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COMMENTARY

Hybrid closed-loop therapy: Where are we in 2021?

Lalantha Leelarathna[1,2] | Pratik Choudhary[3] | Emma G. Wilmot[4,5] | Alistair Lumb[6,7] | Tim Street[8] | Partha Kar[9] | Sze M. Ng[10,11]

[1]Diabetes, Endocrinology and Metabolism Centre, Manchester University NHS Foundation Trust, Manchester, UK

[2]Division of Diabetes, Endocrinology and Gastroenterology, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

[3]Leicester Diabetes Center, University of Leicester, Leicester, UK

[4]Royal Derby Hospital, University Hospitals of Derby and Burton NHS FT, Derby, UK

[5]University of Nottingham, Nottingham, UK

[6]OCDEM, Oxford University Hospitals NHS FT, Oxford, UK

[7]Oxford NIHR Biomedical Research Centre, Oxford, UK

[8]Diabettech Ltd, London, UK

[9]Portsmouth Hospital NHS Trust, NHS, Portsmouth, UK

[10]Paediatric Department, Southport and Ormskirk NHS Trust, Southport, UK

[11]Department of Women's and Children's Health, University of Liverpool, Liverpool, UK

Correspondence
Sze M. Ng, MBBS (Hons) FHEA FRCPCH SFFMLM MSc LLM MBA PhD, Honorary Associate Professor & Consultant Paediatric Endocrinologist Southport and Ormskirk NHS Trust, Wigan Road Ormskirk UK L39 2AZ.
Email: may.ng@nhs.net

Abstract

Hybrid closed-loop systems are characterized by the coexistence of algorithm-driven automated insulin delivery combined with manual mealtime boluses. Used correctly, these insulin delivery systems offer better glucose control and reduced risk of hypoglycaemia and represent the most advanced form of insulin delivery available for people with type 1 diabetes. The aim of this paper was to compare the currently available commercial hybrid closed-loop systems in the UK: the Medtronic 670G/780G, Tandem t:slim X2 Control IQ and CamAPS FX systems. The Medtronic 670G/780G systems use Guardian 3 sensor (7-day use, two to four calibrations per day), while Tandem and CamAPS systems use the calibration-free Dexcom G6 sensor (10 days). The CamAPS system is available as an android app, whereas the other two systems have the algorithm embedded in the insulin pump. During pivotal studies, depending on the study population and baseline glycated haemoglobin level, these systems achieve a time spent in the target range 3.9 to 10 mmol/L (70 to 180 mg/dL) of 65% to 76% with low burden of hypoglycaemia. All three systems allow a higher glucose target for announced exercise, while the Tandem system offers an additional night-time tighter target. The CamAPS system offers fully customizable glucose targets and is the only system licensed for use during pregnancy. Additional education is required for both users and healthcare professionals to harness the best performance from these systems as well as to troubleshoot when "automode exits" occur. We provide consensus recommendations to develop pragmatic pathways to guide patients, clinicians and commissioners in making informed decisions on the appropriate use of the diabetes technology.

KEYWORDS
continuous glucose monitoring (CGM), health economics, type 1 diabetes

1 | INTRODUCTION

Type 1 diabetes is a lifelong endocrine condition related to insulin deficiency caused by pancreatic β-cell dysfunction.[1] People with type 1 diabetes therefore need to be able to self-adjust their insulin dose in order to achieve normoglycaemia and minimize the risk of micro- and macrovascular complications. High blood glucose levels over time may cause complications associated with diabetes including damage to small and large blood vessels and nerves. Achieving glycaemic targets substantially reduces the risk of blindness, kidney failure, heart disease, stroke and amputations.[2,3] Diabetes remains responsible for a large number of additional deaths, with the greatest relative risk in younger people.[4] There has been major progress in the available technology in type 1 diabetes to support diabetes management including insulin pump therapy, intermittently scanned glucose monitoring and real-time glucose monitoring, as well as increasing access to structured education in the context of advances in type 1 diabetes care.[5] Despite this, fewer than 10% of patients reach a target glycated haemoglobin (HbA1c) level of 48 mmol/mol (6.5%), approximately 20% reach a level below 53 mmol/mol (7.0%) and fewer than 35%

TABLE 1 Current commercial hybrid closed-loop systems

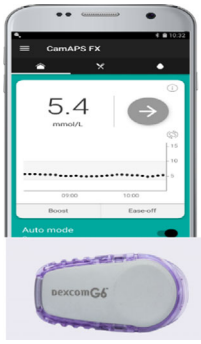
	Medtronic 670G-Guardian 3 sensor Medtronic 780G- Guardian 3 sensor	Tandem t:slimX2-Dexcom G6 -control IQ	CamAPS FX DanaRS-Dexcom G6
Hybrid closed-loop systems			
Integrated pump	670G, 780G (coming soon)	Tandem t:slimX2	Dana RS pump
Sensor	Guardian 3	Dexcom G6	Dexcom G6
Sensor duration	7 days	10 days	10 days
Number of fingersticks	4 to 6 per day, may be less for 780G	Rarely (factory calibrated)	Rarely (factory calibrated)
Licence	7 years and above	4 years and above	1 year and above
Pregnancy licence	No	No	Yes
Algorithm used	Treat to target proportional integral derivative with insulin feedback. 780G system also contain elements of MPC	Treat to range predictive algorithm	Treat to target adaptive MPC
Adaptive learning	Overall	Not reported by manufacturer	Overall, diurnal, meals
Customizable glucose target	670G: Target 6.7 mmol/L (120 mg/dL) non-customizable (optional exercise target at 8.3 mmol/L, 150 mg/dL). Correction target 8.3 mmol/L (150 mg/dL) 780G: Target 6.7, 6.1 or 5.5 mmol/L correction target 6 mmol/L, exercise target 8.3 mmol/L	Target range 6.2–8.9 mmol/L (112.5–160 mg/dL) (Sleep range 6.2–6.7 mmol/L [112.5– 120 mg/dL], exercise range 7.8–8.9 mmol/mol [140–160 mg/dL]) Non-customizable	Target 5.8 mmol/L (105 mg/dL) customizable between 4.4 and 11 mmol/L (80 and 200 mg/dL). Optional activity target set
Exercise mode	Yes	Yes	Yes
Boost mode	No	No	Yes
Insulin compatibility	Rapid only	Rapid only	Rapid and ultra-rapid
Compatible downloading software	Carelink Manual downloading required for 670G. Automated app compatibility with 780G	Clarity (sensor data), Diasend, manual downloading of pump required	Diasend Automated download
Automatic cloud storage of data	670G no 780G yes	Dexcom yes, pump no	Yes, full system
% TIR (3.9–10 mM) achieved in pivotal trials	670G: Adolescents 67% (baseline HbA1c 7.7% or 61 mmol/mol) and adults 74% (baseline HbA1c 7.3% or 56 mmol/mol)[11,12] 780G: Adolescents 73% (baseline HbA1c 7.6% or 60 mmol/mol) and adults 75% (baseline HbA1c 7.5% or 58 mmol/mol)[13]	Adolescents and adults 71% (age range 14–71 years, baseline HbA1c 7.6% or 60 mmol/mol). Children 67% (age range 6–13 years, baseline HbA1c 7.7% or 61 mmol/mol))[14,15]	Well-controlled adults (baseline HbA1c 6.9% or 52 mmol/mol) 76% Poorly controlled adults and children (baseline HbA1c 8.3% or 67 mmol/mol) 65%–68%[16–18]
Waterproofing	Pump and transmitter are waterproof. Sensor is waterproof up to12 feet (3.7 metres) for up to 24 hours	Pump is waterproof for up to 3 feet (0.91 metres) for 30 minutes and transmitter is waterproof for 8 feet (2.4 metres)	Pump is fully waterproof (IPX8) and transmitter is waterproof for 8 feet (2.4 metres)
Approximate yearly cost in UK NHS[a]	Pump = £612.50 Consumables = £1400 Medtronic sensor = £3186	Pump = £838 Consumables = £1588 Dexcom G6 sensor = £2645	Pump = £575 Consumables = £1400 Dexcom G6 sensor = £2645

TABLE 1 (Continued)

	Medtronic 670G-Guardian 3 sensor Medtronic 780G- Guardian 3 sensor	Tandem t:slimX2-Dexcom G6 -control IQ	CamAPS FX DanaRS-Dexcom G6
	SMBG = £500 App = £0 Total yearly cost if new to pump = £5698.50	SMBG = £100 App = £0 Total yearly cost if new to pump = £5171	SMBG = £100 App = £840 Total yearly cost if new to pump = £5560
Yearly additional cost if already on pump	Cost of sensors £3186	Cost of sensors + extra cost of control IQ pump - (savings from reduced SMBG) (2645 + 50–400) = £2295	Cost of sensors + extra cost of app - savings from reduced SMBG 2645 + 840–400 = £3045
Advantages	Well established pump Robust training and support Strong clinical experience with 670G closed loop	Strong evidence base No need for fingerstick Attractive pump interface Online training for HCPs and users	Strong evidence base No need for fingerstick Wide age range and pregnancy licence Mobile app with customizable targets Bolusing from phone for added privacy Online training for HCPs and users
Disadvantages	Limited RCT evidence. Need for multiple finger-sticks, relatively conservative system Alarm fatigue with substantial discontinuation rates Auto mode exists with 670G which is likely to improve with 780G	Limited real-world clinical experience with the system as recently launched Cannot revert to previous basal suspend mode if closed-loop is not suitable Not compatible with faster-acting insulins Relies on users' basal rates, carbohydrate ratio and corrections	Limited real-world clinical experience with the system as recently launched App only available for androids Need to carry the phone. Loss of Dexcom follow feature at present but "follow" planned later this year 2020.

Abbreviations: HbA1c, glycated haemoglobin; HCP, healthcare professional; MPD, model predictive control; NHS, National Health Service; SMBG, self-monitoring of blood glucose; TIR, time in range. [a]Prices are approximate in GBP based in the UK NHS and are correct at the time of publication, but these prices could vary in different countries.

achieve a target of 59 mmol/mol (7.5%) or below based on the UK National Diabetes Audit.[6] Similarly in the US T1D Exchange registry, the American Diabetes Association HbA1c goal of <58 mmol/mol for youth was achieved by only 17% of patients, and the goal of <53 mmol/mol for adults by only 21%. Mean HbA1c levels changed little between 2010 and 2012 or between 2016 and 2018, except in adolescents who had a higher mean HbA1c in the period 2016 to 2018.[7] Evolving technology offers the potential to improve glycaemic management, and reduce the above-mentioned complications and the burden and risks of hypo- and hyperglycaemia, while improving quality of life.

Closed-loop insulin delivery systems (also known as "artificial pancreas" systems) take the technology to the next level by integrating continuous glucose monitoring with an insulin pump and an algorithm which automates insulin delivery. Hybrid closed-loop systems are characterized by the coexistence of automated insulin delivery (via the algorithm) and user-initiated insulin delivery, for example, providing mealtime boluses. These insulin delivery systems offer better glucose control and reduced risk of hypoglycaemia and represent the most advanced form of insulin delivery available for people with type 1 diabetes.[8–10] The objective of the present paper was to compare the currently available commercial closed-loop systems in the United Kingdom, thereby providing up-to-date information for people living with type 1 diabetes and healthcare professionals to make an informed decision in a rapidly changing market.

2 | CURRENT CLOSED-LOOP SYSTEM AVAILABILITY IN THE UNITED KINGDOM

Currently, three commercial closed-loop systems are available in the United Kingdom. In order of introduction to the UK market these are: the Medtronic 670G system (and planned introduction of the 780G system in late 2020; Minimed Medtronic, Northridge, California); CamAPS FX, developed by CamDiab Ltd (www.camdiab.com, Cambridge, UK); and the Tandem Control IQ system (Tandem Inc., San Diego, California). The Medtronic and Tandem systems have the algorithm embedded in the pump software. In contrast, CamAPS FX is a smartphone app, a home-use medical device, that manages glucose levels continuously and autonomously via Bluetooth connection to a compatible insulin pump and glucose sensor. In addition to the commercially available products, as outlined below, people with type 1 diabetes are also using self-built "D.I.Y." artificial pancreas systems. These products are unlicensed and users take responsibility for any risks associated with use. Table 1 shows a comparison of the three commercial hybrid closed-loop systems currently available in the UK.

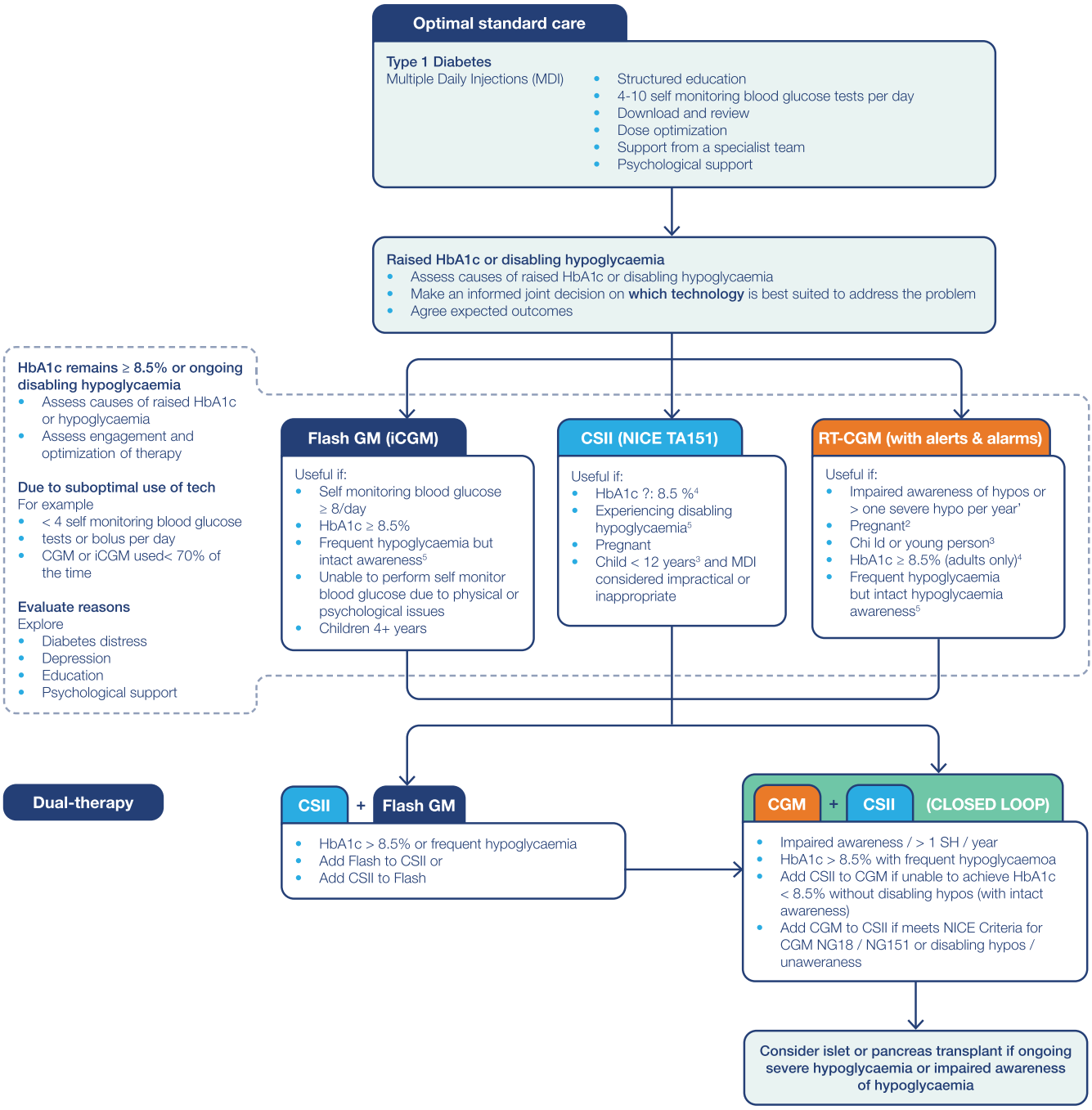


FIGURE 1 Recommendation of hybrid closed-loop therapy in the diabetes technology pathway. Adapted from the Diabetes UK position statement. CGM, continuous glucose monitoring; CSII, continous subcutaneous insulin infusion; GM, glucose monitoring; HbA1c, glycated haemoglobin; NICE, National Institute of Health and Care Excellence; RT-CGM, real-time CGM

Figure 1 details a pragmatic pathway with particular relevance to funding constraints within the UK healthcare system which is adapted from the type 1 diabetes technology pathway.[19] At present, there are no international data to highlight the variations in the use of hybrid closed-loop systems, and current global access is constrained by funding challenges.

3 | OPEN-SOURCE CLOSED-LOOP SYSTEMS

While commercial offerings have appeared in the past 2 years, there has been a vibrant community of people with type 1 diabetes writing their own insulin-dosing algorithms that work with existing pump

technology and releasing the code to open-source repositories making it freely available for others to build.[20–23] These are commonly known as D.I.Y. artificial pancreas systems (DIYAPS). As of writing, there are over 4700 people worldwide using the various systems, with the preferred choice of system varying by geography depending on availability of different pumps. There are three systems available: OpenAPS (2015, running on small Linux computer); AndroidAPS (2017, running the same algorithm as OpenAPS on an Android phone) and Loop (2016, running on iPhone with RileyLink to talk to pumps).[20] In the United Kingdom, the most popular is AndroidAPS (used by 66% of users) due to the range of pumps and continuous glucose monitors it works with. Various retrospective studies have shown that, through the use of DIYAPS, there are reductions in HbA1c and increases in time in range and that the glycaemic benefit of DIYAPS is in reducing hyperglycaemia without compromising the low occurrence of hypoglycaemia.[20]

4 | DISCUSSION

New and improved hybrid closed-loop technologies for the treatment of diabetes are continuing to emerge at an impressive rate. The Pivotal Omnipod Horizon™ Automated Glucose Control System clinical trials are currently underway and are due to be completed in December 2021[24] as well as the Insulin-Only Bionic Pancreas (iLET) Pivotal Trial.[25] Another closed-loop system currently in use in France is the Diabeloop system.[26,27] The DBLG1 algorithm developed by Diabeloop is hosted on a dedicated handset and acts as a user interface. It is connected to a continuous glucose monitor and an insulin pump. The DBLG1 artificial intelligence analyses the data in real time, while considering the patient's physiology, history and data entries (meals or exercise) to determine the correct dose of insulin to administer.

At present, hybrid closed-loop systems do not "automate" diabetes management but are likely to mostly benefit motivated individuals who are committed to maximizing the clinical benefit. The need for appropriate education to maximize the benefits of novel diabetes technology is well established.[28] Some education is common to most novel diabetes technology, for example, the need to count carbohydrates and deliver meal bolus with food. In addition there is also a need for specific education with hybrid closed-loop systems, for example, how to deal with and minimize "automode exits", how to deal with connection problems software issues and updates, and how to safely use standard sensor-augmented pump therapy at times when closed loop is not working for whatever reason.[29,30] Users and healthcare professionals also need to be educated about interpretation of data outputs from various closed-loop software systems and how to adjust existing pump settings based on closed-loop performance. Optimal user settings are more critical for some systems, for example, Tandem Control-IQ, than other systems, such as CamAPS. For some individuals, such technology may be an additional burden of care, as reported in some studies where there has been a high rate of automode exits while using the hybrid closed-loop functions.[31,32] It is important for future trials to focus on higher-risk populations such as those with persistently high HbA1c and/or low socioeconomic status to ensure that a skewed evidence base does not develop to exacerbate existing socioeconomic disparities in health outcomes and access to advanced technology. The success of diabetes technology implementation should emphasize the importance of creating technology which places the lowest possible demands on the user and helps to minimize disparities in access. Ultimately, the goal in the future would be to provide full closed-loop systems to all people living with type 1 diabetes.

5 | SUMMARY

As technology for insulin delivery systems continues to advance rapidly, healthcare professionals need to stay current to better guide their patients and provide the necessary education, support and patient choice when accessing appropriate technology. Digital revolutions in diabetes management will continue to progress; however, digital gaps continue to exist, with variations in care between areas of least and most socially deprived populations. The information provided in this paper should help to develop robust and pragmatic pathways and information to guide clinicians and commissioners in making informed decisions on the most appropriate use of diabetes technology.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

not required

ORCID

Emma G. Wilmot https://orcid.org/0000-0002-8698-6207
Sze M. Ng https://orcid.org/0000-0002-3449-0541

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