Automated Insulin Delivery: Benefits, Challenges, and Recommendations. A Consensus Report of the Joint Diabetes Technology Working Group of the European Association for the Study of Diabetes and the American Diabetes Association

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A technological solution for the management of diabetes in people who require intensive insulin therapy has been sought for decades. The last 10 years have seen substantial growth in devices that can be integrated into clinical care. Driven by the availability of reliable systems for continuous glucose monitoring, we have entered an era in which insulin delivery through insulin pumps can be modulated based on sensor glucose data. Over the past few years, regulatory approval of the first automated insulin delivery (AID) systems has been granted, and these systems have been adopted into clinical care. Additionally, a community of people living with type 1 diabetes has created its own systems using a do-it-yourself approach by using products commercialized for independent use. With several AID systems in development, some of which are anticipated to be granted regulatory approval in the near future, the joint Diabetes Technology Working Group of the European Association for the Study of Diabetes and the American Diabetes Association has created this consensus report. We provide a review of the current landscape of AID systems, with a particular focus on their safety. We conclude with a series of recommended targeted actions. This is the fourth in a series of reports issued by this working group. The working group was jointly commissioned by the executives of both organizations to write the first statement on insulin pumps, which was published in 2015. The original authoring group was comprised by three nominated members of the American Diabetes Association and three nominated members of the European Association for the Study of Diabetes. Additional authors have been added to the group to increase diversity and range of expertise. Each organization has provided a similar internal review process for each manuscript prior to submission for editorial review by the two journals. Harmonization of editorial and substantial modifications has occurred at both levels. The members of the group have selected the subject of each statement and submitted the selection to both organizations for confirmation.

A biological cure for type 1 diabetes (T1D) is not realistic in the near future (1–4). However, a "technical" solution for diabetes management has developed under

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A consensus report of a particular topic contains a comprehensive examination and is authored by an expert panel (i.e., consensus panel) and represents the panel's collective analysis, evaluation, and opinion. The need for a consensus report arises when clinicians, scientists, regulators, and/or policy

Table 1—AID systems terminology

Sensor-augmented pump (SAP)	Insulin pump with use of a CGM either on a separate device or displayed directly on the pump. These systems allow for viewing of the sensor data, but insulin delivery is not altered on the basis of sensor glucose values.
Low glucose suspend (LGS) or predictive low glucose suspend (PLGS)	Insulin pump system that suspends insulin delivery for actual hypoglycemia due to sensor glucose value (LGS) or for predicted hypoglycemia (PLGS).
Hybrid AID (also known as hybrid closed loop)	Insulin pump system that automatically increases or decreases basal insulin delivery in response to sensor glucose values; user still needs to dose prandial insulin manually. Advanced hybrid AID systems are also available now. These next-generation systems not only adjust basal insulin delivery but also have the capacity to deliver automatic correction boluses. However, they still require the person with diabetes to dose prandial insulin.
Full AID	AID system that automatically adjusts all insulin delivery, including prandial insulin.
DIY AID (also known as Loop, OPEN APS, Android APS)	"Do-it-yourself" AID system using a commercially available CGM system and insulin pump, plus an open-source algorithm; currently not approved by regulatory agencies.
Artificial pancreas (AP)	This term was used often in the past as a synonym for AID, but the AP does not take into account the exocrine functions of the pancreas.
Bihormonal (bionic pancreas)	AID systems that incorporate two hormones (insulin and glucagon); insulin and pramlintide are also being studied.

the umbrella of automated insulin delivery (AID) systems (5). These AID systems integrate data from a continuous glucose monitoring (CGM) system, a control algorithm, and an insulin pump to automate subcutaneous insulin delivery. Many different terms for AID systems are in use; however, all describe the same fundamental approach (Table 1). Overall, the term "AID" is becoming standard and is also used by regulatory agencies like the U.S. Food and Drug Administration (FDA).

Current, commercially available AID systems require user input for optimal prandial insulin dosing with a mix of manual and/or automated insulin correction dosing, yet these systems represent a significant movement toward optimizing glucose management for individuals with diabetes. However, expectations need to be set adequately so that individuals with diabetes and providers understand what such systems can and cannot do. The use of AID systems does not mean that diabetes is "cured"; instead, when integrated into care, AID systems hold promise to relieve some of the daily burdens of diabetes care by adjusting basal insulin delivery and providing automatic correction doses. However, issues seen with medical products like CGM systems and insulin pumps (e.g., regarding skin irritations induced by adhesives, occlusion of insulin infusion sets [IIS], inaccurate sensor readings and early sensor failure, and adequacy of the adjustment algorithm for individual users) are also of relevance when these devices are combined to build AID systems. Individuals with diabetes who are considering this type of advanced diabetes therapy should not only have appropriate technical understanding of the system but also be able to revert to standard diabetes treatment (i.e., nonautomated subcutaneous insulin delivery by pump or injections) in case the AID system fails. They should be able to independently troubleshoot and have access to their health care provider (HCP), if needed (see below). In addition, their HCP should have easy remote access to their AID system data. Simply giving a person with diabetes an AID system without support and adequate training presents safety issues without improving outcomes. Presently, AID systems are not available to all people with diabetes due to the high costs associated with this advanced version of diabetes therapy. It is hoped that all parts of AID systems (including insulin and digital access to the data) will become more affordable in the future.

This statement is not a scientific review of all publications involving AID systems; its focus is on safety issues in line with previously published statements (6–8). We provide a short overview on the benefits, limitations, and challenges of current AID systems, followed by a review of a number of critical safety aspects. Finally, we make a series of consensus recommendations for all concerned parties to further enhance and refine the safe use of these systems.

makers desire guidance and/or clarity on a medical or scientific issue related to diabetes for which the evidence is contradictory, emerging, or incomplete. Consensus reports may also highlight gaps in evidence and propose areas of future research to address these gaps. A consensus report is not an American Diabetes Association (ADA) position but represents expert opinion only and is produced under the auspices of the ADA by invited experts. A consensus report may be developed after an ADA Clinical Conference or Research Symposium.

Setting the Stage: Using Time in Range to Contextualize the Impact of Diabetes Technologies

For an understanding of the impact of various technologies used to treat diabetes, a uniform way to assess the wealth of data generated is required. Hemoglobin A_{1c} (HbA_{1c}) is a useful measure of the 2- or 3-month average glucose level and is prospectively validated in terms of its association with microvascular risks (9,10); however, it does not provide detailed information regarding a person's lived experience with diabetes. This holds particularly true in terms of frequency and severity of episodes of hypo- and hyperglycemia. Recognition of the limitations inherent to HbA_{1c} resulted in release of consensus guidelines in 2017 regarding key metrics that could be derived from CGM systems (11). Indeed, time in range (TIR) and visualization of data through standardized reports such as the Ambulatory Glucose Profile (AGP) are now being leveraged in both research studies and clinical practice. Furthermore, benchmarks for time in various glucose ranges based on CGM data have been developed (12,13). The backbone of this approach personalizes targets for individual patients; yet, the goal for most people with T1D, except during pregnancy, is to achieve $\geq$70% of the time with glucose levels in the target range of 3.9–10.0 mmol/L (70–180 mg/dL), with relaxation of this target in older adults and high-risk populations. Importantly, even a 5% increase in TIR is deemed clinically significant (14). However, while agreeing that TIR is an important metric, there is still a need to standardize reporting of this parameter (e.g., in the way that the Diabetes Control and Complications Trial [DCCT] aligned HbA_{1c}) to ensure that data duration, sampling frequency, device accuracy, completeness, handling of missing data, and analytical performance of different CGM systems (of which standardization is missing) in different studies do not skew individual or population data.

A Rapidly Evolving Landscape—Benefits of AID Systems

The dawn of AID systems dates back over 40 years with the advent of Biostator, which consisted of an algorithm on a microcomputer that would adjust intravenous insulin infusion rates based on real-time whole blood glucose measurements (15–17). Much progress has since been made in the development of AID systems, and there has been exponential growth in the field over the past 10 years (18,19). Regardless of the AID system used, a clear picture has emerged with this technology demonstrating improvements in glycemic control—as reflected by improvement in HbA_{1c}—in adults and also in children and adolescents (20). Findings of two meta-analyses, with their limitations acknowledged, support that AID use is associated with improvement in TIR (21,22). Furthermore, early studies indicate how usage of such AID systems benefits quality of life—namely, by improving sleep, reducing anxiety, and relieving some of the burden of daily diabetes management (23). However, future research is needed to demonstrate whether such improvements will also be present on a population level—versus in selected study populations. Future AID systems might use artificial intelligence to adjust responses of the system to the needs of the individual with diabetes. Such systems might also make use of additional hormones and medications like glucagon, glucagon-like peptide 1 receptor agonists, amylin analogs, and sodium–glucose cotransporter 2 inhibitors to improve the performance of the systems; however, the benefits of using noninsulin adjuncts have to be carefully evaluated.

Limitations of AID Systems

Despite the clear benefits of AID, limitations also exist. These limitations can be classified into categories of physiological, technological, and behavioral (Table 2).

Foremost, among the physiological limitations of AID systems lie the issues of where glucose is being sensed and where insulin is being delivered. As CGM sensors are placed in interstitial fluid (ISF), there is an inherent lag time in the sensor glucose value as compared with blood glucose measurements (24). This issue is exacerbated at times of rapid changes in glucose. Even with the currently available rapid-acting insulin analogs, the pharmacodynamic response of insulin is impeded by delivery via insulin pumps into the subcutaneous space (25–27). The hybrid approach adopted for AID systems, in which users need to bolus manually for carbohydrate intake, was developed secondary to these limitations (28). Yet, development of more suitable insulin products and algorithms with inclusion of meal detection and the ability to sense the glucose level every minute may allow for the eventual creation of a full AID system (29,30). Usage of information about the level of physical activity measured by wearables or smartphones will help with adjustment of insulin dosage based on the current needs of the patient; currently, it is not clear how well AID systems generally handle patient insulin requirements during physical activity. Artificial intelligence may eventually assist with such an individualization and customization (31); an example demonstrating such work being done is development of applications for smartphones to determine carbohydrate content based on pictures of a meal.

Although there has been substantial progress in diabetes technologies, other fundamental limitations with devices still exist. For example, finger-stick calibrations to "translate" sensor glucose data measured in ISF into blood values were a requisite of early-generation CGM systems. In recent years, factory-calibrated CGM systems have reduced this issue. Yet, issues with "missing" CGM data and so-called "compression lows" can still occur. At other times, CGM values can be "inaccurate" or otherwise different from blood glucose values measured at the same time with no explainable cause. With compression lows, aberrant CGM glucose readings may be due to sleep position leading to decreased blood flow to tissues near the tip of the glucose sensor in the subcutaneous tissue (32). Missing CGM data and loss of connectivity lead to reversion to preprogrammed manual pump settings in AID systems, which could be incorrect for the individual in a specific situation. Furthermore, individuals with diabetes may have challenges obtaining their CGM devices consistently due to reordering or supply problems. The CGM may stop functioning or fall off before the full expected duration of use is reached, requiring patients to go through the process of obtaining replacement sensors or devices.

Integral to AID systems are the insulin pumps used as one of their foundational components. As with traditional pump

Table 2—Limitations of AID systems

Physiological
1. Time lag in sensor glucose values as measured in ISF vs. blood
2. Delayed absorption of insulin from subcutaneous depot; pharmacodynamic effects of applied insulin are different from physiological secreted insulin
Technological
1. Suboptimal analytical accuracy of CGM systems in low glucose range
2. Compression of tissue around sensor insertion site leads to falsely detected hypoglycemia
3. Missing sensor glucose data (e.g., due to transmission failures) and sensor warm-up time
4. Glucose sensor overreading and inadvertent overdelivery of insulin
5. Infusion set failures or pod failure
6. Outright pump failure due to software or hardware issues
7. Issues with data uploading, regular exchange of batteries, loss of communication between components of the AID system/cloud network
8. Server interruptions leading to inability to remotely track data
9. Cybersecurity/data protection/data privacy
10. Need for regular update of software/operating systems/apps
11. Impact of work or environmental conditions has to be considered (i.e., exposure to high or low temperatures, magnetic fields, or water)
Behavioral
1. Patient needs to bolus prandial insulin
2. Requirement of correction boluses
3. Problem-solving for hyperglycemia (i.e., detect failed infusion sets, broken system components)
4. Avoidance of hyperglycemia overcorrections and avoiding adding fake carbs, etc.
5. Overtreatment of hypoglycemia
6. Limitations and challenges of exercise
7. Need for backup supplies

therapy, IIS will continue to be the "Achilles heel" of AID systems because of the many ways in which infusion of insulin can be interrupted (33). Without algorithms for site failure detection, it will be essential for people with diabetes and providers to problem solve hyperglycemia and include the possibility that insulin flow through the IIS has been either partially or completely blocked as the etiology for the issue. Even patch pumps can be prone to infusion set issues (see Table 2). The development of more consistent methods for subcutaneous insulin infusion could benefit all insulin pump wearers. Integration of continuous ketone monitors, which have been assessed in small clinical feasibility trials, might provide an added safety feature to AID systems in the future (34,35). Exploration into how environmental factors, including temperature variation and electromagnetic fields, impact sensor and pump technology is warranted.

Data management by individuals with diabetes and their providers is essential to understand the effectiveness of AID and impact of behavioral modifications, particularly with regard to meal bolusing and exercise. With increasing use of cloud-based automatic data uploading to servers, the need to educate and encourage patients to manually transmit data from their devices to the cloud is reduced. However, in the present landscape, some systems still require manual, cumbersome data-handling procedures (by patients or HCPs), and operating system updates can affect the ability of medical devices to transfer data for analysis; thus, clinical practices need to account for the time required into clinical workflow. Data from other systems can be readily accessed by clinicians (if permission is granted by users) in real time via dedicated password-protected websites.

While the ability to remotely monitor CGM data has transformed how HCPs and caregivers can be involved in the care of those with diabetes (thus increasing support connectivity), power outages and server failures may lead to data disruptions that can impact an enormous number of patients (36). Contingency plans for how such lapses in data transfer will be managed may help to mitigate the fear of consequences, especially for pediatric populations. Additionally, with plans for smartphone control of AID systems, consideration must be given to how updates to smartphone operating systems may impact insulin delivery and potentially lead to loss of connectivity and impair functionality or what may occur if a smartphone's battery is depleted.

Undoubtedly, the AID systems that are commercially available, as well as those that are in late phases of clinical development, are by no means perfect, and manufacturers of these AID systems have already announced successor products to overcome some of the limitations present with currently available products. The next generations of AID systems will be improved with respect to not only technological performance/components but also algorithms that will cover more aspects of insulin therapy, including unannounced meals and improved management of physical activity.

Education and Expectations: A Critical Component of AID Systems for Both Patients With Diabetes and Providers

Explaining the nuances of the CGM system used for AID may help patients with diabetes in selecting the system that best suits them (37). Points of discussion include whether finger-stick calibrations are necessary, as well as the expected duration of glucose sensor wear. Since medical devices become part of a person's daily "uniform" and even identity, size and appearance of the system components may be a distinguishing factor for some people as they consider device integration. The various AID systems in development can use algorithms embedded in the pump or pod or as an application on a

smartphone device, which can be one's personal device or a dedicated device solely for diabetes management. Additionally, with the advent of remote data monitoring, understanding the data-sharing capabilities of AID systems is crucial. Sharing features may include only CGM data or additional data regarding insulin delivery. These features may be used by a caregiver, such as a parent of a young child; family member of a senior; or the person with diabetes who prefers using their smartphone to check their data on a more regular basis rather than assessing information from the insulin pump itself.

It is important to recognize that in devising a treatment plan, providers should work together with patients and their caregivers to broach the topic of AID systems. Using a structured method to review currently available AID systems will lay the framework upon which patients with diabetes can choose what features are most important to them. This shared decision-making will lead to successful integration of therapy into the care plan. Having the key AID data and action plan automatically available in the electronic health record would also facilitate coordination of care across a team of health care professionals supporting patients on AID systems.

In the European Union (EU) and other countries outside the U.S., diabetes technology including AID systems is usually prescribed by a physician. This means clinicians may find themselves in a "gatekeeping" role, such as assessing suitability. Although access to an AID system may be less physician restricted in the U.S. and more determined by insurance coverage or ability to meet costs, a methodical approach to system selection is still needed. Overall, the approval and reimbursement process of AID systems varies considerably between countries. Given rapid iterations in technological advancements, it is likely that the lifetime of a device or warranty provided by an insurance company may lead to prolonged use of "outdated" algorithms. Thus, it will be imperative to have software updates of hardware to ensure continued access to the latest technologies.

Patient Perspective

Paramount in the transition to using AID systems is setting realistic expectations of what the available systems can and cannot do. For example, with hybrid AID systems, the timing of meal bolusing should ideally occur prior to eating and with accurate assessment of carbohydrate content, with consideration also of the impact of the meal composition (e.g., proteins, fat). While future iterations of AID systems may allow for automatic detection of meal-related glycemic excursions, first-generation AID systems need meal announcements by the user. Accurate and well-timed bolusing will clearly minimize postprandial glycemic excursions and increase TIR. In some systems, delayed meal dosing can result in hypoglycemia because of the overlap between insulin given automatically by the AID system in response to the postprandial glycemic excursion and the relative overbolusing of giving a delayed full meal bolus. If bolusing postprandially, some patients may need to reduce the meal bolus to account for the insulin already provided by the AID system. Patients are also expected to announce any upcoming physical activity to avoid hypoglycemia.

Concern exists that patients transitioning to AID systems may become less skilled in dosing insulin as they rely more heavily on their technology. Thus, it will be essential that patients, as well as providers, understand that like any technology, components of AID systems can fail. When hyperglycemia occurs, patients may need to return to fundamental diabetes management, such as assessing ketones and considering whether an IIS occlusion or failure has led to the hyperglycemia. They will need clear instructions on how to restore normoglycemia, even possibly returning to conventional continuous subcutaneous insulin infusion (CSII) or insulin injection therapy so preprogrammed basal rates are used and appropriate correction doses can be administered. Contingency planning should include access to batteries, charging cables, IIS, reservoirs, a vial of insulin, syringes (or insulin pens and needles), a glucose meter and test strips, glucagon, ketone test strips, and a backup glucose sensor and transmitter for the CGM system. In addition, a plan for transition to insulin injection therapy, as well as a supply of unexpired insulin pens or vials with rapid-acting and long-acting insulins, should be available for use until a replacement for the AID system is available.

It is also critical to consider potential disruption in availability of supplies, as has been noted during the coronavirus disease 2019 era. For example, if there is a supply issue with glucose sensors or transmitters, if the sensors or transmitters do not last for their intended duration of time, or if there is a change in insurance plans and a prior authorization is required, individuals with diabetes may find themselves running out of supplies. The challenge, however, is the difficulty of "stockpiling" extra supplies.

Furthermore, traveling can be exceptionally challenging, especially if key components break unexpectedly. Thus, it is essential to always have a backup subcutaneous insulin therapy plan, as described above. Devices that require charging through USB electric cable can be difficult to charge in certain regions (e.g., during a vacation).

Medical imaging can also be a challenge because certain scans (e.g., computed tomography scans, MRIs) require removal of pumps and CGM systems. IIS can stay in place, but removing the glucose sensor can be a problem if sensors are in short supply. However, the recommendations for removing CGM systems are based on caution, largely in the absence of data from device testing under these conditions. In at least one simulation it was found that CGM can stay in place during radiographic and MRI procedures (38,39).

Discussions regarding treatment of hypoglycemic events in patients using an AID system need to highlight that since basal insulin will be suspended, fewer carbohydrates will need to be consumed to return to euglycemia. Even though hypoglycemia can be corrected with fewer carbohydrates, people with diabetes need to be educated to overcome fear of hypoglycemia and avoid overcorrecting hypoglycemia, which often causes hyperglycemia with the use of AID systems. Also, AID users have noticed (anecdotally) that the AID system assumes that the person with diabetes is still in a state of hypoglycemia with delivery suspension long after the hypoglycemia has been corrected with rapid-acting glucose, and people with diabetes find themselves experiencing hyperglycemia 30–40 min after having corrected hypoglycemia

even if they use fewer carbs. This is driven by the exacerbated/prolonged glucose sensor lag time in the setting of hypoglycemia (40).

While not always commonplace with CSII, explaining the concept of "insulin-on-board" may help patients with their transition to an AID system. Since AID systems increase insulin delivery based on elevated glucose levels, patients may find they are limited in the manual correction bolus that can be given. Helping patients understand that this is due to insulin being proactively delivered by the AID system may help minimize frustration in the initial transition period.

Educating patients with diabetes on AID system functionality and how to determine whether insulin delivery is being increased or suspended may allow for trust to be established with this automated process. Indeed, for those who have achieved targeted glycemia with traditional CSII or multiple daily insulin injections, delegating the decision-making process to this new technology may be difficult.

Education also needs to focus on the different modes that these AID systems have. The most common feature allows the AID algorithm to adapt, for example, to exercise. Alternatively, overnight algorithms may allow some systems to tighten targets, thereby allowing for more aggressive insulin delivery.

Provider Perspective

As commercial AID systems become more widely used, education regarding what to do with an urgent question will be crucial. There should be a clear distinction between technical support delivered by the manufacturer and clinical support delivered by the clinical support team. Clinical questions may be best posed to a provider through contacting a 24/7 emergency call line. Such a helpline should be staffed by people with specific diabetes experience, i.e., good understanding of handling CGM systems and insulin pumps. Most practices do not have the capacity to provide this level of support, especially where general practitioners may treat those with diabetes due to the limited number of subspecialists in a region.

An additional level of complexity with technical support arises with multiple manufacturers contributing to a given AID system. For example, in the case of an unknown failure of an AID system built using components from different manufacturers, who should be contacted? However, with the understanding that AID system issues may necessitate contacting the manufacturer of the given system, a hotline created by the company should also be available for the product's users. Calls must be promptly answered, and multiple language options (based on regional need) should be easily chosen. Those employed to answer calls must be familiar with the given AID system so they can support the patient with most, if not all, questions regarding system use. The questions asked by the call center staff must be simple and nonconfrontational, as individuals with lower literacy, numeracy, and technical skills may not be able to provide detailed information. The most common concern that may arise could be whether the AID system or one of its components needs to be replaced. Trained call-line workers will need to help patients troubleshoot a given situation, help them check and change the pump settings, and potentially provide authorization for new components of the AID system to be sent if it is deemed that the current system is not functioning as intended. Potential AID system issues may include repeated loss of data transfer from the transmitter of the CGM system or an insulin pump that has a cracked screen.

Essential to helping patients integrate AID systems into their care regimen is recognition that the AID system that will work "best" for an individual patient is the one that they choose (https://consumerguide.diabetes.org). However, this requires that the patient have the choice of different AID systems available in the country and through the health care system. Just as CSII offers a plethora of options of different insulin pumps, IIS, and other components, it is anticipated that a number of AID systems will be commercially available in the not-too-distant future. Paramount to having an open dialogue with the patient in considering therapeutic options is presenting information in a standardized and adequate manner. Ideally, the patient would have the chance to evaluate different AID systems before making a decision for a given system.

With certain differences in technology and handling of AID systems currently available, a systematic approach for defining how each advanced diabetes technology works has been proposed. The "CARES" paradigm consist of five domains that should be addressed to achieve optimal use of advanced diabetes devices:

- C: Calculate—How does the algorithm calculate insulin delivery and which components of insulin delivery are automated?
- A: Adjust—How can the user adjust insulin delivery, which parameters can be adjusted to influence insulin delivery during automation, and which parameters are fixed?
- R: Revert—When should the user choose to revert to open loop/no automation and when will the system default to open loop/no automation?
- E: Educate—What are the key education points for the advanced diabetes device?
- S: Sensor/Share—What are relevant sensor characteristics for each device, and what are the system capabilities for remote monitoring and cloud-based data sharing (41,42)?

With conventional CSIIs, the same parameters for system setup are held constant across a range of devices; however, this does not hold true for AID systems. Two approaches exist for AID targets: a treat-to-target AID system that has a singular set point (e.g., 6.7 mmol/L [120 mg/dL]) that the system tries to reach, while advanced hybrid closed loop with treat-to-target algorithms may have multiple targets to choose from (e.g., 5.6 mmol/L [100 mg/dL]) that could range between 4.4 and 11.1 mmol/L (80 and 200 mg/dL). Conversely, for treat-to-range systems there are CGM values between which the system tries to maximize the TIR (e.g., 6.3–8.9 mmol/L [112.5–160 mg/dL]). Thus, the first step may be understanding which type of target a given AID system uses, followed by assessment of the threshold at which these targets are set.

While it is beyond the scope of practice for most clinicians to understand all the intricacies of how each AID algorithm works, it will be critical as AID systems are more widely adopted for HCPs

to know which parameters can be adjusted to optimize insulin delivery. The variables that can impact insulin delivery within AID systems may include the basal rates, active insulin time, insulin-to-carbohydrate ratios, insulin sensitivity/correction factors, and total daily insulin dose. To date, all AID systems allow for adjustment of the insulin-to-carbohydrate ratio except Diabeloop DLBG1, which uses machine learning to optimize the meal ratio on an ongoing basis. Some of the newer AID systems on the market will give automated correction boluses, while others may not. The strategy for determining the dose allowed to be given by automated correction, as well as the frequency with which these autocorrections can be provided, will differ by system. Indeed, without comprehension of what parameters are adjustable, some clinicians may alter settings that have no impact on AID, thereby increasing frustration of both patients and providers in their experience with the product. With commercialization of AID systems, companies should seek to include materials that clearly delineate the settings that can be adjusted. Companies should also provide clinical scenarios to highlight when such optimization would be needed and how to successfully implement the changes.

Providers will need to inform patients of when AID systems may automatically revert to manual mode (i.e., stop automatically adjusting insulin delivery). With manual mode, the preprogrammed basal rates and bolus factors are resumed; however, these settings may not reflect the patient's current insulin dose requirements, as settings may have been altered for AID. Thus, it is a good practice to update these manual settings intermittently while patients are using AID systems, as overall insulin needs may be changing, particularly in the pediatric population. Another critical factor to understand is whether any "low glucose suspend" or "predictive low glucose suspend" features remain in place with the transition back to manual mode. Should such features not be available, it may be critical to consider altering the low-glucose thresholds and predictive low alerts when not using the AID feature so that the patient with diabetes can manually respond to the hypoglycemic event.

It may not be prudent to continue with AID in certain situations, and patients may be instructed to revert to conventional CSII. These situations include illness, when there may be temporarily increased insulin resistance and elevated glucose levels, as well as reduction in oral intake and ketosis without elevated glucose levels. Resolution of ketones will be contingent on increased insulin delivery; however, this may not be possible if a patient is solely relying on the AID system. Likewise, should a clinical situation arise in which treatment necessitates use of systemic steroids, it is possible that the AID system does not respond rapidly enough to account for the increased insulin requirements often necessitated with steroids. Finally, the lower targets needed in pregnancy may not be achievable on an AID system.

Given that AID systems are new in diabetes care and subject to ongoing rapid development, many practitioners may not be fully aware of how to teach individuals with diabetes how to use them. As a result, manufacturers may need to provide training either directly to patients or diabetes care and education specialists or by means of online videos. The pandemic has highlighted that this education can be delivered in person or remotely (43). With the initiation of AID, patients should be provided with clear instructions on how to ensure data are available for providers to view (i.e., whether they need to upload information) and who to follow up with regarding dose optimization. Particularly during early use, providers will need to take a more proactive approach than with previous nonintegrated insulin pumps.

Although teaching tools for medical devices like AID systems include user guides, these are often not easy to read. They are hundreds of pages long, and the chances that patients and even HCPs will read them are slim. In the case of troubleshooting, often it is not easy to find appropriate support. Many learn from videos, which, if available, are often very helpful. However, such teaching tools need to be available in multiple languages, created for learners of all skill levels, and sensitive to the inclusion of people from varying ethnicities. Communication with the HCP may be through the use of interpreter services in case of language barriers. Undoubtedly, there will be a steep learning curve as use of AID systems becomes more prevalent. Patient acceptance and safety will come through education and adjustments to ensure safe use. For people with diabetes whose management strategies have been primarily focused on permissive hyperglycemia, the return to more targeted glucose levels may lead to the sensation of hypoglycemia. Instructions on this phenomenon and encouragement that the threshold for symptoms will be lowered may help patients adapt to this transitional period as they initiate AID therapy.

Providers will need to understand how to access data so that dose optimization on AID systems can be made. They may need to assure they have programs installed for local uploading of devices in their offices. There is a call for standardized reports for AID data, similar to the standardized reports that have been created for CGM data (44). Just as consistent terminology (Table 1) use can help clarify for all what a given system does or does not do, standardized reports will help ensure easy readability of the data for individuals with diabetes as well as their provider.

Special Populations—What Is Needed?

AID holds the promise to improve care for all individuals living with diabetes who require insulin. However, the vast majority of studies to date have focused on those with T1D (45–50). Nevertheless, for people meeting their individualized treatment goals without excess burden or distress, usage of AID systems may not be an appropriate therapy, and recognition of the choice to not use an AID system is important. The current evidence base is mostly built on studies where selected participants were able to engage with self-management and had received structured education or an equivalent level of support, which may impact the outcome of these studies and therefore their generalizability. There is a need for well-conducted studies in populations who differ from those included in the studies, who may, in some cases, be most apt to benefit. However, more data from real-world studies were published recently (e.g., 51).

A handful of studies have demonstrated the short-term benefit of systems in patients with type 2 diabetes (T2D) (52–54). Indeed, for people with T2D whose endocrine pancreatic function

mimics those with T1D, such as those with lower serum C-peptide levels, usage of AID systems may prove to be the optimal way to attain glycemic targets while avoiding hypoglycemia. Additionally, application of AID systems for patients with insulin dependency following pancreatitis or those with cystic fibrosis–related diabetes may be warranted, since improvements in lung function are noted when dysglycemia is treated (55).

Since AID is integrated into the care of patients, certain factors may arise based on the patient's age and clinical condition. For young children, the ability of parents to remotely view both CGM data and insulin delivery is critical. Similarly, for older adults in assisted living facilities, such remote monitoring tools may be of great help. Additionally, in both of these circumstances, it may be best to have only basic functionality on the insulin pump itself in order to prevent errant and unwanted bolus insulin delivery. However, as youth with diabetes achieve greater independence in their care, access to greater functionality of AID systems is likely to be appropriate over time. Including an option for the HCP to individualize pump settings for this purpose is recommended.

Different insulin pumps have regulatory approval for different age ranges, and this must be considered in prescribing an AID system (18,56). To assure systems work across a broad patient population, AID systems in clinical development have been tested in both transitional environments and home-based outpatient assessments of even very young age-groups (<6 years old). Some older studies suggested that dilution of rapid-acting insulin analogs may allow for a reduction in the frequency of hypoglycemic events (57,58); however, in a more recent outpatient assessment in this age-group a benefit was not seen with dilution (59).

Transition from pediatric to adult diabetes care requires specific attention. While youth may have relied on parents at an earlier stage, increasing autonomy of care is essential during transition (60). This will require specific training—or retraining—on how AID systems work at an appropriate time prior to transition to an adult provider.

In patients who may experience acute metabolic events where insulin sensitivity can change rapidly (e.g., acute illness or with use of steroids), more robust algorithms may be required to manage alterations in insulin need. Assessment of these situations in a standardized manner to determine safety of various devices would be prudent. Evidence is now emerging regarding use of AID systems during times where insulin action time may be changing due to reduced or changed insulin clearance (e.g., chronic kidney disease, dialysis) and has suggested that use of AID systems may be of help (61).

Finally, pregnancy poses a unique situation, as the targets for glycemia are inherently much more ambitious (12,62). Early studies in pregnancy have demonstrated the ability of AID systems to improve glycemia (63–65). However, in these studies, women continued to perform self-monitoring of blood glucose (SMBG) multiple times daily. In the Continuous Glucose Monitoring in Women With Type 1 Diabetes in Pregnancy Trial (CONCEPTT), fetal outcomes were evaluated in comparison of CGM plus SMBG monitoring with SMBG alone (66). Clear benefits were illustrated in those on sensor therapy (66). However, no benefit in glycemia was seen in those preparing for pregnancy. Moreover, data on outcomes are lacking from individuals with preexisting T2D or gestational diabetes mellitus. Because pregnancy glycemic targets are currently lower than the targets allowed by most commercially available AID systems, it is important to follow glycemic guidelines for pregnant women and find the best method for achieving these outcomes in an individual patient. One study has shown the adaptability of AID systems to respond to the ever-changing insulin requirements in pregnancy, which are most pronounced immediately after delivery, when insulin requirements are drastically decreased (67). Currently, the CamAPS FX system is the only AID system approved for pregnant women with diabetes (18).

Overall, there is need for good AID teaching and training programs, with emphasis on support for AID use. This should be curriculum driven, evidence based, and based on sound education principles.

Considerations for Patient Selection for Current AID Systems

As previously described, there are many obvious advantages for using AID systems, but there are also some important limitations of the current and near-future AID systems. The following users are more likely to find greater and safer success with these systems:

1. Those who are technically capable of using insulin pump therapy. For example, those who have been trained in the rigors of reservoir/set changes (needed with AID systems with use of conventional insulin pumps) have a basic understanding of carbohydrate counting and the glycemic impact of fats and proteins (which is beneficial with current AID systems), comprehend the need to calibrate their sensor (if needed), and have the ability to troubleshoot. This includes understanding the limitations of all components of the AID system and knowing when to revert to manual insulin delivery and/or seek help.
2. Those with realistic a priori expectations of systems, which may help mitigate feelings of frustration given system limitations (68).
3. Those who are appropriately trained, as noted above, and properly supported. Ideally, they have a social environment supporting them and insurance coverage of AID systems. They also should have the ability to transmit their ongoing AID data to the health care professional team.
4. Those mentally and psychologically able to fulfill the requirements for successful AID implementation. People with diabetes and eating disorders or severe psychiatric comorbidities (e.g., severe depression, anxiety), and people who are not currently committed to change or are lacking desire to improve metabolic control, may not be suited to initiate AID.

A caveat to the abovementioned is the experience of the growing group of patients using do-it-yourself (DIY) AID systems (covered in greater detail below) and achieving impressive glycemic outcomes in the context of community support (69).

Current AID algorithms may be less effective for those with either very low or very high insulin requirements. Visual impairment may prevent some patients

from using AID systems, though creative solutions for this issue have already been developed to allow for incorporation of insulin pumps and CGM systems (70). Finally, while there is concern regarding integration of these devices for those with diabetes complications, reports have demonstrated improvements in glycemia with AID systems in those on hemodialysis, as well as in a cohort of patients with gastroparesis (53,71).

The patient group described above is deemed most likely to be the safest group for use of AID systems; however, they might not be the group that derives the greatest benefit, as they are generally already close to target. Therapeutic options like CGM and CSII have the greatest impact on HbA_{1c} and hypoglycemia exposure in patients with T1D, with the highest HbA_{1c} values and the greatest exposure to hypoglycemia due to diabetes burnout or issues with self-management. Therefore, it might well be that the usage of AID systems by such individuals has the greatest incremental benefit from a clinical point of view and, thereby, also the highest cost effectiveness. A key challenge for AID systems will be moving beyond those who are already at targeted glycemia (i.e., HbA_{1c} $<$53 mmol/mol [7%]) with minimal hypoglycemia, who likely better mirror some study populations. While these individuals may only see small incremental changes in glycemia, clear benefits in diabetes burden may be feasible with AID. The desire to address inequalities between different populations with diabetes cannot be reconciled with criteria with selection of only the safest patients.

Safety Aspects to Be Considered for AID Systems

Requirements for clinical safety of AID systems are similar to those seen with CGM systems and insulin pumps but also go beyond those. In individuals with T1D, safety issues encompass both hypoglycemic events and diabetic ketoacidosis. Such events can be induced by system malfunctioning (e.g., inadequate insulin delivery driven by the algorithm) or user error (i.e., patients who do not understand how AID algorithms work or may manually administer additional bolus insulin doses, whether via pump or injection, to treat persistent hyperglycemia). Conversely, there is potential to override the system and unintentionally give too little insulin, thus increasing risk for ketosis; however, this might be induced mainly by infusion set/pump failures. Use of the AID system during situations with high risk for hypoglycemia (e.g., sports, illness, intentional weight loss) or situations in which hypoglycemia is especially dangerous (e.g., driving) requires additional consideration.

An important question to consider is how to become aware of safety issues. Are currently implemented mechanisms to detect safety issues adequate? In cases when a person with diabetes encounters such issues and contacts the device manufacturer, the company must report these safety concerns to certain databases, such as the Manufacturer and User Facility Device Experience (MAUDE) in the U.S., which are monitored by regulatory agencies. Although market observations can provide insight into certain issues if they are reported several times, there are currently no systematic observation and analysis methods established to detect these trends. Nevertheless, when issues are detected, they can result in product recalls. For example, there was a class 1 recall for the Medtronic MiniMed 670G system following issues with the retainer ring of the pump, which could have impacted insulin delivery (72).

On determination of adverse reactions, properly recognizing issues takes time, as does development of a method to minimize the issue. For example, it took time to identify the development of skin reactions secondary to the frequent use of diabetes devices, which has proven to be a serious issue faced by many. In recent years, severe skin reactions, including contact dermatitis (both irritant and allergic), have been reported with a number of medical products (73–76). In some cases, this has been linked to the presence of isobornyl acrylate, which is a skin sensitizer that can cause additional allergic reactions (77–80). Patch testing can be done in some cases to identify the cause of contact dermatitis (81). Identifying and eliminating tape allergens, which can also be a part of the plastic housing of medical products, is important to ensure comfortable use of devices and enhance patient engagement (82–85). Other device safety issues are possible, which can range from breakage of physical pieces of the pump to issues with the algorithms. Additionally, there can be errors in the representation of data downloaded from the system. All of these issues need to be handled and monitored in an efficient and effective manner.

Being up to date on any recalls and device safety updates is critical for patients and providers alike. Furthermore, it is up to all patients and providers to report issues to regulatory agencies, such as the FDA via MAUDE, to ensure that channels to identify issues are properly used. Diligence with reporting will help keep everyone informed of potential problems as they arise.

Cybersecurity, Data Privacy, Data Protection, General Data Protection Regulation, and Data Donation

Another critical issue is cybersecurity and data privacy. Concerns about cybersecurity for diabetes devices was heightened in 2019 by the FDA's Safety Communication announcing a report that an "unauthorized person" (i.e., someone other than a patient, caregiver, or HCP) could potentially connect wirelessly to a nearby insulin pump with cybersecurity vulnerabilities. This person could change the pump's settings to either overdeliver insulin to a patient, leading to hypoglycemia, or stop insulin delivery, leading to hyperglycemia and ketoacidosis (86). Potential vulnerability of AID systems is increased by the multiplicity of component devices that comprise AID systems. Efforts before and after that discovery by FDA, other regulators, industry, and professional organizations have been aimed at reducing risks of device interference and data theft (87–89). As all who live in the digital world understand, vigilance by AID users, HCPs, manufacturers, and regulators is essential. Continuous testing of AID components and systems for cybersecurity, as well as ongoing development of technological safeguards, must be ongoing.

Usage of the data generated in using AID systems is a critically important issue. Data privacy and data protection are of high relevance; manufacturers are starting to make widespread use of data collected in their databases for "real-world studies." A clear advantage of such studies is that in principle, such analysis would include data from all patients using AID systems, whereas clinical trials would dictate patient selection

with inclusion/exclusion criteria. Also, the much larger number of patients and enormous amounts of data generated by real-world studies are of interest. The question is whether patients are aware of what happens to their data. Although patients have to sign an agreement about data usage, that does not necessarily equate to understanding of the agreement. In contrast, if patients are willing to donate their data for research (e.g., the concept of data altruism/data donation), this is a different matter.

Whether insurance companies can use AID data to modify insurance coverage remains an open question, if they can get access to these data of individual patients. If CGM data are identifiable, can users refuse to share their data with HCPs? Is there a risk to doing so? Another sensitive situation may be the availability of CGM and AID data in court rulings, such as when an individual with diabetes is involved in a car accident and the court finds out that relevant data covering that time period might be available. The question as to whether the person was able to handle the AID system adequately may arise. Could data be downloaded to prove what occurred (i.e., severe hypoglycemia caused loss of patient consciousness)? Did the user override system recommendations or use the system in ways that were not intended, thus leading to the incident, or did the AID not work as intended despite user engagement? Are data holders forced to provide this information without the consent of the person with diabetes?

Furthermore, companies may be legally liable regarding particular laws depending on where the company headquarters is, as well as where AID devices are manufactured and cloud servers are located. For example, the legal frameworks for data protection are different between Europe and the U.S. There is an initiative in Europe, the "European Health Data Space," to ease and regulate the access to data (90).

In Europe, the sensitivity for data privacy is high. Since the General Data Protection Regulation (GDPR) came into force in 2018, manufacturers have to take these matters very seriously (91). This also includes the "right to be forgotten." For example, if a patient wants to stop using a given AID system, what happens with the individual's data, and can they be properly deleted? When it comes to data safety and data usage, a number of technical issues are of concern (i.e., data interoperability). Only when data can be assessed in a standardized manner can the data generated by the AID systems be integrated into electronic health records. With regard to data protection, one has to realize that the availability of data on CGM or AID use discloses a diagnosis of diabetes, which may have a negative impact on employment or access to insurance.

Evaluation and Approval of AID Systems in the U.S. and Europe

In general, the regulation of medical devices in the U.S. and EU differs substantially in requirements and organizational structure (92). In 2016, the European Commission issued the Medical Device Regulation (EU MDR), which represents a major change in how medical devices will be regulated. The implementation of EU MDR started in May 2021. Traditionally medical devices, but not necessarily diabetes-related products, have reached the market sooner in the EU than in the U.S. The EU MDR may have the effect of reducing differences in data requirements and marketing approval times.

The FDA has been highly supportive of diabetes device development through the release of clear and detailed guidance. The FDA has been especially supportive of the development of AID systems over the last decade starting with its 2012 guidance (93). This FDA guidance document describes multiple forms of flexibility for developing AID products including with regard to *1*) use of CGM systems, *2*) primary end points that can be used to measure safety and effectiveness, *3*) the stated therapeutic indication, *4*) clinical study progression, and *5*) the size and duration of each study phase. This guidance explicitly expresses the intent of applying the least burdensome approach to investigating and developing AIDs and making them available to patients.

The FDA has also approved AID systems rapidly. FDA review panels that included patient representatives and patient-led organizations that have supported device approval demonstrate the agency's concern for the perspective of the person with diabetes.

The FDA's landmark approval of the Dexcom G6 integrated CGM (iCGM) permitted that device to be used as an integrated system with other compatible medical devices and electronic interfaces, which "may include automated insulin dosing systems, insulin pumps, blood glucose meters or other electronic devices used for diabetes management" (94). Later the Libre 2 by Abbott also got this status. Importantly, this approval had the effect of changing the risk category for iCGM products from class III to class II while stipulating conditions and special controls to ensure safe interoperability. This new provision also enables bringing future iCGM systems to market with the least burdensome requirements possible. At the end of 2019, the FDA then approved the Tandem Diabetes Care Control-IQ, an interoperable automated glycemic controller device that automatically adjusts insulin delivery by connecting to an "alternate controller enabled" infusion pump (ACE pump) and iCGM. This was the first controller device that could be used with other interoperable devices and integrated into a customizable diabetes management system for AID (94). However, the FDA's interoperable provision only allows an option for AID. A self-contained AID product can still be developed and approved as noninteroperative. Such products could require a more burdensome Premarket Approval (PMA) process.

The EU does not have an interoperable diabetes device pathway comparable with that in the U.S. In the EU, the manufacturer specifies the intended purpose, technical specifications, and indications and limits of use for its product, which are supported by the clinical evidence and documented in the instructions/information for users and the technical documentation. Technical documentation can demonstrate conformance with the essential requirements at the product or system level, but it must take into account system components and interactions used to achieve the intended purpose. Therefore, the manufacturer of a system component defines the interoperability with other components. This results in the availability of AID system components intended to be combined only with other specified system components (e.g., from

the same manufacturer), as well as system components intended to be used with a wider range of components (e.g., from different manufacturers).

In contrast with the FDA as the single national agency for device approval in the U.S., independent notified bodies that conform with EU MDR evaluate and approve medical devices (approved devices are allowed to bear a CE mark). As noted above, the EU MDR brings a higher burden for the manufacturer with respect to technical documentation and clinical evaluation. It should be noted that a number of questions and issues related to AID remain to be addressed by the notified bodies and the EU Commission.

A key question with respect to the EU MDR regulation is, in what risk categories will AID systems and components be placed, class IIb or class III? Four different options for AID systems are conceivable as follows:

1. A fully integrated system (i.e., one manufacturer offers a CGM system, insulin pump, and algorithm)
2. A system that combines products of different manufacturers (e.g., an insulin pump from one company, a handheld with an algorithm from a different company, and the CGM system from another company)
3. An app that consists of an algorithm that controls other devices
4. DIY AID systems that are built by people with diabetes using commercially available hardware combined with an algorithm downloaded from the internet, for which no regulatory approval is available

The second and third types of AID systems might belong to a different risk class than the first. AID systems are viewed as requiring special attention, since they involve infusion of a therapeutic product, insulin, which has a narrow therapeutic index. Such products are scrutinized more intensively. In the case where components of different manufacturers are combined (i.e., similar to FDA's interoperability provision), interoperability has to be explicitly demonstrated. An important consideration is, who is responsible for the "combined product" in terms of liability and warranty? Another question is how the safety and efficacy of the different combinations can be meaningfully demonstrated to the satisfaction of the emerging EU MDR.

According to the EU Product Liability Directive, the manufacturer is liable for the device and should make sure it is working according to the product's specificities as formalized in the CE mark and the instructions for use (per Council Directive 85/374/EEC of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States concerning liability for defective products). Patients with diabetes will be expected to use the device according to the instructions for use provided by the manufacturer, and these instructions will need to be clear, transparent, and understandable. Some manufacturers provide specific warnings to the patient in case of misuse or modifications of the device, such as, "Modifying the devices can cause serious injury, interfere with your ability to operate the device, and void your warranty."

With regard to DIY AID systems, the French Competent Authority National Agency for the Safety of Medicines and Health Products (ANSM) has published a recommendation that people with diabetes not use software and applications that offer DIY AID systems, indicating that these applications usually do not have the CE mark and expose users to risks (95,96). The FDA's designation of interoperable devices enables patients to "build their own" AID system by using devices offered by different manufacturers. Such an approach requires that system components be able to exchange data. In other words, they must be able to "speak" with each other and, hence, be classified as interoperable.

The U.K. left the EU trading bloc in January 2020 with a transition period until the end of 2020. However, the U.K. Medicines and Healthcare products Regulatory Agency (MHRA) has issued guidance that generally harmonizes with EU MDR requirements (i.e., the route to the British market and marking requirements are still based on the medical devices requirements derived from current EU legislation) (97). Since 1 January 2021, all medical devices placed on the U.K. market need to be registered with MHRA (a grace period existed until September 2021 for pumps and CGM systems), but CE marking and certificates issued by EU-recognized notified bodies will continue to be recognized in the U.K. until June 2023. Any manufacturer based outside the U.K. will need to appoint a single U.K. "Responsible Person" to place a device on U.K. market.

Access to AID Systems

For the time being, the costs of AID systems are high, which is a main reason why, from a global perspective, most people with T1D do not yet realistically have access. An important factor to consider is the costs of devices, as well as coverage of devices by insurance companies, which varies widely between countries. This means out-of-pocket costs can be vastly different, and access to particular devices may be restricted in some regions, even if the devices have achieved regulatory approval. Fortunately, use of modern diabetes technology is increasingly being covered by health care systems given the proven benefits they bring for many people with diabetes. However, coverage includes not only the up-front costs of AID systems but also ongoing supply costs for IIS, batteries, and insulin, as well as increasing use of cell phones and adequate Wi-Fi coverage for transmitting data to health care professionals. Furthermore, AID systems require extensive use of nonmonetary resources, such as up-front education of the users. Patients must also have access to HCPs who can support and troubleshoot a given AID system when the need arises, such as malfunction of a component or interruptions in the supply chain. In view of the costs associated with widespread use of AID systems, insurers will likely request more cost-effectiveness studies, which will also be dependent on baseline characteristics of individuals with diabetes.

Underserved and rural patients often lack access to consistent and/or qualified endocrinologists, a problem often encountered in the U.S. Even with adjustment for socioeconomic status and access to care, health care disparities in outcomes exist for those from minority populations (98). Patients with lower incomes often face multiple issues that limit their ability to adopt technology, including insulin pumps and CGM

systems (99), not to mention complex AID systems. These issues include lack of consistent access to health care, insufficient or inconsistent coverage for devices, lower literacy and numeracy skills, lack of access to healthy food, psychosocial stressors, language barriers, and other issues related to social determinants of health that make diabetes management extremely challenging. Furthermore, implicit bias may affect who is offered such devices (100,101).

Liability

One interesting question to raise about AID systems is liability. At first glance, this might be obvious. Questions to consider are as follows: How does a given AID system respond to issues and challenges? How do the algorithms implemented in the system respond to avoid too low glucose values (i.e., hypoglycemia safety measures)? How do we know if the algorithms implemented work adequately under all circumstances? How do we hear about issues?

DIY AID Systems

Less than 10 years ago, upon recognition of the myriad data generated by diabetes devices and the inability to access this data in real time, efforts led by individuals with diabetes demonstrated to manufacturers that remote monitoring of CGM data was feasible. Building on this momentum, an online community of devoted individuals whose lives were touched by diabetes sought next steps and built their own AID systems using a DIY approach (102). The advantages of such an approach are the flexibility and rapidity with which the DIY AID systems can be adjusted to new needs and options. For example, adaptations of algorithms allow for incorporation of insulins with improved pharmacodynamic properties. In contrast to commercial AID systems, with a "one size fits all" approach, a DIY AID system can be adjusted to meet the needs and specific situation of an individual patient. Compared with commercial AID systems, DIY AID systems offer more tunable parameters, thus offering a truer possibility of personalized medicine.

However, the entry bar for a patient who wants to start a DIY AID system is high. This is not merely downloading an app and transitioning to AID. In fact, creation of such systems requires extensive knowledge and frequent monitoring of diabetes therapy.

Additional complications tied to DIY AID systems are differences in legalities and liabilities between different countries. For example, one of the present authors (L.H.) described the German perspective on DIY AID systems in a recent publication (69). Later, a letter that challenged the views expressed in the publication as not being patient centered enough was published (103). Afterward, the reply to the letter clarified that DIY AID systems were a positive development but should be assessed with thorough scientific evaluation (104). Recently, an international consensus statement was published detailing the current state of DIY AID systems, including a description of the systems, evidence of their use, and considerations for clinical implementation. Further, the authors discussed both the ethical and the legal implications of system use, with the understanding that legal consequences of unregulated systems vary between jurisdictions (105).

To date, the benefits of using DIY AID systems have not been fully evaluated in randomized controlled trials, though studies are underway. However, results of a number of real-world studies showed remarkably positive outcomes (106), even during pregnancy and in remarkably challenging patient situations, such as running a half-marathon (107,108). Nevertheless, DIY AID systems are not recommended by regulatory agencies or scientific societies due to the lack of current evidence on safety and "gray zones" and the risk-benefit balance, as well as unsolved liability issues. Overall, DIY AID systems represent a useful tool to learn about how an optimal AID system might operate. Although there is the need for rigorous devotion and intent focus on details in operating DIY AID systems, there is a lot to learn from the users of such systems.

If a provider is asked by an individual with diabetes about using a DIY AID system, the provider should act as follows:

1. The provider should tell the individual that these systems are not approved by regulatory agencies (i.e., they are used off-label), which in turn means that the manufacturer of the components used to build such a system (i.e., the CGM system and insulin pump) are not liable.
2. The provider should tell the individual that although these systems cannot be prescribed by a provider, and the patient assumes responsibility for their use, the provider can make recommendations regarding patient safety and assist with developing a backup plan in case the system fails.
3. The provider should document/report problems (including in electronic health records) if they arise not only to support the ongoing development of such systems but also to enable assessment of the safety of these systems (69,109).

It should be noted that these recommendation are somewhat country specific, depending on the legal framework in the given country.

Patients should be encouraged to review all training material available on social media by groups who support these systems, carefully build (and rebuild) the application on their smartphones, be aware that changes in smartphone operating systems can interfere with proper function of the DIY algorithm, and realize that inquiries about system function will need to be answered by the DIY support group rather than the patient's clinician, who generally does not have any training on/responsibility for the technical use of these systems.

The question of liability becomes exponentially larger in considering DIY AID systems. Since these systems are created by the user through the bridging of different system components, who is liable should a system malfunction occur?

Conclusions and Outlook

We outline a list of considerations for regulatory agencies, manufacturing companies, international and national professional societies, funding bodies, researchers, health care professionals, and people with diabetes to take into careful consideration. These can be categorized into the following themes:

- More systematic and structured guidelines for AID systems usage (1*a–c* and

3*d* and *e* in *CONSENSUS REPORT RECOMMENDATIONS*, below)
- Improved consistency and accessibility of safety reports (2*a*, *b*, and *d*)
- Greater investment in collecting of clinical data to provide evidence for or against use of AID systems (4*a* and *b* and 5*a* and *b*)
- Increased accessibility for all consumer populations to use AID systems confidentially and securely (2*c*, *g*, and *h* and 3*c*)
- Increased communication and cooperation across stakeholder groups (1*d*–*g*, 2*e* and *f*, 3*a* and *b*, 6*a*–*e*, and 7*a*–*c*)

Consensus Report Recommendations

1. Regulatory agencies should:
   - *a*) Harmonize their activities.
   - *b*) Establish and update standards to be met by manufacturing companies.
   - *c*) Provide a regulatory pathway with clear steps and guidance on how to obtain approval for future AID systems.
   - *d*) Construct guidance for conducting both pivotal trials of new devices and postmarketing trials with a focus on evidence regarding how to assess safety and efficacy of systems. Postmarket studies and registry data may elucidate evidence on effectiveness of systems.
   - *e*) Encourage manufacturers to perform randomized trials and not single-arm studies.
   - *f*) Foster a commitment to conduct long-term studies of AID systems to evaluate persistence of glycemic benefits and to explore how this may translate into rates of long-term complications of diabetes.
   - *g*) Consider the potential for head-to-head studies comparing different AID systems.
   - h) Determine methods to evaluate DIY AID systems in larger-scale real-world observational and clinical settings.
   - *i*) Create, publicize, and maintain a single publicly accessible international database of available AID systems.
   - *j*) Publish an annual summary of regulatory activities, which can be linked to the database created.
   - *k*) Mandate that device manufacturers provide information on the population studied in pivotal trials and any updates based on real-world studies that may highlight the clinical data regarding who would derive most benefit from the product. These demographics and characteristics could be updated at least annually based on real-world and/or registry data, allowing clinicians and people with diabetes to better assess what device may best suit their needs. The time commitment involved may not align with that of product cycles; however, this would help to avoid the scenario where a system is licensed based on data that only includes the "safest" participants.
2. Manufacturing companies should:
   - *a*) Comply with regulations, industry standards, and best practices established for AID systems.
   - *b*) Perform long-term (>1 year) studies with collection of real-world data with prespecified data collection requirements, including clear delineations of primary and secondary outcomes at the outset of the study, while monitoring the frequency/intensity of study site contacts to make the data generated more easily translated to clinical care.
   - *c*) Create training modules that are readily available and written at an accessible reading level to ensure these modules will meet the needs of individuals with diabetes. Additionally, help-desk resources should be clear and provide 24/7 access for technical support to ensure optimal use of AID systems.
   - *d*) Assess the usability of device interfaces, with the goal of creating user-friendly platforms for all demographic groups. Further, it should be possible to personalize the interfaces with real-time insights and suggestions for individual users.
   - *e*) Report all safety-related data promptly and transparently to the regulatory authorities.
   - *f*) Cooperate with academic and health care professionals to provide balanced and adequate information both to providers and patients with diabetes.
   - *g*) Package output data from devices in standardized formats for ease of access, and potentially integration, in electronic health records.
   - *h*) Provide users the option to submit their data, including demographic information, anonymously, which will provide real-world metrics of device use to be monitored and reported annually.
   - *i*) Incorporate a high degree of data security and patient confidentiality.
3. International and national professional societies and advocacy organizations should:
   - *a*) Engage all stakeholders including people with diabetes, health care professionals, manufacturing companies, and regulatory authorities together to facilitate discussion on how to advance AID while prioritizing safety and privacy of people with diabetes.
   - *b*) Encourage academia and medical associations to advance research in AID systems and conduct large-scale clinical trials in diverse populations.
   - *c*) Help set expectations for HCPs and consumers about the strengths and limitations of AID systems.
   - *d*) Provide evidence-based guidelines on the effectiveness of AID systems.
   - *e*) Recommend appropriate forms of structured education required for HCPs to support patients with diabetes to ensure benefit from the chosen AID system.
4. International and national research funding bodies should:
   - *a*) Provide or facilitate funding for well-designed acquisition of independent clinical evidence on safety, effectiveness, outcomes, and use of AID systems in real-world settings; this may include sponsorship or registries able to collect such data.
   - *b*) Provide or facilitate significant financial support for long-term data collection by registers.
   - *c*) Provide a harmonized/standardized approach to reporting results obtained with AID systems. This would help HCPs and people with diabetes to assess the performance of AID systems and highlight where action is needed to improve safety and efficiency of AID therapy in an individual.

5. Researchers/academics should:
   a) Share patient-level data only in accordance with local law.
   b) Develop and validate specific and appropriate patient-related outcome measures.
6. Health care professionals should:
   a) Be knowledgeable of AID systems and nuances of different systems, including their distinguishing features as well as strengths and weaknesses.
   b) Inform patients with diabetes about AID systems, including review of currently available systems, and create realistic expectations for device use.
   c) Involve patients with diabetes in shared decision-making when considering use of AID systems.
   d) Share information with people with diabetes, as well as their peers, about general standards set by national and international guidelines on AID systems.
   e) Provide an on call number, or method by which a person with diabetes can access support from an HCP, at the practice to be available at all times including weekends and nights. This will allow for support for patients with diabetes in critical situations. Protocols may be implemented on times when AID systems should not be used.
   f) Use an individual's health data to improve quality of care and health outcomes.
7. Consumers of AID systems—people with diabetes, family members, and caregivers—should:
   a) Have realistic expectations of AID systems; these are a tool to help with optimizing glycemic management, rather than an onerous system, but one must remain engaged in care.
   b) Discuss available AID systems with their health care professionals.
   c) Submit data for HCPs to review and report issues with device components to their HCPs, manufacturers, and/or regulatory authorities.
8. Evidence-based access policies for AID should:
   a) Be set by policy makers and ideally reflect the evidence base, including acknowledgment of the challenge in diabetes technology research as the evidence base and the product cycle move so rapidly that dynamic review is required but is almost never undertaken.
   b) Be frequently and regularly reviewed.
   c) Embed structured consideration of health inequalities in the access policy.
   d) Include patient-reported outcomes when forming policy.

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