Emerging Technologies and Therapeutics for Type 1 Diabetes

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KEYWORDS

• Type 1 diabetes • Continuous glucose monitoring • Hybrid closed loop
• Smart insulin pens

KEY POINTS

- Diabetes technologies are evolving, and new generation continuous glucose monitors and hybrid-closed loop systems are changing lives of the people with type 1 diabetes.
- The efforts for a cure have been moving forward with stem cell research and gene editing.
- New adjunctive therapies in type 1 diabetes are ready for phase 3 clinical trials.
- Digital technologies and smart pen sleeves and caps are helping day-to-day diabetes management and decreasing the burden of type 1 diabetes.

INTRODUCTION

Advancements in diabetes technologies in recent years changed the landscape of type 1 diabetes (T1D) management.[1] Increasing the use of continuous glucose monitors (CGM) and hybrid closed loop (HCL) insulin pumps decrease A1c and hypoglycemia while improving time in range and quality of life.[1–3] A recent study investigated the changes in diabetes technology use from 2016 to 2020 in 1455 patients with T1D.[4] CGM use increased from 32.9% to 75.3%, and HCL use increased from 0.3% to 27.9%. Overall, A1C decreased from 8.9% to 8.6% ($P < .0001$).[4] Early initiation of the diabetes technologies have better outcomes, such as initiation of CGM in the first year of T1D diagnosis has been shown to be associated with significantly lower A1c in 7 years.[5] However, access to these technologies are still a problem in the United States for some, especially for minorities, due to many reasons including implicit bias, insurance, lack of endocrinologists, and lack of knowledge about these technologies.[6]

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CONTINUOUS GLUCOSE MONITORING SYSTEMS

CGM use has been increasing in the United States in the last decade with the improvements in the systems. New generation CGMs are smaller, have better accuracy as measured with a mean absolute relative difference (MARD), and integrate with HCL systems.[7] New generation FDA-approved CGMs include Dexcom G7, Libre 3, and Eversense E3.

The FreeStyle Libre 3 is a single-use, disposable sensor that is applied to the back of the upper arm and can be worn for 14 days.[8] It is the smallest CGM to date and is a real-time CGM with 1 piece applicator unlike the 1st and 2nd generation Libre series. It has vitamin C interference over 500 mg, similar to Libre 2. Recently, the FDA approved a reader device that displays real-time glucose readings. The US FDA cleared FreeStyle Libre 2 and FreeStyle Libre 3 sensors for integration with automated insulin delivery systems. The modified sensors were also cleared for use by children as young as 2 years old and for wear time up to 15 days. Current FreeStyle Libre 2 and FreeStyle Libre 3 sensors available today in the United States are approved for people of 4 years and older and have a wear time of up to 14 days. Additionally, the clearance allows for FreeStyle Libre 2 and FreeStyle Libre 3 sensors—both those available today and the modified sensors available in the future—to be used by women with all types of diabetes (type 1, type 2, and gestational) who are pregnant.

Dexcom G7 is 60% smaller than the 6th generation and it has a simplified applicator. Unlike Dexcom G6's 2 hour warm up, the G7 is functional after 30 minutes.[9] Additionally, the sensor and transmitter are combined into one piece with an additional 12 hours of CGM use in between sensor changes.[9] Dexcom G7 users can delay the first alert for high sensor glucose until the sensor reading is at or past the alert setting. It is also FDA-approved to be used in pregnancy. In 316 adults, for arm- and abdomen-placed sensors, overall MARDs were 8.2% and 9.1%, respectively.[10] Overall %15/15, %20/20, and %30/30 agreement rates were 89.6%, 95.3%, and 98.8% for arm-placed sensors and 85.5%, 93.2%, and 98.1% for abdomen-placed sensors.[10] In 127 children, for arm-placed sensors, the overall MARD was 8.1% and overall %15/15, %20/20, and %30/30 agreement rates were 88.8%, 95.3%, and 98.7%, respectively.[11] For abdomen-placed sensors, the overall MARD was 9.0% and overall %15/15, %20/20, and %30/30 agreement rates were 86.0%, 92.9%, and 97.7%, respectively.[11] Not surprisingly based on the studies, the FDA-approved Dexcom G7 for only used in the arm.

The Eversense E3 by Senseonics is a 6 month implantable CGM. To date, it is the only FDA-approved implantable CGM in the United States. It is approved to be used in adults with diabetes and should be calibrated 2 times a day in the first 21 days and then once a day rest of 6 month use. It has a 24 hours warm-up time and it is the only CGM with vibration alerts with a wearable transmitter.[12] In a study with 90 adults with diabetes, using the current version of the sensor, modified (sacrificial boronic acid) sensor, the percent CGM readings within 20%/20% of yellow springs instruments (YSI) values was 93.9%; overall MARD was 8.5%.[12] The confirmed alert detection rate at 70 mg/dL was 94% and 180 mg/dL was 99%. The median percentage of time for one calibration per day was 63%.[12] About 90% of the sacrificial boronic acid (SBA) sensors survived 180 days.[12]

The use of digital apps may improve diabetes care and quality of life in T1D. One study showed that increased engagement with a CGM app can increase time in range, decrease hypoglycemia rate, and help remote monitoring of loved ones with T1D.[13] More research is necessary to determine their benefits in long term in T1D care.

HYBRID CLOSED LOOPS

Currently, the FDA-approved HCL systems in the United States are Medtronic 670/770/780G series, Tandem Control IQ, Omnipod 5, and iLet Bionic Pancreas.

Medtronic 780G is the latest HCL from Medtronic that has been in use in Europe since 2020 and was recently FDA approved in April 2023 for T1D patients aged 7 years or older. Compared with 770G, the main differences include an adjustable glucose target for "SmartGuard," that is called auto mode in this system. Glucose targets can be 100, 110, and 120 mg/dL.[14] Of note, 100 mg/dL is the lowest target in any FDA-approved HCL system to date. The new autocorrect feature delivers small auto boluses for high glucose that can be turned on and off independently. The 780G can be used in patients requiring between 8 and 250 units of insulin per day and can be used with Medtronic Guardian 3 or 4 CGM.[14] The Guardian 4 sensor does not require any fingerstick calibrations, and users reported fewer requirements for fingerstick confirmation when going to automation mode with the new system.[15] There is smartwatch access with a mobile app. Users can also use FDA-approved extended infusion set up to 7 days with this system.

As the 780G was recently approved by the FDA in the United States, most of the literature is from Europe and other parts of the world. A recent study with 109 children aged 7 to 17 years and 67 adults with T1D showed that 3 month use of 780G with Guardian 4 CGM was safe and effective.[15] Pediatric and adult A1C were 7.2% ± 0.7% and 6.8% ± 0.7%, respectively, and there were no serious adverse events.[15] Smartguard exits averaged 0.1/d, and there were few blood glucose measurements (0.8/day–1.0/d).[15] Another multicenter observational real-world study investigated the first 6 month of 780G use in 111 children and adolescents aged 7 to 18 years.[16] International Consensus targets for a time in the range were met by 72.1% of the participants.[16] A shorter duration of active insulin time and a lower target of sensor glucose were significant predictors for optimal glycemic control.[16]

A randomized parallel group study evaluated the 780G in insulin pump and CGM naïve adults with T1D transitioning from multiple daily injection (MDI) and self-monitoring blood glucose (SMBG) to 780G.[17] Participants from the 780G group had significant improvements in A1c levels (treatment effect, −0.6% [95% CI −0.9, −0.2]; $P = .005$) and in quality of life compared with MDI + SMBG group.[17] Time spent in the target range (70–180 mg/dL) increased from 69.3% ± 12.3% at baseline to 85.0% ± 6.3% at 3 months in the 780G group, while remaining unchanged in the control group (treatment effect, 21.5% [95% CI 15.7, 27.3]; $P < .001$).[17] The time below range (<70 mg/dL) decreased from 8.7% ± 7.3% to 2.1% ± 1.7% in the HCL group and remained unchanged in the MDI + SMBG group (treatment effect, −4.4% [95% CI −7.4, −2.1]; $P < .001$).[17] On the basis of the data and clinical experience, it seems most useful to use a glucose target of 100 mg/dL and a 2 hour active insulin time with the 780G system.

The Omnipod 5 is an HCL system that uses a patch insulin pump which is controlled with a smartphone app or a controller device.[18,19] It is the only system that considers CGM trends in decision making in the algorithm. The target can be customized from 110 to 150 mg/dL in 10 mg/dL increments.[18] In a study including 111 children and 124 adults with T1D in 3 months, A_{1c} was significantly reduced in children by 0.71% (mean ± SD: 7.67% ± 0.95% to 6.99% ± 0.63%, $P < .0001$) and in adults by 0.38% (7.16% ± 0.86% to 6.78% ± 0.68%, $P < .0001$).[18] Time in range was improved from standard therapy by 15.6% ± 11.5% or 3.7 hour/day in children and 9.3% ± 11.8% or 2.2 hour/day in adults (both $P < .0001$).[18]

iLet Bionic Pancreas is the newest FDA-approved HCL system. The system is programed using the user's weight and can be alerted to meal announcements by the individual, but it does not require carb counting. In a 13 week clinical trial of 219 participants of 6 to 79 years of age with T1D assigned to the bionic pancreas or standard of care,[20] the A1c decreased from 7.9% to 7.3% in the bionic-pancreas group

and remained unchanged in the standard-care group (mean adjusted difference at 13 weeks, −0.5% points; 95% confidence interval [CI], −0.6 to −0.3; $P < .001$).[20] Of note, the minorities (all non-White participants) decreased A1c more than Whites. In Whites ($n = 240$), the mean baseline-adjusted difference in 13 week A1c between the bionic pancreas group and standard of care group was −0.45% (95% CI −0.61 to −0.29; $P < .001$), while this difference among Minorities ($n = 84$) was −0.53% (−0.83 to −0.24; $P < .001$).[21]

The Tandem Control IQ system works by automatically increasing the programed basal insulin delivery rate when glucose levels are predicted to exceed 160 mg/dL.[22] In addition to modulating the basal rates, the system can also deliver an automatic correction bolus dose of insulin if glucose levels are predicted to increase above 180 mg/dL. This occurs up to once per hour during normal operation and delivers 60% of the dose calculated based on the user's insulin sensitivity (ISF) factor.[12] In a real-world use study with 9451 users, at baseline, the median percent time in range was 63.6 (interquartile range [IQR]: 49.9%–75.6%) and increased to 73.6% (IQR: 64.4%–81.8%) for the 12 months of Control IQ technology use with no significant changes over time.[23] A study with 4243 Medicare and 1332 Medicaid users of Control IQ showed that after starting Control IQ, the Medicare group had significant improvement in TIR (64% vs 74%; $P < .0001$), and the Medicaid group also had significant improvement in TIR (46% vs 60%; $P < .0001$).[24]

The auto bolus feature in the newer HCL systems has the ability to compensate for missed boluses, which is advantageous for busy professionals, adolescents, those facing challenges with carbohydrate counting, adolescents, and older adults with T1D. A recent study with 780G with 34 adolescents with T1D compared the fix group (simplified meal announcement by preset of 3 personalized fixed carbohydrate amounts) or the flex group (precise carbohydrate counting) and followed for 12 weeks.[25] The TIR was 73.5% ± 6.7% in the fix and 80.3% ± 7.4% in the flex group, with a between-group difference of 6.8% in favor of flex ($P = .043$).[25] Time greater than 250 mg/dL was better in the flex group ($P = .012$), whereas A1c ($P = .168$), time below range ($P = .283$), and time between 180 and 250 mg/dL ($P = .114$) did not differ.[25] Another study evaluated Tandem Control IQ in 30 adults with groups ($n = 10$) with minimal or no user-initiated boluses (auto >90%) compared with age, gender, and diabetes duration-matched adults with T1D with intermediate (auto 50%–90%) and high bolusing behavior (auto 10%–49%).[22] Compared with baseline, there was a significant decrease in A1c by 1.6%% ± 0.8% and an increase in time in range by 19.3% ± 6.4% ($P < .001$ for both) over 12 months of Tandem Control IQ use in auto greater than 90% use group without increasing time below range.[22] While it is not advised to miss boluses or bolus late with these HCL systems, newer generation HCL systems can compensate which opens the door for individuals who are not strict carbohydrate counters to still be candidates for HCL systems.

HCL systems have been reported to be used successfully in special situations such as pregnancy, diabetic gastroparesis, and cystic fibrosis-related diabetes; however, their safety and efficacy should be investigated in larger clinical trials.[26–29]

SMART INSULIN PENS, PEN CAPS

The development of new smart insulin pens with connectivity is a promising approach for improving and simplifying the management of T1D. The published literature on smart insulin pens with connectivity is limited.[30] However, they may offer the potential for increased adherence to quality of life and monitoring with the documentation of insulin administrations and mimicking an insulin pump use with some features for bolusing.[30]

Smart Insulin Pens

Smart insulin pens are devices that assist individuals with T1D in insulin dosing calculations. Currently, there are 2 smart insulin pens available in the United States: InPen and NovoPen Echo. The InPen device connects with the users with compatible Android or iOS smartphones to an app that can be programed by their diabetes provider. The InPen app can store fixed doses of mealtime insulin, provide meal-estimated insulin doses or operate on insulin-to-carbohydrate and ISF inputs. The InPen allows for connectivity to the Medtronic Guardian 3 sensor and to Dexcom G6 CGM. It has other features that allow for reminders to be set for insulin administration and tracking of the expiration of insulin in the cartridge and insulin on board.[31] Reports can be generated for providers to review and discuss with the patient. The InPen is compatible with Lispro, Aspart, and faster Aspart cartridges. The pen injector allows the user to dial the desired dose from 0.5 to 30 units in one-half unit increments.[31]

The NovoPen Echo stores both the timing and the amount of insulin delivered which can later be downloaded for review.[32] This pen works with Aspart 100 unit/mL cartridges containing a total of 300 units and can deliver in 0.5 unit increments up to 30 units. The digital display shows how many units of insulin are injected in hourly segments and tracks battery life.[32]

Pen Caps

The Bigfoot Unity Diabetes Management System, approved in August 2021, uses a smart insulin pen cap that is compatible with the typical disposable insulin pens. It works by scanning the FreeStyle Libre 2 sensor with the pen cap.[33] On basis of settings, the recommended insulin dose is displayed along with the CGM glucose and glucose trend arrow. The BigFoot Unity system includes 2 types of pen caps: one for rapid-acting bolus insulin and one for long-acting basal insulin.[33] The timing of the insulin is recorded. Two real-time glucose alarms are available, including a mandatory alarm for glucose at 55 mg/dL or lower and an optional glucose alarm at 70 mg/dL. If the basal insulin dose is missed over a 24 hour period, the patient is also alerted. The pen cap itself lasts 2 years and is rechargeable.

Tempo pen cap with its app from Eli Lilly, works with all Eli Lilly insulins, bolus, and basal. The app can combine the data with readings from Tempo Blood Glucose Meter and/or Dexcom G6 CGM and provides personalized progress reports to assist with the self-management of diabetes.[34]

DISPARITIES IN THE USE OF DIABETES TECHNOLOGY IN TYPE 1 DIABETES

Despite major advances in diabetes technology over the last 2 decades, it is clear that there are substantial disparities in their utilization.[35] Much of the data to date on disparities in technology utilization are generated by the T1D Exchange QI Collaborative, a network of adult and pediatric diabetes centers in the United States. Overall, the T1D data show that technology utilization is low in individuals from minority and lower socioeconomic backgrounds in both pediatric and adult populations.[36–39]

Outside of the T1D registry, disparities in insulin pump utilization have been demonstrated by studies examining large electronic health databases in the United States. In a retrospective cohort analysis of young adult patients with T1D, low insulin pump utilization was shown, particularly in Black and Hispanic minorities, males and individuals with governmental insurance despite insulin pump showing superior HbA1c control without an increase in DKA events.[40] This study also noted that it was unclear why Black and Hispanic subjects had lower odds of receiving insulin pump therapy but wrote that it may, in part, be due to the provider's unconscious or conscious bias.[40]

Overall, there is a movement to have greater racial/ethnic diversity in diabetes technology trials to overcome these barriers and move toward more equitable prescribing of these life-changing technologies.

INPATIENT USE OF CONTINUE GLUCOSE MONITORING

Few areas of medicine have advanced as quickly as the landscape of diabetes technology including major leaps forward in insulin pumps, CGM, and automated insulin delivery systems. As the utilization of these devices expands in the outpatient setting, invariably, they have made their way into the hospital. Before coronavirus-19 (COVID-19), CGM was studied with a vision for glucose telemetry by Spanakis.[41] In March 2020, the World Health Organization declared COVID-19 a pandemic and subsequently the FDA issued emergency authorization of inpatient use of CGM to preserve personal protective equipment (PPE) which was in short supply.[42] After these measures, several observational studies aimed to establish the feasibility and accuracy of inpatient CGM were published demonstrating the utility of inpatient CGM to reduce both hypo and hyper glycemia. Additional benefits included decreased frequency of point-of-care (POC) glucose checks and decreased utilization of PPE.

In a retrospective study analyzing 218 patients with matched-pair CGM (Dexcom G6) and capillary POC glucose data from 3 inpatient CGM studies of noncritically ill hospitalized patients, the overall MARD was 12.8%.[43] The results of the Clarke error grid analyses showed 98.7% of values where in zones A and B indicating that discrepancies between CGM and POC glucose data would have little-to-no effect on the clinical outcome. Overall, these findings are reassuring that in noncritically ill hospitalized patients, CGM is a reliable tool for monitoring glucose values.

In terms of clinical outcomes, inpatient CGM-guided (Dexcom G6) insulin administration in hospitalized patients with diabetes has been shown in a randomized clinical trial to produce similar glycemic control but a significant reduction in hypoglycemic events when compared with usual care POC-guided insulin adjustment.[44]

According to an Endocrine Society Clinical Practice Guideline, adults with insulin-treated diabetes hospitalized for noncritical illness who are at high risk of hypoglycemia, CGM with adjunctive POC glucose monitoring is recommended.[45]

STEM CELL THERAPIES

The history of islet cell transplantation brought to light the ability of β cells to engraft and function after transplantation, giving rise to an arm of regenerative therapies for T1D.[46] A promising technique currently under study is the ability to transplant human stem cell (SC)-derived β cells, which has advantages over traditional islet transplantation which is limited by pancreatic tissue availability and the need for immunosuppression.[47] Human pluripotent SCs, both embryonic and induced pluripotent, garner the most enthusiasm for creating functional β cells that will be able to divide and differentiate.[48,49]

Recently, ViaCyte created a SC-derived pancreatic endoderm cell population, referred to as PEC-01, which matured into insulin-producing endocrine cells in rodent models.[50] The first iteration of this technology in 2014 was flawed by a foreign body response to the device encapsulation component, which led to fibrosis and loss of insulin secretion.[50] In the second iteration in 2017, the PEC-direct device was engineered to allow for an opening where vasculature could penetrate allowing for nutrient exchange.[50] This technique was overall successful, and the grafts showed measurable c-peptide. However, the vasculature allowed for interaction between the host cells and the device, which led to the need for immunosuppression.

Interestingly, in addition to demonstrating β cell function, many of the cells stained positive for α cells secreting glucagon.[50]

To overcome the issues of graft fibrosis and the need for immunosuppression, the Vertex Pharmaceuticals began a human clinical trial with T1D patients in 2021 where a SC-derived product, VX-880, was transplanted without an immune-protective device. Initial findings seem promising and await peer review.[50]

In March 2023, Vertex announced FDA Clearance of Investigational New Drug Application for VX-264, a novel encapsulated cell therapy for the treatment of T1D.[51] VX-264, an allogeneic human SC-derived islets are encapsulated in a channel array device designed to shield the cells from the body's immune system and to be surgically implanted. Vertex initiates a Phase 1/2 clinical trial to study the safety, tolerability, and efficacy of VX-264 in patients with T1D. The company previously received approval from Health Canada on the Clinical Trial Application for VX-264, and the Phase 1/2 trial is ongoing in Canada. The clinical trial is a Phase 1/2, single-arm, open-label study in patients who have T1D. Approximately 17 patients will be enrolled in the global clinical trial.

Challenges in the regenerative SC therapies for T1D remain, particularly in terms of the ability to generate a highly functional, uniform cell-based product for transplantation that does not require immunosuppression.[50]

ADJUNCTIVE THERAPIES IN TYPE 1 DIABETES

Despite advanced diabetes technologies and therapeutics, many people with T1D do not achieve target A1c levels and have problems with high postprandial blood glucose, weight gain, and increased insulin resistance.[52] A need exists for adjunctive therapies to insulin in the management of T1D to prevent long-term complications and achieve better glycemic profiles. In the last decade, many medications used in the treatment of type 2 diabetes have been tried in T1D such as metformin, glucagon-like peptide-1 receptor agonists, and sodium-glucose cotransporter 2 inhibitors (SGLT2i).[53] The use of SGLT2i in T1D as an adjunctive therapy has been approved in Europe and Japan with some limitations; however, the US FDA denied its use in T1D due to an increased risk of diabetic ketoacidosis.[54] Since then, new molecules have been developed as an adjunct therapy in T1D.

Volagidemab, an antagonistic monoclonal glucagon receptor antibody, was evaluated in a phase 2 placebo-controlled randomized trial in 13 weeks as an adjunctive therapy to T1D.[55] Eligible participants ($n = 79$) were randomized to receive weekly subcutaneous injections of placebo, 35 mg volagidemab, or 70 mg volagidemab.[55] At week 13, the placebo-corrected reduction in A1c percentage was −0.53 (95% CI = −0.89 to −0.17, nominal $P = .004$) in the 35 mg volagidemab group and −0.49 (95% CI = −0.85 to −0.12, nominal $P = .010$) in the 70 mg volagidemab group.[55] There was no change in weight or increase in hypoglycemia. However, there was an increase in liver transaminase levels, blood pressure, and LDL cholesterol.

TTP399, a novel hepatoselective glucokinase activator, was investigated in a phase 1b/2 study in people with T1D.[56] The SimpliciT1 was a placebo-controlled randomized study that used 800 mg TTP399 or matched placebo for 12 weeks.[56] The difference in change in A_{1c} from baseline to week 12 between TTP399 and placebo was −0.7% in CGM and insulin pump users.[56] There was no increase in hypoglycemia frequency.

SUMMARY

Diabetes technologies and therapeutics for the management of T1D rapidly evolved in the last decade. CGM, HCL, smart insulin pens, digital apps, and newer rapid and

long-acting insulins are the mainstay of current T1D management. Emerging therapies for a cure in T1D are ongoing, and they are more promising than ever, while newer adjunctive therapies are likely to be approved to decrease insulin requirements, weight, and A1c. Future focus areas for diabetes technology include decreasing disparities in T1D care and increasing utilization of these devices in inpatient settings and pregnancy. As new developments materialize, the hope is to reach the lowest rates of complications in diabetes in history and decrease the burden of diabetes for those living with this disease.

CLINICS CARE POINTS

- Diabetes technologies should be used in all people with T1D with a motivation, a follow plan, and a good comprehension.
- Providers should discuss diabetes technologies with all people with T1D to find a good fit for their lives.
- Providers should focus on decreasing disparities in diabetes technology use and encourage minorities to be involved in clinical trials.

DISCLOSURES

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REFERENCES

1. Akturk HK, Garg S. Technological advances shaping diabetes care. Curr Opin Endocrinol Diabetes Obes 2019;26:84–9.
2. Berget C, Akturk HK, Messer LH, et al. Real-world performance of hybrid closed loop in youth, young adults, adults and older adults with type 1 diabetes: Identifying a clinical target for hybrid closed-loop use. Diabetes Obes Metabol 2021; 23:2048–57.
3. Akturk HK, Giordano D, Champakanath A, et al. Long-term real-life glycaemic outcomes with a hybrid closed-loop system compared with sensor-augmented pump therapy in patients with type 1 diabetes. Diabetes Obes Metabol 2020; 22:583–9.
4. Alonso GT, Triolo TM, Akturk HK, et al. Increased Technology Use Associated With Lower A1C in a Large Pediatric Clinical Population. Diabetes Care 2023; 46:1218–22.
5. Champakanath A, Akturk HK, Alonso GT, et al. Continuous Glucose Monitoring Initiation Within First Year of Type 1 Diabetes Diagnosis Is Associated With Improved Glycemic Outcomes: 7-Year Follow-Up Study. Diabetes Care 2022;45:750–3.
6. Akturk HK, Rompicherla S, Rioles N, et al. Factors Associated With Improved A1C Among Adults With Type 1 Diabetes in the United States. Clin Diabetes 2022;41: 76–80.
7. Garg SK, Akturk HK. A New Era in Continuous Glucose Monitoring: Food and Drug Administration Creates a New Category of Factory-Calibrated Nonadjunctive, Interoperable Class II Medical Devices. Diabetes Technol Therapeut 2018;20:391–4.

8. Nguyen A, White JR. FreeStyle Libre 3. Clin Diabetes 2022;41:127–8.
9. Welsh JB, Psavko S, Zhang X, et al. Comparisons of Fifth-, Sixth-, and Seventh-Generation Continuous Glucose Monitoring Systems. J diabetes science and technology 2022. 19322968221099879.
10. Garg SK, Kipnes M, Castorino K, et al. Accuracy and Safety of Dexcom G7 Continuous Glucose Monitoring in Adults with Diabetes. Diabetes Technol Therapeut 2022;24:373–80.
11. Laffel LM, Bailey TS, Christiansen MP, et al. Accuracy of a Seventh-Generation Continuous Glucose Monitoring System in Children and Adolescents With Type 1 Diabetes. J Diabetes Sci Technol 2022. 19322968221091816.
12. Garg SK, Liljenquist D, Bode B, et al. Evaluation of Accuracy and Safety of the Next-Generation Up to 180-Day Long-Term Implantable Eversense Continuous Glucose Monitoring System: The PROMISE Study. Diabetes Technol Therapeut 2022;24:84–92.
13. Akturk HK, Dowd R, Shankar K, et al. Real-World Evidence and Glycemic Improvement Using Dexcom G6 Features. Diabetes Technol Therapeut 2021; 23. S21-s6.
14. Silva JD, Lepore G, Battelino T, et al. Real-World Performance of the MiniMed™ 780G System: First Report of Outcomes from 4120 Users. Diabetes Technol Therapeut 2022;24:113–9.
15. Cordero TL, Dai Z, Arrieta A, et al. Glycemic Outcomes During Early Use of the MiniMed™ 780G Advanced Hybrid Closed-Loop System with Guardian™ 4 Sensor. Diabetes technol ther 2023. https://doi.org/10.1089/dia.2023.0123.
16. Lombardo F, Passanisi S, Alibrandi A, et al. MiniMed 780G Six-Month Use in Children and Adolescents with Type 1 Diabetes: Clinical Targets and Predictors of Optimal Glucose Control. Diabetes Technol Therapeut 2023;25:404–13.
17. Matejko B, Juza A, Kieć-Wilk B, et al. Transitioning of People With Type 1 Diabetes From Multiple Daily Injections and Self-Monitoring of Blood Glucose Directly to MiniMed 780G Advanced Hybrid Closed-Loop System: A Two-Center, Randomized, Controlled Study. Diabetes Care 2022;45:2628–35.
18. Brown SA, Forlenza GP, Bode BW, et al. Multicenter Trial of a Tubeless, On-Body Automated Insulin Delivery System With Customizable Glycemic Targets in Pediatric and Adult Participants With Type 1 Diabetes. Diabetes Care 2021;44: 1630–40.
19. Cobry EC, Berget C, Messer LH, et al. Review of the Omnipod(®) 5 Automated Glucose Control System Powered by Horizon™ for the treatment of Type 1 diabetes. Ther Deliv 2020;11:507–19.
20. Russell SJ, Beck RW, Damiano ER, et al. Multicenter, Randomized Trial of a Bionic Pancreas in Type 1 Diabetes. N Engl J Med 2022;387:1161–72.
21. Castellanos LE, Russell SJ, Damiano ER, et al. The Insulin-Only Bionic Pancreas Improves Glycemic Control in Non-Hispanic White and Minority Adults and Children With Type 1 Diabetes. Diabetes Care 2023;46:1185–90.
22. Akturk HK, Snell-Bergeon J, Shah VN. Efficacy and Safety of Tandem Control IQ Without User-Initiated Boluses in Adults with Uncontrolled Type 1 Diabetes. Diabetes Technol Therapeut 2022;24:779–83.
23. Breton MD, Kovatchev BP. One Year Real-World Use of the Control-IQ Advanced Hybrid Closed-Loop Technology. Diabetes Technol Therapeut 2021;23:601–8.
24. Forlenza GP, Carlson AL, Galindo RJ, et al. Real-World Evidence Supporting Tandem Control-IQ Hybrid Closed-Loop Success in the Medicare and Medicaid Type 1 and Type 2 Diabetes Populations. Diabetes Technol Therapeut 2022;24:814–23.

25. Petrovski G, Campbell J, Pasha M, et al. Simplified Meal Announcement Versus Precise Carbohydrate Counting in Adolescents With Type 1 Diabetes Using the MiniMed 780G Advanced Hybrid Closed Loop System: A Randomized Controlled Trial Comparing Glucose Control. Diabetes Care 2023;46:544–50.
26. Kaur H, Schneider N, Pyle L, et al. Efficacy of Hybrid Closed-Loop System in Adults with Type 1 Diabetes and Gastroparesis. Diabetes Technol Therapeut 2019;21:736–9.
27. Daly A, Hartnell S, Boughton CK, et al. Hybrid Closed-loop to Manage Gastroparesis in People With Type 1 Diabetes: a Case Series. J Diabetes Sci Technol 2021; 15:1216–23.
28. Polsky S, Akturk HK. Case series of a hybrid closed-loop system used in pregnancies in clinical practice. Diabetes/metabolism research and reviews 2020; 36:e3248.
29. Scully KJ, Palani G, Zheng H, et al. The Effect of Control IQ Hybrid Closed Loop Technology on Glycemic Control in Adolescents and Adults with Cystic Fibrosis-Related Diabetes. Diabetes Technol Therapeut 2022;24:446–52.
30. Heinemann L, Schnell O, Gehr B, et al. Digital Diabetes Management: A Literature Review of Smart Insulin Pens. J Diabetes Sci Technol 2022;16:587–95.
31. Gildon BW. InPen Smart Insulin Pen System: Product Review and User Experience. Diabetes Spectr 2018;31:354–8.
32. Klonoff DC, Nayberg I, Stauder U, et al. Half-Unit Insulin Pens: Disease Management in Patients With Diabetes Who Are Sensitive to Insulin. J Diabetes Sci Technol 2017;11:623–30.
33. Bigfoot Unity System Features. 2023. at https://www.diabeteseducator.org/danatech/insulin-medicine-delivery/find-compare-delivery-devices/product-detail/bigfoot-unity#:~:text=Bigfoot%20Unity%20System%20includes%3A%20long,readings%20on%20demand%20without%20fingersticks.
34. Lilly Tempo pen features. 2023. Available at https://www.lillytempo.com/how-tempo-works/temposmart-app.
35. Akturk HK, Agarwal S, Hoffecker L, et al. Inequity in Racial-Ethnic Representation in Randomized Controlled Trials of Diabetes Technologies in Type 1 Diabetes: Critical Need for New Standards. Diabetes Care 2021;44:e121–3.
36. Agarwal S, Hilliard M, Butler A. Disparities in Care Delivery and Outcomes in Young Adults With Diabetes. Curr Diabetes Rep 2018;18:65.
37. Agarwal S, Kanapka LG, Raymond JK, et al. Racial-Ethnic Inequity in Young Adults With Type 1 Diabetes. J Clin Endocrinol Metabol 2020;105:e2960–9.
38. Lai CW, Lipman TH, Willi SM, et al. Racial and Ethnic Disparities in Rates of Continuous Glucose Monitor Initiation and Continued Use in Children With Type 1 Diabetes. Diabetes Care 2021;44:255–7.
39. Addala A, Auzanneau M, Miller K, et al. A Decade of Disparities in Diabetes Technology Use and HbA(1c) in Pediatric Type 1 Diabetes: A Transatlantic Comparison. Diabetes Care 2021;44:133–40.
40. McKee AM, Al-Hammadi N, Hinyard LJ. Disparities in Utilization and Outcomes With Continuous Subcutaneous Insulin Infusion in Young Adults With Type 1 Diabetes. Endocr Pract 2021;27:769–75.
41. Levitt DL, Silver KD, Spanakis EK. Inpatient Continuous Glucose Monitoring and Glycemic Outcomes. J Diabetes Sci Technol 2017;11:1028–35.
42. Gothong C, Singh LG, Satyarengga M, et al. Continuous glucose monitoring in the hospital: an update in the era of COVID-19. Curr Opin Endocrinol Diabetes Obes 2022;29:1–9.

43. Davis GM, Spanakis EK, Migdal AL, et al. Accuracy of Dexcom G6 Continuous Glucose Monitoring in Non-Critically Ill Hospitalized Patients With Diabetes. Diabetes Care 2021;44:1641–6.
44. Spanakis EK, Urrutia A, Galindo RJ, et al. Continuous Glucose Monitoring-Guided Insulin Administration in Hospitalized Patients With Diabetes: A Randomized Clinical Trial. Diabetes Care 2022;45:2369–75.
45. Korytkowski MT, Muniyappa R, Antinori-Lent K, et al. Management of Hyperglycemia in Hospitalized Adult Patients in Non-Critical Care Settings: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2022;107:2101–28.
46. Sordi V, Monaco L, Piemonti L. Cell Therapy for Type 1 Diabetes: From Islet Transplantation to Stem Cells. Horm Res Paediatr 2022;1–12.
47. Velazco-Cruz L, Goedegebuure MM, Millman JR. Advances Toward Engineering Functionally Mature Human Pluripotent Stem Cell-Derived β Cells. Front Bioeng Biotechnol 2020;8:786.
48. Pellegrini S, Piemonti L, Sordi V. Pluripotent stem cell replacement approaches to treat type 1 diabetes. Curr Opin Pharmacol 2018;43:20–6.
49. Migliorini A, Nostro MC, Sneddon JB. Human pluripotent stem cell-derived insulin-producing cells: A regenerative medicine perspective. Cell Metabol 2021;33:721–31.
50. Hogrebe NJ, Ishahak M, Millman JR. Developments in stem cell-derived islet replacement therapy for treating type 1 diabetes. Cell Stem Cell 2023;30:530–48.
51. Vertex FDA clearance for VX-264 new drug application. 2023. Available at: https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-fda-clearance-investigational-new-drug.
52. Akturk HK, Rewers A, Joseph H, et al. Possible Ways to Improve Postprandial Glucose Control in Type 1 Diabetes. Diabetes Technol Therapeut 2018;20. S224-s32.
53. Garg SK, Rewers AH, Akturk HK. Ever-Increasing Insulin-Requiring Patients Globally. Diabetes Technol Therapeut 2018;20. S21-s4.
54. Akturk HK, Rewers A, Garg SK. SGLT inhibition: a possible adjunctive treatment for type 1 diabetes. Curr Opin Endocrinol Diabetes Obes 2018;25:246–50.
55. Pettus J, Boeder SC, Christiansen MP, et al. Glucagon receptor antagonist volagidemab in type 1 diabetes: a 12-week, randomized, double-blind, phase 2 trial. Nat Med 2022;28:2092–9.
56. Klein KR, Freeman JLR, Dunn I, et al. The SimpliciT1 Study: A Randomized, Double-Blind, Placebo-Controlled Phase 1b/2 Adaptive Study of TTP399, a Hepatoselective Glucokinase Activator, for Adjunctive Treatment of Type 1 Diabetes. Diabetes Care 2021;44:960–8.