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Authors

Kompala, Tejaswi
Neinstein, Aaron B

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Smart Insulin Pens: Advancing Digital Transformation and a Connected Diabetes Care Ecosystem

Tejaswi Kompala, MD[1] and Aaron B. Neinstein, MD[1,2]

Abstract

With the first commercially available smart insulin pens, the predominant insulin delivery device for millions of people living with diabetes is now coming into the digital age. Smart insulin pens (SIPs) have the potential to reshape a connected diabetes care ecosystem for patients, providers, and health systems. Existing SIPs are enhanced with real-time wireless connectivity, digital dose capture, and integration with personalized dosing decision support. Automatic dose capture can promote effective retrospective review of insulin dose data, particularly when paired with glucose data. Patients, providers, and diabetes care teams will be able to make increasingly data-driven decisions and recommendations, in real time, during scheduled visits, and in a more continuous, asynchronous care model. As SIPs continue to progress along the path of digital transformation, we can expect additional benefits: iteratively improving software, machine learning, and advanced decision support. Both these technological advances, and future care delivery models with asynchronous interactions, will depend on easy, open, and continuous data exchange between the growing number of diabetes devices. SIPs have a key role in modernizing diabetes care for a large population of people living with diabetes.

Keywords
digital health, diabetes mellitus, insulin delivery, telehealth

Background

Prevalence of People With Diabetes on Insulin Therapy Is Increasing

As the worldwide diabetes prevalence continues to increase, the prevalence of insulin users is also rising. In 2018, 34.2 million people in the Unites States had diabetes,[1] and more than 10 million of those individuals used insulin.[2]

Until recently, digital advances in insulin delivery were limited to insulin pump users, whereas traditional methods of insulin delivery—vial and syringe or insulin pen—remained untouched by modern digital technology. However, with the recent commercialization of the first generation of digital, "smart" insulin pens (SIPs), a much larger population of people with diabetes (PWD) have the potential to access a digital tool to facilitate improved and easier insulin therapy. We explore the role of SIPs in an increasingly connected diabetes care ecosystem, with special focus on use of device-generated data by patients, clinical teams, and health systems.

Healthcare, Including Diabetes Care, Is Digitizing

The delivery of healthcare and the way patients consume healthcare are changing. Diabetes care is shifting from synchronous, in-person, face-to-face office visits to synchronous telehealth (eg, video visits) and, increasingly, asynchronous digital care, offered mostly by newer market entrants.[3,4]

The paper glucose logbook—with its legacy of inaccuracies and missing data—is being replaced with automated data capture that is easier and more efficient for patients to produce and for providers to review. Continuous glucose monitoring (CGM) data, for example, can now be reviewed continuously through cloud-based data sharing. Patients take on zero additional work beyond normal device use to share data. Providers, during visits or asynchronous care, can access and review data. Aggregated data in standardized glucose reports can assist with decision-making, and over time, machine learning-based recommendations will be increasingly possible. In other chronic conditions, digital technologies are increasingly leveraged to improve and personalize

[1]Department of Medicine, University of California, San Francisco, San Francisco, CA, USA
[2]Center for Digital Health Innovation, University of California, San Francisco, San Francisco, CA, USA

Corresponding Author:
Tejaswi Kompala, MD, University of California, San Francisco, 1700 Owens Street, Suite 541, San Francisco, CA 94158, USA.
Email: Tejaswi.Kompala@ucsf.edu

the care delivery experience and outcomes for patients, such as in asthma,[5] heart failure,[6,7] and oncology.[8]

Insulin Pens Are the Preferred Mode of Insulin Therapy in the United States

Increasingly chosen by insulin users as their delivery mode, insulin pen use in the United States has steadily increased in the past decades in both type 1 diabetes (T1D) and type 2 diabetes (T2D), and now represents the largest market share in the commercially insured population.[9,10] Compared to use of insulin vial and syringe, insulin pens are preferred by patients, citing high satisfaction and ease of use.[10,11] Pens are better for dose accuracy and associated with better adherence to insulin use.[11-14] Use of insulin pens, as compared to vial and syringe, also confers glycemic improvements with decreased A1c, as well as decreased hypoglycemia.[10,15] Despite higher upfront costs related to pen use, total all-cause and diabetes-related costs are lower.[15] Insulin pen users have significantly fewer hospitalizations, diabetes-related hospitalizations, and hypoglycemia-associated health care utilization.[14,16]

Insulin Pumps Offer Many Benefits of Digital Technology, but Are not Available to All, nor Desired for All

While we commonly refer to insulin pump therapy as "CSII," or continuous subcutaneous insulin infusion, the reality is that many of the benefits have to do with the *digitization* of insulin delivery rather than the continuous insulin infusion itself.[17] Insulin pumps have evolved following a common path in digital transformation (see Table 1), where what was once an analog activity (injecting insulin) became a digital tool connected with other networked digital tools, using machine learning to provide automated insulin delivery and better glucose control.

Insulin pumps, however, are not accessible to all, nor are they always the desired delivery mechanism for all PWD.[18] For many potentially eligible patients, cost barriers, variable insurance coverage, and authorization hurdles prevent use.[19] Others may lack accessibility to diabetes specialists or the ability to participate in the time- and resource-intensive training required to successfully start using an insulin pump.[19-21]

Smart Insulin Pens

Though there have been iterative improvements and modifications to connected pens and attachments in previous years,[22] we argue that an SIP requires a set of core components: digital dose capture, real-time wireless connectivity, real-time connectivity with glucose-sensing devices, and integration with insulin-dosing decision support. The Companion InPen, released in December 2017, is the first FDA-approved "smart pen" for insulin to meet these criteria.

Table 1. Common Sequence of Steps in Digital Transformation.

Common sequence of steps in digital transformation	Insulin pump example
1. Simplify and automate a complex manual operation	Bolus calculator function
2. Capture and store data	Time log data of insulin delivery
3. Provide simple statistics	Insulin pump data summary
4. Develop advanced statistics	Personalized recommendations
5. Network data sources together	Connected pump and CGM
6. Apply machine learning	Automated insulin delivery

Abbreviation: CGM, continuous glucose monitoring.

In reviewing key functionalities of the InPen, we highlight general principles of user design and interoperability that will be key for future SIPs.

At its core, the InPen is an insulin delivery device, augmented with Bluetooth connection to a paired smartphone application, which provides bolus calculator functionality and automatic data capture. The current model of InPen depends on predetermined therapy settings programmed into the smartphone app, but as Kerr and Warshaw describe in their roadmap to smart insulin pens (see Figure 1), future SIPs should enable advanced decision support, to aid individualized insulin therapy.[23]

In practice, the InPen allows the programming of personalized insulin delivery settings—target glucose, insulin to carbohydrate ratio (ICR), insulin sensitivity factor (ISF), duration of insulin action (DIA)—into a user's smartphone application. Based on these settings, calculations guide users to manually deliver personalized doses of rapid acting insulin for mealtime and corrections. Importantly, because the InPen captures dose history, the calculations automatically subtract "insulin on board." Thus, users benefit from individualized digital tools similar to those found in an insulin pump, but with a lower cost and with the freedom of not being continuously connected to a pump.

Smart Insulin Pens: The Future of Digitized Insulin Delivery

Insulin pens are likely to remain the predominant insulin delivery device for the foreseeable future, in part due to familiarity and preferences by patients and primary care providers, and in part due to limited access or interest in insulin pumps. By bringing digital technology and connectivity to insulin pens, we believe that SIPs have the potential to dramatically improve quality of care and the care experience for millions of people living with diabetes.

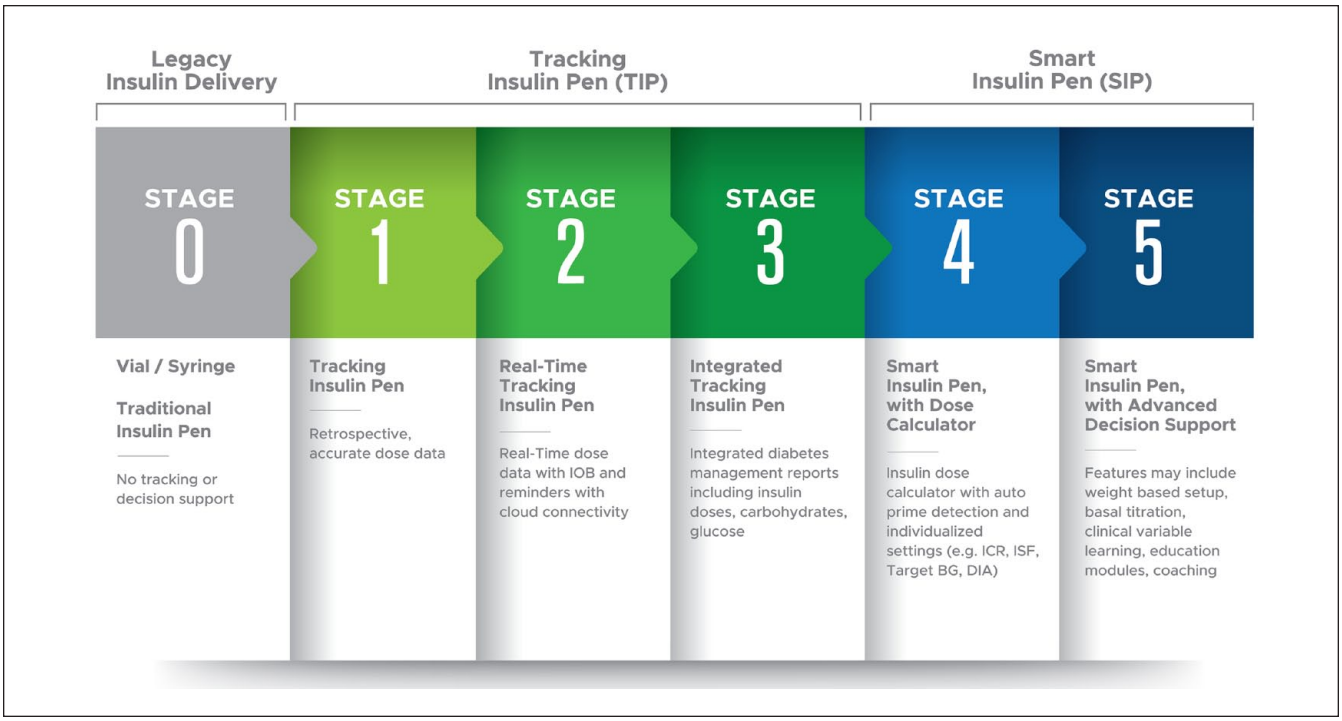

Figure 1. Roadmap to smart insulin pens.

While some benefits of these devices accrue directly between device and user, many other potential benefits require that we both develop and leverage a more connected data ecosystem and clinical delivery system using device data in care delivery.[24] Historical experience with CGM and insulin pumps shows that, when clinical infrastructure and device connectivity are inadequate, patients and providers underutilize retrospective data review.[25] Because the vast majority of PWD receive diabetes care in the primary care setting, achieving spread and use of SIPs at scale will require much more seamless data flows and easy-to-use toolkits within the typical clinical practice setting. We explore here the opportunities and challenges in leveraging SIPs to create a more connected diabetes care ecosystem.

Smart Insulin Pens: The Patient Perspective

The SIP promises a series of patient-directed digital technology interventions that have the potential to improve diabetes management decisions for patients in real time, enhance decision-making based on retrospective review, and create future opportunities in data connectivity, ownership, and sharing.

SIPs Promote Adherence and Safety in Multiple Daily Injections Therapy

PWD on insulin therapy rely on numeracy skills to make dosing decisions multiple times per day, yet we know that these skills are heterogeneous, and frequently lead to errors in dosing that impact diabetes self-management and glycemic control.[26-28]

Bolus advisors (BAs) were developed to assist patients using multiple daily injections (MDI) therapy with the complex decision-making involved in insulin dosing. BAs demonstrate benefit in glycemic control and allow patients to take more accurate doses.[29-31] Though the evidence base is building for BAs within SIPs, we expect similar positive findings on treatment satisfaction and glycemic control as have been demonstrated previously with bolus calculators.[29,31-33]

Missed or delayed boluses are common with MDI therapy[34-37] and can negatively impact glycemic control.[38] SIPs and connected software can be enabled with real-time dosing alerts and reminders.[22] Early observational evidence suggests that SIPs may reduce the frequency of missed mealtime boluses.[39]

Retrospectively, SIPs can help identify patterns of missed or mistimed meal boluses, providing feedback to the patient.[39] Further, because SIPs represent ground-truth, precise digital capture of the timing of each insulin dose, when combined with CGM data, these data could enable fine-tuning and personalized improvements on the precise and optimal timing of a meal bolus for an individual.[40]

A critical aspect of SIPs is to promote safety with insulin dosing. Insulin is a frequent culprit in adverse events primarily related to hypoglycemia from overt dosing errors and also from insulin dose stacking.[41,42] By automatically accounting for insulin on board based on captured dose data, SIPs may

help reduce hypoglycemia occurrence and associated fear of hypoglycemia.[29,32]

SIPs Will Iteratively Improve

At present, most bolus calculators consider ISF, ICR, and DIA, but many other variables impact BG levels and insulin sensitivity, and we expect these will be increasingly incorporated into future calculators.[43] Personalized suggestions for insulin regimen and dose adjustments based on machine learning, currently possible with insulin pump therapy, should also be leveraged with SIPs. To make this possible, data will need to be connected between various devices and cloud systems. For example, CGM data and wearable activity data should directly integrate into the same software tool as insulin dosing.

One benefit of the digitization of insulin pens is the ability to have software updates. Without any change to the device hardware, vendors can make software upgrades with iterative adjustments to features like algorithms and calculators, as done recently with InPen adding a mode for small, medium, and large mealtime dose calculations rather than dosing only by carbohydrate counting. Software updates and their separation from hardware upgrades represents a paradigm shift in medical devices—product upgrade cycles can be dramatically faster, more iterative, and incorporate ongoing learning through agile process, in contrast to long, expensive, multi-year product cycles that can impede innovation. In the United States, FDA's Digital Health Innovation Action Plan is helping to speed existing and create new approvals processes for "software as a medical device."[44]

Cost and accessibility of the requisite components for SIP therapy—the smartphone, SIP, and insulin—necessitate ongoing attention. Though most adults in the United States have smartphone access,[45] reliance on smartphones for insulin therapy does require that patients and providers have back up plans when phone access is not possible (eg, battery failure, faulty Bluetooth connection, lost phone). Programs will be needed to facilitate setup, training, and education on the features of the SIP smartphone applications. Additionally, beyond the existing challenges to insulin coverage and access, SIP manufacturers will need to limit pen cost and ensure interoperable functionality across different insulin types.

Future Considerations for Patients: Data Integration and Data Access

Individuals in the United States want electronic access to their health data.[46] The Health Insurance Portability and Accountability Act of 1996 (HIPAA) gives an individual the right to request all of his or her health data from a covered entity, such as a healthcare payor or provider. Bolstering this right, the 21st Century Cures Act of 2016 states that health systems must give patients electronic access to their health data via application-programming interfaces (APIs) "without special effort," and increasingly health systems are doing so.[47] However, this right has not yet been applied by federal policy or enforcement to a patient's right to access his or her own medical device data. Device makers are currently left to decide on their own what level of data access to provide to patients.

Patients should have the ability to use their data personally, to view all their data integrated together, and to share this information with family members, clinicians, or even with researchers if they desire.[48] A system like Apple Health enables an individual to integrate together different sources of health data into one place, and then direct access to those data for use by any other software application. To date, some diabetes device makers have chosen to allow their data to be accessible in Apple Health. However, other device makers have chosen to keep their data access proprietary, limiting data access to only those companies with whom they have formed one-to-one business partnerships. Without full interoperability and easy API-based access to data, the utility patients can gain from diabetes device data will continue to be limited and restricted.

As an example, the Companion InPen allows extensive data sharing—insulin dose data are shared with Apple Health as well as with Dexcom. This means that a user can choose to view InPen data in either the InPen app, Dexcom's Clarity software, Tidepool, or Glooko, and conversely, Dexcom CGM data are viewable in the InPen app. When data are integrated like this, they are more easily visualized, facilitating more efficient and accurate interpretation (see Figure 2). In stark contrast, it is not currently possible to view data from a Freestyle Libre CGM and the Companion InPen in the same data visualization, hindering efficient provision of care for the patients who choose this combination of devices.

Smart Insulin Pens Within Clinical Practice

With the digitization of insulin dose history, SIPs can support providers in optimizing diabetes care, with even greater impacts when combined with CGM data. Additional work is required for effective team-based care and a satisfactory provider experience.

Insulin Dosing Data Promotes Active Diabetes Management

Software-based diabetes data review has been shown to improve diabetes outcomes.[49] Retrospective CGM review can be a powerful educational tool and has been shown to increase patient-provider discussion in clinical visits.[50] On the other hand, lack of timely data access to facilitate a diabetes visit can lead to therapeutic inertia.[51] Therefore, by filling

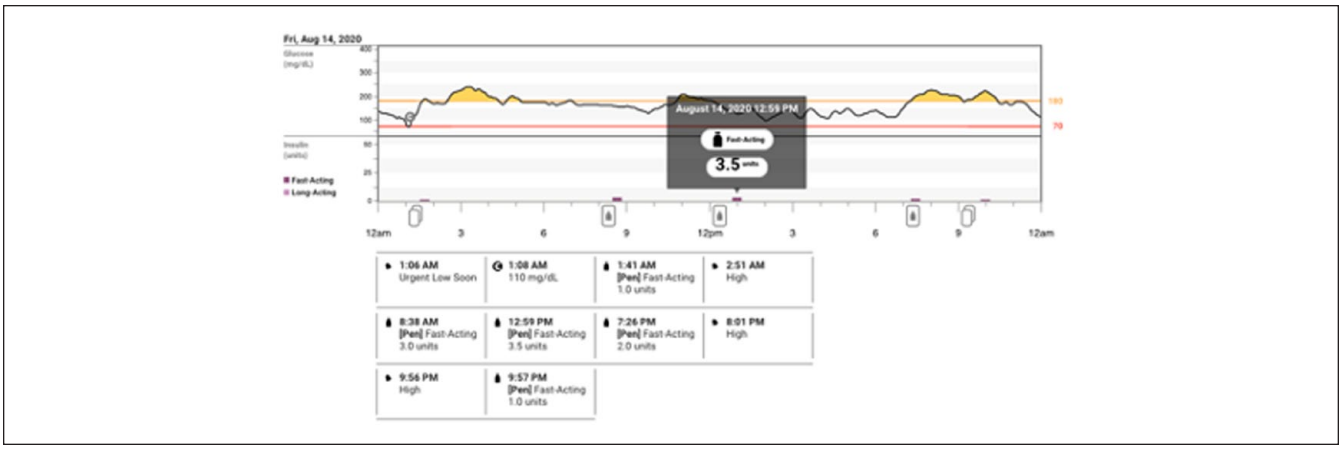

Figure 2. (Provider-facing): Dexcom + InPen data visualized together; Integrated data is more easily visualized and facilitates efficient interpretation.

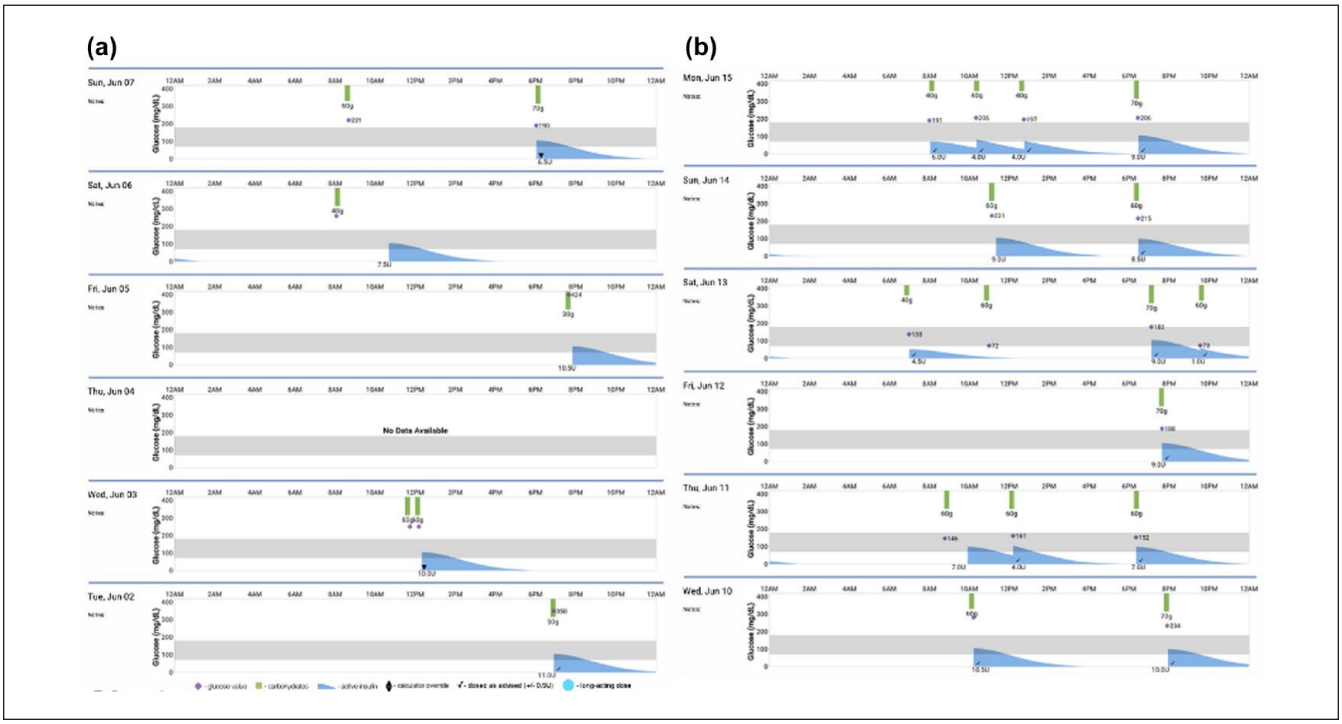

Figure 3. (Patient-facing): Patient with identification of frequent missed boluses (a) before viewing retrospective InPen data download and (b) after viewing data download.

data gaps and adding complete and accurate information about insulin dosing data in the context of glucose control, SIPs present an opportunity to facilitate the patient-provider interaction and aid in timely clinical decision-making.

Issues such as fear, stigma, and cost often drive a patient's reluctance to use insulin therapy as prescribed.[52] When using SIPs, discussions about a PWD's insulin delivery history can be objective, and more easily seen by patient and provider, potentially leading to more frequent and open conversations about patient concerns, reluctance, or other habits around insulin dosing. In a recent patient encounter in our practice, a retrospective review of insulin data made it clear that the patient was frequently missing mealtime insulin boluses (see Figure 3). After reviewing the SIP report together, and without requiring significant discussion or explanation on part of provider or patient, the patient changed his behavior and increased his frequency of meal-time insulin boluses.

As new sources of diabetes data emerge and are connected to care, effective engagement of the full diabetes care team is possible. In addition to providers, data can also be reviewed by dieticians, diabetes educators, and health coaches to encourage behavior change with food, adherence,

Table 2. Focus Areas for Optimizing Clinic and Provider Experience.

1.	Require use of standard APIs to make diabetes device data easily accessible from any device to any software, at patient's direction
2.	Enable SMART-on-FHIR launch of diabetes software applications from EHR
3.	Integrate discrete diabetes device data directly into EHR
4.	Simplify EHR-based electronic prescribing process for SIPs
5.	Streamline patient onboarding and confirm data sharing with diabetes software
6.	Automate pre-visit reminders for data upload

Abbreviations: API, application-programming interface; EHR, electronic health record; FHIR, fast healthcare interoperability resources; SIPs, smart insulin pens; SMART, substitutable medical applications and reusable technologies.

or other aspects of daily diabetes management. When patients need access to additional support, coaching from digital services is an option.

Data Integration and Machine Learning Will Augment Diabetes Management

While providers benefit from the additional data captured by SIPs and are better able to fine-tune individualized treatment parameters, this work takes time and energy. Humans are inherently unable to leverage the vast quantities of available data. Machine learning may prove to be more effective and efficient in reviewing the data and aiding in recommending adjustments to insulin settings. To date, companies exist to do this for hospitalized patients on insulin infusions[53-55] and for outpatients using insulin pumps,[56,57] and we expect to see similar technology emerge to better aid in interpretation and titration of insulin pen doses. While tailored adjustments of insulin dosing regimens have traditionally been the job of an Endocrinologist, advanced decision support driven by machine learning may increasingly empower primary care providers to care for patients using complex MDI therapy.

Provider Experience and Clinic Integration Need to be Optimized

Currently, routine integration of diabetes devices into office-based care is inefficient and cumbersome. Broad uptake of these new devices will require a focus on data accessibility and usability for the clinic staff, provider, and clinical team, with improvements required in several areas (see Table 2):

(1) Data from diabetes devices should be accessible and able to be aggregated across all software systems, so that providers can easily view all relevant data in one source.[58] To facilitate this data exchange, device makers should leverage standard APIs.

(2) Enable launch of diabetes data apps from the electronic health record (EHR) via SMART-on-FHIR, so that providers and clinic staff do not need to maintain separate accounts and passwords (akin to using OAuth technology to use your Google, Twitter, or Facebook ID to authenticate and log you on to a different website).[59]

(3) Directly integrate diabetes device data into the EHR, avoiding time-intensive, frustrating, error-prone manual entry. This would also facilitate analytics and longitudinal tracking of changes in time-in-range or insulin dosing regimens, largely impossible today.

(4) Simplify the prescribing of SIPs. Prescribing an InPen to date has required an order form that asks for insulin dose settings much like an insulin pump start form. This may erect a barrier to prescribing from a broader set of providers who may be intimidated by this or put off by the friction and time required.

(5) Easily onboard patients to connect their data to cloud and clinic accounts. Investing time upfront to help patients share data, connect devices, and learn how to access retrospective data is time-saving and will facilitate telehealth-based digital care delivery.

(6) Automate reminders to patients to connect or upload data before a check-in, avoiding clinic visit time wasted trying to upload device data.

Leveraging SIPs for Improved Population Health

As the focus in health care increasingly shifts toward high value care, allocating resources strategically within a group of patients becomes important. One could foresee identifying patients with poor diabetes control, frequent healthcare utilization, or otherwise medically complex as ideal candidates to receive SIP therapy. With the digital tools to promote insulin safety, high risk patient groups may benefit from SIP use.

Objective data capture allows better evaluation of adherence, and providers can more closely offer support. It has been shown with insulin pump therapy that individuals with poor diabetes control and those considered medically complex still benefit from the technology,[60,61] and we expect the same to apply with SIPs.

Just as CGM data can be used to stratify patients into risk categories,[62] and as insulin pump reports have been used to identify behavioral patterns, SIP data could similarly be used. A clinic dashboard could identify PWD who are frequently missing boluses and allow targeted outreach to promote improved dosing strategies. The dashboard could identify those with sudden changes in insulin usage and escalate their care to a provider. We could identify people who consistently struggle with carbohydrate estimation and offer focused education. Achieving these opportunities also requires a connected data ecosystem where population-level dashboards enable simultaneous visualization of aggregated data from the EHR, CGM, and SIPs.

Table 3. Summary of Smart Insulin Pen Benefits for Patients, Providers, and Health Systems.

Category	Feature	Summary
Patients	Safety and hypoglycemia avoidance	Bolus calculator on paired smartphone app accounts for insulin on board and recommends tailored insulin doses based on user input.
	Smartphone app supports dosing reminders	Users can enable reminders and alarms. Smartphone app tracks dose history so users rely less on memory.
	Software updates deliver frequently improved digital tools	Without requiring a new insulin pen, smartphone app can continuously update bolus calculator and other features.
	Data integration with glucose sensing	Data flow between InPen and Dexcom CGM allows users to see relevant data together.
Providers	Automatic data capture facilitates retrospective review	Objective data allows for data-driven discussion between patient and provider. Providers can discuss adherence, safety, and adjust insulin recommendations.
	Machine learning can support therapeutic decisions	Artificial intelligence can be used for advanced decision support, which may support primary care providers and specialists in adjusting complex MDI therapy.
Health Systems	Identify and support high risk patients	SIPs can be used in high-risk patients as therapeutic tools. SIP data can identify patients who need escalation of care.
	Connected data ecosystem promotes asynchronous care	Integrated insulin pen and CGM data can be accessed at any time by patients and providers; data-driven recommendations can occur between scheduled visits.

Abbreviations: CGM, continuous glucose monitor; MDI, multiple daily injections; SIPs, smart insulin pens.

The Future of Connected Care Is Increasingly Asynchronous and Continuous

Current typical practice involves a periodic clinic visit at standard intervals, which may then take advantage of data review from devices. In the future, patient care should involve more targeted, frequent, data-driven check-ins leveraging glucose monitoring and insulin dosing data.

To meet this future state, every diabetes device must contain the ability for seamless, passive, real-time data flow.[63] Cloud-based continuous streaming of data allows patients to be connected with care teams and offers the possibility for asynchronous, virtual connection. For example, after an initial synchronous consultation, subsequent care could be conducted asynchronously and virtually, with integrated SIP and CGM data reviewed within a few weeks of the original visit.[64] These easier, quicker interactions might drive more frequent check-ins and reduce clinical inertia.

Shifting to a model of care driven by patient need, rather than by provider availability and clinic schedules will require systemic changes. Providers will need new reimbursement models, along with sufficient time, and administrative and leadership support.

Conclusion

The SIP, as a connected digital diabetes tool, has the potential to improve diabetes care for millions of PWD on insulin therapy (see Table 3). Users of SIPs benefit from digital tools that provide easier insulin dose calculation, dose reminders, and facilitate hypoglycemia avoidance. Iterative software updates will speed new benefits to SIP users. Automatic data capture of insulin dose data, particularly when paired with glucose data, can help counter therapeutic inertia, and allow patients and providers to make data-driven decisions. As we move toward a connected care future, the benefits of broad use of SIPs—machine learning, asynchronous and virtual care, risk stratification—hinge on the success of a connected diabetes data ecosystem in which data flow is frictionless, data integration is standard, and care delivery workflows are reimagined.

Abbreviations

API, application-programming interface; CGM, continuous glucose monitor; CSII, continuous subcutaneous insulin infusion; DIA, duration of insulin action; EHR, electronic health record; FDA, Food and Drug Administration; FHIR, fast healthcare interoperability resources; HIPAA, Health Insurance Portability and Accountability Act; ICR, insulin to carbohydrate ratio; ISF, insulin sensitivity factor; MDI, multiple daily injections; PWD, people with diabetes; SIPs, Smart Insulin Pens; SMART, substitutable medical applications and reusable technologies; T1D, Type 1 Diabetes, T2D; Type 2 Diabetes.

Declaration of Conflicting Interests

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ORCID iDs

Tejaswi Kompala https://orcid.org/0000-0002-4492-5035

Aaron B. Neinstein https://orcid.org/0000-0002-9774-7180

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