One Year Clinical Experience of the First Commercial Hybrid Closed-Loop System

Rayhan A. Lal,[1,2,3] Marina Basina,[1,3] David M. Maahs,[2,3] Korey Hood,[2,3] Bruce Buckingham,[2,3] and Darrell M. Wilson[2,3]

OBJECTIVE

In September 2016, the U.S. Food and Drug Administration approved the Medtronic 670G "hybrid" closed-loop system. In Auto Mode, this system automatically controls basal insulin delivery based on continuous glucose monitoring data but requires users to enter carbohydrates and blood glucose for boluses. To track real-world experience with this first commercial closed-loop device, we prospectively followed pediatric and adult patients starting the 670G system.

RESEARCH DESIGN AND METHODS

This was a 1-year prospective observational study of patients with type 1 diabetes starting the 670G system between May 2017 and May 2018 in clinic.

RESULTS

Of the total of 84 patients who received 670G and consented, 5 never returned for follow-up, with 79 (aged 9–61 years) providing data at 1 week and 3, 6, 9, and/or 12 months after Auto Mode initiation. For the 86% (68 out of 79) with 1-week data, 99% (67 out of 68) successfully started. By 3 months, at least 28% (22 out of 79) had stopped using Auto Mode; at 6 months, 34% (27 out of 79); at 9 months, 35% (28 out of 79); and by 12 months, 33% (26 out of 79). The primary reason for continuing Auto Mode was desire for increased time in range. Reasons for discontinuation included sensor issues in 62% (16 out of 26), problems obtaining supplies in 12% (3 out of 26), hypoglycemia fear in 12% (3 out of 26), multiple daily injection preference in 8% (2 out of 26), and sports in 8% (2 out of 26). At all visits, there was a significant correlation between hemoglobin A$_{1c}$ (HbA$_{1c}$) and Auto Mode utilization.

CONCLUSIONS

While Auto Mode utilization correlates with improved glycemic control, a focus on usability and human factors is necessary to ensure use of Auto Mode. Alarms and sensor calibration are a major patient concern, which future technology should alleviate.

[1]Division of Endocrinology, Department of Medicine, Stanford University School of Medicine, Stanford, CA

[2]Division of Endocrinology, Department of Pediatrics, Stanford University School of Medicine, Stanford, CA

[3]Stanford Diabetes Research Center, Stanford, CA

Corresponding author: Rayhan A. Lal, inforay@stanford.edu

Insulin replacement treatment is a significant burden, with a narrow therapeutic margin. Too much insulin results in acutely debilitating hypoglycemia, and too little over long periods results in hyperglycemia with subsequent microvascular complications and cardiovascular disease (1,2). One method of reducing disease burden is to use continuous glucose monitoring (CGM) data to alter insulin delivery from an insulin pump using a software controller. In September 2016, following years of clinical trials (3–12), the U.S. Food and Drug Administration approved the Medtronic 670G "hybrid" closed-loop system (13). In Auto Mode, this system automatically controls basal insulin

delivery based on Guardian 3 CGM data, but requires users to enter carbohydrate intake for meal boluses and finger-stick glucose readings for correction boluses (as the Guardian 3 is not approved for nonadjunctive use). Prior studies have demonstrated improved time in range associated with the use of Auto Mode (14). There have been recent case series presenting clinical experience with the 670G in the pediatric setting (15). To track our real-world experience with this first commercial closed-loop device, we followed pediatric and adult patients placed on the 670G in our clinics.

RESEARCH DESIGN AND METHODS

This was a 1-year prospective observational study of both pediatric and adult patients with type 1 diabetes starting the 670G system at Stanford University Medical Center between May 2017 and May 2018. Those with type 1 diabetes over the age of 7 years who had received the Medtronic 670G insulin pump and Guardian 3 CGM were eligible. This was an observational study based on a convenience sampling for those patients who were interested in starting the 670G closed-loop system. As such, there was no formal power calculation, and we report on all participants recruited over 1 year. A little over one-quarter of participants were upgrading from the prior 630G pump with Guardian 2 CGM through the priority access program and free upgrade pathway. The majority of participants had used Medtronic pumps in the past. The Stanford University Institutional Review Board approved the research protocol. The trial was registered on Clinicaltrials.gov as NCT03017482.

Observational data gathered through routine clinical care were collected on those patients providing informed consent. Study data were collected in REDCap electronic data capture tools hosted at Stanford University (16). The proposed start-up protocol included a thorough explanation of expectations, risks, and benefits of starting the 670G system. This discussion was to take place with the physician, diabetes educators, and device representatives. Participants would wear the pump and Guardian 3 sensor for 1 week with suspend before low enabled. During this same period, a 48-h Auto Mode warmup occurs, even

before Auto Mode is activated. Thereafter, Auto Mode is started in clinic. Weekly CareLink downloads occur for the first month with provider calls and intervention as needed. Patients would then be seen for routine follow-up at 3, 6, 9, and 12 months.

Demographics collected included age, diabetes duration, race/ethnicity, highest education achieved by the patient or

Table 1—Baseline demographic data subdivided by age-groups

	All participants	Age <18 years	Age ≥18 years
n (%)	79 (100)	26 (33)	53 (67)
Age (years), mean ± SD	27.2 ± 14.4	14.8 ± 2.2	33.3 ± 13.9
Diabetes duration (years), mean ± SD	14.6 ± 10.5	7.0 ± 4.3	18.3 ± 10.7
Sex			
Male	46 (58)	16 (62)	30 (57)
Female	32 (41)	10 (38)	22 (42)
Transfeminine	1 (1)	0 (0)	1 (2)
Baseline HbA$_{1c}$, % (mmol/mol), mean ± SD	7.9 ± 1.4 (63 ± 15.3)	8.3 ± 1.7 (67 ± 18.6)	7.8 ± 1.2 (62 ± 13.1)
Percent time using CGM prior to Auto Mode initialization, mean ± SD	77 ± 25	73 ± 28	80 ± 22
Baseline time in range (70–180 mg/dL) (%), mean ± SD	60 ± 17	58 ± 18	61 ± 17
Number of visits (total 5 possible), mean ± SD	4.1 ± 1.0	4.3 ± 0.9	4.0 ± 1.1
Race			
African	3 (4)	2 (8)	1 (2)
Asian	9 (11)	5 (19)	4 (8)
Caucasian	57 (72)	18 (69)	39 (74)
Middle Eastern	3 (4)	0 (0)	3 (6)
Native American	1 (1)	1 (4)	0 (0)
Unknown	3 (4)	0 (0)	3 (6)
Declined	3 (4)	0 (0)	3 (6)
Highest education for subject or guardian			
Some high school	5 (6)	0 (0)	5 (9)
High school degree	2 (3)	2 (8)	0 (0)
Some college	8 (10)	7 (27)	1 (2)
College degree	19 (24)	13 (50)	6 (11)
Graduate degree	23 (29)	15 (58)	8 (15)
Other	4 (5)	4 (15)	0 (0)
Declined	18 (23)	12 (46)	6 (11)
Prior insulin delivery systems			
Animas	13 (9)	3 (8)	10 (10)
Medtronic, older	62 (45)	19 (49)	43 (44)
Medtronic 630G	37 (27)	13 (33)	24 (24)
Omnipod	5 (4)	1 (3)	4 (4)
Roche	1 (1)	0 (0)	1 (1)
Tandem	4 (3)	0 (0)	4 (4)
Multiple daily injections	4 (3)	1 (3)	3 (3)
Other	11 (8)	2 (5)	9 (9)
Prior CGM			
Abbott FreeStyle Libre	3 (3)	2 (6)	1 (1)
Dexcom, G5 or older	54 (51)	16 (47)	38 (54)
Medtronic Enlite	35 (33)	11 (32)	24 (34)
None	8 (8)	3 (9)	5 (7)
Other	5 (5)	2 (6)	3 (4)

Data are n (%) unless otherwise indicated.

patient's guardian, and the prior pump systems (four maximum) and CGM systems (three maximum) used by the participants. With the exception of seven participants, baseline HbA$_{1c}$ was available 1 month prior to Auto Mode initialization. At the time of Auto Mode initialization, participants had a minimum of 1 week of data regarding CGM usage and time in range (defined as 70–180 mg/dL) collected from Guardian 3 sensor downloads.

The data were analyzed using MATLAB (2018; MathWorks, Natick, MA), and violin plots were generated using code from Holger Hoffmann. Qualitative and quantitative measures are compared for those using Auto Mode at 1 year versus those who discontinued use of Auto Mode. We summarize quantitative measures using means and SDs with comparisons made using an unpaired statistical hypothesis test. A two-proportion z test is used to compare differences in qualitative measures. Linear regression was performed on percent time in Auto Mode and HbA$_{1c}$ at each time point.

Reasons for continuing and discontinuing use of the system were derived from chart review. During the observation period, sensor technology advanced considerably. Dexcom released the G6 system, which is the first CGM not requiring calibrations, resistant to acetaminophen interference, and approved for nonadjunctive use (17,18). Given these benefits over the Guardian 3, we assessed Dexcom G6 use among participants at the end of the trial.

RESULTS

Eighty-four patients with type 1 diabetes received 670G and consented to be in the study. Five never returned for follow-up. Of the remaining 79 participants (aged 9–61 years), 26 (33%) were <18 years of age. These 79 individuals provided data for at least one visit at 1 week, 3 months, 6 months, 9 months, and/or 12 months after Auto Mode initiation. Demographic data for the group are presented in Table 1 and further subdivided by the age of the participants.

Not every patient came to a 1-week, 3-month, 6-month, 9-month, or 12-month visit. For example, more participants had data available at 3 months than at 1 week. For the 86% (68 out of 79) with Auto Mode initiation data, 99% (67 out of 68) successfully started. Among the 79 participants providing some data, Auto Mode use was as follows:

- 3 months: 22 (28%) discontinued, 50 (63%) continued, and 7 (9%) provided no data
- 6 months: 27 (34%) discontinued, 40 (50%) continued, and 12 (15%) provided no data

- 9 months: 28 (35%) discontinued, 35 (44%) continued, and 16 (20%) provided no data
- 12 months: 26 (33%) discontinued, 30 (38%) continued, and 23 (29%) provided no data

Figure 1 illustrates this decline in the use of Auto Mode over time for those with available data. By 3 months, 31% (22 out of 72) stopped using Auto Mode; at 6 months, 40% (27 out of 67); at 9 months, 44% (28 out of 63); and by 12 months, 46% (26 out of 56). Use of Auto Mode >70% of the time was 43% (31 out of 72) at 3 months, 40% (27 out of 67) at 6 months, 30% (19 out of 63) at 9 months, and 32% (18 out of 56) at 12 months.

Variations in demographics between those using Auto Mode and discontinuing at 1 year are presented in Table 2. (Further delineation by age-groups is provided in Supplementary Tables 1 and 2.) Age (P = 0.02), CGM use prior to initiating Auto Mode (P = 0.001), and self-report of college or graduate degree (P = 0.02) were significantly different between those using Auto Mode and those who discontinued after 12 months. Among participants with available data, 61% of those <18 years of age discontinued, while 39% of those ≥18 years discontinued.

Among those for whom data were available at 12 months, we conducted
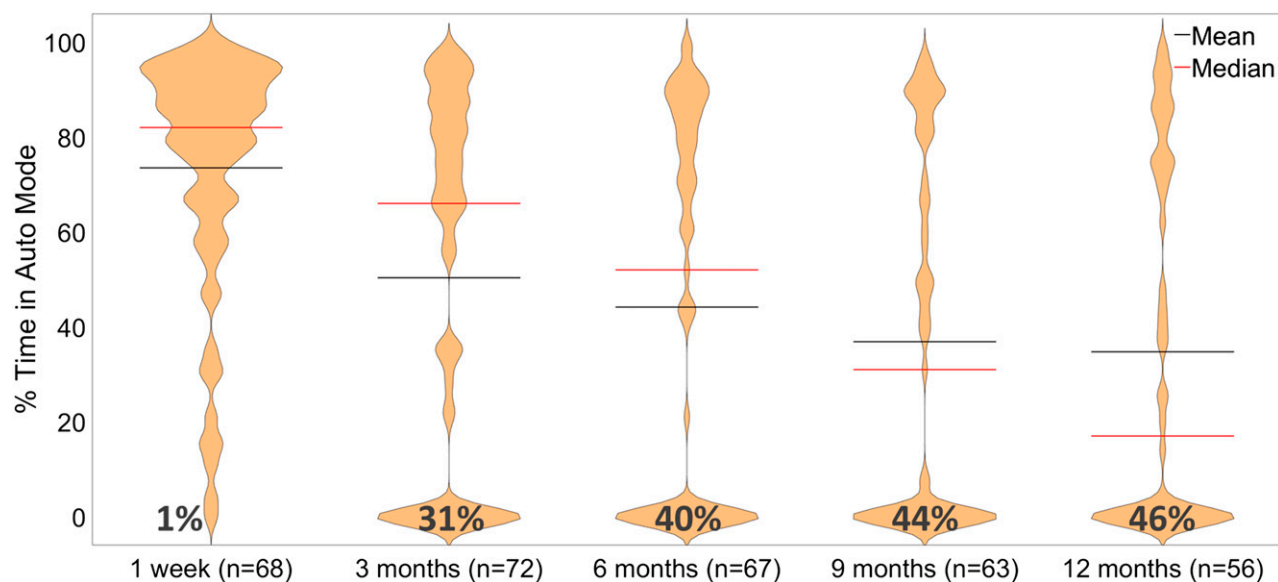
Figure 1—Violin plot reflecting percentage of time in Auto Mode by time of follow-up, with the number of participants with available data noted. For the available data, usage of Auto Mode diminishes over time. At 1 week, mean 74% and median 82%; at 3 months, mean 50% and median 66%; at 6 months, mean 44% and median 52%; at 9 months, mean 37% and median 31%; and at 12 months, mean 35% and median 17%.

Table 2—Demographic differences among those who use and do not use Auto Mode at 1 year

	Using Auto Mode	Discontinued Auto Mode	P value
n (%)	30 (54)	26 (46)	NA
Age (years), mean ± SD	31.5 ± 17.8	22.3 ± 10.0	0.02*
Percent time using CGM prior to Auto Mode initialization, mean ± SD	84 ± 13	61 ± 32	0.001*
Diabetes duration (years), mean ± SD	17.0 ± 13.1	11.1 ± 9.3	0.06
Sex, n (%)			
Male	15 (50)	17 (65)	0.25
Female	14 (47)	9 (35)	0.36
Transfeminine	1 (3)	0 (0)	0.35
Baseline HbA$_{1c}$, % (mmol/mol), mean ± SD	7.7 ± 1.1 (61 ± 12.0)	8.3 ± 1.7 (67 ± 18.6)	0.13
HbA$_{1c}$ at 1 year, % (mmol/mol), mean ± SD	7.6 ± 0.8 (60 ± 8.7)	8.3 ± 1.2 (67 ± 13.1)	0.06
Number of visits (total five possible), mean ± SD	4.7 ± 0.7	4.6 ± 0.5	0.57
Race			
African	0 (0)	2 (8)	0.12
Asian	6 (20)	1 (4)	0.07
Caucasian	23 (77)	17 (65)	0.35
Middle Eastern	0 (0)	3 (12)	0.06
Native American	0 (0)	1 (4)	0.28
Unknown	0 (0)	1 (4)	0.28
Declined	1 (3)	1 (4)	0.92
Highest education for subject or guardian			
Some high school	1 (3)	3 (12)	0.23
High school degree	2 (7)	0 (0)	0.18
Some college	1 (3)	5 (19)	0.05
College degree	9 (30)	6 (23)	0.06
Graduate degree	13 (43)	5 (19)	0.05
Other	2 (7)	2 (8)	0.88
Declined	2 (7)	5 (19)	0.16
Prior insulin delivery systems			
Animas	4 (7)	4 (9)	0.81
Medtronic, older	24 (44)	20 (43)	0.10
Medtronic 630G	15 (28)	14 (30)	0.77
Omnipod	2 (4)	3 (7)	0.52
Roche	1 (2)	0 (0)	0.35
Tandem	1 (2)	1 (2)	0.91
MDI	1 (2)	1 (2)	0.91
Other	6 (11)	3 (7)	0.42
Prior CGM			
Abbott FreeStyle Libre	1 (2)	1 (3)	0.84
Dexcom, G5 or older	23 (55)	16 (50)	0.68
Medtronic Enlite	13 (31)	11 (34)	0.76
None	1 (2)	4 (13)	0.09
Other	4 (10)	0 (0)	0.07
Concurrent Dexcom G6 use	4 (13)	8 (31)	0.11

Data are n (%) unless otherwise indicated. MDI, multiple daily injections; NA, not applicable. *P < 0.05.

chart review on all to assess for themes in those who continued and discontinued use of the system. Broadly speaking, the primary reason for continuing the system was desire for increased time in range. This includes prevention of both hypoglycemia and hyperglycemia. At all time points, there was a significant correlation between HbA$_{1c}$ and time in Auto Mode (Fig. 2). This held true even when comparing baseline HbA$_{1c}$ just prior to initiation of Auto Mode versus Auto Mode use 1 week after initialization.

At 1 year, reasons for discontinuation included sensor issues (16 out of 26; 62%), issues obtaining supplies (3 out of 26; 12%), fear of hypoglycemia (3 out of 26; 12%), preference for multiple daily injections (2 out of 26; 8%), and incompatibility with playing sports (2 out of 26; 8%). Sensor issues reported include multiple requests for calibrations, alarms relevant to sensor use, and the system exiting Auto Mode requiring additional blood glucose checks. Eight participants who discontinued use of Auto Mode

moved to the Dexcom G6. Four participants who continued Auto Mode wore a Dexcom G6 to calibrate the Guardian 3 sensor.

CONCLUSIONS

The objective of this study was to track real-world experience with the first commercial closed-loop device, the Medtronic 670G. Results indicate that at least 33% stop using Auto Mode at 1 year, and primary reasons for discontinuation were sensor issues including
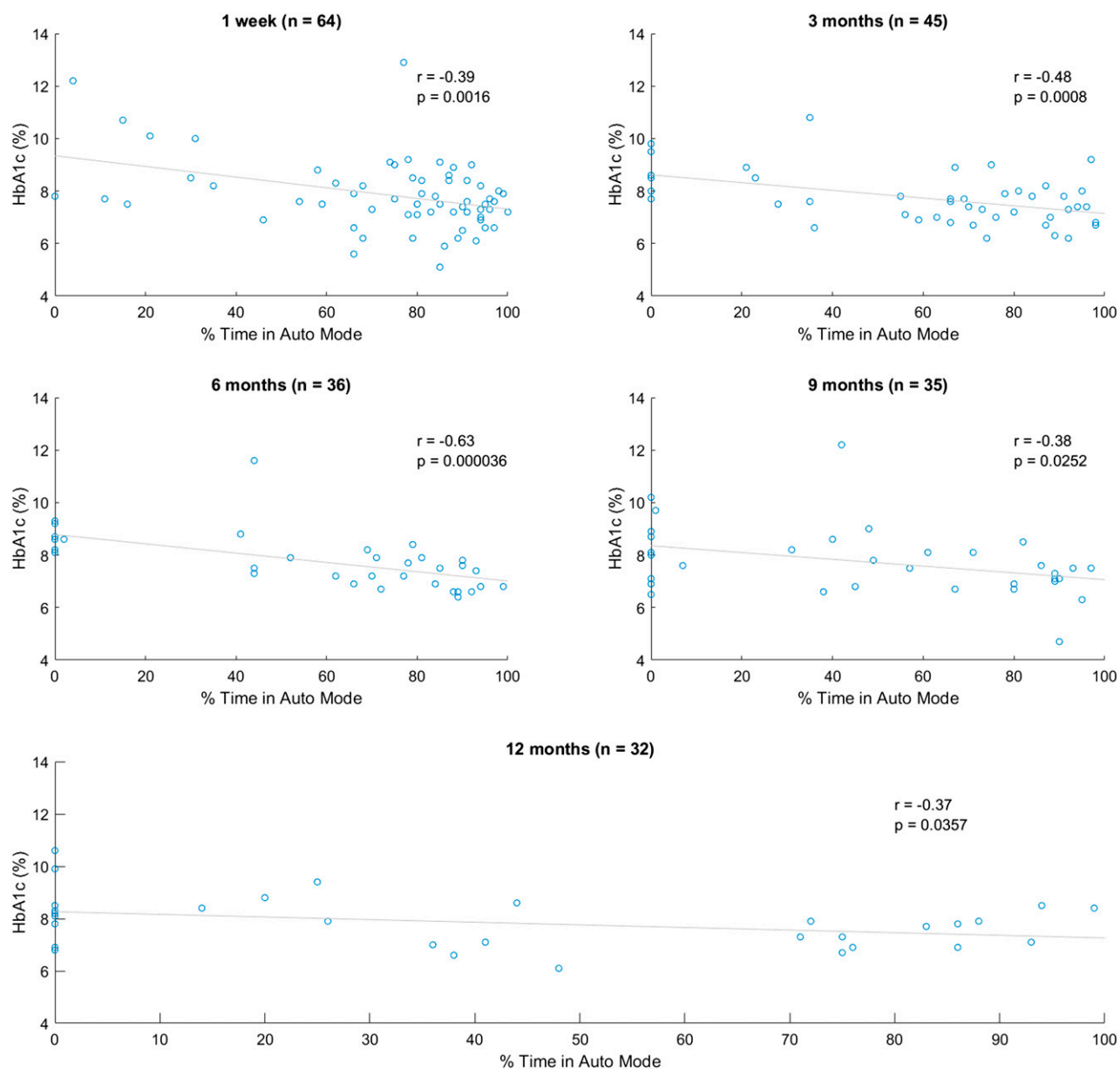
Figure 2—Scatter plots of percentage of time in Auto Mode vs. HbA$_{1c}$ by time of follow-up. Linear regression demonstrates significant correlation at every time point. One-week data are constructed from baseline HbA$_{1c}$ compared with Auto Mode use 1 week after initiation of the 670G system.

alarms for calibrations. Even among those continuing Auto Mode, average utilization fell over time. When continued, Auto Mode was associated with lower A1C and more time in range. These findings highlight the promise of hybrid closed-loop while illuminating significant variables related to user experience that limit its potential benefits.

Older age, increased Guardian 3 CGM use prior to Auto Mode initialization, and college education may be predictors of continued use of Auto Mode. Less than 60% Guardian 3 CGM use prior to Auto Mode initialization is a particularly early

marker of Auto Mode discontinuation at 1 year and could serve as a point of critical educational and behavioral intervention. Utilization of Auto Mode correlated with improved glycemic control. Notably, baseline HbA$_{1c}$ just prior to Auto Mode initialization also correlated with the use of Auto Mode at 1 week. Because Auto Mode played no part in the baseline HbA$_{1c}$ measure, it draws causality of this relationship into question. One might hypothesize that those with lower HbA$_{1c}$ were able to keep themselves in Auto Mode longer and that this may contribute to the association. Additionally, the

relationship between HbA$_{1c}$ and time in Auto Mode may simply be an expression of compliance.

The primary concern of those who stopped using Auto Mode was difficulty with the sensor. Requests for blood glucose checks coupled with alarms and exiting Auto Mode due to prolonged maximal basal insulin were common. Medtronic has recognized this problem and issued a transmitter upgrade for those experiencing significant repeated blood glucose requests (https://info .medtronicdiabetes.com/bgcheck). None of the participants in the current study

had upgraded to this new transmitter version. Over time, the difficulty obtaining supplies has reduced (19). While hypoglycemia is reduced with use of Auto Mode (11,20–23), it can still occur in the context of sports and large insulin boluses. In spite of the data supporting reduction in hypoglycemia, some users who experienced lows reported hypoglycemia as a reason for discontinuing. Education and adequate preparation are crucial in setting realistic expectations for closed-loop systems (24,25). We are strong believers that technology should be offered to everyone interested. Anecdotally, those who continue to use Auto Mode report benefits. In clinical trials, Auto Mode improved glycemic control even in the poorly controlled (26). In this real-world experience, usability was a barrier to Auto Mode utilization. We must provide the same care, attention, follow-up, and discussion of risks and benefits as we do in clinical trials. Most importantly, a focus on usability and human factors is necessary to ensure patients stay on treatment (27–29). Next-generation technology must balance safety concerns with simplified device operation.

While one might expect that those using the system at 1 year would continue thereafter, this was not always the case. Among the 30 participants using Auto Mode for any percentage of time at 1 year, at least 1 moved to Decom G6 with 670G insulin pump, and another discontinued after the 1-year follow-up for Loop, a do-it-yourself system.

There are limitations inherent to this prospective observational study. While we can demonstrate correlations, we cannot establish causality, and findings are merely hypothesis generating. The design is prone to selection and volunteer bias. Especially important, only participants with insurance covering the system were included, introducing a socioeconomic discrepancy. Indeed, these same individuals may have access to alternative technologies like the Dexcom G6 or do-it-yourself systems. Because this was clinical care, patients did not attend every visit, and thus, there are gaps in the data. Additionally, themes for continuing and discontinuing 670G use were derived from analysis of notes in the electronic medical record. Despite this, the strengths of the study include a varied clinical patient population receiving training at a center, which

established an educational program for initialization of 670G therapy. The data present the challenges encountered with first-generation technology, the need for setting realistic expectations, and the importance of human factors and usability in the design and clinical implementation of closed-loop insulin delivery systems.

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