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New and Emerging Technologies in Type 1 Diabetes



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KEYWORDS

- Continuous glucose monitoring (CGM) • Automated insulin delivery (AID)
- Artificial pancreas (AP) • Bionic pancreas • Closed-loop • Insulin • Glucagon
- Ultrarapid-acting insulin

KEY POINTS

- Innovative and novel technologies for the management of type 1 diabetes hold promise for improving glycemia, decreasing burden of disease management, and improving long-term outcomes.
- Improvements in the accuracy of real-time continuous glucose monitoring (CGM) have allowed for the development of automated insulin delivery systems that can adjust insulin delivery based on CGM glucose input.
- The development of new drugs, such as ultrarapid-acting insulins that better mimic physiologic insulin secretion, may lead to improved postprandial glycemia. The advent of stable glucagon formulations may allow for development of dual-hormone closed-loop systems that could further improve glycemic regulation.

NEW TECHNOLOGIES IN TYPE 1 DIABETES

Intensive insulin therapy for the management of type 1 diabetes (T1D) was established as the standard of care based on the results of the Diabetes Control and Complication Trial (DCCT), which conclusively demonstrated the benefits of tight glycemic control.¹ However, those who received intensive insulin management were at increased risk for severe hypoglycemia, which can be acutely life threatening and can result in seizures, coma, or death. Based on DCCT and other data, the American Diabetes Association (ADA) recommends glycosylated hemoglobin (HbA1c) less than 7% in adults, and recently also in many children and adolescents, in order to decrease the risk of both macrovascular and microvascular complications.² To achieve these recommended glycemic targets, patients must monitor blood glucose multiple times a day, closely

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Endocrinol Metab Clin N Am 49 (2020) 667–678

<https://doi.org/10.1016/j.ecl.2020.07.006>

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estimate carbohydrate intake to calculate appropriate meal coverage, and administer multiple doses of insulin, which can have varying effects based on several physiologic factors such as physical activity, illness, or stress. This program results in a significant burden of disease management. Recently published data from the T1D Exchange, which includes more than 22,000 children and adults in the United States, show that less than a quarter of patients with T1D are meeting HbA1c goals.³ Diabetes technologies are being developed to help decrease disease burden and improve glycemic outcomes. In this article, the authors highlight diabetes technology and therapies including new insulin analogues, continuous glucose monitoring systems (CGM), continuous subcutaneous insulin infusion (insulin pump therapy), as well as automated insulin delivery (AID) systems that integrate CGM and insulin pump technology with mathematical algorithms that automatically adjust insulin delivery (**Box 1**).

GLUCOSE MONITORING

Self-monitoring of blood glucose (SMBG) with finger-stick glucose (FSG) concentrations has become a key component of diabetes care. The ability to obtain a blood glucose measurement and adjust therapy accordingly is a mainstay of treatment to reach glucose targets and prevent hypoglycemia. Glucometer accuracy has increased throughout the years, but not all meters available on the market today meet standards set forth by the Food and Drug Administration (FDA) and International Organization for Standardization.⁴ Identifying glucose trends and patterns based on SMBG to make insulin adjustments had been the standard of care set forth by the DCCT, and increased frequency of SMBG is associated with improved glycemic control.⁵ Some newer glucometers are Bluetooth enabled and can pair with smartphone applications for patients

Box 1	
Key definitions	
Real-time continuous glucose monitoring (CGM)	Wearable technology that provides real-time continuous glucose measurements with the options of alerts for hyperglycemia, hypoglycemia, or projected glucose out of target ranges
Flash glucose monitoring (FGM)	Glucose monitoring system in which data are stored in a wearable sensor and obtained by scanning the sensor with dedicated receiver or smartphone
Automated insulin delivery, artificial pancreas system, closed-loop system, bionic pancreas	Terms that refer to an insulin delivery system that uses mathematical algorithms that can adjust insulin delivery based on CGM input
Threshold suspend	Automated insulin suspension when glucose level drops less than a specified threshold
Predictive low glucose suspend	Automated insulin suspension when glucose level is predicted to be less than a specified glucose threshold (eg, 70 mg/dL) in a specific period of time (eg, 30 min)
Hybrid-closed loop system	An automated insulin delivery system that modulates insulin delivery but still requires quantitative announcement of carbohydrate intake by the user
Fully closed-loop system	Automated insulin delivery not dependent on user input
Bihormonal (dual hormone) system	An artificial pancreas technology that uses insulin plus an additional hormone (eg, glucagon) intended to achieve better glycemic control than possible with an insulin-only system

to better track and identify patterns.⁶ However, FSG has limitations in that they provide only an instantaneous snapshot in time of current glucose and do not provide information on glucose trends or direction of change.

CGM and FGM devices measure interstitial glucose and estimate plasma glucose every 5 to 15 minutes, depending on the system. Real-time CGM systems (Dexcom G6, Senseonics Eversense, Medtronic Guardian) actively transmit glucose information to a dedicated receiver, insulin pump, smartphone/watch, and to a cloud network if desired and can provide real-time information to the user regarding (1) rate of glucose change, (2) hyperglycemia and hypoglycemia based on individualized thresholds, and (3) impending hypoglycemia alarms based on glucose trends. The glucose measurements can also be shared by patients with others, such as family members, in real-time for an added degree of security. In the only currently available FGM system (Abbott Freestyle Libre), data are stored within the sensor and can be obtained by scanning the device with dedicated receiver or smartphone. Of note, the next-generation Freestyle Libre 2 CGM recently approved by the FDA is capable of “pushing” optional real-time threshold alerts to a receiver or smartphone. Both CGM and FGM devices can be used in blinded mode to record glucose data on the device for later analysis of glycemic patterns to assist health care professionals in making therapeutic decisions.

Externally worn CGM (Dexcom G6, Medtronic Guardian) and FGM (Abbott Freestyle Libre) devices measure interstitial glucose via a transcutaneous sensor, a filament placed in the subcutaneous tissue connected to an overlying transmitter. More recently a CGM with an implantable sensor system with an externally worn transmitter, the Senseonics Eversense, has been approved for 3 or 6 months of use before replacement in the United States and Europe, respectively. Some devices require regular calibration, with FSG input required at least twice daily (Medtronic Guardian and Senseonics Eversense), or are factory calibrated with no additional measurements required (Dexcom G6 and Abbott Freestyle Libre).

Data from CGM and FGM devices can be downloaded by clinicians and provide a standardized ambulatory glucose profile with information regarding percentage of time spent in hypo- and hyperglycemic ranges, time in target range, and glucose variability. Mean glucose as determined by CGM can be used to calculate the glucose management indicator, which provides an estimate of HbA1c⁷ to help determine if patients are achieving target glucose goals.⁸ In fact, because the relationship between HbA1c and average glucose can be modified by the mean red blood cell lifespan, mean CGM glucose may be a better predictor of long-term complications than HbA1c when the measured HbA1c and GMI are not in agreement.⁷ Recently the ADA has published consensus guidelines regarding the recommended percentage of time in target range as well as hyper- and hypoglycemic targets for patients with T1D.⁹ Time in target range of 70 to 180 mg/dL (TIR) has been shown to correlate with mean glucose and HbA1c. TIR of 70% correlates to an HbA1c of approximately 7%. TIR has been suggested as a new treatment standard based on the argument that TIR is easier for people with diabetes to understand and is more actionable on a day-to-day basis.^{2,10} Targets for time below range (TBR) and time above range (TAR) have also been established (Table 1).

CGM accuracy has improved significantly since its inception, and many CGM devices have obtained approval for nonadjunctive use (Dexcom G6, Senseonics Eversense, Freestyle Libre), meaning that CGM data can be used as a replacement for FSG when making insulin-dosing decisions.¹¹ Studies have shown that CGM use is associated with improved HbA1c and a reduction in hypoglycemia.^{12,13} More recently,

	Glycemic Target (mg/dL)	% of CGM Readings
Time below range (TBR)	<54	<1%
	<70	<4%
Time in range (TIR)	70–180	>70%
Time above range (TAR)	>180	<25%
	>250	<5%

^a For a target HbA1c of 7.5% TIR goal is greater than 60%.

Data from Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care*. 2019;42(8):1593-1603.

the FDA has created an interoperable integrated continuous glucose monitoring system standard, which allows an approved CGM device to be used as part of an integrated system with other compatible medical devices and electronic interfaces, including insulin delivery systems. Approved systems (currently, the Dexcom G6 and the Freestyle Libre 2) meet accuracy and reliability standards set forth by the FDA, securely transmit glucose data to other devices, and may be used interchangeably with AID devices for the purpose of managing glycemia.

INSULIN

One of the major challenges to managing glycemia in patients with diabetes is the inability of currently available insulin formulations to mimic the kinetics and action of endogenous insulin secretion.¹⁴ In individuals without diabetes, incretin-stimulated insulin release and a rapid hepatic exposure to insulin in response to a meal occur and lead to decreased hepatic glucose production.¹⁵ This physiology is no longer intact in patients with T1D. Exogenous insulin administered in the subcutaneous tissue takes time to be absorbed in the systemic circulation. This delayed systemic delivery of exogenous insulin is a major physiologic difference with the immediate entry of endogenous insulin into the hepatic circulation for rapid effects.¹⁶

Since the discovery of insulin in 1921, insulin therapy has greatly advanced from porcine and bovine insulin derivatives to the development of rapid-acting, and then ultrarapid-acting, insulin analogues. Older insulins such as Neutral Protamine Hagedorn and regular human insulin have a slow action of onset and long duration, which require patients to have rigid food consumption timing and routines to match the kinetics of insulin action. Rapid-acting insulin analogues (aspart, lispro, and glulisine) have a faster onset of action and quicker time to peak insulin action, which help better match postprandial glucose excursion. These rapid-acting insulins permit greater flexibility for patients: doses can be adjusted based on the timing and quantity of carbohydrates consumed rather. However, rapid-acting insulin analogues still require injection 10 to 15 minutes before meal intake for optimal action.¹⁴

New ultrarapid-acting insulins have even faster on-off kinetics than rapid-acting insulin.^{17–21} Faster aspart (also known as Fiasp) is currently FDA approved for adults and children with diabetes and uses nicotinamide as an excipient and L-arginine to increase stability. Ultrarapid lispro (URLi), which has recently completed a phase 3 trial, uses treprostinil to promote vasodilation and citrate as an excipient.²¹ BioChaperone lispro, which uses BC222, an oligosaccharide modified with natural molecules and

citrate as an excipient, is currently in development. Postprandial glucose were found to be lower with use of faster aspart in both pump and MDI delivery.^{19,22} Overall rates of blood glucose–confirmed hypoglycemia and severe hypoglycemia have been reported to be similar between aspart and faster aspart.¹⁹ Faster aspart is labeled for use to be administered up to 20 minutes after meal, which can provide further flexibility to patients. A trial of URLi in patients with T1D showed decreased postprandial glycaemic excursions at 1 and 2 hours compared with lispro.²¹ A short-term, cross-over trial comparing BioChaperone Lispro with insulin lispro has also shown decreases in early postprandial hyperglycemia.²⁰ In a head-to-head study, BioChaperone Lispro had slightly faster on-off kinetics than insulin lispro and may more closely mimic normal postprandial insulin secretion.¹⁷ Inhaled insulin (Afrezza) is FDA approved and has much more rapid kinetics than injectable insulin delivered subcutaneously. Limitations in clinical use include lack of dose equivalency with injectable insulin and possible respiratory side effects including lung function decreases that are reversible on discontinuation.²³

INSULIN DELIVERY MODALITIES

Multiple Daily Injection

Insulin has been traditionally administered via MDI therapy via insulin syringe or insulin pen. *Smart pen* technology pairs the insulin pen with a smartphone to allow patients to more easily calculate and track insulin administration. The InPen (Companion Medical) is currently the only FDA-approved smart pen device, although others are in development. The InPen connects with a smartphone app via Bluetooth allowing patients to track insulin dosing history, calculate insulin doses, keep track of “insulin on board” (an estimate of rapid-acting insulin still in effect) and adjust calculated dosing accordingly, and set dosing reminders.²⁴ In addition, the phone application can also receive CGM data directly and in real time. Patients can export data collected from the application and share it with their health care team. Smart pen technology may have extra utility in certain patient populations or clinical scenarios, such as those who have difficulty remembering insulin dosing (eg, pediatric patients or those with cognitive or memory impairment) or those with limited health numeracy.²⁵ Accurate tracking of insulin dose administration is also of use to treatment teams to aid in insulin regimen adjustments. Further research is needed to determine clinical benefits of this technology, and other companies (including major insulin manufacturers) have announced plans to release smart pens in the future.

Insulin Pumps

Insulin pumps deliver a continuous infusion of insulin via a cannula placed in the subcutaneous tissue, sometimes referred to as continuous subcutaneous insulin infusion (CSII). Most of the pumps available use an infusion set with tubing to deliver insulin (in the United States, pumps from Tandem and Medtronic), but some systems known as patch pumps attach directly to the skin without the need for tubing (in the United States, the Insulet Omnipod system). Insulin pumps have programmable basal and bolus settings that can vary based on the time of the day. Insulin pumps track insulin usage and contain bolus calculators to assist in the calculation of meal-time insulin coverage and glucose correction. The pump also keeps track of “insulin on board” and adjusts calculated doses accordingly. The abilities to use different basal rates at different times of the day, to make temporary basal rate adjustments in response to glucose trend or activity level, and to deliver meal-time bolus insulin over extended periods of time based on user input are all unique to insulin pumps.

Patients can achieve target HbA1c goals with either MDI or insulin pump therapy, and extensive research has sought to determine if glycemic control with pump therapy is superior to that of MDI management. A systematic review and meta-analysis showed that both MDI and pump therapy resulted in comparable levels of glycemic control and incidence of severe hypoglycemia in children and adolescents with T1D and that pump therapy may have favorable effects on glycemic control in adults with T1D.²⁶ Insulin pump therapy is also associated with improved quality of life in both pediatric and adult populations.^{27,28} By allowing varied basal rates, insulin pumps permit more flexible and physiologic insulin delivery that can be changed based on time of day and other factors such as exercise, as well as varied delivery of meal-time insulin bolus (eg, dual-wave or square-wave delivery set by the user) based on the type of food consumed. In addition, pump therapy eliminates the need for multiple daily injections of insulin, instead requiring only infusion set be changed every 2 to 3 days. Uptake of CSII has increased over the past decade, and currently nearly half of all patients with T1D in the United States manage their diabetes with pump therapy.³

Automated Insulin Delivery

AID systems (also known as closed-loop, artificial pancreas, or bionic pancreas systems) use real-time glucose measurements fed into a control algorithm that automatically adjusts the rate of subcutaneous insulin delivery via an insulin pump (Table 2). The earliest approved AID systems used threshold suspend, in which insulin delivery way automatically suspended when blood glucose level dropped less than a certain threshold.²⁹ Predictive glucose suspend improves on this feature by suspending insulin delivery when a hypoglycemic event is predicted in the future. Predictive low glucose suspend functionality decreases the percentage of time spent in hypoglycemic ranges in both the daytime and overnight.³⁰ By suspending insulin before a hypoglycemic event, this feature also reduces the duration of hypoglycemic events when they do occur.

Later generation AID systems entail more complex algorithms to not only suspend insulin delivery based on hypoglycemia but continuously adjust insulin delivery in response to glycemic trends. The most advanced AID systems that are commercially available today are referred to as hybrid closed-loop systems. Patient input is still required to count carbohydrates and administer correction boluses, but the system will additionally modulate insulin delivery in the background, and in some systems deliver partial correction boluses, based on glycemic trends. Other systems that have been studied but are not yet available use qualitative meal announcements to estimate carbohydrate content, describing meals as “typical,” “more than typical,” “less than typical,” or “a small bite,” rather than requiring quantitative carbohydrate counting.³¹

Table 2

Current Food and Drug Administration–approved automated insulin delivery systems

	MiniMed 530G (Medtronic)	MiniMed 630G Pump (Medtronic)	Basal-IQ System (Tandem)	MiniMed 670G (Medtronic)	Control IQ System (Tandem)
AID system type	Threshold suspend	Predictive low glucose suspend	Predictive low glucose suspend	Hybrid- closed loop	Hybrid- closed loop

Currently available FDA-approved hybrid closed-loop systems include the Medtronic 670G and Tandem t:slim X2 with Control IQ. The first hybrid closed-loop system available in United States, the Medtronic 670G, was approved in 2017 for adult and pediatric patients as young as age 7 years. The approval relied on a nonrandomized study without a control arm.³² The system can be used as a traditional pump or in “auto mode,” in which the pump automatically adjusts basal insulin rates up to every 5 minutes by increasing, decreasing, or suspending delivery of insulin based on CGM trends. Patients are still required to count carbohydrates and enter them into the system, and meal boluses are calculated based on a programmed carbohydrate ratio. As a safety feature, the system may exit auto mode and revert to preprogrammed delivery if insulin delivery approaches maximum or minimum insulin delivery thresholds, if POC and CGM readings are discrepant, or if CGM signal is lost. In a real-world, prospective observational study of 92 youth who started this system, 30% discontinued use of the auto mode within the first 6 months. Another real-world cohort study of 79 pediatric and adult patients reported that 33% discontinued auto mode use within 12 months.^{33,34} Reasons cited included the number of alarms, challenges with requiring calibrations, and dissatisfaction with glycemic control.³⁴

The second hybrid closed-loop device in the United States, the Tandem t:slim X2 with Control-IQ using the Dexcom G6 as the input CGM, was approved in 2019 for adults and pediatric patients older than or equal to 6 years. In the 6-month, randomized, controlled pivotal trial of this device, participants were randomized to closed-loop control or usual diabetes care with sensor-augmented pump therapy.³⁵ Patients randomized to closed-loop control had improvements in target range, mean CGM glucose, and HbA1c, as well as reduced rates of hypoglycemia. Unlike the Medtronic 670G, Control-IQ only reverts to preprogrammed insulin delivery when CGM signal is lost and does not require finger-stick calibration to continue AID. Trials are underway evaluating this device in younger children (NCT03844789).

Experimental Automated Insulin Delivery Systems

Several AID systems that rely on different sets of mathematical algorithms, including proportional integral derivative, fuzzy logic, and model predictive control algorithms, are in development. These AID systems have been associated with increased time in target glucose range (typically 70–180 mg/dL) and in some cases with decreased mean glucose, lower HbA1c, and decreased time in the hypoglycemic range. Pivotal trials for several of these AID systems are currently ongoing, including the Omnipod Horizon hybrid closed-loop system (NCT04196140) and the Beta Bionics iLet Bionic Pancreas (NCT04200313).

One class of AID systems, called bihormonal or dual hormone systems, is capable of delivering a second hormone to further improve glycemic control. Given the kinetics of subcutaneous insulin delivery, the reduction and/or suspension of insulin may be insufficient to prevent hypoglycemia, especially in certain scenarios that may result in changes in insulin sensitivity such as exercise. Several bihormonal systems use microdosing of glucagon to prevent and treat hypoglycemia when suspension of insulin delivery is not sufficient. Glucagon has rapid on and off kinetics, and the addition of glucagon can allow for more aggressive glucose targets compared with insulin-only systems by reducing the potential for hypoglycemia. In short-term studies of bihormonal systems, subjects achieved increased time in target range, lower mean glucose, and decreased rates of hypoglycemia compared with sensor-augmented pump therapy.^{31,36} Additional studies comparing bihormonal with insulin-only closed-loop systems suggest that bihormonal systems may further improve mean glucose, time in range, as well as reduce the time spent in hypoglycemic ranges.³⁷

Other classes of dual hormone systems that have been studied administer pramlintide (an amylin analogue) or glucagon-like peptide-1 (GLP-1) receptor agonist in combination with insulin.^{38,39} Amylin is cosecreted with insulin from pancreatic beta cells and helps moderate postprandial glucose excursions by slowing gastric emptying, inhibiting glucagon secretion, and promoting satiety. A recent study examining an automated system delivering fixed dose ratio of insulin and pramlintide found increase in time in range compared with the insulin-only system.³⁸ Long-term studies of bi-hormonal systems are needed to establish their potential benefits.

A recent meta-analysis³⁷ reviewed published studies of artificial pancreas systems including insulin-only and dual hormone systems delivering glucagon in more than 500 adult and pediatric subjects with T1D. Most of these trials were small and for a short duration, but the analyses showed that AID systems achieved higher TIR compared with conventional pump therapy and that dual hormone systems resulted in greater improvements in TIR than insulin-only systems. Both classes of AID systems deliver improved glycemia overnight, which is a substantial benefit to patients, as fear of nocturnal hypoglycemia is a primary concern for patients and families.^{37,40}

Challenges to Fully Automated Insulin Delivery

One of the main challenges to achieving fully automated closed-loop insulin delivery is overcoming the kinetics of nonphysiologic subcutaneous insulin administration related to postprandial glucose excursions. Given the kinetics of subcutaneous insulin delivery, increased insulin dosing that occurs only after the glucose excursion has begun may lead to prolonged hyperglycemia. Furthermore, because of variations in physiologic insulin needs and the kinetics of current insulin formulations, increased insulin delivery can result in late hypoglycemia. Exercise can compound these challenges by altering insulin sensitivity and increasing insulin-independent glucose uptake into muscles. Several approaches have been studied to ameliorate this issue. Adjunctive therapies including pramlintide (an amylin analogue), GLP-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and sodium-glucose cotransporter 2 inhibitors have all been studied in patients with T1D with the goal of decreasing postprandial glycemic excursions and reducing the need for aggressive insulin dosing.⁴¹ Alternate approaches to insulin delivery, such as delivery of insulin directly to intraperitoneal space, enable faster pharmacokinetics/pharmacodynamics than subcutaneous insulin delivery.⁴² Studies examining the utility of new ultrarapid-acting insulins in AID systems have suggested decreased glycemic variability with these newer insulin analogues.⁴³

DATA MANAGEMENT AND TELEHEALTH

Technology including CGM, smartphones, smartwatches, and activity trackers generate large amounts of high-density data that can be difficult for clinicians to synthesize in the limited time available during visits. At present, SMBG, CGM, and pump data can be downloaded to review for patterns and make adjustments in treatment. Currently available software allows patients to download their pump and CGM at home and then share these data via cloud-based services with the patient's clinical team to review, potentially allowing for more frequent patient contact between in-person visits. With advancement of artificial intelligence and machine learning, these data could be analyzed for automated generation of recommendations for therapy adjustment. Software systems have been developed to automatically generate insulin dose decision support recommendations.⁴⁴

The prevalence of technology at home and in clinics has led to great interest in telehealth—a broad term used to describe health care delivery with the aid of technology, which includes video visits, web-based portals, or text messaging. Telehealth has been applied across multiple specialties and conditions and can be used to conduct remote patient visits and patient education and behavioral management sessions. Telehealth strategies can help increase access to health care and reduce barriers to reaching providers, especially in resource limited settings or for those living far from treatment facilities. A recent meta-analysis found that telehealth intervention in patients with diabetes led to HbA1c improvements.⁴⁵ Concerns about spread of SARS-CoV-2 have dramatically increased use of telehealth visits for diabetic patients over a very short period of time in the first quarter of 2020 and will likely accelerate the movement of diabetes management visits to virtual formats.

Availability of data in the cloud has allowed companies to publish “real world” studies describing glycemic control in patients using their technologies.⁴⁶ The development of virtual diabetes clinics is likely on the horizon, as patient data are obtained from wearable devices including CGM and insulin pumps and then transmitted into the electronic health record for analysis with machine learning and decision support.⁴⁷

SUMMARY

Diabetes technology holds promise for improving glycemic outcomes and decreasing burden of disease for patients and families with T1D. Rapid advancement of diabetes therapeutics and technologies have enhanced diabetes monitoring and insulin delivery capabilities. Devices that partially automate insulin delivery improve glycemic control, and more capable automated closed-loop systems will likely be available in the near future. Further research should determine the long-term benefits of these devices on glycemic control and quality of life in T1D.

DISCLOSURE

J.S. Sherwood has nothing to disclose. S.J. Russell has patents and patents pending on aspects of the bionic pancreas that are assigned to Massachusetts General Hospital and are licensed to Beta Bionics, has received honoraria and/or travel expenses for lectures from Novo Nordisk, Roche, and Ascensia, serves on the scientific advisory boards of Unomedical and Companion Medical, has received consulting fees from Beta Bionics, Novo Nordisk, Senseonics, and Flexion Therapeutics, has received grant support from Zealand Pharma, Novo Nordisk, and Beta Bionics, and has received in-kind support in the form of technical support and/or donation of materials from Zealand Pharma, Ascensia, Senseonics, Adocia, and Tandem Diabetes. M.S. Putman has nothing to disclose.

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