An illustration of the use of the d-Nav® diabetes insulin guidance service: An insulin titration aid for type 2 diabetes

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Article points

1. An increasing number of people are being treated with insulin therapy in the UK, and most do not achieve their therapeutic HbA_{1c} goals.
2. The key element for successful insulin therapy is frequent dosage titrations to overcome variations in insulin requirements. Yet, due to high workload and the large number of patients, healthcare providers rarely have time to adjust dosage.
3. The diabetes insulin guidance service (DIGS) combines d-Nav® (a handheld device) with the clinical expertise of a diabetes nurse team. DIGS is a scalable and practical solution to aid frequent insulin titrations for people with type 2 diabetes who use insulin without overburdening healthcare systems.

Key words

- d-Nav®
- Dose recommendations
- Insulin guidance service
- Titration

Authors

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About a quarter of the people with diabetes progress to require life-long insulin therapy, and the majority of individuals using insulin have type 2 diabetes. Despite the introduction of the deficient hormone, many people who inject insulin continue to experience persistent hyperglycaemia while complications escalate. Studies have shown that insulin therapy can be successful if combined with frequent dosage adjustments in narrowing the gap between the initially prescribed dosage and the individual optimal therapeutic dosage. Additionally, due to constant variations in insulin demands, frequent titration is needed to maintain optimal control while avoiding hypoglycaemia. In reality, insulin titration is done sporadically, and provider-based, frequent insulin titration is unlikely to be feasible. This article describes a scalable and practical solution, the d-Nav® diabetes insulin guidance service, which assists insulin titration for people in type 2 diabetes.

Mrs Smith is a 62-year-old woman who has had type 2 diabetes for 14 years. She was successfully using metformin until 2 years ago when her HbA_{1c} started to trend upwards. Her primary care provider has added a variety of agents over this time to control her hyperglycaemia, and all have been effective but only for a short period of time.

About a year ago, Mrs Smith started using soluble/isophane insulin 30/70 mix at an initial dosage of 20 units with breakfast and 15 units with dinner. She has seen her primary care provider three times over the previous year and has been reviewed twice by a consultant endocrinologist. At present, she continues to use soluble/isophane insulin 30/70 mix, 38 units with breakfast and 22 units with dinner but her HbA_{1c} is still 78 mmol/mol (9.3%), while her peripheral neuropathy and chronic kidney disease are worsening. The following questions arise:

- How common is Mrs Smith's problem?
- How much insulin does Mrs Smith need per day?
- Why is it so difficult to make insulin therapy effective?
- How can Mrs Smith's providers help to improve her glycaemic balance?

In this article, we will attempt to answer these questions and offer a solution to what we believe is one of the most substantial medical challenges of our generation. The diabetes insulin guidance service (DIGS) discussed, features a handheld device called d-Nav® (short for diabetes navigator), and is available by prescription. It provides users with an insulin dose recommendation for each injection and, by analysing stored glucose patterns, d-Nav titrates insulin dosage without provider supervision or behaviour modifications of the user. The service nurse specialists provide patients with on-going support and clinical triage.

How common is Mrs Smith's problem?

Type 2 diabetes is a progressive, multifactorial condition resulting ultimately in insulin deficiency. The management of this condition tends to be relatively simple during the first decade after diagnosis. Characteristically, in the majority of the cases adequate glycaemia can be maintained with lifestyle modification and metformin without significant complications or expenses (UnitedHealth Center Group, 2010). However, as individuals with diabetes progress beyond 10 years with the condition, they become resistant to medications, HbA_{1c} trends up and only insulin replacement therapy is able to improve

hyperglycaemia (UK Prospective Diabetes Study Group, 1998). Despite the introduction of the deficient hormone (i.e. insulin), unlike other hormone replacement therapies (e.g. levothyroxine for hypothyroidism, hydrocortisone for adrenal insufficiency and testosterone for male hypogonadism), most patients who use insulin continue to experience persistent hyperglycaemia while complications escalate (UnitedHealth Centre Group, 2010) – also referred to as "the insulin paradox" (Hodish, 2015).

In the UK, about 500 000 people with diabetes inject insulin (mainly for type 2 diabetes; Holden et al, 2014). These individuals experience the most complications and require the majority of resources (McBrien et al, 2013). Among insulin users in the UK, the average HbA_{1c} exceeds 64 mmol/mol (8%), and it is likely that more than a third experience an HbA_{1c} of 75 mmol/mol (9%) and above (Hillson, 2011; Holden et al, 2014). This reality is similar in other nations and unlikely to have changed since the 1990s (Hoerger et al, 2008; Hillson, 2011; Ali et al, 2013).

How much insulin does Mrs Smith need per day?

Fasting insulin levels in individuals without diabetes are about 10 mcU/mL (Fesinmeyer et al, 2013). Earlier physiology research has alluded that this level corresponds to pancreatic insulin secretion of about 1 unit/kg per day (Waldhausl et al, 1979; Polonsky et al, 1988a; 1988b). Endogenous pancreatic insulin secretion occurs in the portal system, where the main organ responsive to the hormone is the liver. Once a patient becomes insulin deficient, no longer secretes enough insulin and requires insulin replacement therapy, insulin is administered peripherally outside the portal system. Due to peripheral metabolism of the hormone, mainly in the kidney, the required dosage needed to achieve similar levels of insulin in the portal system doubles (i.e. approximately 2 units/kg per day; Ishida et al, 1984). This does not take into account cutaneous degradation of injected insulin (Freidenberg et al, 1981), and is not the case for individuals with type 1 diabetes who typically need low insulin dosage (Campbell et al, 2014).

In diabetes, endogenous insulin secretion fails gradually, so it can take a few years to build the required individual daily dosage once insulin therapy is initiated (Holman et al, 2009). In the majority of cases, fluctuations in blood glucose or the tendency to develop hypoglycaemia worsens a few years after diabetes onset (UK Hypoglycaemia Study Group, 2007) and more complex insulin regimens are needed to maintain optimal glycaemia while avoiding hypoglycaemia (Holman et al, 2009). Not surprisingly, in clinical studies that supervise insulin therapy in people with advanced diabetes to achieve predefined HbA_{1c} goals, individual daily insulin requirements average at 1.5–2 unit/kg with a wide variance of distribution (Bergenstal et al, 2008; Riddle et al, 2014).

Why is it so difficult to make insulin therapy effective?

Given the wide variation in total daily insulin requirements between individuals (Bergenstal et al, 2012) and the gradual development in insulin deficiency (Holman et al, 2009), it is impossible to predict how much insulin an individual patient requires, which can be less than 0.5 unit/kg per day or more than 3 unit/kg per day. Thus, the initial dosage needs to be low and frequent titration is needed to close the gap between the initial dosage and the individual therapeutic need. In the current standard of care, insulin dosage adjustments are done during clinic encounters that occur two to four times a year. Thus, it may take years to recognise or determine each patient's individual insulin requirements.

Identification of total daily insulin requirements is not the only challenge in maintaining therapy goals. Once optimal HbA_{1c} goals are initially achieved, insulin requirements continue to change (Bashan et al, 2015; examples in *Figure 1*). Transient or prolonged decrease in insulin requirements may expose individuals to frequent hypoglycaemia or bouts of hyperglycaemia. In reality, dosage adjustments are done sporadically (Blak et al, 2012); mainly during outpatient clinic visits and thus it is challenging for providers to recognise such changes in insulin requirements. Indeed, it has been demonstrated that the considerable clinical effort required to achieve therapy goals is similar to the effort needed to maintain them

Page points

1. Unlike other hormone deficiencies, when insulin is administered in diabetes, hyperglycaemia can still persist.
2. It can be difficult to predict how much insulin an individual patient requires; it can be less than 0.5 unit/kg per day or more than 3 unit/kg per day. Insulin requirements will continue to change even when the initial HbA_{1c} goal has been achieved.
3. Insulin dosage adjustments are mostly done sporadically, but it is recommended that titration adjustments are completed weekly.

(Rosenthal et al, 2011). In extreme cases, which are typically associated with acute or subacute medical conditions (e.g. deterioration in kidney function), total daily insulin requirements can decrease by more than 70% over a period of a few weeks (example in *Figure 2*).

Clearly, insulin therapy can be effective if combined with frequent insulin dosage adjustments continually rather then sporadically during outpatient clinic visits. Commonly used titration protocols suggest weekly titrations are preferable (Bastyr et al, 2015; Bergenstal et al, 2008; Riddle et al, 2015). Evidently, in clinical trials where insulin therapy is frequent adjusted every few days, insulin therapy is predominantly effective (e.g. Bergenstal et al, 2008; Buse et al, 2009; Bastyr et al, 2015). Additionally, in studies where insulin is one of the main agents used, optimal HbA_{1c} is usually lost 1–2 years after the completion of the protocol perhaps due to the loss of frequent adjustments (e.g. Hayward et al, 2015).

How can Mrs Smith's providers help her to improve her glycaemic balance?

Since frequent insulin dosage adjustments are needed at all times, can Mrs Smith's providers facilitate this by weekly clinic visits or phone calls? The process of insulin dosage adjustment is a teachable skill, but it is lengthy and requires resources that tend to only available in well-funded trials. For illustration, it may take more then 15 minutes to contact a patient, deliberate and then convey adjustment in dosage. Even if a provider was to spend their entire professional time adjusting insulin dosage, they would only be able to support about 150 people if weekly interactions occurred. In the UK, there are about 500 000 people who use insulin (Holden et al, 2014). According to the aforementioned provider-to-patient ratio needed for weekly insulin dosage adjustments, it would require over 3200 providers dedicated only to insulin dosage adjustments. Currently, in the UK there are about 2000 providers who possess the required

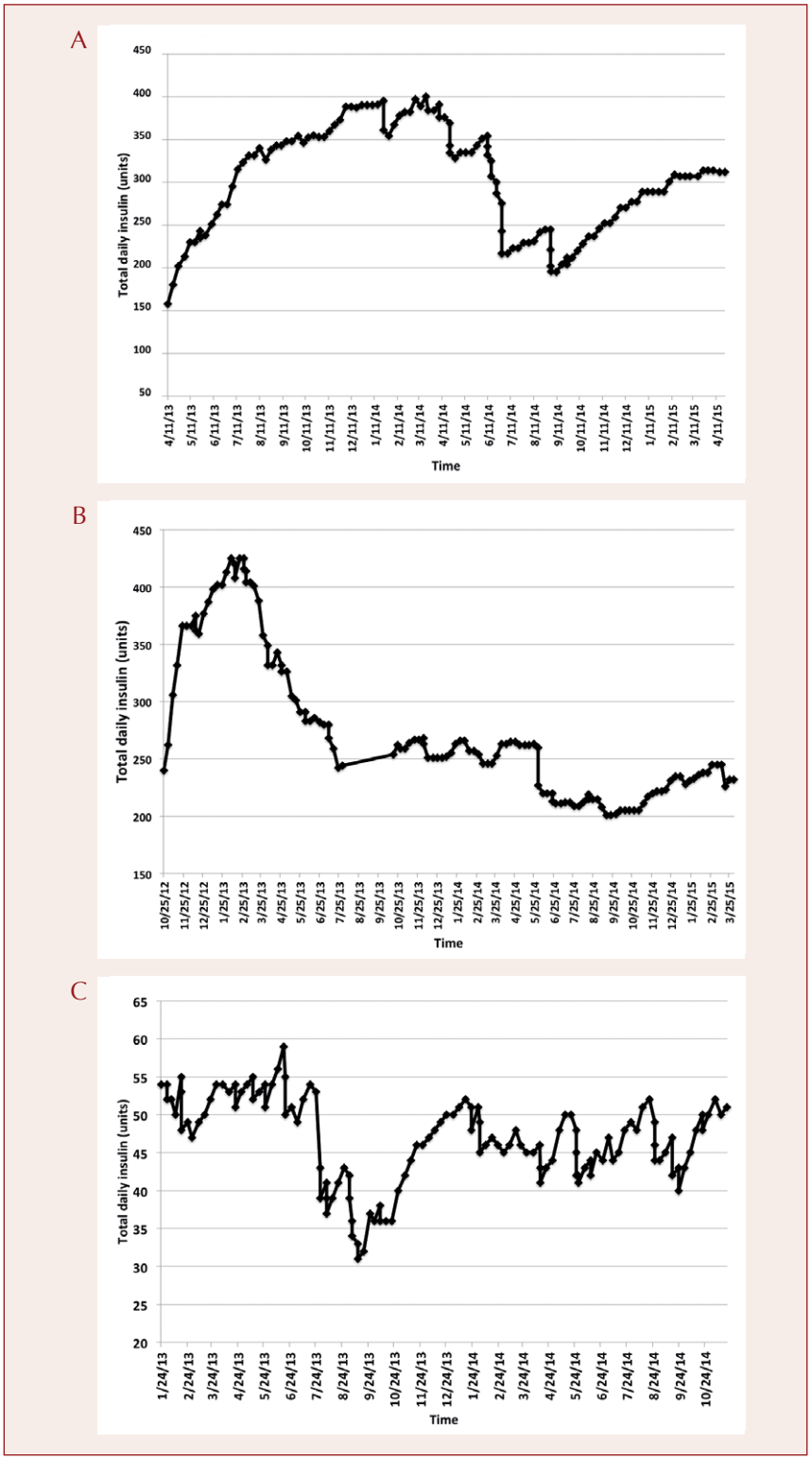

Figure 1. Dynamics in insulin requirements. Examples of patients treated with frequent insulin dosage adjustments for about 2 years. A) In this individual's case, total daily insulin maximised after about 7 months, decreased by about 50% over a period of additional 7 months and then started to rise again. B) In this patient's case, total daily insulin reached a peak after about 4 months and gradually decreased to a nadir that was lower than the initial total daily dosage. C) In this patient's case, total daily insulin remained fairly stable for 6 months and then decreased by about 40% for 4 months, before it increased to a level that was lower then the initial dosage and remained stable for at least an additional 10 months. Date is in MM/DD/YYYY format.

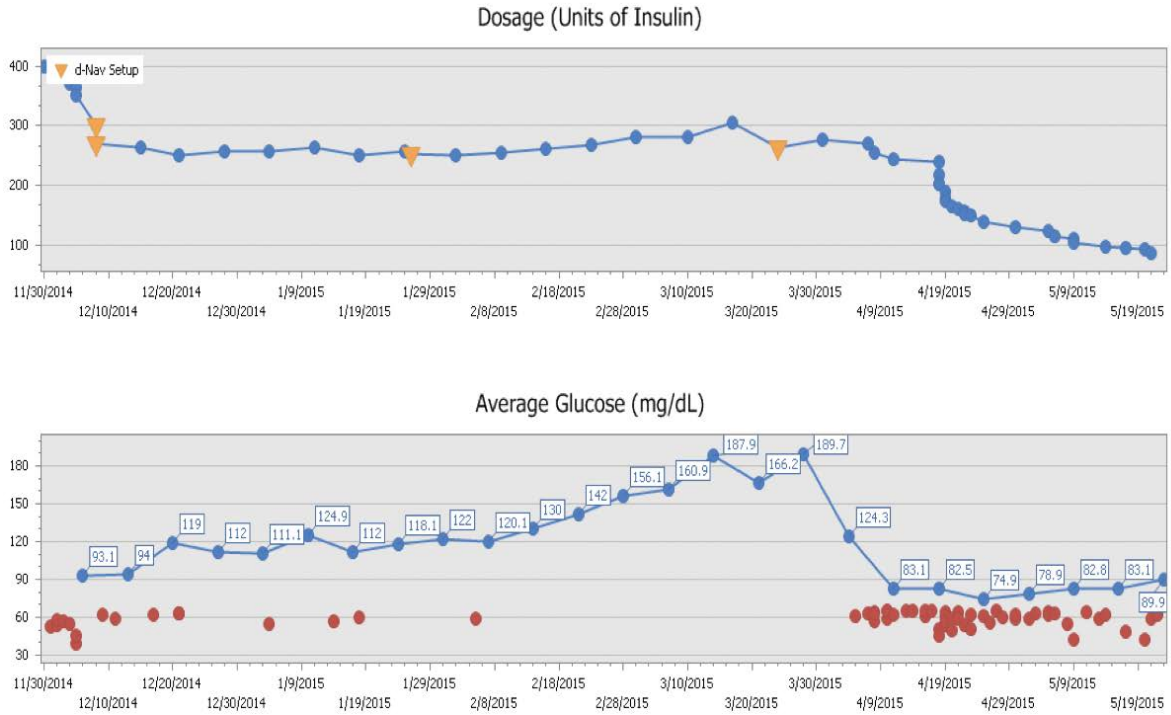

Figure 2. A d-Nav® download from a person with type 2 diabetes treated with basal–bolus insulin therapy with atypical clinical course. The upper graph denotes total daily insulin (in insulin units). The lower graph denotes weekly mean glucose (in mg/dL) and episodes of minor daytime hypoglycaemia (glucose ≤65 mg/dL [3.6 mmol/L]) are shown as red dots. From the end of March 2015 over a period of a few weeks, total daily insulin requirements dropped by about 66% due to a development of a post-operative small intestinal fistula. Due to the rapid change in insulin demands, over this entire 25-week period d-Nav performed 45 dosage adjustments (about twice a week). Date is in MM/DD/YYYY format.

expertise, but it is not possible for them to devote all their time to insulin titration (Blak et al, 2012). Even if insulin dosage adjustments were done every other week, the need would still surpass healthcare resources.

Most importantly, the challenge is not in the collection and delivery of glucose data to the provider, for which a breadth of advanced technological solutions are available. It is not even in the deliberation process and medical decision. The main impediment is the need to "close the loop". In other words, the need to deliver the recommendation to the individual with diabetes in a way that they understand and become comfortable with, so they incorporate the new dosage in their daily life until the next time adjustment is needed. Accordingly, only a solution that does not increase the burden on the healthcare system can enable frequent insulin dosage titration to realize the full benefit of insulin therapy.

The d-Nav® diabetes insulin guidance service

Hygieia Inc (Ann Arbor, MI, USA) has developed a scalable solution for continuous and consistent insulin titration. The DIGS is a scalable solution to the challenge and comprises a handheld device and a diabetes nurses service that aims to improve glycaemic control in people with diabetes without overburdening healthcare systems.

People with diabetes use d-Nav (a European Conformity [CE-marked] handheld device) to monitor their glucose level before each insulin injection, and, in addition to their glucose level, it provides a recommended insulin dose. By analysing glucose patterns (stored on the on-board sensor in

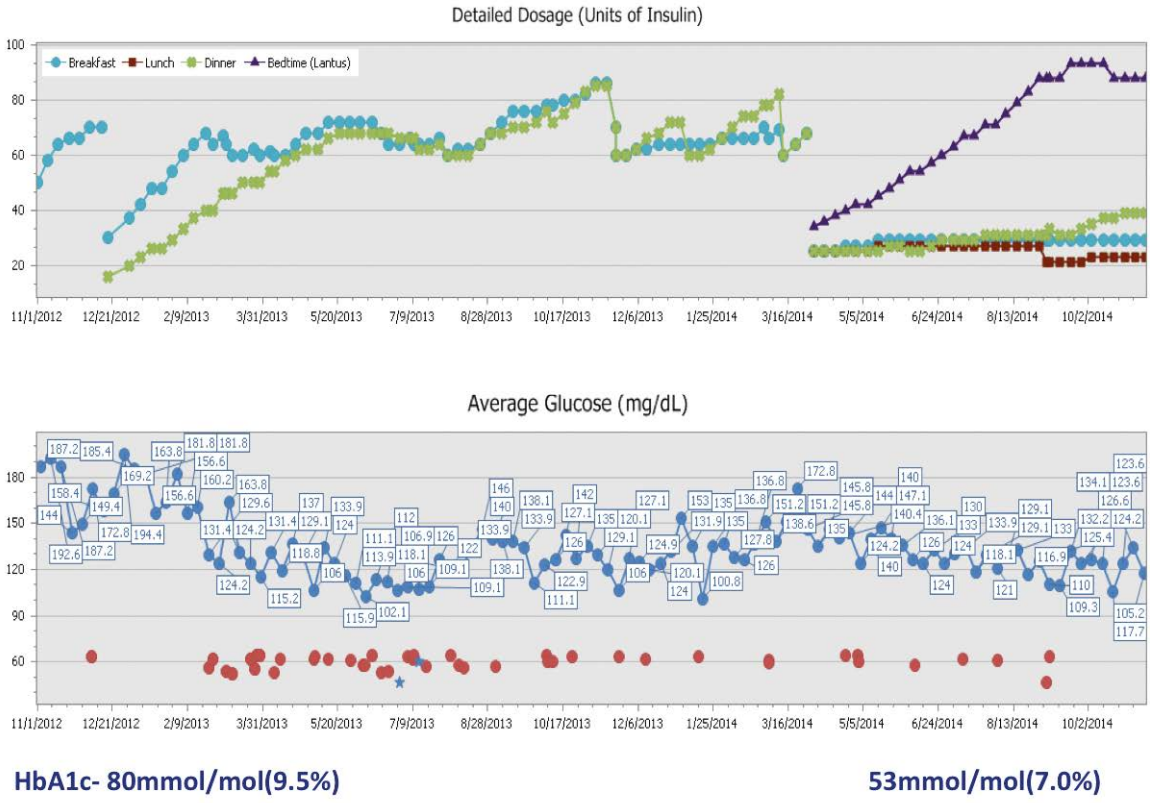

Figure 3. A d-Nav® download from a person with type 2 diabetes. The upper graph denotes each therapy component dosage (in insulin units). The lower graph denotes weekly mean glucose (in mg/dL). Episodes of minor daytime hypoglycaemia (glucose ≤65 mg/dL [3.6 mmol/L]) are shown as red dots and nocturnal events are shown as blue stars. From November to December 2012, the individual was treated with once-daily injection of basal insulin. Since average glucose remained elevated, it was clear that prandial coverage was needed. The individual's providers changed their regimen to pre-mixed insulin (see dynamics in breakfast and dinner dosage). To allow more treatment flexibility given their lifestyle, it was felt that the patient required more intensive therapy. In April 2014, therapy was changed to basal–bolus insulin therapy (see dynamics for bedtime long-acting insulin and pre-prandial rapid-acting insulin dosage). Average glucose became stable at about 120 mg/dL (6.7 mmol/L). HbA_{1c} at the end of 2012 and 2014 are displayed under the graphs. Date is in MM/DD/YYYY format.

the device), d-Nav automatically adjusts insulin dosage without provider supervision and without behavioural changes from the user. A physician prescribes the initial regimen and dosage, and d-Nav adjusts the dosage onwards. Adjustments are typically made weekly by the device. Yet, if insulin requirements drop or hypoglycaemia ensues, d-Nav can make immediate adjustments. This dynamic insulin system first closes the gap between the initial prescribed total daily dose and the therapeutic dose, and then continually evaluates each component of the therapy to fit users' changing needs while preventing an increase in hypoglycaemia.

Since d-Nav provides insulin dose recommendations, it is typically used before every insulin injection (i.e. one to four times a day depending on the regimen). d-Nav adjusts most types of insulin regimens (e.g. once-daily basal insulin, twice-daily premixed long- and short-acting insulin, and intensive insulin therapy involving long-acting and fast-acting insulin with or without carbohydrate counting [Bergenstal et al, 2012]; see *Figure 3*).

The DIGS nurses periodically follow-up users with telephone calls and in-person consultations to encourage user confidence, correct use errors and triage and identify uncharacteristic clinical courses. Downloads from d-Nav can be viewed via a dedicated software. The software, which is used by DIGS nurses and providers during clinic visits, can

help with clinical evaluation to recognise atypical clinical course (e.g. *Figure 2*) and to recognise if a more complex regimen is required.

As of June 2015, 172 people have been using the DIGS for more than 9 months. During enrolment to the service, average(±standard deviation) HbA_{1c} was 79.2(±16.4) mmol/mol (9.4[±1.5%]). HbA_{1c} is now 56.3(±12.0) mmol/mol (7.3[±1.1%]) for this group and hypoglycaemic burden has been stable and low. The frequency of severe hypoglycaemia has been less than 1 event per 100 patient years. Data pertaining to the service evaluation can be found elsewhere (Bashan et al, 2015; Donnelly et al, 2015). To our knowledge, this is the only service available of its kind at present.

Conclusion

DIGS serves as an extension of the diabetes care team to follow patients and it provides simple and safe instructions to modify treatment between clinic visits. It simplifies diabetes management for the patient and does not increase the burden on the healthcare system. We believe that DIGS has the potential to transform the standard of care (both in primary and secondary settings) by improving glycaemic balance in the growing population who require lifelong insulin therapy. ■

Further information is available at www.hygieia.com. Any further inquiries can be directed to Hygieia at d-Nav@hygieia.com.

Conflicts of interest disclosure

Israel Hodish is a co-founder of Hygieia Inc (Ann Arbour, MI, USA), the developer of the d-Nav® insulin guidance service. **Roy Harper** has no financial interest in Hygieia.

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