanced diabetes technology, this task force believes that advanced diabetes technology can be integrated safely and effectively into the care of persons with diabetes, affording a personalized approach to this complex, heterogenous condition. These recommendations should be interpreted with the understanding that diabetes technology is constantly evolving.

Limitations of the Literature

In the continually expanding literature on diabetes technology, evidence is not available to compare every technology in each category to all available devices, partly due to the rapidly evolving development cycle. The field consists of many studies with small sample sizes, homogeneous populations, and of short duration. There are limited well-designed and adequately powered RCTs to assess effectiveness and clinical targets. Several RCTs have employed an open-label design with potential bias or implemented a crossover design with an inherent limitation, since the order of treatments may affect outcomes. There is a significant heterogeneity among studies, including but not limited to differences in study design, and age or duration of diabetes among participants. The majority of studies were sponsored to some degree by industry, which presents another challenge to interpreting the literature on advanced diabetes technology. Recognizing these limitations, the grading of the evidence base was informed by trial design and potential generalizability.

Methods

The AACE Clinical Practice Guidelines Oversight Committee and AACE Board of Directors identified the necessity of this guideline on advanced diabetes technology, confirmed the extent of literature, and empaneled a task force of clinicians for its development in adherence to the 2017 AACE Protocol for Standardized Production of Clinical Practice Guidelines.[1](Appendix Tables 1-4).

A methodologist conducted comprehensive literature searches in PubMed using medical subject headings, field descriptions, and free-text terms to identify all possible studies that included human participants, were published in English between January 1, 2012 and February 1, 2021, and met inclusion criteria (Appendix Table 5). The designation of a specific period of time in such a rapidly evolving field represented a challenge, and it was partially secondary to the tenet that studies from an earlier period represent a marked difference from the devices used in clinical care today. We believed that roughly choosing the past decade would strike the appropriate balance between the currently used technologies and the foundational studies on which they were built. Bibliographies of select articles were also reviewed to ensure the inclusion of all possibly relevant studies. The literature searches and examination of reference lists from primary and review articles yielded 2478 studies, of which 357 citations—343 articles and 14 web links—were included to support this guideline's recommendations and background information.

At least 2 task force authors screened titles and abstracts of broad pools of evidence found in literature searches for each topic and submitted decisions to include or exclude each article along with rationale for exclusion. Disagreements about inclusion among reviewers were resolved by consensus with the chairs. Through this process, authors conducted a thorough appraisal of evidence based on the full scope of available literature to determine studies that best support each recommendation.

AACE methodologist and staff assigned evidence levels and study types to included studies according to established AACE evidence ratings (Appendix Table 1) and extracted data from each full-text article into a structured table to document authors, title, journal citation, study design and population, limitations, comparison group/controls, intervention, outcomes, and limitations. The methodologist and staff assigned a grade for the quality of each article, which informed assigned grades for the confidence and strength of evidence in aggregate for each recommendation (Appendix Table 2-3). There is little evidence available for some issues related to advanced diabetes technology and clinical practice. When the task force determined guidance to be necessary despite a lack of available supporting literature, a recommendation was developed based on expert opinion and consensus of task force authors' collective experience, knowledge, and judgment. Recommendation qualifiers and subjective factors informed the overall grade assigned for each recommendation (Appendix Table 4). Through discussion and consensus of the full task force, task force members confirmed recommendation grades and grades for strength of evidence. Task force chairs provided oversight throughout the development process.

Clinical questions provide the framework for this guideline with answers in the form of recommendations. Task force authors submitted contributions to specific clinical questions, which were integrated into the final document and discussed to achieve unanimous consensus for each of the recommendations. Semantic

descriptors of "must," "should," and "may" generally, although not strictly, correlate with Grade A (strong), Grade B (intermediate), and Grade C (weak) recommendations, respectively; each semantic descriptor can be used with Grade D (no conclusive evidence and/or expert opinion) recommendations, based on the AACE protocol.[1] Deviations from this mapping take into consideration further decision-making based on clinical expertise. AACE followed a rigorous developmental process based on strict methodology to systematically collect and objectively evaluate and clearly summarize available scientific literature to develop trustworthy recommendations for clinical practice regarding advanced diabetes technology.

Table 1
Summary of Recommendations
Q = Question; **R** = Recommendation

Question 1:
What glucose metrics should be used in clinical practice to assess glycemic status?

Q1.1 What are the priority metrics for clinical decision-making regarding the use of diabetes technology?

R1.1.1 Established clinical targets should be used to individualize glycemic targets and adjust therapy based on each individual's overall health status, concomitant medical condition (eg, pregnancy, frailty), and risk for hypoglycemia:

All Persons with Diabetes
- Number of days of active CGM use: 14 days preferred
- Percentage of data available from active CGM use: >70% of data from 14 days
- Mean glucose: Individualized to targets
- Glucose management indicator (GMI): Individualized to targets
- Glycemic variability, percent coefficient of variation (%CV [coefficient of variation]): ≤36%

Type 1 Diabetes (T1D)/Type 2 Diabetes (T2D)
- Percentage of time in range (%TIR) 70 to 180 mg/dL: >70%
- Percentage of time below range (%TBR) <70 mg/dL: <4%
- %TBR <54 mg/dL: <1%
- Percentage of time above range (%TAR) >180 mg/dL: <25%
- %TAR >250 mg/dL: <5%

Older/High Risk T1D/T2D
- %TIR 70 to 180 mg/dL: >50%
- %TBR <70 mg/dL: <1%
- %TBR <54 mg/dL: ~0%
- %TAR >250 mg/dL: <10%

Pregnancy: T1D
- %TIR 63 to 140 mg/dL: >70%
- %TBR <63 mg/dL: <4%
- %TBR <54 mg/dL: <1%
- %TAR >140 mg/dL: <25%

Grade C; Low-Intermediate Strength of Evidence; BEL 2

R1.1.2 Two metrics, %TIR and %TBR, should be used as a starting point for the assessment of quality of glycemic control and as the basis for therapy adjustment, with emphasis on reducing %TBR when the percentages of CGM values falling below 54 mg/dL or 70 mg/dL are close to or exceed targets.
Grade B; Low-Intermediate Strength of Evidence; BEL 1

Question 2:
Who would benefit from diabetes technologies?

Glucose Monitoring Technologies

Q2.1 Who would benefit from routine use of continuous glucose monitoring?

R2.1.1 CGM is strongly recommended for all persons with diabetes treated with intensive insulin therapy, defined as 3 or more injections of insulin per day or the use of an insulin pump.
Grade A; High Strength of Evidence; BEL 1

R2.1.2 Structured SMBG is recommended for individuals on insulin therapy who have limited success with or are unable or unwilling to use CGM.
Grade A; High Strength of Evidence; BEL 1

R2.1.3 CGM is recommended for all individuals with problematic hypoglycemia (frequent/severe hypoglycemia, nocturnal hypoglycemia, hypoglycemia unawareness).
Grade A; Intermediate-High Strength of Evidence; BEL 1

R2.1.4 CGM is recommended for children/adolescents with T1D.
Grade A; Intermediate-High Strength of Evidence; BEL 1

R2.1.5 CGM is recommended for pregnant women with T1D and T2D treated with intensive insulin therapy.
Grade A; Intermediate-High Strength of Evidence; BEL 1

R2.1.6 CGM is recommended for women with gestational diabetes mellitus (GDM) on insulin therapy.
Grade A; Intermediate Strength of Evidence; BEL 1

R2.1.7 CGM may be recommended for women with GDM who are not on insulin therapy.
Grade B; Intermediate Strength of Evidence; BEL 1

R2.1.8 CGM may be recommended for individuals with T2D who are treated with less intensive insulin therapy.
Grade B; Intermediate Strength of Evidence; BEL 1

Q2.2 What is an efficient approach to interpreting continuous glucose monitoring data?

R2.2.1 The AGP may be utilized to assess glycemic status in persons with diabetes.
Grade B; Low Strength of Evidence; BEL 1

R2.2.2 When using the AGP, a systematic approach to interpret CGM data is recommended:
1. Review overall glycemic status (eg, GMI, average glucose)
2. Check TBR, TIR, and TAR statistics, focusing on hypoglycemia (TBR) first. If the TBR statistics are above the cut-point for the clinical scenario (ie, for most with T1D >4% <70 mg/dL; >1% <54 mg/dL), the visit should focus on this issue. Otherwise, move on to the TIR and TAR statistics.
3. Review the 24-hour glucose profile to identify the time(s) and magnitude(s) of the problem identified.
4. Review treatment regimen and adjust as needed.

Grade B; Low Strength of Evidence; BEL 1

Table 1 (*continued*)

Q2.3 When is one method of continuous glucose monitoring (real-time continuous glucose monitoring versus intermittently scanned continuous glucose monitoring) preferred over the other?
R2.3.1 Real-time continuous glucose monitoring (rtCGM) should be recommended over intermittently scanned continuous glucose monitoring (isCGM) to persons with diabetes with problematic hypoglycemia (frequent/severe hypoglycemia, nocturnal hypoglycemia, hypoglycemia unawareness) who require predictive alarms/alerts; however, the lifestyle of persons with diabetes and other factors should also be considered. **Grade B; Low-Intermediate Strength of Evidence; BEL 1**
R2.3.2 isCGM should be considered for persons with diabetes who meet 1 or more of the following criteria: • Newly diagnosed with T2D • Treated with nonhypoglycemic therapies • Motivated to scan device several times per day • At low risk for hypoglycemia, but desire more data than SMBG provides **Grade D; Low Strength of Evidence/Expert Opinion of Task Force; BEL 4**
Q2.4 When should diagnostic/professional continuous glucose monitoring be considered?
R2.4.1 Diagnostic/professional CGM should be used in the management of persons with diabetes who meet 1 or more of the following criteria: • Newly diagnosed with diabetes mellitus • Not using CGM • May have problematic hypoglycemia, but no access to personal CGM • Persons with T2D treated with non-insulin therapies who would benefit from episodic use of CGM as an educational tool • Persons who would like to learn more about CGM before committing to daily use Importantly, in those using "masked" or "blinded" diagnostic/professional CGM, they must have and continue using adjunctive SMBG to assist in daily diabetes self-care. **Grade B; Intermediate Strength of Evidence; BEL 1**
Q2.5 When should intermittent/occasional use of continuous glucose monitoring be considered?
R2.5.1 Intermittent/occasional CGM may be recommended for the management of persons with diabetes who are reluctant or unable to commit to routine CGM use. **Grade C; Intermediate Strength of Evidence; BEL 1**
Insulin Delivery Technologies
Q2.6 Who would benefit from the use of connected pens?
R2.6.1 Connected pens may be recommended for all persons with diabetes who are treated with intensive insulin management, with 3 or more injections per day and who are not on insulin pump therapy, in whom an assessment of insulin dosing may help the person with diabetes and the clinician to further optimize the insulin regimen and avoid the stacking of rapid-acting insulin doses that could lead to hypoglycemia. **Grade C; Intermediate Strength of Evidence/Expert Opinion of Task Force; BEL 2**
Q2.7 Who would benefit from the use of an insulin pump without continuous glucose monitoring?
R2.7.1 The use of an insulin pump without CGM could be used to manage persons with diabetes who are achieving glycemic targets with minimal TBR, who report infrequent episodes of symptomatic hypoglycemia, and who are using SMBG on a regular basis (at least 4 times per day for persons with T1D). **Grade B; Intermediate-High Strength of Evidence; BEL 1**
Q2.8 Who would benefit from the use of an insulin pump with continuous glucose monitoring (separate devices or sensor-augmented pump)?
R2.8.1 Insulin pump with CGM or SAP is recommended to manage all persons with diabetes treated with intensive insulin management who prefer not to use automated insulin suspension/dosing systems or have no access to them. **Grade A; Intermediate-High Strength of Evidence; BEL 1**
Q2.9 Who would benefit from the use of more advanced insulin pump technologies: low-glucose suspend, predictive low-glucose suspend, and hybrid closed loop?
R2.9.1 Low-glucose suspend (LGS) is strongly recommended for all persons with T1D to reduce the severity and duration of hypoglycemia, whereas predictive low-glucose suspend (PLGS) is strongly recommended for all persons with T1D to mitigate hypoglycemia. Both systems do not lead to a rise in mean glucose, and lead to increased confidence and trust in the technology, more flexibility around mealtimes, and reduced diabetes distress for both persons with diabetes and caregivers. Therefore, anyone with frequent hypoglycemia, impaired hypoglycemia awareness, and those who fear hypoglycemia leading to permissive hyperglycemia should be considered for this method of insulin delivery. **Grade A; High Strength of Evidence; BEL 1**
R2.9.2 AID systems are strongly recommended for all persons with T1D, since their use has been shown to increase TIR, especially in the overnight period, without causing an increased risk of hypoglycemia. Given the improvement in TIR and the reduction in hyperglycemia with AID, this method of insulin delivery is preferred above other modalities. For persons with diabetes with suboptimal glycemia, significant glycemic variability, impaired hypoglycemia awareness, or who allow for permissive hyperglycemia due to the fear of hypoglycemia, such AID systems should be considered. **Grade A; High Strength of Evidence; BEL 1**
Q2.10 In what settings or special situations is the use of diabetes technologies beneficial?
R2.10.1 The continuation of CGM and/or CSII (insulin pump, SAP, LGS/PLGS) should be considered in hospitalized persons with diabetes without cognitive impairment and ideally with the presence of a family member who is knowledgeable and educated in the use of these devices or with a specialized inpatient diabetes team available for advice and support. **Grade A; Intermediate Strength of Evidence; BEL 1**
R2.10.2 rtCGM is recommended for persons ≥65 years old with insulin-requiring diabetes to achieve improved glycemic control, reduce episodes of severe hypoglycemia, and improve QoL; however, glycemic goals should be individualized due to increased comorbidities and reduced capacity to detect and counter-regulate against severe hypoglycemia in this population. **Grade A; Intermediate-High Strength of Evidence; BEL 1**
R2.10.3 Clinicians should prescribe CGM as a tool to track glucose before, during, and after exercise in persons with diabetes; monitor the glycemic response to exercise; and help direct insulin and carbohydrate consumption to avoid hypoglycemia and hyperglycemia. When this technology is utilized as part of AID systems, it can reduce glycemic excursions during exercise. **Grade A; Intermediate Strength of Evidence; BEL 1**

(*continued on next page*)

Table 1 (*continued*)

Q2.11 What is the role of telemedicine in the implementation and ongoing use of diabetes technology?
R2.11.1 Telemedicine, including periodic phone calls, smartphone-web interactions, and periodic supervision by health care professional interactions, is strongly recommended to treat persons with diabetes, provide diabetes education, remotely monitor glucose and/or insulin data to indicate the need for therapy adjustments, and improve diabetes-related outcomes/control with better engagement. **Grade A; Intermediate-High Strength of Evidence; BEL 1**
Q2.12 Do smartphone applications have utility in the management of diabetes?
R2.12.1 Clinically validated smartphone applications should be recommended to persons with diabetes to teach/reinforce diabetes self-management skills, encourage engagement (eg, coaching), and support/encourage desired health behaviors (healthy eating instruction, physical exercise tracking). **Grade B; Intermediate-High Strength of Evidence; BEL 1**
Question 3: **What are safety considerations for the use of diabetes technologies?**
Q3.1 What are safety considerations for the use of continuous glucose monitoring?
R3.1.1 With the use of CGM, clinicians should make a reasonable effort to ascertain that a person with diabetes is not inadvertently ingesting a substance or medication that will cause the CGM to deliver false or misleading information. Furthermore, clinicians should make a reasonable effort to make persons with diabetes aware of the theoretical risk of radiation exposure to diabetes technologies. **Grade C; Low Strength of Evidence/Expert Opinion of Task Force; BEL 3**
R3.1.2 Persons with diabetes who have a care provider, such as a spouse, adult child of a geriatric person with diabetes, or parent of a child with diabetes, who remotely monitors glucose data, should be cautioned that remote glucose monitoring is dependent upon server functionality and that data interruption can result. Back-up plans of having persons with diabetes revert to SMBG or methods to communicate CGM data to those who remotely follow will be needed until functionality can be restored. **Grade D; Low Strength of Evidence/Expert Opinion of Task Force; BEL 4**
Q3.2 What are safety issues for the use of insulin delivery devices?
R3.2.1 All persons with diabetes using an insulin delivery technology should receive comprehensive training in its proper use and care. **Grade A; Intermediate Strength of Evidence/Expert Opinion of Task Force; BEL 2**
R3.2.2 The use of United States (U.S.) Food and Drug Administration (FDA) – cleared and clinically validated smartphone bolus calculators, in the absence of pump therapy, is strongly recommended to decrease the frequency of hypoglycemia or severe postprandial hyperglycemia. **Grade A; High Strength of Evidence; BEL 1**
R3.2.3 Clinicians should ensure that persons with diabetes using an insulin delivery technology are aware of the frequency and relative risk of pump malfunction, receive instruction for identifying signs of pump malfunction, know who to contact in the event of a pump malfunction, and have a defined plan for emergency measures (eg, back-up insulin pen, remediation). **Grade A; Low Strength of Evidence/Expert Opinion of Task Force; BEL 2**
Q3.3 What are safety issues for the use of integrated devices to manage persons with diabetes?
R3.3.1 Persons with diabetes using integrated devices should receive requisite training in the use of their device(s) and that the devices are being safely and properly used according to manufacturer instructions. **Grade A; Low-Intermediate Strength of Evidence/Expert Opinion of Task Force; BEL 2**
Q3.4 Are open-source automatic insulin-dosing systems, which currently are not approved by the U.S. Food and Drug Administration, safe and effective in the management of persons with diabetes mellitus?
R3.4.1 Clinicians should caution persons with diabetes who are using do-it-yourself systems that these devices have not undergone rigorous review by the FDA for safety and efficacy. **Grade B; Low Strength of Evidence/Expert Opinion of Task Force; BEL 4**
Q3.5 What are the criteria for discontinuing the use of insulin pumps in persons with diabetes?
R3.5.1 Clinicians should strongly consider the discontinuation of insulin pump therapy based on an individual's ability to use it effectively and safely or based on the personal preference of a person with diabetes to discontinue this insulin delivery modality. **Grade A; Intermediate Strength of Evidence; BEL 1**
Question 4: **How should the use of diabetes technologies be implemented in clinical practice?**
Q4.1 Who should prescribe/direct/supervise the implementation of diabetes technologies?
R4.1.1 Initiation and use of diabetes technology should be implemented by health care professionals who are trained, committed, and experienced to prescribe and direct the use of these tools. Clinicians should have the infrastructure to support the needs of persons with diabetes using the technology. **Grade B; Intermediate Strength of Evidence/Expert Opinion of Task Force; BEL 1**
Q4.2 How should patient education programs be structured?
R4.2.1 Training of persons with diabetes should utilize a structured, comprehensive training program that covers all aspects of safe and effective use of diabetes technologies. **Grade C; Low Strength of Evidence/Expert Opinion of Task Force; BEL 2**
R4.2.2 Diabetes self-management education and support program specialists should assess knowledge base, review data with the person with diabetes, and provide individualized feedback for initiating therapy, adjustments, and/or behavioral modifications as needed to support the attainment of individualized glycemic goals. **Grade B; Intermediate-High Strength of Evidence/Expert Opinion of Task Force; BEL 1**

Overview of Advanced Diabetes Technology

Continuous Glucose Monitoring

CGM is emerging as a standard of care for persons with diabetes who are treated with intensive insulin therapy.[2–8] CGM systems continuously measure glucose concentrations in the interstitial fluid, which correlate with blood glucose levels.[9] Although the imprecision of early CGM systems required persons with diabetes to continue the use of SMBG to confirm their blood glucose results prior to adjusting therapy, today's CGM systems have now achieved a level of accuracy comparable to SMBG systems[10] Most CGM

systems are now approved for use in insulin dosing without capillary glucose confirmatory testing.

Personal Continuous Glucose Monitoring

Unlike SMBG, which provides static and "point-in-time" glucose measurements, current CGM devices additionally present data in numerical and graphical formats, reporting current glucose level, glucose trends, and trend arrows, which indicate the direction and velocity of changing blood glucose levels. These data enable persons with diabetes to respond in a more timely fashion to mitigate or prevent acute glycemic events and allow them to make informed decisions in their insulin dosing and other areas of their daily self-management as they are alerted to glucose perturbations prior to a time they may have chosen to perform an SMBG measurement. Historical data can be viewed in the device reader/receiver or smartphone application and downloaded for retrospective analysis, similar to what can be gathered with SMBG; however, the wealth of data generated is exponentially greater. Most of today's CGM systems also feature active alarms and alerts that are critical for individuals who experience problematic hypoglycemia, which encompasses frequent hypoglycemia, severe hypoglycemia, and/or impaired hypoglycemia awareness.[11,12] Those with lower risk of hypoglycemia may choose devices that do not have real-time alerts/alarms or may choose to keep such features disabled. As an added safeguard, current CGM systems offer the ability to share data remotely with clinicians, caregivers, family, and friends.

Currently, there are 2 types of CGM system technologies available for personal use: rtCGM and isCGM, which historically was referred to as "flash" CGM. rtCGM systems automatically transmit data to the receiver and/or smartphone of a person with diabetes, whereas isCGM systems require a person to "swipe" the receiver and/or smartphone close to the sensor to obtain current and historical sensor glucose data. Until recently, a key differentiator between these technologies was the added safeguard of active alarms/alerts that can warn a person with diabetes of immediate or impending glycemic events, such as hypoglycemia and hyperglycemia. New isCGM systems offer optional alerts that warn users when glucose levels fall below or rise above the programmed threshold; however, the current iteration of these technologies do not warn users of predicted low or high glucose levels. Both rtCGM and isCGM technologies are available as standalone devices. However, only the current rtCGM systems can be linked to SAP or AID systems.

It is important to consider and address the expectations of a person with diabetes as well as their care partners. Critical to understanding expectations is ensuring that the person with diabetes knows what is feasible with the use of CGM systems. For example, while CGM provides data, it will not automatically adjust insulin delivery unless used in conjunction with an integrated, CGM sensor-augmented insulin delivery device (see below). Furthermore, understanding the need for blood glucose testing is crucial. Although most current systems no longer require calibration, a person with diabetes needs to be aware that there may be times when a fingerstick blood glucose measurement will be needed. If a person with diabetes runs out of sensor supplies or the sensor does not last for its intended duration or if their symptoms do not match the sensor glucose reading, a confirmatory fingerstick glucose measurement would be prudent. Because some persons with diabetes may not want to incorporate CGM into their daily routine, clinicians may consider intermittent use, which would allow those persons to experience the use of a CGM as a first step and garner the wealth of data such reports can generate. Another option is the use of diagnostic/professional/blinded CGM.

Diagnostic/Professional/Blinded Continuous Glucose Monitoring

Diagnostic/professional/blinded CGM is purchased by the clinician's practice and worn by a person with diabetes for short periods. This version of CGM can have data collected in a "blinded" mode, whereby the user is passively collecting data for retrospective interpretation but not viewing data during device wear or, with some systems, it is possible to have the data displayed in real time. These professional CGM systems can gather 7 to 14 days of data and thus provide insight into the effects of current treatment regimens. With real-time data display, the person with diabetes can assess glycemic patterns in real time. Regardless of whether using real-time or blinded modes, the clinician can use the data collected to assess current glycemic status and variability, enable a conversation to ground and advance education on certain topics of diabetes management, and determine how to optimize treatment whether through behavioral modifications or through adjustments in the medications used or doses prescribed to achieve more targeted glycemia.[13] The use of diagnostic/professional CGM may provide a means to familiarize persons with diabetes with CGM wear and may lead to the integration of personal CGM.

Insulin Delivery Systems

Connected Pens

A recent development in insulin injection technology is the "smart" pen, which automatically tracks insulin dosing and provides dose-decision support via a bolus calculator. Connected pens, which became available recently, provide objective data regarding insulin administration and can be combined with SMBG or with CGM for a better understanding of the patterns of insulin use. Importantly, these pens differentiate between priming and therapeutic doses, thereby allowing for the accurate tracking of active insulin. Additionally, smart insulin pens feature the ability to send missed dose alerts when doses are not delivered within a specified time frame, both for rapid-acting analogs and for daily basal insulin doses. This feature is particularly significant in avoiding adverse glycemic outcomes due to suboptimal treatment engagement.[14] In addition, current and future pens provide integrated insulin, glucose, and carbohydrate/meal data that can be transmitted to the health care team. Some smart pens include a memory function, which can recall insulin dose amounts and timing, either retrospectively or in real time.

Insulin Pumps

The use of CSII pumps has led to improvement in the quality of care for people with T1D in terms of lowered hemoglobin A1c (A1C) and reductions in the frequency and severity of hypoglycemia. Insulin pumps provide convenience for the use of multiple boluses per day without the need for separate injections. Ongoing innovations in CSII technology have since led to the development of a diverse array of insulin infusion products, ranging from disposable patch-like devices to sophisticated insulin pumps with advanced features to automate insulin dosing.

Conventional Pumps

Conventional insulin pump systems allow persons with diabetes to program precise basal insulin rates that deliver preset hour-by-hour doses of insulin that can vary throughout the day and night. Other features may include bolus calculators that use data from the

current glucose level and grams of carbohydrates that are manually entered, active insulin (insulin-on-board), and the person's individual insulin parameters (eg, insulin-to-carbohydrate ratio, insulin sensitivity factor, glucose targets). While all systems deliver insulin via a subcutaneous catheter, whether it is plastic or steel based, some conventional pump systems have infusion sets connected to these cannulas, whereas others are considered tubeless patch pumps that hold the insulin in a pod that sits directly on the skin. A wearable insulin delivery system, V-Go (Zealand Pharma US, Inc.), requires replacement every 24 hours, delivers one preset basal rate, and requires users to manually deliver boluses before meals.

Continuous Subcutaneous Insulin Infusion with Continuous Glucose Monitoring

During the past decade, manufacturers have integrated CGM into pump technologies across a wide spectrum of devices, from SAP to LGS and PLGS systems to hybrid closed loop (HCL) systems, referred to as AID systems. With SAP systems, CGM values are transmitted to the pump; however, the dosing of insulin functions independently.

The first technology to allow alteration of insulin delivery based on sensor glucose values was the LGS system. Building on this concept, PLGS systems interrupt basal insulin delivery when hypoglycemia is predicted, not when a threshold is met.

Advances in technology have led to the development of AID systems, which have the ability to increase basal insulin delivery for hyperglycemia, in addition to suspending insulin infusion to mitigate hypoglycemia. Additionally, some AID systems have algorithm-derived automated correction doses. Currently available AID systems are considered to be HCL devices because meals must be announced by inputting carbohydrate contents of each meal to facilitate meal insulin-bolus administration. These systems allow persons with diabetes to achieve greater TIR, while minimizing TBR and frequency of hypoglycemia treatment. The greatest benefit derived from these systems is in the overnight period given the variable insulin delivery based on the corresponding sensor glucose data.

The ultimate goal is to achieve fully closed-loop control, whereby a user would not need to announce meals or input carbohydrate intake. This may be achieved with an insulin-only system or with a dual-hormone system, combining insulin delivery with a secondary hormone, like glucagon or pramlintide. Additionally, the input of data from wearable devices, providing relevant bio signals for delivery may also allow for a more refined management of physical activity.

Telemedicine Technologies

Telemedicine has the potential to improve the quality of diabetes care by expanding access to care for individuals who are unable to attend clinic visits and those who live in geographic areas where clinical care is limited. The ability of persons with diabetes to interact remotely with their clinicians via smartphones and other communication devices can significantly increase their access to clinical care and support programs, such as diabetes coaching and online support groups.

The use of telemedicine technologies first began in the 1960s as a form of health care delivery; however, the adoption of these technologies in diabetes management has been slow due to the lack of reimbursement and regulatory restrictions. However, in 2020, the integration of telemedicine into clinical care was swift, given the global SARS-CoV-2 pandemic starting in 2019 (coronavirus disease 2019 [COVID-19]). Indeed, with the goal of keeping persons with diabetes and health care professionals safe in the COVID-19 era, telemedicine has been an essential tool. Recognizing the utility of telemedicine, the question remains as to how these services will be used in the post-COVID-19 era, how reimbursement strategies may change, and how delivery of care across state lines may be viewed for established patients.

Smartphone Applications

The rapid growth in digital communications technologies has spurred the development of a large offering of health-related smartphone applications for persons with diabetes, mainly focusing on self-management skills, lifestyle modification, and motivation for medication adherence. A 2017 report identified 346 smartphone applications specifically for self-diabetes management that were available from smartphone application stores.[15]

While the majority of these applications provide simple tools for daily diabetes management (for example, glucose logbook, carbohydrate counting assistance, exercise tracking, healthy eating, insulin dosage calculation), others function as mediators between users and large, for-profit health care professionals who provide remote coaching, education, and clinical advice. Diabetes applications have an enormous potential, given that more than 5.2 billion individuals in the world use smartphones[16] and approximately 0.5 billion individuals already use mobile applications for diet, physical activity, and chronic disease management.[17]

Rationale for Achieving Optimal Glycemic Management

Clinical Impact

Large clinical trials have demonstrated that achieving and sustaining near-normal glycemia reduces the incidence and progression of diabetes-related complications.[18–21] However, a substantial proportion of persons with diabetes are not achieving glycemic goals,[22–24] leading to increased acute and chronic complications and associated costs.[25]

Indeed, data from the U.S.-based T1D Exchange Registry have demonstrated that despite the increased penetrance of technology, including the greater use of CGM, in a cohort of 22 697 participants, only 17% and 21% of youth and adults, respectively, were achieving glycemic targets.[26] Further, by assessing the U.S. electronic health record databases, a retrospective observational study demonstrated that in a cohort of >30 000 persons with T1D, a similar proportion (~20%) of the cohort had an A1C of <7% (27). When stratified by glycemic control, those with A1C $\geq$9% had the highest rates of both severe hypoglycemia and diabetic ketoacidosis (DKA) as well as the highest prevalence of neuropathy and nephropathy.[27] While conventional wisdom has suggested avoiding hypoglycemia for fear of the impact on the developing brain, newer studies have highlighted the potential detrimental impact of hyperglycemia on both structural and functional neurodevelopment compared with age-matched health controls.[28–30] However, despite more than a quarter century with the knowledge that the avoidance of complications is feasible with the attainment of glycemic targets, this remains elusive for the majority of those living with diabetes.

Severe hypoglycemia is a common acute complication in insulin-treated diabetes, and several individuals with insulin-treated diabetes are unable to meet their glycemic targets without experiencing frequent and/or severe hypoglycemia. Severe hypoglycemia is not defined by a specific glucose threshold, but rather by an altered mental and/or physical functioning, requiring assistance for recovery.[31] As reported in the large prospective DIALOG survey ($N = 3743$), 85.3% and 43.6% of participants with T1D and insulin-treated T2D, respectively, reported at least 1 hypoglycemic event over 30 days; 13.4% and 6.4% of participants with T1D and T2D, respectively,

reported at least 1 severe hypoglycemic event within the same period.[32] A retrospective analysis of severe hypoglycemia in a population with T1D ($N = 206$) reported that the incidence rate of severe hypoglycemia was 0.49 events/patient-years, with higher rate ratios in individuals with prior severe hypoglycemia (3.71), neuropathy (4.16), and >20 years duration of diabetes.[33]

In addition to the immediate effects of severe hypoglycemia, recent studies have shown a strong association between severe hypoglycemia and risk for major adverse cardiovascular events among insulin-treated individuals with T2D and suboptimal glycemia.[34–36] In the recent LEADER study, individuals with severe hypoglycemia were more likely to experience major adverse cardiovascular events, cardiovascular-related death, and all-cause death, with an even higher risk shortly following hypoglycemia.[36]

Frequent episodes of hypoglycemia in insulin-treated diabetes can result in the development of impaired hypoglycemia awareness, which significantly increases the risk for recurrent severe hypoglycemia.[37,38] Approximately 25% of children/adolescents and adults with T1D have impaired hypoglycemia awareness.[39–41] Early single-center studies showed wide variance in the reported prevalence of impaired hypoglycemia awareness in insulin-treated T2D, ranging from 7% to 46%.[37,38,42–44] However, in a recent national cohort study of 2350 individuals with insulin-treated T2D, 9.7% were found to have impaired hypoglycemia awareness, and 31.6% of the full cohort had a history of severe hypoglycemia within the 12-month observation period.[45] Importantly, studies have shown that the avoidance of hypoglycemia can result in meaningful restoration of hypoglycemia awareness without compromising overall glycemic status, even in adults with long-standing diabetes.[46–49]

Severe hypoglycemia is a notable concern for older adults with diabetes. These individuals are at a significantly higher risk for severe hypoglycemia compared with younger persons due to age, diabetes duration, glucose variability, and higher prevalence of impaired hypoglycemia awareness.[32,33,50–52] The risk of severe hypoglycemia among older adults with diabetes is further exacerbated by cognitive impairment, physical limitations, and other comorbidities.[50] A retrospective study of Medicare beneficiaries ≥65 years of age from 1999 to 2011 showed an 11.7% increase in inpatient admission rates for severe hypoglycemia (from 94 to 105 admissions/100 000 person-years).[53]

Similar to the older adults, very young children also have an increased risk of hypoglycemia and progression to severe hypoglycemia given a multitude of factors, including grazing instead of adhering to fixed mealtimes as well as an inability to communicate symptoms of hypoglycemia with care providers.[54] Studies have demonstrated an increased variability in insulin delivery requirements with closed-loop systems in youngsters with T1D compared with older persons with T1D.[55] A recent trial of CGM use in children aged 2 to <8 years demonstrated that CGM primarily was utilized to reduce TBR with no change in TIR noted, indicating that families may allow permissive hyperglycemia given the fear of hypoglycemia.[56]

As noted above, severe hypoglycemic events or fear of such events, may also impact a person's willingness to follow their prescribed therapy for diabetes management, which can result in suboptimal glycemic control and increase the risk of long-term complications.[57,58] In a large international survey of 27 585 persons with diabetes, 25.8% to 46.7% of individuals with T2D reported reducing their insulin dosages in response to hypoglycemia.[59]

Given the immediate and long-term effects of suboptimal glycemic control, it is imperative that individuals have access to the tools they need to achieve their diabetes targets, namely advanced diabetes technologies. These devices have the potential to enhance the quality of diabetes care and improve the QoL for individuals who must contend with the daily burden of managing this chronic condition.

Economic Impact

Continuous Glucose Monitoring Technologies

The growing prevalence of diabetes has created a public health crisis that is threatening to overwhelm U.S. health care systems. The total cost of diagnosed diabetes in 2017 was estimated to be $327 billion.[60] Approximately 73% of these costs are directly related to treating avoidable complications of suboptimal glycemia, which include hospitalizations, emergency room services, and indirect costs associated with lost/reduced productivity.[60] In a 2014 analysis of the SWITCH RCT with a crossover design of 79 adults and 72 children with T1D analyzed, use of CGM with CSII showed a potential cost offset by fewer missed days of school among children with >70% sensor use compared with children in the sensor-off arm ($P = .0046$), resulting in less burden in the use of this technology.[61] In addition to their clinical benefits, it is important to consider the economic impact that advanced diabetes technologies may have for both health systems and payers.

Although the long-term health benefits of intensive glycemic control in persons with T1D have been well established, many individuals continue to have suboptimal glycemic control.[26,62] Suboptimal glycemic control invariably increases the risk of long-term complications, including microvascular and macrovascular complications, which greatly increase the costs of diabetes care.[20,31] A barrier to intensive glycemic management is the increased risk of hypoglycemia (severe and nonsevere), which negatively affects QoL and further increases treatment costs.[63,64]

Numerous recent studies have evaluated and demonstrated the cost-effectiveness of advanced glucose monitoring[65–70] and insulin delivery technologies[69,71–82] discussed in this clinical practice guideline.

As demonstrated in a recent study in the United Kingdom, the use of rtCGM versus SMBG was associated with a mean incremental gain in quality-adjusted life expectancy of 1.49 quality-adjusted life years (QALYs), with lower rates of eye disease, end-stage renal disease, cardiovascular disease, and severe hypoglycemia requiring medical assistance.[70]

An economic analysis of the DIAMOND trial cohort,[83] which included 158 persons with MDI-treated T1D and A1C ≥7.5% who were randomly assigned in a 2:1 ratio to rtCGM or SMBG, found that the use of rtCGM initially increased costs ($15.20/d) without immediately improving QoL as measured by the health-related EQ-5D questionnaire.[69] However, rtCGM significantly reduced A1C (0.6%), daily strip test use (201 strips/y), and nonsevere hypoglycemic events (25 episodes/y).[69] When these clinical benefits were extrapolated over a lifetime, rtCGM emerged as a cost-effective intervention with an incremental cost-effectiveness ratio (ICER) of $98 108 per QALY, with participants gaining 0.54 QALYs.[69] ICER is a ratio of the incremental cost of the new therapy divided by the incremental measure of the benefit. The authors concluded that the real-world use of rtCGM can be highly cost-effective.

Another modeling study evaluated the cost-effectiveness of isCGM versus SMBG in a hypothetical cohort of 1000 persons with T1D living in Spain.[68] The total annual cost/patient was $5405 for SMBG versus $3077 for isCGM (converted from Euros to USD). The investigators determined that the use of isCGM would be associated with an annual savings of $2328 per patient-year due to reductions in the costs of monitoring and managing hypoglycemic events. It was found that in this cohort of 1000 persons, the use of isCGM could avoid approximately 4900 severe hypoglycemic events and 93 hospitalizations in 1 year compared with SMBG, generating a total savings of up to $2 326 916 per year. A similar modeling study of pregnant women with T1D reported that the use of rtCGM would

result in significant cost savings from reductions in neonatal intensive care unit (NICU) admissions and shorter duration of NICU care.[67]

In a hypothetical commercial health plan with 10 million members aged 18-64 years, a cost study estimated that 9.3% had diagnosed diabetes, 20% of whom had hypoglycemia unawareness.[65] Their analysis showed that the use of rtCGM was estimated to reduce the cost of annual hypoglycemia-related hospitalizations in this population by $54 369 000, with an estimated net cost savings of $8 799 000 to $12 519 000 and a savings of $946 to $1346 per patient.[65]

In a recent prospective, observational study that assessed the impact of isCGM in a real-world cohort of 1913 adults with T1D over a 12-month period, admissions for severe hypoglycemia and/or DKA were reduced from 3.3% to 2.2% ($P = .031$), with significantly fewer individuals reporting a severe hypoglycemic event (7.8% vs 14.6%, $P < .0001$) or hypoglycemic coma (1.1% vs 2.7%, $P = .001$).[84] Similar findings were reported in the RESCUE trial, another prospective, observational study that demonstrated significant reductions in hospitalizations for severe hypoglycemia (from 11.9% to 3.17%) and DKA (4.6% to 1.06%) following 12 months of rtCGM use in conjunction with insulin pump therapy.[85]

Using evidence from an earlier RCT of adults with T2D treated with non-intensive insulin therapy,[86] investigators of a 2016 cost-effectiveness modeling study assessed the projected lifetime clinical and economic outcomes of rtCGM use and determined that intermittent, short-term use of rtCGM is both clinically effective and a cost-effective disease management adjunct in this population.[66]

Insulin Delivery Technologies

Insulin Pumps. A 2018 well-designed economic study suggested that intensive management of participants in the Diabetes Control and Complications Trial (DCCT) over 30 years was more expensive than treatment with conventional therapy, accomplished with 1 to 2 injections of insulin per day; however, if pumps are used for all persons with T1D, there would be no cost benefit to pump use.[87] The disposable device V-Go (Zealand Pharma US, Inc.) was associated with greater reduction in A1C, required less insulin, and proved more cost-effective than administering intensive insulin therapy with MDI.[88] A pragmatic, pediatric-based RCT showed no financial benefit of CSII versus MDI in children (median age, 9.8 years) newly diagnosed with T1D; conclusions are generalizable for the 12 months after pump initiation in this population.[89] A 2019 RCT with economic analysis showed that CSII was not cost-effective.[90] Data from the Swedish National Diabetes Register showed a lower incidence of some cardiovascular events and all-cause mortality for individuals with T1D on insulin pump therapy from 2005 to 2012.[91] The registration of insulin pump therapy started in 2002 in the National Diabetes Register, and the use of pump therapy among individuals with T1D increased from 10% in 2002 to 22% in 2015.[92]

Cost-effectiveness of insulin pump therapy is dependent upon therapeutic effects beyond resource use and costs as well as how much a payer is prepared to invest in additional QALYs. If the payer's cost-effectiveness threshold is $50 000 per QALY gained, treatment needs to provide an average annual additional 0.1 QALY or, on the basis of the subgroup analyses, gains in the range of 0.06 to 0.12 QALY. Similarly, with a threshold of $100 000, the required gain in annual QALYs would have to be between 0.03 and 0.06. A 2019 cohort study based on registry data found that the average cost difference between insulin therapies and a 20-year time horizon approximately corresponded to a discounted (3%) lifetime cost difference of $62 000 and the corresponding cost for a 40-year time horizon to be $95 000.[82]

Other investigators have noted that the use of non-integrated insulin pumps may increase the risk of treatment-emergent hypoglycemia and may not be cost-effective in managing T1D.[71,78]

Integrated Insulin Delivery Technologies. Although the early versions of SAPs have shown little or no benefit over MDI supported by CGM,[93] an economic simulation that considered SAP systems with alarms compared with MDI showed that SAP improved mean life expectancy by an additional 3.51 years compared with MDI, with a delayed onset of diabetes-related complications and an increase in survival time free of complications.[94] The estimated ICER for integrated pump/CGM was approximately $23 200 per QALY gained.[94] A 2017 economic modeling analysis concluded that SAP with automated insulin suspension was a cost-effective option and associated with better life expectancy and quality-adjusted life expectancy than CSII for the management of persons with T1D and a history of severe hypoglycemic events or poor glycemic control despite the use of CSII in Sweden.[74]

Today's more advanced integrated systems with LGS, PLGS, and HCL technologies have demonstrated both clinical efficacy and cost-effectiveness in T1D compared with insulin pump therapy alone due to improved glycemic control and reductions in hypoglycemia.[72,75,77,80,81,95,96] A 2019 cost-effectiveness model among 2 T1D cohorts in the Netherlands showed that among participants with suboptimal glycemic control, LGS improved quality-adjusted life expectancy by 1.77 QALYs versus insulin pump therapy alone, with higher lifetime costs (EUR 189 855 vs EUR 150 366), resulting in an ICER of EUR 22 325 per QALY gained[81] For those with an increased risk for hypoglycemia, the use of the system was associated with a 2.16 increase in QALYs with higher lifetime costs (EUR 204 013 vs EUR 171 032), leading to an ICER of EUR 15 243 per QALY gained.[81] The investigators concluded that among individuals with suboptimal glycemic control and/or higher risk for hypoglycemia, switching from CSII without CGM to an integrated system with LGS is cost-effective and will likely result in long-term clinical gains.[81]

An earlier cost-effectiveness modeling study also showed that projected improvements in clinical outcomes associated with an LGS system translated into good economic value, particularly in individuals with problematic hypoglycemia.[79] Similar findings were reported in a 2018 cost-effectiveness modeling study,[77] whereas another 2018 cost-effectiveness model showed the cost-effectiveness of the LGS function in individuals with T1D and hypoglycemia unawareness.[72] An earlier Australian study reported that the use of LGS over a 6-month period significantly reduced the incidence of severe hypoglycemia compared with standard pump therapy and SMBG. The ICER per severe hypoglycemic event avoided was $18 257 for all persons and $14 944 for persons aged 12 years and older, and the cost per QALY gained for persons aged 12 years and older was $40 803 (76). The most recent systematic review covering the cost-effectiveness of diabetes technology reported that integrated insulin pump systems with LGS were more cost-effective than CSII with SMBG for 8 of 10 of the relevant studies included in the 2020 systematic review.[96]

Although cost analyses have not been conducted on PLGS systems, several studies have shown reductions in hypoglycemia, particularly at night, similar to results shown in LGS studies. Pooled estimates from a recent meta-analysis showed that overnight periods of PLGS use were associated with an 8.8% lower risk of nocturnal hypoglycemia than non-PLGS use, which would likely lead to significantly reduced costs.[95]

With HCL systems, cost benefits are more definitive. As demonstrated in a 2019 Swedish study, the use of the only HCL system commercially available was associated with a QALY gain of 1.90.[75] Due to higher overall costs compared with CSII, ICER was $19 579 per QALY gained.[75] However, use of the system resulted in a lower cumulative incidence of diabetes-related complications, thereby offsetting the higher cost by reducing complication costs and productivity losses.

Recommendations with Evidence Base

Question 1:
What glucose metrics should be used in clinical practice to assess glycemic status?

Q1.1 What are the priority metrics for clinical decision-making regarding the use of diabetes technology?

Recommendation 1.1.1
Established clinical targets should be used to individualize glycemic targets and adjust therapy based upon each individual's overall health status, concomitant medical condition (eg, pregnancy, frailty), and risk for hypoglycemia:

All Persons with Diabetes
- Number of days of active CGM use: 14 days preferred
- Percentage of data available from active CGM use: >70% of data from 14 days
- Mean glucose: Individualized to targets
- GMI: Individualized to targets
- Glycemic variability, %CV: ≤36%

T1D/T2D
- %TIR 70 to180 mg/dL: >70%
- %TBR <70 mg/dL: <4%
- %TBR <54 mg/dL: <1%
- %TAR >180 mg/dL: <25%
- %TAR >250 mg/dL: <5%

Older/High Risk T1D/T2D
- %TIR 70 to 180 mg/dL: >50%
- %TBR <70 mg/dL: <1%
- %TBR <54 mg/dL: ~0%
- %TAR >250 mg/dL: <10%

Pregnancy: T1D
- %TIR 63 to 140 mg/dL: >70%
- %TBR <63 mg/dL: <4%
- %TBR <54 mg/dL: <1%
- %TAR >140 mg/dL: <25%

Grade C; Low-Intermediate Strength of Evidence; BEL 2

Evidence Base

Ever since the DCCT and United Kingdom Prospective Diabetes Studies, clinicians have set glycemic goals in terms of A1C targets to be achieved. Typically, the initial recommended goals were <7.0% by the American Diabetes Association[31] and ≤6.5%[97] by AACE; however, the organizations clearly acknowledged the need for individualization of the targets. These goals were set with the expectation that the lower the A1C, the risk for long-term, macro-, and microvascular complications were reduced. However, it was recognized by expert panels that these goals should be modified based on the clinical scenario, for example, in those with limited life expectancy or comorbidities, based on frequency and severity of hypoglycemia, hypoglycemia unawareness, occupation, intercurrent illness, travel, and behavioral issues.[98] Classically, A1C has been used by most physicians as a basis for adjustment of antihyperglycemic therapy; however, there are several limitations to the use of A1C for making therapeutic decisions.[99–103] Indeed, hemoglobinopathies, rates of red blood cell turnover, and even race can impact the accuracy of A1C measurements. Furthermore, A1C changes gradually with time (2-3 months) and typically requires a venipuncture, although point-of-care devices with reasonable accuracy using capillary blood are available. Finally, while A1C may help clinicians and persons with diabetes recognize that glycemic targets are not being met, these measurements provide little data on how to alter treatment plans.

With the widespread availability of CGM and its rapidly increasing use in the management of both T1D and T2D, several new sources of information have become available, including mean glucose (preferably measured over a 14-day period), variability (standard deviation [SD] and %CV of glucose, and percentage of time spent in hypoglycemia, target range, and hyperglycemia.

An international panel of experts achieved consensus on the use of CGM and provided information on TIR at the Conference on Advanced Technologies & Treatments for Diabetes in 2017.[6] In 2019, an expert panel of clinicians, researchers, and persons with diabetes determined the clinical cut-points for assessing CGM data in clinical care settings.[4]

The availability of adequate glucose data for evaluation is fundamental to accurate and meaningful interpretation of CGM data. It has been demonstrated that >70% use of CGM over the most recent 14 days strongly correlates with 3 months of mean glucose, TIRs, and hyperglycemia metrics.[104–106] Correlations are weaker for hypoglycemia and glycemic variability in individuals with T1D.[105] Longer durations of CGM data collection periods may be required for individuals with greater glycemic variability (eg, 4 weeks of data) to investigate hypoglycemia exposure.[4,104]

The GMI is a new metric that replaces the estimated A1C. The GMI metric uses a formula based on CGM data from the HypoDE study.[107] The GMI provides an estimate of the A1C based on an average of the CGM glucose levels an individual has been experiencing over a period of several weeks.[107] Table 2 shows the relationship between the average CGM glucose and the GMI values.[107]

Importantly, the GMI value is less influenced by conditions, such as anemia,[102] altered red blood cell lifetime,[100] hemoglobinopathies,[99] iron deficiency,[108] and pregnancy,[103] which can confound A1C measurements.[109] However, because measured A1C results are altered by these conditions, the correlation of the GMI and mean glucose can vary. For example, in a recent study of 641 individuals with T1D, 11% of participants had discordance between the A1C and the GMI of <0.1%, although 50% and 22% had differences of ≥0.5% and ≥1.0%, respectively.[110]

Three groups have shown that it is possible to improve on the GMI as an estimate of A1C using CGM data, estimation of red blood cell lifetime, and rate of glycation of hemoglobin. These methods have been introduced very recently, although are not yet available in commercial software for CGM data processing.[111–113]

Table 2
Relationship Between Continuous Glucose Monitoring-Derived Average Glucose and Glucose Management Indicator Values

Continuous Glucose Monitoring (CGM)-Derived Average Glucose (mg/dL)	Glucose Management Indicator (GMI) (%)*
100	5.7
125	6.3
150	6.9
175	7.5
200	8.1
225	8.7
250	9.3
275	9.9
300	10.5

Derived from: Bergenstal RM, Beck RW, Close KL, Grunberger G, Sacks DB, Kowalski A, Brown AS, Heinemann L, Aleppo G, Ryan DB, Riddlesworth TD, Cefalu WT. Glucose Management Indicator (GMI): A New Term for Estimating A1C From Continuous Glucose Monitoring. Diabetes Care. 2018 Nov;41(11):2275-2280.

* Estimate of expected A1C values.

Table 3
Estimates of Percentage of Time in Range relative to A1C and Average Glucose

Beck 2019 (N = 455 participants with T1D)			Vigersky 2019 (N = 1137 participants with T1D or T2D)			Average - Beck and Vigersky		
%TIR 70–180 mg/dL	A1C, %	Estimated Average Glucose, mg/dL	%TIR 70–180 mg/dL	A1C, %	Estimated Average Glucose, mg/dL	%TIR 70–180 mg/dL	A1C, %	Estimated Average Glucose, mg/dL
20%	9.4	223	20%	10.6	256	20%	10.0	239
30%	8.9	210	30%	9.8	236	30%	9.4	223
40%	8.4	194	40%	9.0	212	40%	8.7	202
50%	7.9	181	50%	8.3	191	50%	8.1	185
60%	7.4	165	60%	7.5	170	60%	7.5	167
70%	7.0	154	70%	6.7	147	70%	6.9	151
80%	6.5	141	80%	5.9	125	80%	6.2	131
90%	6.0	125	90%	5.1	99	90%	5.6	113

Based on: Beck RW, Bergenstal RM, Cheng P, Kollman C, Carlson AL, Johnson ML, Rodbard D. The Relationships Between Time in Range, Hyperglycemia Metrics, and HbA1C. J Diabetes Sci Technol. 2019 Jul;13(4):614-626. and Vigersky RA, McMahon C. The Relationship of Hemoglobin A1C to Time-in-Range in Patients with Diabetes. Diabetes Technol Ther. 2019;21(2):81-85.
Abbreviations: A1C = hemoglobin A1c; T1D = type 1 diabetes; T2D = type 2 diabetes; TIR = time in range.

Multiple studies have observed a nearly linear relationship between %TIR and A1C.[114–116] An analysis of data sets from 4 RCTs, which included central laboratory A1C measurements from 545 T1D adults, showed a strong correlation between the %TIR (70-180 mg/dL) and A1C.[114] On average, an observation of 70% of time spent in the 70 to 180 mg/dL range was found to be nearly equivalent to an average A1C value of 7.0%.[114] Similar observations were reported in a 2019 systematic review that assessed 18 RCTs, which included more than 2500 individuals with T1D and T2D over a range of ages and A1C values.[116] However, there are differences between the findings from the 2 studies, which are likely due to differences in the number of studies analyzed and the nature of the individuals included.[4]

Table 3 shows the numerical relationship between %TIR, A1C, and mean glucose derived from Beck et al[114] and Vigersky et al[116] and presents an average of those findings.

A nearly linear relationship has also been observed between % TIR and mean glucose.[114–116] Recent studies have shown correlations between increased %TIR (70-180 mg/dL) and reductions in diabetic retinopathy,[117] renal disease,[118,119] peripheral neuropathy,[118] and cardiovascular autonomic neuropathy (CAN).[120,121] In a recent study of the associations between CGM-derived TIR, hyperglycemia, hypoglycemia metrics, and CAN in individuals with T2D, investigators reported that a 10% increase in %TIR was inversely associated with the severity of CAN.[121] Each 10% increase in %TAR (>180 mg/dL) was also independently correlated with the presence and severity of CAN. Similar findings of the inverse relationship between %TIR and cardiovascular disease have also been observed.[122,123]

The boundaries for the acceptable %TIR is based on the distribution of glucose values in people with no known diabetes,[124–126] which help to define the lower limit for the target range. Based on the evidence, %TIR has recently been validated as an outcome measure for diabetes clinical trials.[127]

The %TBR metric was derived from a post-hoc analysis of the DCCT data set that showed a strong association between low-glucose values (54 mg/dL to <70 mg/dL and <54 mg/dL) and an increased risk for severe hypoglycemia.[128] The choice of a threshold of <70 mg/dL is also based on multiple studies of hypoglycemia, evaluating both subjective symptoms, neurological and cognitive findings, counterregulatory responses, and other factors.[129–131]

Recommendation 1.1.2

Two metrics, %TIR and %TBR, should be used as a starting point for the assessment of quality of glycemic control and as the basis for therapy adjustment, with emphasis on reducing %TBR when the percentages of CGM values falling below 54 or 70 mg/dL are close to or exceed targets.

Grade B; Low-Intermediate Strength of Evidence; BEL 1

Evidence Base

The primary goal for effective and safe glucose management is to reduce the %TBR, while increasing the %TIR.[4] Beck et al[114] reported that every 10% increase in %TIR corresponds to a decrease in A1C of approximately 0.5%. For most adults with diabetes, an appropriate goal is to achieve a %TIR 70 to 180 mg/dL goal of >70% (>15 hours, 48 min/d), if this can be achieved without an unacceptable risk of hypoglycemia (%TBR of <4% at <70 mg/dL, <1% at <54%)[4] in the absence of other clinical factors. These factors include life expectancy, significant comorbidities, macrovascular and advanced microvascular complications, functional attitude and adherence, diabetes duration, and resources/support system.[98]

The International Society for Pediatric and Adolescent Diabetes has endorsed the recommendations published by the international consensus panel regarding TIR. The 2018 International Society for Pediatric and Adolescent Diabetes clinical practice guideline recommends an A1C target of <7.0% for children, adolescents, and young adults <25 years of age who have access to comprehensive care.[132] This would equate to a TIR goal of 70% for most youth. However, for individuals aged <25 years, if the A1C goal is 7.5%, then the %TIR target would be set to approximately 60%.[4]

The combination of %TIR + %TBR also defines the limits for %TAR because %TIR + %TBR + %TAR metrics are, by definition, equal to 100%. It is important to strive for a %TBR of <1% falling below a threshold of 70 mg/dL, because older and/or frail individuals are at an increased risk for hypoglycemia.[32,33,50,51]

A separate set of goals has been established for women with T1D during pregnancy. These cut-points are based on data from the CONCEPTT trial, which confirmed that achieving %TBR of <4% with a threshold of <63 mg/dL is achievable, especially after the first trimester, and that 68% of women achieved the recommendation of >70% TIR (63-140 mg/dL).[133] Premeal and 2-hour postprandial glucose targets remain (<95 mg/dL and 120 mg/dL, respectively) for diabetes in pregnancy[134] in addition to the new CGM TIR targets for overall glycemia. Due to the lack of evidence supporting pregnancy and CGM targets for women with T2D treated with less intensive regimens or GDM, no recommendations for TIRs have been established. However, it may be reasonable to treat these individuals similar to pregnant women with T1D given the deleterious effects of suboptimal glycemic control on neonatal outcomes. More stringent targets and greater attention to overnight glucose profiles, particularly problematic hypoglycemia, may be required.[135]

These goals are often more challenging to achieve in individuals with T1D than those with T2D, even those treated with MDI or pump therapy. People with T1D generally show more glycemic variability than those with T2D and have a higher risk of

hypoglycemia and severe hypoglycemia.[136,137] This may be due to the longer duration of the condition or greater loss of counter-regulatory mechanisms both at the alpha cell (glucagon) and hypothalamic levels.[130]

The %CV is the most popular metric for assessing glycemic variability and correlated with hypoglycemia[138] and mortality.[139,140] Monnier et al reported that a %CV target of <36% is an appropriate means for distinguishing between stable and unstable glycemic variability.[141,142] When %CV exceeds this limit, the frequency of hypoglycemia is significantly increased in relation to the mean SD and nature of the glucose distribution.[115,142–145]

Importantly, all of the clinical targets should be individualized. This is especially true for children, older adults, frail, and pregnant persons with diabetes.[4]

Question 2:
Who would benefit from diabetes technologies?

Glucose Monitoring Technologies

Q2.1. Who would benefit from routine use of continuous glucose monitoring?

Recommendation 2.1.1

CGM is strongly recommended for all persons with diabetes treated with intensive insulin therapy, defined as 3 or more injections of insulin per day or the use of an insulin pump.

Grade A; High Strength of Evidence; BEL 1

Evidence Base

Clinicians should utilize CGM in persons with diabetes on insulin therapy to achieve optimal glycemia, empower persons with diabetes to engage further with their diabetes care, and relieve persons with diabetes of cumbersome and intrusive fingerstick glucose measurements.

Recent studies have demonstrated the clinical efficacy of CGM use in T1D regardless of the insulin delivery method used.[11,83,146–155] Studies have also shown significant reductions in hospitalizations for acute diabetes-related events and absenteeism.[85,156,157]

The large, randomized, 24-week DIAMOND trial demonstrated that the use of rtCGM in persons with T1D treated with MDI compared with SMBG resulted in lower A1C levels (-1.0% vs 0.4%, $P < .001$), with significant reductions in time spent at <70 mg/dL (-22 vs 37 min/d, mean difference 59 min/d, $P = .002$) and >250 mg/dL (-78 vs 78 min/d, mean difference 156 min/d, $P < .001$).[83] Significant reductions in diabetes-related distress and greater hypoglycemic confidence among the rtCGM users were also reported.[158] Similar findings were reported in the GOLD study, a 6-month crossover trial conducted at 15 sites in Sweden. During the 26 weeks of rtCGM use, participants spent an average of 2.79% of time <70 mg/dL and 0.79% at <54 mg/dL compared with SMBG use who spent 4.79% and 1.23%, respectively.[151] More recently, a 2020 real-world, nonrandomized trial showed significant and sustained reductions in A1C over 3 years, with increases in the %TIR and reductions in percentage of TBR in adults with T1D treated with MDI or SAP therapy using rtCGM compared with SMBG.[154]

Glycemic benefits have also been demonstrated with isCGM in adults with T1D treated with intensive insulin therapy.[148,152] In the IMPACT study, which included 239 participants with 6.7% A1C at baseline, the use of isCGM was associated with a 38% reduction in time spent in hypoglycemia (<70 mg/dL).[148] Increases in time spent in range and reductions in glycemic variability were also observed.

Although large clinical studies of isCGM have shown minimal A1C improvements in populations with T2D and treated with intensive insulin therapy, the use of isCGM has been associated with significant reductions in hypoglycemia.[149,150] In the REPLACE trial, a significant reduction in time spent in hypoglycemia was noted among 149 adults with T2D using isCGM versus 75 participants using SMBG with 43% reduction in TBR noted between treatment groups ($P = .0006$).[149] Additionally, the users of isCGM had a reduction of 54.3% in nighttime hypoglycemia (<70 mg/dL) compared with the users of SMBG ($P < .0001$, at 6 months).[149] These decreases were sustained throughout the 6-month follow-up study (150). The use of isCGM has also been shown to improve treatment satisfaction within this population and may lead to an improved glycemic status without increasing the frequency of hypoglycemia.[159]

Recommendation 2.1.2

Structured SMBG is recommended for individuals on insulin therapy who have limited success with or are unable or unwilling to use CGM.

Grade A; High Strength of Evidence; BEL 1

Evidence Base

Although the use of CGM is the preferred method for glucose monitoring, many individuals may not be ready to transition from SMBG to this technology. Others may be unable to use CGM due to physical and/or cognitive limitations or cost issues. These individuals would therefore benefit from utilizing structured SMBG for their daily diabetes management. Conversely, the ability to perform SMBG may be limited by other impairments, including tremors, neurological deficits, and visual impairments. Thus, clinicians will be tasked with the need to constantly and consistently remember to individualize therapy for each person with diabetes.

Structured SMBG involves gathering blood glucose data within a defined testing regimen, interpreting the data, and then utilizing the data to make appropriate pharmacologic and/or lifestyle adjustments.[160] The early landmark DCCT showed that intensive insulin therapy supported by structured SMBG, with a minimum of 4 checks per day, lowered A1C and reduced the development/progression of long-term diabetes complications.[161] Some studies have shown the beneficial effects of structured SMBG in persons with newly diagnosed T2D and individuals with suboptimally controlled non-insulin–treated T2D[160,162] and could contribute to improved self-efficacy.[163] Although the use of structured SMBG in adults with non-insulin-treated T2D has not been associated with a deterioration of QoL and locus of control,[162] worsening A1C and low adherence to prescribed SMBG have been observed in youth-onset T2D.[164]

Recommendation 2.1.3

CGM is recommended for all individuals with problematic hypoglycemia (frequent/severe hypoglycemia, nocturnal hypoglycemia, hypoglycemia unawareness).

Grade A; Intermediate-High Strength of Evidence; BEL 1

Evidence Base

The HypoDE study demonstrated that the use of rtCGM in MDI-treated adults with T1D ($N = 141$) with problematic hypoglycemia resulted in reductions in hypoglycemic events and fewer episodes of severe hypoglycemia.[11] At 6 months, the average number of hypoglycemic events among users of rtCGM decreased from 10.4 to 3.4; reductions among control participants were negligible (from 13.5 to 13.2). Moreover, rtCGM participants had a significantly lower incidence rate ratio (IRR, 0.28; $P < .0001$).

The GOLD-3 study also showed that the use of rtCGM resulted in significant reductions in nocturnal and daytime hypoglycemia in individuals with MDI-treated T1D.[165] Among rtCGM users, time spent in nocturnal hypoglycemia <70 mg/dL decreased from 19.6 to 10.2 min/night, and time spent <54 mg/dL decreased from 8.9 to 3.1

min/night (both, $P < .001$). Daytime hypoglycemia <70 mg/dL decreased from 49 to 29 min/d. Investigators also reported an improved confidence in avoiding hypoglycemia (P=0.002) among users of rtCGM.

The use of rtCGM has also been shown to be beneficial in older persons with diabetes. In a recent RCT of 203 adults with T1D aged >60 years, the use of rtCGM resulted in a significantly lower percentage of glucose values <70 mg/dL than the use of SMBG.[166] During the 6-month study period, median time spent at <70 mg/dL decreased from 73 to 38 min/d among rtCGM users compared with that of the SMBG group, with a slight increase from 68 to 70 min/d ($P <$ .001).

Similar improvements in reducing hypoglycemia have also been observed with the use of isCGM. In a subgroup analysis of participants in the IMPACT trial,[148,152] time spent in hypoglycemia <70 mg/dL was reduced by 46.0% (from 3.44 to 1.86 h/d) among isCGM users versus SMBG users in whom reductions were negligible (from 3.73 to 3.66 h/d; $P < .0001$). Treatment satisfaction and perception of hypoglycemia and hyperglycemia were also improved in the isCGM group.

Recent observational and prospective studies have also shown notable improvements in both A1C and hypoglycemia as well as reductions in diabetes-related hospitalizations with the use of both rtCGM and isCGM.[84,156,157] In the RESCUE study, the use of rtCGM was associated with significant reductions in the number of participants with severe hypoglycemia and DKA hospitalizations, decreasing from 11.9% to 3.17% and from 4.6% to 1.06%, respectively, after 1 year.[156]

A similar study assessed the impact of isCGM in a real-world cohort of 1913 adults with T1D (84). During the 12-month observation period, admissions for severe hypoglycemia and/or DKA decreased from 3.3% to 2.2% ($P = .031$), and fewer participants reported severe hypoglycemic events (7.8% vs 14.6%, $P < .0001$) or hypoglycemic coma (1.1% vs 2.7%, $P < .001$). Reductions in hypoglycemia and diabetes-related hospitalizations were also observed in a similar study that included 1365 users of isCGM enrolled in the Dutch diabetes registry.[157]

Recommendation 2.1.4

CGM is recommended for children/adolescents with T1D.

Grade A; Intermediate-High Strength of Evidence; BEL 1

Evidence Base

The use of rtCGM and isCGM has been shown to improve glycemic control without increased hypoglycemia in pediatric and adolescent populations with T1D.[167–173] In a recent crossover study, investigators assessed glycemic control with rtCGM in 30 adolescents and young adults with T1D. During the 8-week study period, the percent of TIR was significantly associated with rtCGM use compared with SMBG (35.7% vs 24.6%, respectively, $P < .001$) and greater reductions in A1C (-0.53% vs 0.24%, respectively, $P < .001$).[173] A larger 2020 RCT investigated the impact of rtCGM versus SMBG use on A1C among 153 adolescents and young adults with T1D, with a baseline A1C of 8.9%.[168] At 26 weeks, rtCGM was associated with significantly greater A1C reductions compared with SMBG (-0.4% vs 0.1%, $P < .01$), improvements in TIR (37% to 43% vs 36% to 35%, $P < .001$), with significant reductions in percent of time spent <70 mg/dL (from 3.2% to 2.2% vs 3.7% to 3.2%, respectively, $P = .02$).[168] Similar improvements in A1C and hypoglycemia risk have been reported in earlier studies of young adolescents with T1D.[167] The use of rtCGM with remote monitoring has also been shown to improve QoL measures for parents of children with T1D[174] and facilitate glycemic control during exercise.[175]

The glycemic benefits of isCGM have also been demonstrated in a real-world, observational study of 335 children and adolescents with T1D.[170] Among the 278 participants who switched from SMBG to isCGM, the proportion of individuals who experienced a severe hypoglycemic event decreased by 86% ($P = .037$) compared with no change in those who continued SMBG ($P = .317$), with a 53% decrease in the rate of severe hypoglycemia ($P = .012$) with continued isCGM use at 12 months.[170] Importantly, 234 participants were still using their device, suggesting a high acceptability within this population. Reductions in A1C[171] and improvements in QoL measures[171,176,177] have also been observed in smaller studies.

Recommendation 2.1.5

CGM is recommended for pregnant women with T1D and T2D treated with intensive insulin therapy.

Grade A; Intermediate-High Strength of Evidence; BEL 1

Evidence Base

Some RCTs have demonstrated that the use of rtCGM during pregnancy improves glycemic control and neonatal outcomes.[133,152,178] The CONCEPTT trial assessed the clinical impact of rtCGM versus SMBG within a cohort of 325 women with T1D who were pregnant (≤13 weeks' gestation) or planning to become pregnant.[133] Investigators reported significant increases in TIR with rtCGM compared with the use of SMBG (68% vs 61%; $P = .0034$, respectively) with lower incidence of large-for-gestational age ($P = .0210$), fewer NICU admissions lasting more than 24 hours ($P = .0157$), fewer incidences of neonatal hypoglycemia ($P = .0250$), and 1-day shorter length of hospital stay ($P = .0091$). A secondary analysis of the CONCEPTT trial involving 225 pregnant women and their infants showed modest increases in %TIR (5%-7%) with rtCGM during the second and third trimesters, which were associated with a reduced risk for neonatal hypoglycemia.[178] The use of isCGM in pregnant women with well-controlled T1D treated with MDI showed significant reductions in time in hypoglycemia without compromising A1C.[152] However, a large, multicenter RCT of pregnant women with T1D and T2D found no significant advantage in the use of intermittent (blinded) CGM versus SMBG on neonatal or glycemic outcomes.[179]

The accuracy of a factory-calibrated rtCGM was assessed in a cohort of pregnant women with diabetes. The cohort included women with T1D ($n = 20$), T2D ($n = 3$), and GDM ($n = 9$). Based on frequent sample testing that was conducted, it was determined that sensor accuracy was similar to what has been previously described and that the arm as a site for sensor insertion demonstrated the highest level of accuracy.[180]

Recommendation 2.1.6

CGM is recommended for women with GDM on insulin therapy.

Grade A; Intermediate Strength of Evidence; BEL 1

Recommendation 2.1.7

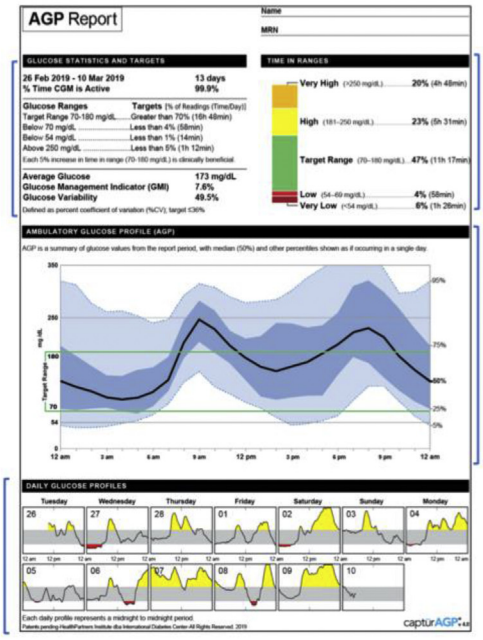
CGM may be recommended for women with GDM who are not on insulin therapy.

Grade B; Intermediate Strength of Evidence; BEL 1

Evidence Base

Although the use of rtCGM for GDM has not been well studied in randomized trials, a large prospective cohort study of rtCGM use in women with GDM reported significantly improved daily blood glucose levels and lower glycemic variability assessed by mean amplitude of glycemic excursion compared with SMBG.[181] The mean amplitude of glycemic excursion score was significantly associated with birth weight ($P < .001$) and found to be an independent factor for preeclampsia and composite neonatal outcomes. A 2016 RCT showed an association between rtCGM use and reductions in body weight in women with GDM.[182] A more recent

- **Glucose Ranges** provide statistics regarding percentage of time within, above, and below target range.
- **Glucose Management Indicator (GMI)** indicates the average A1C level that would be expected based on mean glucose measured in a large number of individuals with diabetes.
- **Glucose Variability** is reported as the percentage of coefficient of variation
- **Daily Glucose Profiles** present a glucose profile for each day covered.



- **High (Level 1 Hyperglycemia) and Very High (Level 2 Hyperglycemia)** indicate percentage of time above range (TAR) for each of the high glucose levels.
- **Target Range** indicates the percentage of time in range (TIR) within a person's with diabetes target glucose range.
- **Low (Level 1 Hypoglycemia) and Very Low (Level 2 Hypoglycemia)** indicate percentage of time below range (TBR) for each of the low glucose levels.
- **The Ambulatory Glucose Profile (AGP)** combines daily profiles to create a 1-day (24-hour) graphic. The black line indicates the median glucose level at all day parts. The dark and light blue shaded areas graphically depict the degree of glycemic variability (SD or %CV), which in this case is well above the recommended goal of ≤36%.

Figure 1. Ambulatory glucose profile. Modified from: Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, Bosi E, Buckingham BA, Cefalu WT, Close KL, Cobelli C, Dassau E, DeVries JH, Donaghue KC, Dovc K, Doyle FJ 3rd, Garg S, Grunberger G, Heller S, Heinemann L, Hirsch IB, Hovorka R, Jia W, Kordonouri O, Kovatchev B, Kowalski A, Laffel L, Levine B, Mayorov A, Mathieu C, Murphy HR, Nimri R, Nørgaard K, Parkin CG, Renard E, Rodbard D, Saboo B, Schatz D, Stoner K, Urakami T, Weinzimer SA, Phillip M. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019 Aug;42(8):1593-1603. Permission granted by the American Diabetes Association and the Copyright Clearance Center

study found no difference in glycemic measures between rtCGM and intermittent (blinded) rtCGM; however, differences in outcomes between CGM and SMBG were not assessed.[183] Importantly, each of these studies included a subset of women who were using insulin therapy, which tended to be higher in the group using sensor technology, with insulin use noted in ~30% in the CGM group versus 12% in the SMBG group in most of these studies.[181,182]

Recommendation 2.1.8

CGM may be recommended for individuals with T2D who are treated with less intensive insulin therapy.

Grade B; Intermediate Strength of Evidence; BEL 1

Evidence Base

The benefits of rtCGM and isCGM use have been reported in individuals with T2D treated with basal insulin only or non-insulin therapy.[86,184] A 40-week RCT evaluated the long-term effects of intermittent rtCGM compared with SMBG use among participants with T2D and treated with diet and exercise alone or other glucose-lowering therapies except prandial insulin.[86] Participants performed 4 cycles of rtCGM use (2 weeks on/1 week off) for 3 months. Investigators observed a significant reduction in A1C at 12 weeks among the rtCGM group versus the SMBG group, with a sustained improvement for the duration of the study.[86] Importantly, the improvement seen in the rtCGM group occurred without a greater intensification of medication.[86]

Q2.2 What is an efficient approach to interpreting continuous glucose monitoring data?

Recommendation 2.2.1

AGP may be utilized to assess glycemic status in persons with diabetes.

Grade B; Low Strength of Evidence; BEL 1

Recommendation 2.2.2

When using AGP, a systematic approach to interpret CGM data is recommended:

1. Review overall glycemic status (eg, GMI, average glucose)
2. Check TBR, TIR, and TAR statistics, focusing on hypoglycemia (TBR) first. If the TBR statistics are above the cut-point for the clinical scenario (ie, for most with T1D >4% <70 mg/dL; >1% <54 mg/dL), the visit should focus on this issue. Otherwise, move on to the TIR and TAR statistics.
3. Review the 24-hour glucose profile to identify the time(s) and magnitude(s) of the problem identified.
4. Review treatment regimen and adjust as needed.

Grade B; Low Strength of Evidence; BEL 1

Evidence Base

The use of the AGP is recommended as a template for data presentation and interpretation (Fig. 1).[4,6,185–192] AGP reports can be derived from either SMBG or CGM data. For CGM data, it is critical to ensure that adequate data are available, and it has been demonstrated that >70% use of CGM over the most recent 14 days correlates strongly with 3 months of mean glucose, TIRs, and hyperglycemia metrics.[104–106] AGP presents core metrics in a standardized format, facilitating a rapid assessment of TIR, TBR, and TAR as well as other pertinent data.

Q2.3 When is one method of continuous glucose monitoring (rtCGM vs isCGM) preferred over the other?

Recommendation 2.3.1

rtCGM should be recommended over isCGM to persons with diabetes with problematic hypoglycemia (frequent/severe hypoglycemia, nocturnal hypoglycemia, hypoglycemia unawareness) who require predictive alarms/alerts; however, the lifestyle of persons with diabetes and other factors should also be considered.

Grade B; Low-Intermediate Strength of Evidence; BEL 1

Evidence Base

Studies comparing rtCGM and isCGM are sparse. Available evidence shows that rtCGM was superior to isCGM, when these systems did not include threshold alarms, in reducing hypoglycemia and improving TIR in adults with T1D with normal hypoglycemia awareness.[12,193] Apart from hypoglycemia risk, reviews have suggested that rtCGM may be preferred for persons with diabetes who are physically active or have busy lifestyles that would inhibit frequent scanning of an isCGM sensor, require uninterrupted monitoring by parents/caregivers, choose to use advanced insulin delivery technologies (SAP, LGS/PLGS, AID), or cannot achieve desired glycemic targets with isCGM.[194,195]

Recommendation 2.3.2

isCGM should be considered for persons with diabetes who meet 1 or more of the following criteria:

- Newly diagnosed with T2D
- Treated with nonhypoglycemic therapies
- Motivated to scan device several times per day
- At low risk for hypoglycemia, although desire more data than SMBG provides

Grade D; Low Strength of Evidence/Expert Opinion of Task Force; BEL 4

Evidence Base

Lacking formal studies, expert opinion suggests that the use of isCGM may be more appropriate for persons with diabetes: with low risk of hypoglycemia; with newly diagnosed T2D; treated with less intensive regimens (basal insulin, non-insulin therapy); motivated to scan frequently; or who prefer to monitor glucose without the support of predictive alarms/alerts.[194,195]

Q2.4 When should diagnostic/professional continuous glucose monitoring be considered?

Recommendation 2.4.1

Diagnostic/professional CGM should be used in the management of persons with diabetes who meet 1 or more of the following criteria:

- Newly diagnosed with diabetes mellitus
- Not using CGM
- May have problematic hypoglycemia, but no access to personal CGM
- Persons with T2D treated with non-insulin therapies who would benefit from an episodic use of CGM as an educational tool
- Persons who would like to learn more about CGM before committing to daily use

Importantly, in those using “masked” or “blinded” diagnostic/professional CGM, they must have and continue using adjunctive SMBG to assist in daily diabetes self-care.

Grade B; Intermediate Strength of Evidence; BEL 1

Evidence Base

The majority of studies assessing the use of professional CGM are blinded studies, whereby the user cannot view the data in real time. Early studies have shown that professional rtCGM can lead to reductions in A1C, bodyweight, and/or reductions in the incidence of hypoglycemia in persons with T2D[86,196–200] when the clinician uses the data to guide therapeutic changes. A 2014 RCT demonstrated that the initiation and titration of basal-bolus therapy with adjunctive retrospective rtCGM was safe and improved A1C with low rates of hypoglycemia in individuals with T2D.[196] Recent RCTs have demonstrated similar benefits of isCGM in the management of persons with T1D and T2D.[201,202]

Q2.5 When should intermittent/occasional use of continuous glucose monitoring be considered?

Recommendation 2.5.1

Intermittent/occasional CGM may be recommended for the management of persons with diabetes who are reluctant or unable to commit to routine CGM use.

Grade C; Intermediate Strength of Evidence; BEL 1

Evidence Base

Few studies have suggested that the use of intermittent/occasional CGM with less intensive treatment regimens is associated with significant glycemic improvements[86,184] and is effective in promoting desired self-care behaviors.[184] A 2020 observational study of 594 T2D adults treated with basal insulin only or non-insulin therapy assessed the impact of intermittent use of rtCGM. Participants wore their sensors for a mean of 31.1 ± 26.5 days over a period of 4.8 ± 3.2 months.[184] During that time period, significant reductions in A1C from baseline were observed within the total cohort (from 7.7% ± 1.6 to 7.1% ± 1.2, $P < .0001$). Importantly, the mean overall rtCGM satisfaction score was 4.5 out of 5, and the majority of respondents indicated agreement or strong agreement that rtCGM use increased their diabetes knowledge, improved their understanding of medication importance, made it easier to perform other self-management behaviors, improved their understanding of how food impacts their diabetes control, and helped improve their diabetes when not wearing the rtCGM device. The majority of participants (88.4%) indicated that they would like to use rtCGM again.

Insulin Delivery Technologies

Q2.6 Who would benefit from the use of connected pens?

Recommendation 2.6.1

Connected pens may be recommended for all persons with diabetes who are treated with intensive insulin management, with 3 or more injections per day and who are not on insulin pump therapy, in whom an assessment of insulin dosing may help the person with diabetes and the clinician to further optimize the insulin regimen and avoid the stacking of rapid-acting insulin doses that could lead to hypoglycemia.

Grade C; Intermediate Strength of Evidence/Expert Opinion of Task Force; BEL 2

Evidence Base

Connected smart pens and attached caps for insulin delivery may assist in better diabetes management. These devices offer individuals the ability to have a record of insulin dosing, including when insulin was administered and how much was given. Further, some devices have the ability to set notification reminders to help prevent missed doses of insulin. These pens provide data regarding insulin administration that can be combined with glucose data, from either SMBG or with CGM, to allow for better assessment of glycemic patterns. This technology also allows a person with diabetes to connect to management software, which can provide information on carbohydrate count and an algorithm to help make decisions about insulin dosing. As such, connected pens help improve engagement and provide more precise diabetes care. Smart connected pens, devices, and attachments provide people who are not on pumps or have CGMs with up-to-date management information, which otherwise would not be available. Thus, connected pens allow for behavioral modifications to be based on

retrospective review of data captured. Available studies that have assessed clinical outcomes related to connected smart insulin pens are limited; however, a recent systematic review summarized published data that confirm preference for this device among persons with diabetes and indicate this technology's potential for positive impact relative to diabetes self-management.[203]

Q2.7 Who would benefit from the use of an insulin pump without continuous glucose monitoring?

Recommendation 2.7.1

The use of an insulin pump without CGM could be used to manage persons with diabetes who are achieving glycemic targets with minimal TBR, or who report infrequent episodes of symptomatic hypoglycemia, and who are using SMBG on a regular basis (at least 4 times per day for persons with T1D).

Grade B; Intermediate-High Strength of Evidence; BEL 1

Evidence Base

Early studies demonstrated that the use of insulin pumps was associated with significant glycemic improvements compared with MDI therapy in adults with T1D. A 2015 observational study based on Swedish national registry data assessed the long-term effects of insulin pump therapy compared with SMBG on cardiovascular disease and mortality among adults with T1D; at a 6.8-year follow-up, the adjusted hazard ratios were significantly lower for fatal coronary heart disease (0.55), fatal coronary heart disease or stroke (0.58), and all-cause mortality (0.73).[91] Following the completion of the larger DIAMOND trial,[83] which described the impact of CGM in those on MDI therapy, a follow-up study was conducted in which 75 persons with T1D were randomized to either CSII or MDI.[204] In that trial, TIR of 70 to 180 mg/dL was improved among randomized adults with T1D who switched to CSII and continued CGM compared with those who were randomized to continue MDI plus CGM.[204]

While pump therapy did not significantly improve glycemic outcomes in adults with T1D >12 months in the REPOSE trial compared with MDI, secondary outcomes related to QoL and treatment satisfaction statistically and significantly improved at 12 and 24 months.[73] Treatment satisfaction also was higher with CSII than that of MDI ($P = .0003$) in the HypoCOMPaSS trial among adults with T1D and impaired awareness of hypoglycemia in the CSII and rtCGM (encouraged, not mandatory) group versus those in the MDI with SMBG group.[205]

More recent studies on insulin pump use have focused on persons with T2D. A 2018 single-center, crossover RCT reported significant reductions in A1C (-0.9%) among insulin pump users, but not the MDI-treated group at 6 months.[206] At 12 months, participants who crossed over from MDI to insulin pump showed significant A1C reductions (-0.5%), whereas those who continued insulin pump therapy achieved an additional 0.7% reduction in A1C.[206] The 12-month follow-up phase to the prior OpT2mise trial reports[207,208] showed similar findings, as insulin pump use was associated with significantly greater A1C reductions in the first 6 months of use compared with MDI therapy (-1.1 vs -0.4, $P < .001$).[209] This improvement was sustained for the next 6 months, while those who switched over from MDI to insulin pump use achieved a 0.8% reduction at 12 months. A small ($N = 29$) randomized, crossover study compared a patch pump system with traditional insulin pump use over 2 consecutive 12-week periods.[210] Although significant reductions in A1C were seen with both devices, the majority (76%) of participants reported that they preferred the patch pump over the traditional pump, and 56% believed it fit in better with their lifestyles.[210]

In a long-term study that investigated the glycemic effects of sustained use of insulin pumps versus MDI in children, investigators reported a 0.3% difference in A1C, favoring pump therapy at 6 months, which was sustained with the greatest difference in A1C (0.4%) at 6 years.[211] However, the A1C was not significantly lower beyond 6 years. In a 3-year comparison of insulin pump in children and young adolescents, the MDI group had higher A1C levels than the insulin pump group at study end (7.98% vs 7.56%, $P = .002$) with no differences in hospitalizations due to acute events, but with a 1.25-day shorter duration of hospital stays.[112] An international observational study of children and young adults after a 7-year insulin pump use found similar glycemic improvements.[212] A cross-sectional study of 669 children with retrospective longitudinal analysis of 1904 young children (<6 years) with T1D showed lower A1C values following the initiation of pump therapy compared with continued MDI use (7.9 vs 8.5%, $P < .001$).[213] In this longitudinal study, A1C was decreased by 0.2% after the initiation of CSII ($P < .001$).[213] Although there were no between-group differences in severe hypoglycemia frequency, parent-reported DKA events in the prior year were greater among pump versus MDI users (10% vs 8%, $P = .04$).[213] Insulin pump use was associated with a lower mean A1C than injection use ($P < .001$) among children and adolescents with T1D in a pooled analysis of data from the Prospective Diabetes Follow-Up, T1D Exchange, and National Paediatric Diabetes Audit registries.[214]

Among pregnant women with T1D, insulin pump use without the integration of CGM throughout pregnancy does not appear to be beneficial. In a prespecified analysis of CONCEPTT involving 248 pregnant women with T1D, investigators reported that the participants treated with MDI were more likely to have better glycemic outcomes and less likely to have gestational hypertension, neonatal hypoglycemia, and NICU admissions than insulin pump users.[215] However, in women who are currently using insulin pump therapy, continuation during labor and delivery has been shown to be safe and efficacious. Indeed, women who remained on pump therapy had better glycemic control during delivery than those who switched to intravenous insulin infusion.[216]

Q2.8 Who would benefit from the use of an insulin pump with continuous glucose monitoring (separate devices or sensor-augmented pump)?

Recommendation 2.8.1

Insulin pump with CGM or SAP is recommended to manage all persons with diabetes treated with intensive insulin management who prefer not to use automated insulin suspension/dosing systems or have no access to them.

Grade A; Intermediate-High Strength of Evidence; BEL 1

Evidence Base

The use of CGM with an insulin pump, either as independent devices or as an integrated SAP system has shown glycemic benefits over SMBG in children, adolescents, and adults.[83,154,167,217,218] Children using SAP were more likely to achieve their age-specific glycemic targets with reduced glycemic variability compared with use of MDI therapy in a 2012 RCT.[218] Another 2012 RCT resulted in significant reductions in A1C with less time spent <70 mg/dL and greater treatment adherence in children and adults using an SAP device in the "sensor-on" versus "sensor-off" mode.[167] In addition, measures for treatment satisfaction and QoL rated significantly higher ($P < .001$) among adults and children with T1D and their caregivers in the SAP group than those managed with MDI and SMBG.[219]

A trial that included hospitalized persons with T2D who were treated with SAP versus MDI reported significantly reduced time to reach glycemic targets ($P < .001$) as well as less hypo- ($P < .05$) and hyperglycemia ($P < .05$).[220] In an earlier study of persons with T2D, which compared CSII and MDI therapy with SAP for 6 days, the use of SAP resulted in a reduced blood glucose fluctuation with no increased risk of hypoglycemia.[221]

A cohort of adults with T1D from the 2017 DIAMOND T1D trial[83] was randomly assigned to continue MDI or switch to an insulin pump, with the continuation of CGM, for 28 weeks.[204] Over the study period, TIR (70-180 mg/dL) was 791 min/d in the rtCGM plus CSII group and 741 min/d in the rtCGM plus MDI group ($P = .01$). The participants in the rtCGM plus CSII group also experienced greater reductions in rtCGM-measured mean glucose ($P = .005$) and hyperglycemia ($P = .007$), but with an increase in hypoglycemia for <70 mg/dL ($P = .0002$) and <50 mg/dL ($P = .0002$).[204] A four-arm prospective observational study showed sustained reductions in A1C over 3 years, with increases in %TIR and reductions in %TBR in adults with T1D treated with MDI or SAP therapy using rtCGM compared with SMBG.[154]

A recent study using real-world evidence reported that CGM use in conjunction with insulin pump therapy resulted in lower A1C in individuals with T1D than SMBG and insulin pump use.[222] The investigators also noted that an early initiation of CGM plus insulin pump may lead to an improved long-term glycemic control.

Q2.9 Who would benefit from the use of more advanced insulin pump technologies: low-glucose suspend, predictive low-glucose suspend, and hybrid closed loop?

Recommendation 2.9.1

LGS is strongly recommended for all persons with T1D to reduce the severity and duration of hypoglycemia, whereas PLGS is strongly recommended for all persons with T1D to mitigate hypoglycemia. Both systems do not lead to a rise in mean glucose, and lead to increased confidence and trust in the technology, more flexibility around mealtimes, and reduced diabetes distress for both persons with diabetes and caregivers. Therefore, anyone with frequent hypoglycemia, impaired hypoglycemia awareness, and those who fear hypoglycemia leading to permissive hyperglycemia should be considered for this method of insulin delivery.

Grade A; High Strength of Evidence; BEL 1

Recommendation 2.9.2

AID systems are strongly recommended for all persons with T1D, since their use has been shown to increase TIR, especially in the overnight period, without causing an increased risk of hypoglycemia. Given the improvement in TIR and reduction in hyperglycemia with AID, this method of insulin delivery is preferred above other modalities. For persons with diabetes with suboptimal glycemia, significant glycemic variability, impaired hypoglycemia awareness, or who allow for permissive hyperglycemia due to the fear of hypoglycemia, such AID systems should be considered.

Grade A; High Strength of Evidence; BEL 1

Evidence Base

The ASPIRE trial demonstrated that the use of an LGS system resulted in a 38% reduction in nocturnal hypoglycemia compared with CGM alone without increasing A1C.[223] This finding was corroborated by a 2013 RCT that included 95 children and adults with T1D.[224]

PLGS algorithms increase the sophistication of these insulin interruption algorithms by suspending basal insulin for predicted hypoglycemia. To assess the efficacy of PLGS system, 69 participants underwent insulin-induced lowering of their glucose, and the PLGS system tested was found to avoid hypoglycemia in 60% of the cases without causing rebound hyperglycemia.[225] A 2018 randomized crossover trial reported similar findings in 103 participants aging 6-72 years, comparing a PLGS system with SAP.[226]

The use of HCL systems have been shown to improve endpoints in children and adults with SAP systems.[227–234] In a 6-month, multicenter RCT of 168 individuals with T1D aging 14-71 years, the use of a closed-loop system was associated with a greater %TIR, less hyperglycemia and hypoglycemia, and improved A1C levels than the use of an SAP.[228] Two RCTs reported similar improvements in % TIR and reductions in A1C with HCL use compared with the LGS systems.[233,235] Importantly, the 2018 RCT specifically included those with suboptimal glycemia, broadening the generalizability of their study results.[233] A recent 16-week trial involving over 100 children with T1D found that glucose levels were in the target range for a greater percentage of time in individuals who used a closed-loop system compared with those who used an SAP.[236] Meta-analyses have consistently shown that the use of HCL insulin delivery systems lowers mean glucose, increases TIR, and reduces time in hypoglycemia.[234,237,238]

The most recent studies report on an investigational advanced hybrid closed loop (AHCL) system, which is designed to automate the delivery of both basal insulin and provide automated correction boluses every 5 minutes. A recent RCT conducted in New Zealand included participants as young as 7 years old and showed a 13-percentage point overall improvement in TIR in the AHCL system compared with the SAP plus PLGS system.[239] The AHCL system was also tested in adolescents and young adults, a cohort that traditionally struggles with glycemia, who were naive to diabetes technology, in an RCT that compared its use with an HCL system. The AHCL system increased the amount of time spent in target glucose range by 10-percentage points, up to approximately 16 hours across a 24-hour period. The advanced system had a larger number of individuals reaching a TIR target of 70%, with up to a 3-fold increase compared to baseline versus the previous system's 2-fold increase.[240]

Q2.10 In what settings or special situations is use of diabetes technologies beneficial?

Recommendation 2.10.1

The continuation of CGM and/or CSII (insulin pump, SAP, LGS/PLGS) should be considered in hospitalized persons with diabetes without cognitive impairment and, ideally, with the presence of a family member who is knowledgeable and educated in the use of these devices or with a specialized inpatient diabetes team available for advice and support.

Grade A; Intermediate Strength of Evidence; BEL 1

Evidence Base

Hospitalized persons with diabetes are often challenged in retaining their ability to continue the use of their CGM and CSII technologies. This can be due to a lack of uniform hospital policies or lack of expertise among hospital staff in the use of these technologies. Critical to the determination of whether to continue the use of advanced diabetes technologies in hospitalized persons with diabetes is the assessment of both the setting (for example, is the person on a general floor or admitted to an intensive care unit) and the clinical picture of the person with diabetes. The use of diabetes technologies relies on someone familiar with this technology to be readily available, often defined as at the bedside; thus, a family member who is knowledgeable may serve in this role if a person with diabetes is cognitively impaired. The use of technology in the inpatient setting will be augmented by the availability of an inpatient diabetes team or educated nursing staff, but if these are not available and hospital policy allows, the use of diabetes technologies may be feasible if the above prerequisites are met (Expert Opinion).

Although evidence supporting the use of CGM and CSII technologies in hospitalized persons is sparse, results provide a growing body of evidence supporting the benefits of continued patient self-management in the hospital setting.[241,242] The COVID-19 pandemic has offered a unique window into the opportunity of using CGM in

inpatient wards and highlights the success of such strategies,[243] but this has only been feasible with non-objection from the U.S. FDA, given the extraordinary circumstances of the pandemic.[244,245]

Results from a study of 81 insulin-treated hospitalized persons with T2D, ages 18-65 years, who were randomized to SAP or MDI with SMBG and blinded CGM, showed that 21 participants using SAP experienced significantly less hypoglycemia (<50 mg/dL: 0.04% vs 0.32%, $P < .05$) and significantly less hyperglycemia (>180 mg/dL: 21.56% vs 35.03%, $P < .05$).[220]

Further, the question of whether CGM initiation could be beneficial to those with diabetes has recently been explored. In a 2020 RCT, 72 insulin-treated persons with T2D at high risk for hypoglycemia were randomized to rtCGM in conjunction with a glucose telemetry system that wirelessly transmits glucose data from the bedside to a centralized monitor at the nursing station.[246] The rtCGM cohort experienced fewer hypoglycemic events (<70 mg/dL, $P = .024$), fewer clinically significant hypoglycemic events (<54 mg/dL, $P = .003$), and a lower percentage of TBR (<70 mg/dL and <54 mg/dL) than the point-of-care glucose testing group ($P = .17$).[246] No between-group differences in nocturnal hypoglycemia, TIR 70-180 mg/dL, and TAR were observed.

Recommendation 2.10.2

rtCGM is recommended for persons ≥65 years old with insulin-requiring diabetes to achieve improved glycemic control, reduce episodes of severe hypoglycemia, and improve QoL; however, glycemic goals should be individualized due to increased comorbidities and reduced capacity to detect and counter-regulate against severe hypoglycemia in this population.

Grade A; Intermediate-High Strength of Evidence; BEL 1

Evidence Base

Older persons with diabetes are at a significantly higher risk for severe hypoglycemia than younger individuals.[50,51,53] Investigations in the use of CGM within this population have been shown to detect[247] and reduce hypoglycemia,[166,248] reduce A1C,[249] and improve QoL.[248]

In a 2020 RCT, 203 older adults (≥60 years) were randomized to use CGM or SMBG. At 6 months, CGM was associated with a decrease in severe hypoglycemia compared with SMBG, showing significant reductions in severe hypoglycemia incidence rates (per 100 person-years) compared with SMBG (1.9 vs 22.4, respectively, $P = .02$).[166] The use of CGM was also associated with reductions in the percentage of time spent <70 mg/dL (from 5.1% to 2.7%) versus increases with SMBG use (from 4.7% to 4.9%, $P < .001$).[166]

The investigators of a subgroup analysis of the DIAMOND T1D and T2D trial cohorts[204,250] assessed changes in glycemic status among rtCGM versus SMBG users[249] and reported significant A1C reduction with rtCGM versus SMBG use (−0.9% vs −0.5%, $P < .001$).[249]

Recommendation 2.10.3

Clinicians should prescribe CGM as a tool to track glucose before, during, and after exercise in persons with diabetes; monitor the glycemic response to exercise; and help direct insulin and carbohydrate consumption to avoid hypoglycemia and hyperglycemia. When this technology is utilized as part of AID systems, it can reduce glycemic excursions during exercise.

Grade A; Intermediate Strength of Evidence; BEL 1

Evidence Base

Glycemic management during exercise has improved with CGM. Adjustments on insulin doses especially for CSII[251–253] and carbohydrate intake[175] prior to, during, and after exercise have been facilitated by CGM data. CGM studied under differing exercise conditions has shown good and comparable accuracy.[254] However, some studies show diminished accuracy of sensors with physical activity as noted in an assessment of the isCGM system during exercise[255] and rtCGM in a study of 17 adults with T1D.[256]

CGM has been proven to mitigate exercise-induced hypoglycemia in PLGS, wherein there was a reduced need for hypoglycemia treatment after moderate-intensity exercise in an in-clinic setting[257] as well as in AID.[258] An automated exercise-enabled dual-hormone closed-loop system outperformed an exercise-enabled single-hormone system and a PLGS system in hypoglycemia reduction.[259,260]

Announcement of exercise to the algorithm at ≥30 minutes may be required to achieve improved outcomes and to reduce the risk of hypoglycemia.[261] In adults with T1D, to limit the hypoglycemic risk associated with 30 minutes of exercise 3 hours after lunch, without carbohydrate supplements, the best options seem to be to reduce basal rate by 80% or to stop the pump for moderate or intense exercise, or for moderate exercise 90 minutes after lunch, to reduce the prandial bolus rather than the basal rate.[262]

Some trials have shown that automatic suspension of insulin delivery significantly reduced the duration and severity of induced hypoglycemia without causing rebound hyperglycemia.[263,264]

Q2.11 What is the role of telemedicine in the implementation and ongoing use of diabetes technology?

Recommendation 2.11.1

Telemedicine, including periodic phone calls, smartphone-web interactions, and periodic supervision by health care professional interactions, is strongly recommended to treat persons with diabetes, provide diabetes education, remotely monitor glucose and/or insulin data to indicate the need for therapy adjustments, and improve diabetes-related outcomes/control with better engagement.

Grade A; Intermediate-High Strength of Evidence; BEL 1

Evidence Base

Telemedicine is being rapidly adapted and expanded in terms of use, following the COVID-19 pandemic. Telemedicine has the potential as a communication technology to improve access to care with ease of access due to improved time efficiency, improved geographical reach, and greater convenience for persons with diabetes. Telemedicine can provide access to diabetes management and education, initiate remote use of diabetes technology, lead to outcomes that are equal to or better than in-person visits, and facilitate more frequent encounters.

A telemedicine visit includes the same components as an in-person visit with a limited exam (visual only), but for those with diabetes, nearly all essential parts of a visit are possible. Diabetes management is particularly well suited to use for telemedicine because care is driven by the data collected from connected CGM systems, insulin delivery devices, and peripheral devices, including pedometers, weight scales, and applications for smartphones. Data from these devices can be remotely downloaded and analyzed with the person with diabetes during a telehealth visit; however, one limitation might be a person's ability to upload the data.

Numerous studies have shown that in persons with T1D and T2D, various forms of telemedicine visits, including phone calls, internet and phone-based data transmission, and video calls are similar to in-person visits and lead to measures of glycemic control.[265–267] Other studies have demonstrated in persons with both T1D and T2D that telemedicine is associated with improvements in A1C,[184,268–279] reductions in diabetes-related distress,[280] and improvements in medication adherence.[281]

The use of telemedicine also has been associated with improved measures of engagement in diabetes self-management among younger individuals with T1D.[282] A 2016 RCT reported lower body fat and improved lipids in its group assigned to telemedicine visits,[274] and the use of telemedicine in women with GDM in a recent RCT resulted in lower A1C, better engagement, and less maternal weight gain.[272]

In a recent RCT of 240 children (age 1-16 years) with T1D, investigators observed the impact of monthly telemedicine visits on glycemic control and diabetes burden compared with usual care.[283] At 6 months, no between-group differences in A1C were observed. However, parents reported decreased diabetes burden and improved treatment satisfaction. At 12 and 15 months of follow-up, there was a significant improvement in A1C.[283]

Moreover, recent articles as well as the Centers for Disease Control and Prevention have reported that the use of telemedicine technologies addresses several of the obstacles caused by the COVID-19 pandemic.[284–288]

Q2.12 Do smartphone applications have utility in the management of diabetes?

Recommendation 2.12.1

Clinically validated smartphone applications should be recommended to persons with diabetes to teach/reinforce diabetes self-management skills, encourage engagement (eg, coaching), and support/encourage desired health behaviors (healthy eating instruction, physical exercise tracking).

Grade B; Intermediate-High Strength of Evidence; BEL 1

Evidence Base

Despite there being a plethora of applications for those with diabetes, as noted by a consensus report of the American Diabetes Association and European Association for the Study of Diabetes Technology Working Group, there have been few studies to explore the clinical validity of these applications, and the vast majority are not regulated.[289,290] Meta-analyses and systematic reviews have shown that diabetes self-management applications can improve A1C[291–293] and lifestyle modification.[294] A 2017 systematic review reported that smartphone applications that facilitate behaviorally designed interventions can improve an individual's access to diabetes self-management education and ongoing support.[291] Another study showed no benefit of a self-management application when used alone; however, the application could be beneficial when combined with interactive management.[295] A recent meta-analysis reported that smartphone applications can help improve A1C; however, the clinical impact is low.[296]

Although studies have demonstrated the benefits of specific smartphone applications for persons with both T1D and T2D,[291–293] the large majority have not had formalized assessment to determine the clinical validity nor have they received FDA clearance. A 2018 comprehensive study for the U.S. Agency for Health care Research and Quality found only 11 RCTs (clinical vs control) reporting health outcomes among the hundreds of commercially available applications for diabetes self-management.[297] Of these 11 RCTs, only 5 were associated with clinically significant, but small improvements in A1C. None of the studies demonstrated improvements in QoL, blood pressure, weight, or body mass index.[297] A 2019 RCT showed no benefit of a self-management application alone; however, the application could be beneficial when combined with interactive management.[295]

Applications that are used in conjunction with FDA-regulated devices, such as insulin pumps and smart pens, which assist persons in calculating insulin doses, are more highly regulated. "Low-risk" medical applications include software that supports administrative functions, encourages a healthy lifestyle, serves as an electronic patient record, assists in displaying or storing data, or provides limited clinical data support. FDA lists approved/cleared applications in its 510(k), premarket approval (PMA), and establishment registration and device listing databases.[298–301]

Question 3:
What are safety considerations for the use of diabetes technologies?

Q3.1. What are safety considerations for the use of continuous glucose monitoring?

Recommendation 3.1.1

With the use of CGM, clinicians should make a reasonable effort to ascertain that a person with diabetes is not inadvertently ingesting a substance or medication that will cause the CGM to deliver false or misleading information. Furthermore, clinicians should make a reasonable effort to make persons with diabetes aware of the theoretical risk of radiation exposure to diabetes technologies.

Grade C; Low Strength of Evidence/Expert Opinion of Task Force; BEL 3

Evidence Base

Each CGM currently in use can deliver incorrect or misleading information due to interfering substances. For example, the Freestyle Libre (Abbott) systems can be adversely affected by large doses of ascorbic acid (>500 mg/d), which can cause a false elevation of glucose. Earlier CGM devices, such as G4 and G5 (Dexcom), yield falsely elevated values in the presence of acetaminophen. High levels of hydroxyurea can lead to falsely elevated sensor glucose values.[302] The Guardian 3 system (Medtronic) is also vulnerable to interference from acetaminophen, ascorbic acid, and xylose as well as very high levels of bilirubin and uric acid. The Eversense (Senseonics Inc.) sensor does not show a significant interference with ascorbic acid and acetaminophen, although is affected by mannitol and tetracycline.[303,304] Given a theoretical risk of radiation exposure to medical devices and a lack of formalized studies to assess risk, while the risk is believed to be low, it may be prudent to have persons with diabetes remove diabetes devices for imaging that may expose devices to radiation or to request alternate screening methods in situations where medical detectors may be utilized.[305]

Recommendation 3.1.2

Persons with diabetes who have a care provider, such as a spouse, adult child of a geriatric person with diabetes, or parent of a child with diabetes, who remotely monitors glucose data, should be cautioned that remote glucose monitoring is dependent upon server functionality and that data interruption can result. Back-up plans of having persons with diabetes revert to SMBG or methods to communicate CGM data to those who remotely follow will be needed until functionality can be restored.

Grade D; Low Strength of Evidence/Expert Opinion of Task Force; BEL 4

Evidence Base

As with any piece of technology, a device can fail, not last for its intended duration, not transmit a signal to a receiver or phone if not in close proximity and, under some circumstances, other devices, such as powerful magnets, may disable the CGM. Furthermore, servers used to relay signals have the potential of interruptions in service, with the possibility that remote data will not be available. In 2019, an event of this type was noted and caused concern for a number of persons with diabetes and their loved ones.[306] It is wise

for both persons with diabetes and their health care team to problem-solve when the device appears not to be performing as expected and advise users to revert to SMBG, if needed (Expert Opinion). These caveats are not meant to restrict the use of this important device, but rather to make it safer and more efficacious. Additionally, ensuring back-up supplies, like glucometers and test strips, are available will be essential. Accordingly, the coverage of these supplies is a necessity.

Q3.2 What are safety issues for the use of insulin delivery devices?

Recommendation 3.2.1

All persons with diabetes using an insulin delivery technology should receive comprehensive training in its proper use and care.
Grade A; Intermediate Strength of Evidence/Expert Opinion of Task Force; BEL 2

Evidence Base

The assessment of foundational skills for the use of various insulin delivery technologies is an ongoing process, and reinforcement or re-education should be provided as needed by a multidisciplinary team (Expert Opinion). Additionally, re-education may be essential in youth as they become more independent with care or with alternate care providers, for example, adult children of the geriatric population. Understanding that all persons with diabetes learn differently, techniques should include both verbal relay of information with reinforcement through visual cues and tactile skill review on how to utilize the various diabetes technologies. A recent study reported that the use of virtual training of persons with diabetes on an advanced insulin delivery system led to high satisfaction and short-term glycemic results comparable with in-person training.[307] It is often beneficial to have close contact following device initiation to allow for dose optimization while reinforcing concepts related to pump therapy and answer any questions that may arise. A personalized approach to education incorporating the learning style preferred by a person with diabetes may make insulin delivery devices safer. Indeed, structured education programs have been shown to be beneficial during the integration of pump therapy.[308]

Recommendation 3.2.2

The use of FDA-cleared and clinically validated smartphone bolus calculators, in the absence of pump therapy, is strongly recommended to decrease the frequency of hypoglycemia or severe postprandial hyperglycemia.
Grade A; High Strength of Evidence; BEL 1

Evidence Base

Early studies have demonstrated that bolus calculators help insulin pump users more accurately meet prandial insulin dosage requirements, improve postprandial glycemic excursions,[309] reduce hypoglycemic episodes,[310] reduce glycemic variability,[311] and achieve more optimal glycemia with an increased time within target range. Studies have shown that the use of a blood glucose meter with integrated bolus calculators improves glycemic control and treatment satisfaction without increasing severe hypoglycemia[312] and increases confidence in persons treated with MDI therapy. Additionally, many of these bolus calculators incorporate insulin-on-board and will reduce suggested boluses to help prevent the stacking of insulin, thereby preventing episodes of hypoglycemia.

The growing number of bolus calculator smartphone applications increases access to this technology for persons with diabetes. However, the safety and clinical efficacy of these bolus calculators are not known. In 2015, FDA issued guidance on Medical Device Data Systems, which covered smartphone bolus calculators and a number of other mobile technologies[313] FDA has since granted approval to several companies for smartphone bolus calculators that have met the agency's safety and efficacy criteria.

Insulin pump systems with integrated bolus calculators, particularly when used in conjunction with CGM and appropriate algorithms to assist in insulin delivery, have been shown to be superior in the short term in reducing nocturnal hypoglycemia and increasing TIR, and both outcomes significantly increase the personal safety of persons with diabetes and can increase the QoL for both the individual as well as their family.

Recommendation 3.2.3

Clinicians should ensure that persons with diabetes using an insulin delivery technology are aware of the frequency and relative risk of pump malfunction, receive instruction for identifying signs of pump malfunction, know who to contact in the event of a pump malfunction, and have a defined plan for emergency measures (eg, back-up insulin pen, remediation).
Grade A; Low Strength of Evidence/Expert Opinion of Task Force; BEL 2

Evidence Base

Insulin pump malfunctions are a key concern among individuals treated with CSII systems,[314–316] with higher rates in more sophisticated pump systems.[316] Because insulin pump therapy solely relies on rapid-acting analogs, persons with diabetes must be advised that should glucose levels trend high and not come to target following a correction bolus, the infusion set should be assumed to be nonfunctional, and the site should be replaced. Although the majority of reported issues with insulin pumps (traditional and integrated) are with infusion sets and often involve clogging, kinking, or disruption of the infusion site, both problems in the connectivity and malfunction of the pumps have occurred.[316–318] In some reported cases, manufacturing flaws have led to recalls of insulin infusion sets. Preparing persons with diabetes with management strategies for this anticipated issue will help minimize the risk of DKA.

All insulin delivery devices also have potential technological issues. This may include batteries that fail or the device being damaged due to being dropped, crushed, or exposed to strong electromagnetic fields. In certain instances, screens have shattered, making it impossible for a person with diabetes to safely administer a bolus dose of insulin. In these situations, persons with diabetes must be well prepared to revert to injection therapy while they await replacement of the device. For integrated insulin delivery systems, one must consider what occurs if a pump loses connection with either the sensor or the controlling device, if it is not embedded on the pump itself. When a person using an AID turns off the automated functions, it is important to understand the settings the system defaults to.

Although the FDA database, Manufacturer and User Facility Device Experience (MAUDE), has a wealth of information on the many varieties of both common and uncommon causes of adverse events due to insulin pump therapy, the database is not easy to navigate.[319] Furthermore, the system relies on accurate reporting of pump issues, and several authors noted its deficiencies. While the adverse event may be recorded, the cause may not be. Finally, all mechanical devices, such as insulin pumps, may not perform as well later in their usage. Batteries may fail more often, buttons and screens may become less responsive, or signals from connected devices like a sensor may be dropped more often. The assessment of such issues during follow-up will help clinicians assure that persons with diabetes have safe tools for insulin delivery.

Furthermore, human error is a significant challenge and can lead to serious morbidity as well. Robust education in the proper use of

the device and re-evaluation may identify those at higher risk for human error in their use of the insulin pump.

Q3.3 What are safety issues for the use of integrated devices to manage persons with diabetes?

Recommendation 3.3.1

Persons with diabetes using integrated devices should receive requisite training in the use of their device(s) and that the devices are being safely and properly used according to manufacturer instructions.

Grade A; Low-Intermediate Strength of Evidence/Expert Opinion of Task Force; BEL 2

Evidence Base

While there is strong evidence for the efficacy and safety of the use of integrated devices to manage persons with diabetes, clinicians need to consider that these devices are not infallible and can and do malfunction, and each component of the system may be vulnerable, including the reservoir, tubing, and connection to the individual for all insulin pumps.[316,320] Human error also may remain a significant challenge to consider when evaluating the cause of an adverse event. More importantly, since the introduction of commercially approved AID systems is relatively recent (2017), with much of the data derived from well-constructed and supervised trials powered to show efficacy, apart from the FDA's MAUDE database and recent recalls, there are few data for the relative frequency of adverse events with the new systems. Therefore, clinicians must evaluate the willingness and ability of persons with diabetes to use advanced insulin delivery systems properly and safely.

Q3.4 Are open-source automatic insulin-dosing systems, which currently are not approved by the U.S. Food and Drug Administration, safe and effective in the management of persons with diabetes mellitus?

Recommendation 3.4.1

Clinicians should caution persons with diabetes who are using DIY systems that these devices have not undergone rigorous review by the FDA for safety and efficacy.

Grade B; Low Strength of Evidence/Expert Opinion of Task Force; BEL 4

Evidence Base

Thousands of persons with diabetes worldwide are currently using DIY closed-loop insulin delivery systems for managing their diabetes. DIY systems combine FDA-approved components, including insulin pumps and CGM, with open-source software to deliver continuous doses of insulin. However, because these systems have not been formally evaluated for efficacy and safety, the FDA issued a warning that the use of these systems could result in inaccurate glucose measures or unsafe insulin dosing that could lead to adverse events.[321] There is a growing body of literature suggesting a safe and effective utilization of DIY systems; however, in their present form, these systems have not been formally integrated yet into our care model. However, the commercialization of DIY algorithms is currently being sought, with data collected in an observational, real-world trial that demonstrated both the safety and efficacy of these systems.[322]

Recognizing that individuals who use such systems would still benefit from care by a diabetes specialist, clinicians should document the use of the off-label system and continue to assist with clinical care. Similar to care providers of those on commercially available pump systems, clinicians should assist with optimizing pump settings, determining adequacy and appropriateness of CGM alerts, providing back-up plans, including injection therapy for instances where system components may malfunction, and provide instructions on hypoglycemia management and the importance of checking for ketones and assessing for infusion-set failures when prolonged hyperglycemia occurs.

Q3.5 What are the criteria for discontinuing the use of insulin pumps in persons with diabetes?

Recommendation 3.5.1

Clinicians should strongly consider the discontinuation of insulin pump therapy based on an individual's ability to use it effectively and safely or based on the personal preference of a person with diabetes to discontinue this insulin delivery modality.

Grade A; Intermediate Strength of Evidence; BEL 1

Evidence Base

Although most trials show a significant advantage of CSII over MDI therapy,[323–325] some studies have pointed toward higher frequency of hypoglycemia and DKA in CSII users,[204,320,326] which are often due to pump malfunction or suboptimal engagement. Registry-based assessments have shown lower risks of both severe hypoglycemia and DKA with pump use when assessing adolescents and young adults.[327] However, when or why the use of diabetes technologies should be discontinued has not been studied. Absent this guidance, the decision to discontinue the use of these technologies must be driven by clinical judgment for each individual and based on whether the current therapy is enabling the user to achieve desired treatment goals and if continued use of the technology is increasing the risk for adverse events. In addition, clinicians must be respectful of an individual's personal desire and motivation to continue using the technology. More studies are needed to address this issue. Should a person with diabetes not be achieving the jointly developed treatment goals, clinicians should seek to understand obstacles and provide more education on how to successfully integrate diabetes care devices into one's care regimen. This may allow for an open conversation so that persons with diabetes can express their desire, or lack thereof, to continue with a particular insulin delivery modality.

Question 4:
How should the use of diabetes technologies be implemented in clinical practice?

Q4.1 Who should prescribe/direct/supervise the implementation of diabetes technologies?

Recommendation 4.1.1

Initiation and use of diabetes technology should be implemented by health care professionals who are trained, committed, and experienced to prescribe and direct the use of these tools. Clinicians should have the infrastructure to support the needs of persons with diabetes using the technology.

Grade B; Intermediate Strength of Evidence/Expert Opinion of Task Force; BEL 1

Evidence Base

To utilize technologies to their fullest potential, it is necessary to have a multidisciplinary diabetes team that has specific assigned roles. Diabetes-care team members ideally should include an experienced endocrinologist or a primary care physician, with additional staff who may include nurses, certified diabetes care and education specialists (CDCESs), dietitians/nutritionists, advanced practice nurses, physician assistants, and/or other professionals, such as a social worker and behavioral health professional. Diabetes-care teams may be composed of as little as 2 clinicians, such as a

primary care physician and a CDCES, who have the ability to work with industry partners to provide training on devices and refer to local behavioral care specialists. In other circumstances, a more diverse team, including all roles listed above, may be feasible. The goal of this team is to ensure that clinicians have the knowledge and methods of support available to help persons with diabetes integrate advanced diabetes technologies into their lives. The initial step in integrating diabetes technology into practice is to become familiar and comfortable with the most common devices that may be used. In addition, having a clear division of labor can optimize the management and interpretation of remote data.

Individuals responsible for the initiation and supervision of a person with diabetes using diabetes technologies should be experts in diabetes management who are proficient in using and teaching the features and functionality of all prescribed diabetes technologies. The areas of proficiency should include:

- Device setup, troubleshooting, and awareness of common questions, problems, and concerns
- Ability to download and interpret device data (eg, glucose, insulin administration), change device settings as needed, and adjust therapy

There is a paucity of literature that addresses globally the level of expertise and experience needed for health care professionals to implement diabetes technology. Insulin pumps are typically prescribed and started by diabetes specialists, endocrinologists, and CDCESs, although there is no certification requirement. CGMs are prescribed and interpreted both by diabetes specialists and primary care physicians; no certification is required. A 2019 study of 42 pediatric endocrinology fellows showed suboptimal knowledge of insulin pumps and CGM.[328] It is our opinion that there is a need for pediatric and adult endocrinology training programs to include formal training in diabetes technology. Additionally, anyone who would prescribe diabetes technology, such a primary care physician or an advanced practice clinician, would benefit from formal training as well.

An exploratory RCT showed that insulin initiation and use of CGM was safe and improved A1C using CDE-RNs and in the primary care setting.[196] A 2019 cohort study showed that a DSMES team-based approach resulted in improvement in glycemic control and reduction in hospitalizations in a high-risk cohort of adults with uncontrolled T2D as well as potential for monetization.[329] A recent review advocated that diabetes care and education specialists are in a unique position to help persons with diabetes integrate diabetes technology in daily care.[330]

The Stanford University Extension for Community Healthcare Outcomes (Project ECHO) Model[331] recruits primary care clinicians and clinics that care for persons with diabetes. Utilizing telemedicine, knowledge between diabetes specialists and primary care physicians can be shared via regular training sessions that discuss best practices and new technologies and provide feedback on case studies. Recent studies conducted in primary care environments have shown beneficial clinical endpoints, including hypoglycemia detection in people with T2D treated with oral agents[332] and improved TIR at 12 months.[201]

As technology improves and becomes more widespread, more physicians and health care professionals will be able to incorporate diabetes technology into their practices.

Q4.2 How should patient education programs be structured?

Recommendation 4.2.1

Training of persons with diabetes should utilize a structured, comprehensive training program that covers all aspects of safe and effective use of diabetes technologies.

Grade C; Low Strength of Evidence/Expert Opinion of Task Force; BEL 2

Evidence Base

Diabetes education and training are essential to optimizing the use of CGM and other diabetes technologies.[333–335] Persons with diabetes and their care professionals need to understand the factors that can influence sensor accuracy, such as the lag time between CGM and SMBG values and interfering substances. Understanding how to safely and effectively use CGM data for daily diabetes self-management and how to interpret and learn from retrospective data are essential. While many sensors are approved to be independently used without the need for a confirmatory fingerstick check, persons with diabetes should be advised that if their symptoms do not match sensor glucose values or if they believe their sensor glucose is inaccurate, it would be prudent to check a capillary blood glucose level. For persons with diabetes who choose a CGM system with active alarms and alerts, setting up individualized alarms and alerts is important for preventing alarm fatigue. Additionally, it is essential to monitor for skin problems, allergic reactions, sensitivity caused by, or poor CGM sensor adhesion that may affect their persistence in device use. If the sensor is not lasting for its intended duration, there will be gaps wherein no data are available if insurance limits the supply of devices.

It is also important to manage expectations in terms of what CGM can and cannot do and the time and effort required to integrate the use of CGM into one's daily life. The use of direct questioning, ongoing collaboration between the person with diabetes and their clinician, and joint goal setting allow for a person-centered approach, which can overcome most of the obstacles encountered when introducing CGM and other diabetes technologies.[333,336–338]

Once a technology is selected, a person with diabetes will require comprehensive education and training in the setup, operation, and troubleshooting of their device. However, the accurate calculation of prandial and correction insulin dosages is a significant challenge for persons with diabetes using MDI therapy, sometimes due to poor numeracy skills.[339,340] A 2012 cohort study found that bolus dose math errors occur in over 60% of manual dose calculations, although human errors are substantially reduced when a bolus calculator is used.[341] In the SENLOCOR study, metabolic control was improved in persons with T1D who received 6-month training on SAP from a multidisciplinary team, especially home-care providers, with a high level of adherence and satisfaction.[342]

Clinicians need to consider that most technology applied in the management of persons with diabetes is not entirely self-explanatory. Persons with diabetes and their care partners (parents, spouse, and, for the geriatric population, potentially their children) need to receive thorough education both about diabetes management in general and about the devices that are being used as part of the diabetes management plan. A diabetes management plan may also require psychosocial support as well as technical support, with periodic monitoring as appropriate.

Prior to initiating CGM, the health care team should assess an individual's ability to accurately calculate their bolus, prandial, and correction insulin dosage. Initial training should focus on the following:

- Fundamentals of the CGM device operation (system set-up, sensor insertion, troubleshooting)
- Similarities/differences between CGM and SMBG (eg, time delay between blood glucose and interstitial glucose)
- Prevention and treatment of acute glycemic events
- Significance and use of alarms/alerts (if applicable)
- Follow-up training should focus on:

- Use of trend arrows for insulin dosage and adjustment and activity/nutrition modification
- Use of retrospective CGM data
- Use of share functions (if applicable)

DSMES specialists should include a defined plan for structured follow-up with the ability to receive actionable feedback and provide access to a specialist who is available to answer questions, help with setting goals and building skills, and provide immediate support in the setting of extreme glucose excursions. In addition, they should review data with the patient, assess that person's knowledge, provide individualized feedback on health behaviors, and initiate therapy adjustments and/or behavioral interventions as needed to support improved glycemic control.

The team should incorporate a stepped-care approach that provides evidence for the effectiveness of the management of persons with diabetes and impaired awareness of hypoglycemia, initially with structured diabetes education in flexible insulin therapy, which may incorporate psychotherapeutic and behavioral therapies, and progress to diabetes technology, incorporating sensors and insulin pumps.

During the initial start-up period, CGM users should be encouraged to personalize the use of their systems' alarm/alert features. Although clinicians may initiate CGM and insulin delivery concurrently, CGM users should be advised to wait until they are comfortable with the general application of CGM data and learn how their body responds to various meals (quantity/composition) and physical activity before adjusting insulin dose using trend arrows. Clinicians should advise CGM users about the ability to share their data with care partners as an added safeguard; however, some persons with diabetes may elect not to share their data.

As follow-up, DSMES specialists should schedule interactions based on individual needs and provide actionable feedback. The frequency of contact can range from daily, weekly, bi-weekly, monthly, or quarterly. Data should be viewed with hypoglycemia identification as the first priority. If there is significant glucose variability on different days of the week, it would be necessary to obtain at least 2 weeks of CGM recordings, followed by appropriate analyses and recommendations.

Recommendation 4.2.2

DSMES program specialists should assess knowledge base, review data with the person with diabetes, and provide individualized feedback for initiating therapy, adjustments, and/or behavioral modifications as needed to support the attainment of individualized glycemic goals.

Grade B; Intermediate-High Strength of Evidence/Expert Opinion of Task Force; BEL 1

Evidence Base

Diabetes education is a valuable tool to engage persons with diabetes in their self-management and has been shown to improve QoL and result in long-term improved glycemia.[343,344] The value of person-centered education is documented in persons with T1D in several studies.[345–347] A 2019 RCT showed that DSMES programs result in greater empowerment, motivation, and medical adherence in persons with T2D.[348] An earlier study found that the use of an intensive diabetes education program combined with structured SMBG was associated with clinically significant reductions in A1C, increased SMBG frequency, and improved QoL.[349] A 2019 RCT showed that the use of a structured education and treatment program improved glycemic control and lowered diabetes-related distress in isCGM users.[350] Similarly, an education program aimed at optimizing conventional insulin therapy in persons with T2D improved A1C when delivered in both inpatient and outpatient settings.[351]

As with clinical care, DSMES programs may include support by telephone, telehealth visits, or secure internet communications. A 2012 RCT showed that telephone video messages can help in diabetes self-care support.[352] Whether through in-person or remote consultations, a collaborative review of diabetes data makes the data meaningful to persons with diabetes and empowers them to make informed adjustments and decisions about their care.

Although CDCESs play a critical role in self-management education, a 2013 RCT showed that properly trained staff members in primary care practices can be just as effective in DSME delivery.[353]

Future Directions

The field of diabetes technology is rapidly evolving. However, as evidenced above, several areas remain to be explored. Currently, criteria for the use of isCGM instead of rtCGM are largely based on expert opinion and the need to use rtCGM for devices that alter insulin delivery provided via pumps based on sensor glucose profiles. However, studies assessing the ability to use isCGM in AID systems are planned; thus, this differentiating factor may diminish over time.

While connected pens have reached commercialization, further assessment of their utility in the treatment of persons with diabetes in the real-world setting is warranted. Determination of whether systems could allow for seamless transition between connected pens and pumps may provide an opportunity for persons with diabetes to feel less tethered to devices.

Ongoing assessment of the safety of diabetes technologies will be critical. Should safety signals emerge, alterations in the technology and/or investigation into how to alter education to ensure persons with diabetes have the skillset needed to problem-solve will be essential. Recognizing that infusion-set failures plague all pump systems (conventional CSII, SAP, LGS, PLGS, and HCL), a prime area to explore would include strategies to minimize the risk of dislodgement or occlusions through changes of the infusion set product and/or development of algorithms that may alert a user to a potentially nonfunctioning infusion set. Such developments could minimize the risk of DKA. Alternatively, the development of new biosignals, such as continuous ketone measurements, may help in the detection of metabolic deterioration that could occur with infusion-set failures.

For those with hypoglycemia unawareness or nocturnal hypoglycemia, the use of CGM with audible alarms may be essential to help keep them safe. Critical to ensuring that CGM can help minimize the risk of hypoglycemia and hyperglycemia is assisting persons with diabetes with how to set threshold and predictive alerts/alarms.[11] Those with hearing and/or visual impairments may be unable to respond to alerts; thus, the use of vibratory alerts or visual cues on smartphones may be of benefit to those who are hearing impaired. Additionally, the use of remote monitoring by care partners, which may include family members or staff at nursing homes, may be even more essential. Indeed, for youth with diabetes, this practice is common, whereby a school-aged child will have the family remotely monitor sensor glucose data during school hours. This approach has been accepted both by parents and nursing staff in schools.[354] Furthermore, measures of QoL have been improved with the use of such remote monitoring systems as has sleep for parents of children with diabetes.[354] Data on the use of such remote monitoring is scant in the adult population; however, the COVID-19 pandemic has provided information on remote monitoring of hospitalized persons.

Nevertheless, for those with hearing difficulties or cognitive impairment, the integration of a care partner to help respond to alarms would be of great utility and should be explored. However, with the ability to alter insulin delivery based on sensor glucose values, the most valuable tool in the arsenal to treat individuals who have cognitive impairment may be AID systems—especially those systems that allow insulin delivery to not be physically attached to the person with diabetes, making a patch pump an ideal option. Early outpatient studies of an AID-enabled patch pump demonstrated the benefits in glycemia, with larger trial results confirming these findings.[355,356]

Strategies to help clinicians care for persons with diabetes utilizing non-physician–prescribed devices, such as DIY AID, should be refined. However, this may be alleviated as certain algorithms are being currently reviewed by regulatory authorities.

Methods to allow clinicians to monitor the success of implementation of diabetes technologies into the care of their patients also will be of use. With cloud-based data available, which can track not only device use but outcomes from CGM-based metrics, clinicians may be able to deliver care more strategically, namely by focusing on those whose device wear has faltered or whose TBR or TIR are below personalized thresholds. However, concerns regarding data privacy have been raised. Therefore, consideration needs to be given to determine how to afford access to the data while upholding privacy for an individual.

Recognizing the wealth of data generated from diabetes devices, a 2020 RCT highlighted that the use of an automated artificial intelligence decision support tool was non-inferior to clinician recommendations in optimizing insulin doses.[357] Importantly, this tool requires a health care clinician to review and accept dosing recommendations prior to them being sent to the person with diabetes; however, it is feasible that with refinement of these algorithms, one could forgo clinician approval in the future.

With reports of the clinical validity of time in target ranges as an acceptable outcome measure, clinical trials, whether of new therapies or technologies, should include the assessment of CGM-based metrics as prespecified outcome measures. These data may help provide clinicians with concrete means by which to advise persons with diabetes of the clinical benefit derived from the population studied, which also may facilitate the joint decision-making conversation of whether this treatment should be incorporated into an individual's care.

Furthermore, wherever feasible, the assessment of QoL measures in conjunction with CGM-based metrics will be critical to demonstrate that the benefits of therapies extend beyond improvements in the numbers derived by these devices to more meaningful impact on the daily burden of this chronic medical condition. Consideration should be given, including measures of cost-effectiveness, into future trials to help ensure access to devices when they become commercially available.

Continued miniaturization and reduced complexity of devices will surely advance with increased penetrance into clinical care. Further, the integration of devices, including a catheter that has both the ability to sense glucose as well as deliver insulin, may increase the acceptance of devices, since fewer insertion sites will be needed. Extended-wear infusion sets lasting up to 7 days are currently being investigated and should also improve adherence and lessen the burden of care. Finally, the creation of a fully closed-loop system that could function independently of the user would be ideal. Strategies to achieve this may include 1) the use of more physiologic insulin preparations, 2) dual-hormone systems, 3) integration of wearable devices that harness physiological data to inform algorithms, or 4) implanted devices. Many of these areas are being explored actively by a number of academic investigators, in some cases, alongside industry partners.

Conclusions

Advanced diabetes technology holds the promise to be beneficial for all those living with diabetes. However, technology, in its current state, is not a solution, but rather provides greater insight to challenges and refined tools to address them. Ensuring universal access to these technologies is anticipated to result in improved glycemia and allowing more persons with diabetes to achieve glycemic targets, improve QoL, and, hopefully, reduce the burden of this complex, chronic, and heterogenous condition. Refinements in technology, such as moving to a fully closed-loop system and reduction in size and footprint of current CGM technology, are anticipated. Making data collected from diabetes devices easily accessible through direct transmission to the cloud will foster the opportunity for both persons with diabetes and clinicians to view data in real time as well as retrospectively review those data. A number of device manufacturers are investigating the possibility of using artificial intelligence to assist with interpretation of glycemic data and necessary insulin dosing recommendations. However, critical to making this endeavor widely applicable will be the insurance coverage of these devices. As the data have shown improvement in glycemic metrics with advanced diabetes technology, the call to action now is to ensure adequate payer coverage, education of persons with diabetes on available devices, and assistance with the integration of these tools into the care regimen. As with other technological advancements, the field of diabetes technology is rapidly evolving; clinicians and persons with diabetes will need to strive to remain abreast of these developments.

Disclosures

The Task Force was empaneled in accordance with AACE's Conflict of Interest (COI) Policy and approved by the AACE COI Subcommittee. All members of the expert Task Force completed AACE's disclosure form regarding any multiplicities of interests related to commercial and direct financial relationships within the preceding 12 months with companies that develop products connected with endocrine disorders. Categories for disclosure include employment, stock or other ownership, direct financial relationships (eg, speaker or consultant), research funding, authorship or panel involvement on a guideline related to an overlapping topic, or other situations related to a perceived COI. The AACE COI Subcommittee reviewed these disclosures against an AACE-approved list of affected companies for this guideline and reached consensus regarding members who could serve on the task force in the nonconflicted majority, those who could serve in the conflicted minority with management strategy, and those who were disqualified from serving on the task force. The AACE Clinical Practice Guideline Oversight Committee reviewed and approved the AACE COI Subcommittee's decisions regarding manageable COI and empanelment. Members of this task force were reminded to update potential disclosures if new potential conflicts arose during their appointments and to verify currency of disclosures. AACE made every effort to minimize the potential for conflicts of interest that could influence the recommendations of this clinical practice guideline.

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The Task Force was empaneled in accordance with AACE's COI Policy. This evidence-based clinical practice guideline was developed by a group of credentialed medical professionals in the fields of endocrinology and primary care, a methodologic specialist, and a medical writer.

Review Process

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Updating Policy

AACE reviews and updates or retires its evidence-based guidelines every 3 years or after significant scientific developments or change in public policy as determined by the AACE executive leadership, AACE CPG Oversight Committee, and relevant AACE Disease-State Network.

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Note: Reference sources are followed by an evidence level [EL] rating of 1, 2, 3, or 4. The strongest evidence levels (EL 1 and EL 2) appear in red for easier recognition.

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Appendix

Table 1. Step I AACE G4GAC—Evidence Rating[a]

Numerical Descriptor[b]	Semantic Descriptor	Methodology Descriptor
STRONG EVIDENCE		
1 (1)	RCT	Randomized controlled trial[c]
1 (1)	MRCT	Meta-analysis of only randomized controlled trials
INTERMEDIATE EVIDENCE		
2 (2)	MNRCT	Meta-analysis including nonrandomized prospective or case-controlled trials
2 (new)	NMA	Network meta-analysis
2 (2)	NRCT	Nonrandomized controlled trial (or unconfirmed randomization)
2 (2)	PCS	Prospective cohort study (does not include open-label extension study)
2 (2)	RCCS	Retrospective case-control study
2 (new)	NCCS	Nested case-control study
2 (3; reassigned)	CSS	Cross-sectional study
2 (3; reassigned)	ES	Epidemiological study (hypothesis driven; includes survey, registry, data-mining, with or without retrospective uni-multivariate analyses or propensity matching
2 (new)	OLES	Open-label extension study
2 (new)	PHAS	Post-hoc analysis study
WEAK EVIDENCE		

3 (new)	DS	Discovery science (explorative/inductive; includes -omics, "big data," network analysis, systems biology, Bayesian inference, modeling)
3 (new)	ECON	Economic study (includes Markov models, pharmaco-economics)
3 (3)	CCS	Consecutive case series (N > 1)
3 (3)	SCR	Single case report (N = 1)
3 (new)	PRECLIN	Preclinical study (e.g., feasibility, safety)
3 (new)	BR	Basic research (must be high impact and relevant)
NO EVIDENCE		
4 (4)	NE	No evidence (theory, opinion, consensus, review, position, policy, guideline)
4 (new)	O	Other (e.g., lower impact/relevant basic research; any highly flawed study

Abbreviations: AACE = American Association of Clinical Endocrinology; G4GAC = Guidelines for Guidelines, Algorithms, and Checklists

[a]Based on principle that interventions, scientific control, generalizability, methodological flaws, and evidentiary details determine strength, consistent with other evidence-based methodology systems. Numerical and semantic descriptors of evidence levels provided in online supplementary material.

[b]The original numerical description from G4GAC 2004, 2010, and 2014 are provided in parentheses.

[c]The superiority of RCT over all other studies, and in particular MRCT, is discussed in reference elsewhere.

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Table 2. Step II AACE G4GAC—Scientific Analysis and Subjective Factors[a]

Study design[a]	**Data analysis**[b]	**Interpretation of results**
Allocation concealment (randomization)	Intent-to-treat	Generalizability
Blinding[c]	Modeling (e.g., Markov)	Incompleteness
Comparator group	Network analysis	Logical
Endpoints (real clinical vs surrogate)	Statistics	Overstated
Hypothesis	Appropriate follow-up	Validity
Power analysis (too small sample size)	Appropriate trial termination	
Premise		
Type 1 error (e.g., adjusted for PHAS)		

Abbreviations: PHAS = *post hoc* analysis study; AACE = American Association of Clinical Endocrinology; G4GAC = Guidelines for Guidelines, Algorithms, and Checklists

[a]These subjective factors pertain to an individual citation. Subjective factors are provided in online supplementary material from (1).

[b]Are these elements appropriate for the given study?

[c]Including patients, clinicians, data collectors, adjudicators of outcome, and data analysts.

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Table 3. Step III AACE G4GAC—Recommendation Qualifiers

Cascades (are there other recommendation versions based on ethnocultural factors?
Dissenting opinions (based on HCP and patient preferences)
Economic (e.g., cost-effectiveness, cost-benefit, value)
Evidence Base (are there significant gaps or is there overwhelming evidence?)
Relevance (patient-oriented evidence that matters vs disease-oriented evidence; social acceptability)
Resource availability (limited or sufficient)
Risk to benefit
Abbreviations: HCP = healthcare professional; AACE = American Association of Clinical Endocrinology; G4GAC = Guidelines for Guidelines, Algorithms, and Checklists [a]Each of these elements pertains to the recommendation statement with the evidence considered in aggregate. The element may be positive or negative, and therefore modify a final recommendation grade. Recommendation qualifiers are provided in online supplementary material from (1). Reprinted with permission from Mechanick JI, et al. *Endocr Pract*. 2017;23:1006-1021.(1)

Table 4. Step IV AACE G4GAC—Creating Initial Recommendation Grades[a]

Best Evidence Level	Predominantly Negative SF and/or RQ	Predominantly Positive SF and/or RQ	Consensus for Recommendation and for Grade	EL to Grade Mapping	Map to Final Recommendation Grade
1	No	No	>66%	Direct	1 → A
Any[b]	No	No	100%	Rule	Any → A (new)
2	No	Yes	>66%	Adjust up	2 → A
2	No	No	>66%	Direct	2 → B
1	Yes	No	>66%	Adjust down	1 → B
3	No	Yes	>66%	Adjust up	3 → B
3	No	No	>66%	Direct	3 → C
2	Yes	No	>66%	Adjust down	2 → C
4	No	Yes	>66%	Adjust up	4 → C
4	No	No	>66%	Direct	4 → D
3	Yes	No	>66%	Adjust down	3 → D
Any[b]	Yes/no	Yes/no	>66%	Rule	Any → AD (new)

Abbreviations: BEL = best evidence level; EL = evidence level; RQ = recommendation qualifiers; SF = subjective factors; AACE = American Association of Clinical Endocrinology; G4GAC = Guidelines for Guidelines, Algorithms, and Checklists

[a]Recommendation Grade A = "Very Strong"; B = "Strong"; C = "Not Strong"; D = "Primarily Based on Expert Opinion." Mappings are provided in online supplementary material from (1).

[b]Rule-based adjustment wherein any recommendation can be a "Very Strong" Grade A if there is 100% consensus to use this designation. Similarly, if >66% consensus is not reached, even with some degree of scientific substantiation, a "Primarily Based on Expert Opinion" Grade D designation is assigned. The reasons for downgrading to D may be an inconclusive or inconsistent evidence base or simply failure of the expert writing committee to sufficiently agree. Note that any formulated recommendation is omitted from the document if sufficiently flawed, so any Grade D recommendation in the final document must be deemed sufficiently important. Rule-based adjustments are provided in online supplementary material from (1).

Table 5. Inclusion/Exclusion Criteria for Evidence to Support Recommendations

Included:	**Excluded:**
Evidence-level (EL) 1: Randomized controlled trials (RCTs); systematic reviews or meta-analyses of RCTs EL 2 studies: meta-analyses including nonrandomized trials or observational studies; controlled trials without randomization; cohort, case-control, cross-sectional studies; epidemiological studies (including surveys and registry data); open-label extension studies; post-hoc analyses EL 3 economic studies EL 3 modeling studies related to continuous glucose monitoring (CGM) metrics, Glucose Management Indicator EL 3 network analyses EL 4 consensus/position/policy statements and guidelines, when no other evidence is available or as background Human participants English Published, full article in peer-reviewed journal Published January 1, 2012 or later All persons with diabetes mellitus on intensive insulin therapy CGM, including: Real-time CGM Intermittently scanned CGM Integrated CGM In-hospital use of CGM Insulin pump therapy, including Continuous subcutaneous insulin infusion Sensor-augmented insulin pump therapy Patch insulin pumps Closed-loop insulin delivery Automated insulin pump dosing systems Insulin pumps approved in United States Non-US Food and Drug Administration–approved/ do-it-yourself pumps Alternatives to diabetes technology: multiple daily injections and self-monitoring of blood glucose	EL 3 studies: case reports/series, preclinical/feasibility/protocol/pilot studies, studies with hypothetical cohorts, basic research, except when no other evidence is available or as background EL 4 studies: editorials/letters, opinions, reviews, theory (except when no other evidence is available or as background) Animal studies Non-English Studies published before year 2012, except when cited as background Persons without diabetes Studies that focus on diabetes technology that is no longer relevant to practice at the time of publication Studies with a focus on accuracy of a product/device Insulin pumps not approved in United States