Advances in Technology in the Treatment of Diabetes Mellitus 2017

How far have we come-How far are we going?

Is there a final frontier?

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Disclosures

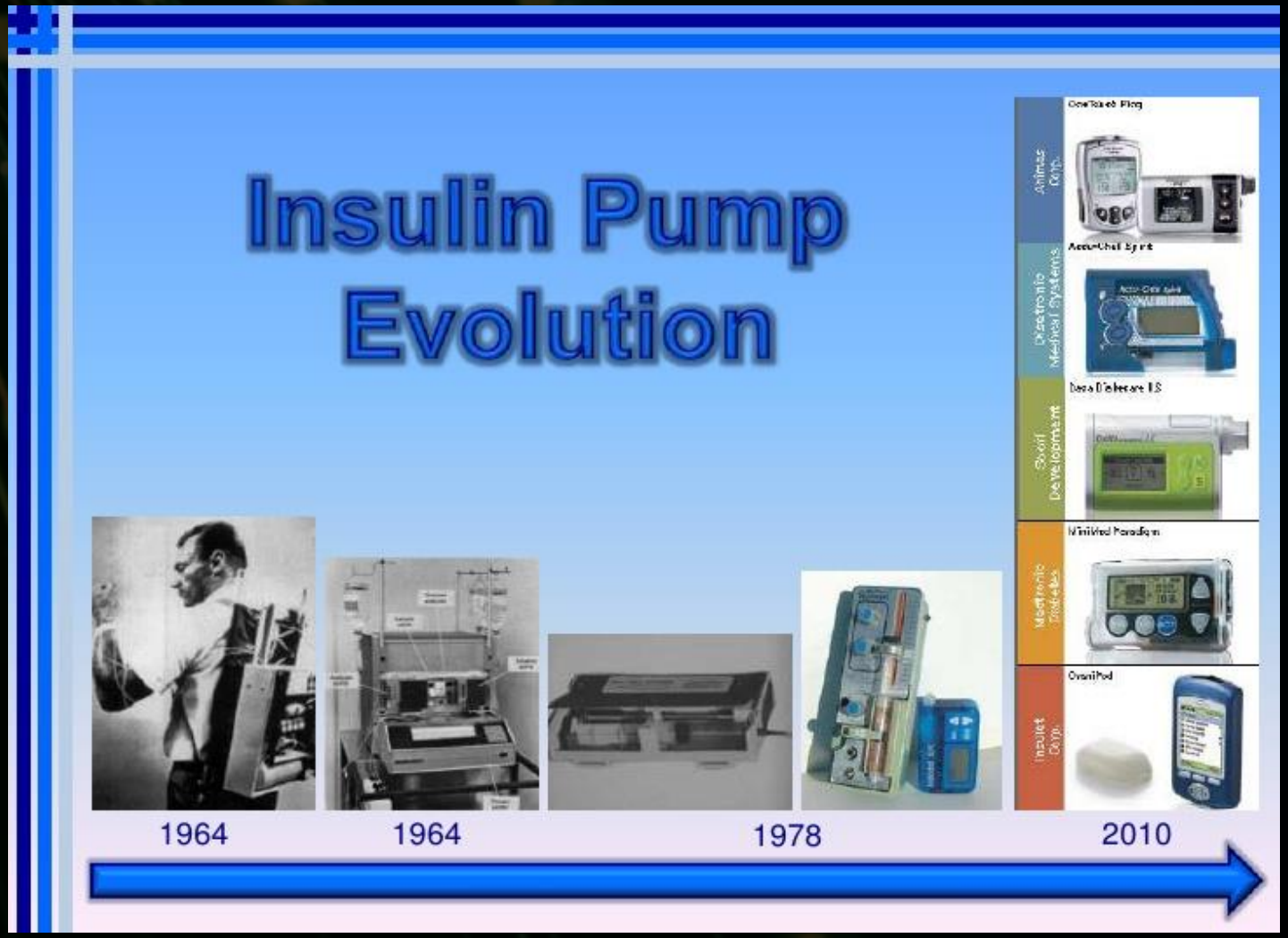
- Member- DSMB and CEC – Medtronic Diabetes
- Speakers Bureau-
  - Sanofi- Toujeo/ Soliqua
  - Astra Zeneca- Symlin only
- Research
  - PI –Aspire Bariatrics
  - Sub Investigator- BMS/ AZ

Early Insulin Pumps

-Generally bulky
-Little or no variables
-Worked on 24 hour basal rate-1 or 2 only

-Simple technology compared to present day systems

Pump Evolution through the years



Newest Technology

What is now and on the Horizon?

Can an Artificial Pancreas (AP) be achieved?

What are the limitations?

Animas Vibe Plus –Newest Version

Uses G5 Technology

Pump Technology has not improved since 2006-2007

Cartridge capacity is limited to 200 units- may limit use in Type 2 patients unless U-500 used

Roche AccuChek Technology

Pump only available in Europe and Asia

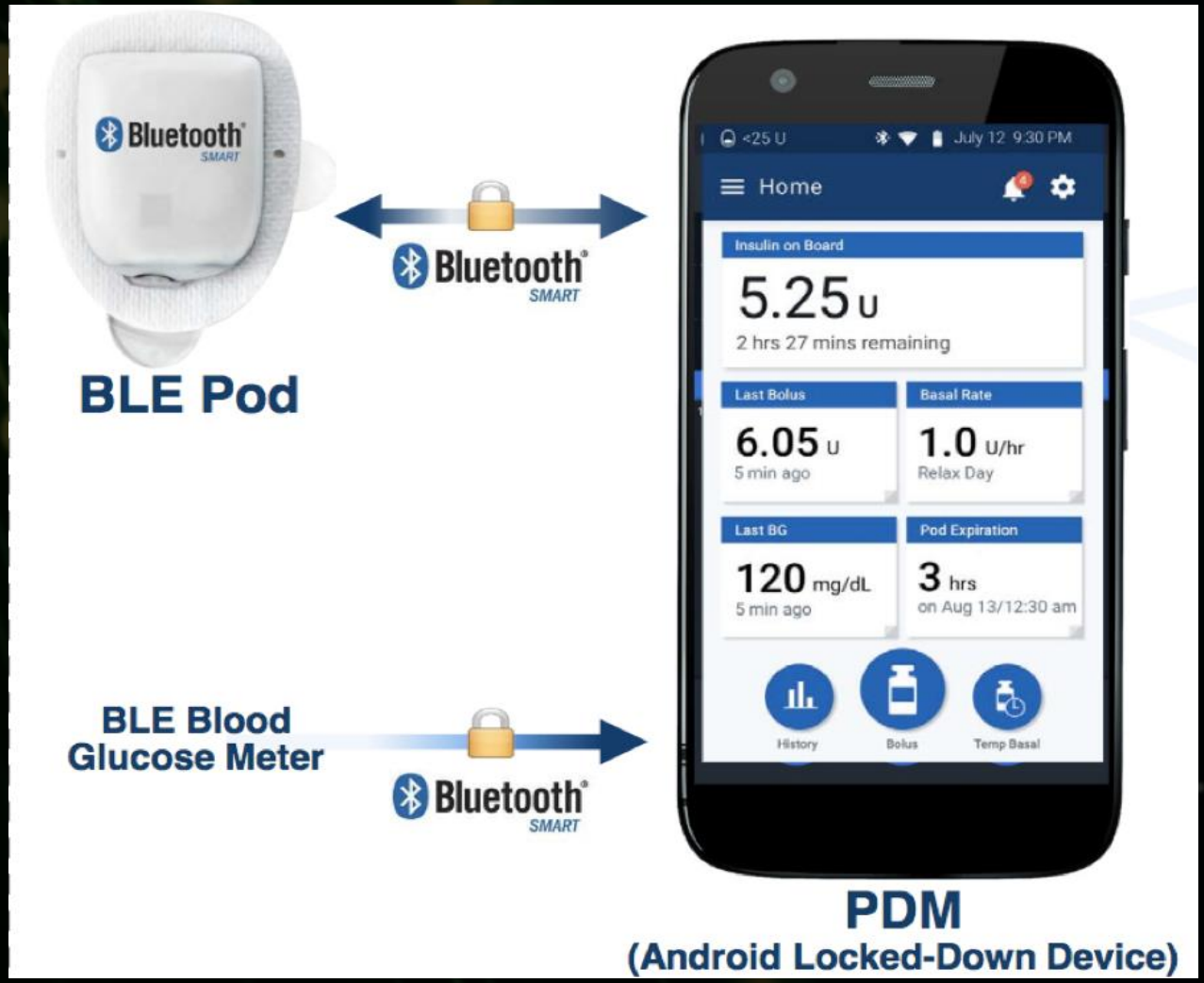
Company exited US market abruptly in 2017 –sold remaining pump assets to Medtronic

Has Bluetooth technology

Very popular pump in UK and Germany

Uses prefilled insulin cartridges- may limit type of insulin used

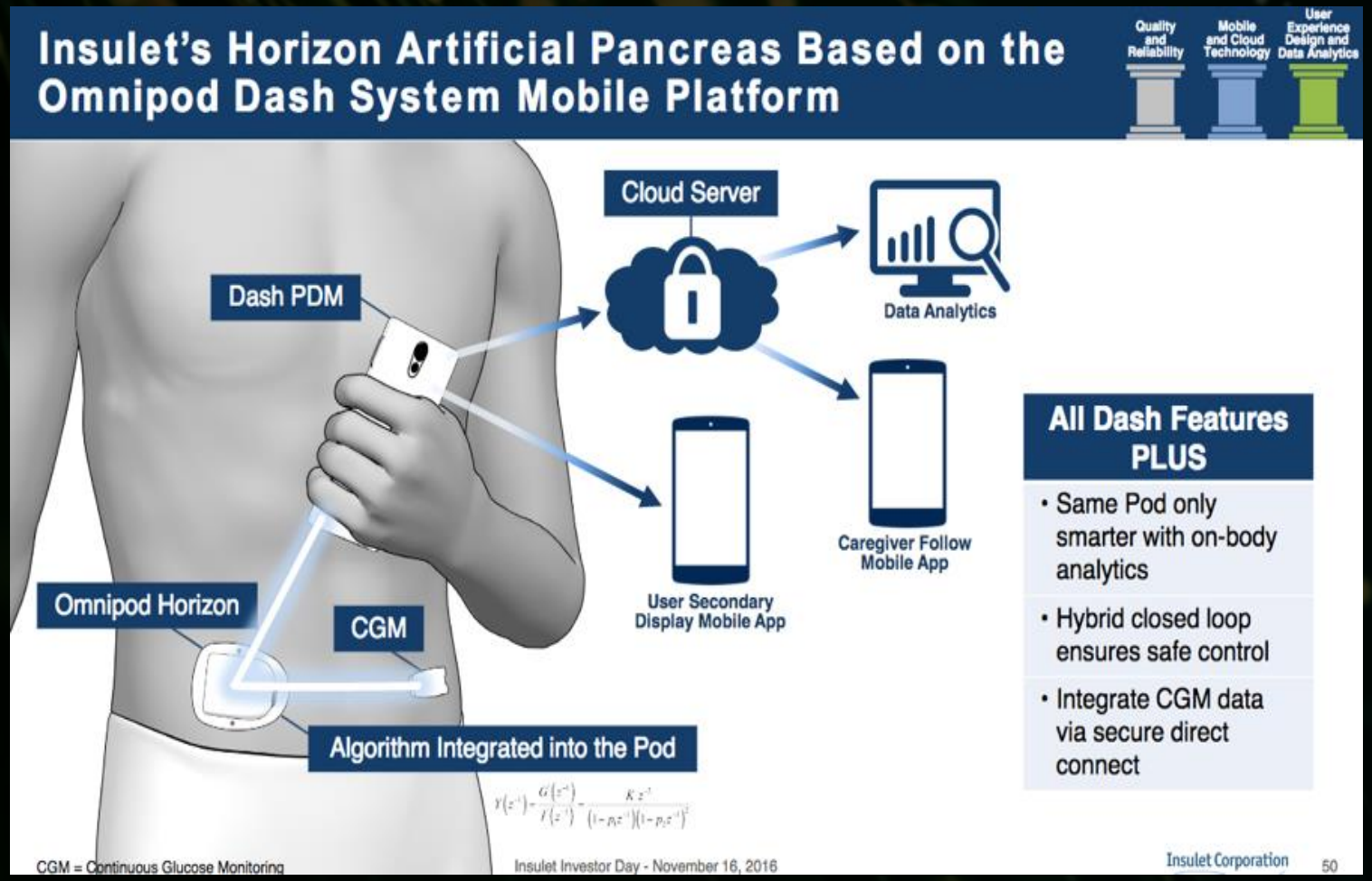
OmniPod Dash System



-Will use Bluetooth technology
-May have capability of U-200 or U-500 insulin volumes in 2 to 3 years
-New PDM
-Android only availability at present

Insulet 2017

Insulet Horizon- Modified AP system



-Modified Hybrid closed loop system

-Integrates with DEXCOM CGM

-Clinical trials in 2018 with possible availability 2019-2020

-Algorithm noted

-Patient will still need to give MB and Correction

Tandem PLGS System

- Will use CGM data – DEXCOM G5 to determine possible hypoglycemia and automatically suspend insulin delivery

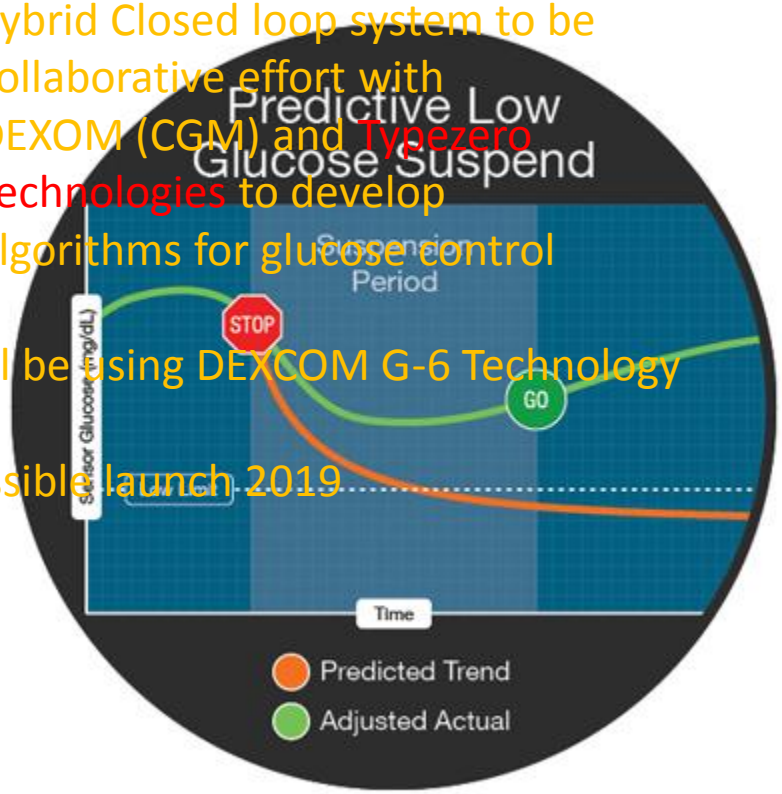
- Launch possibly in 2018
- Ongoing studies in 2017

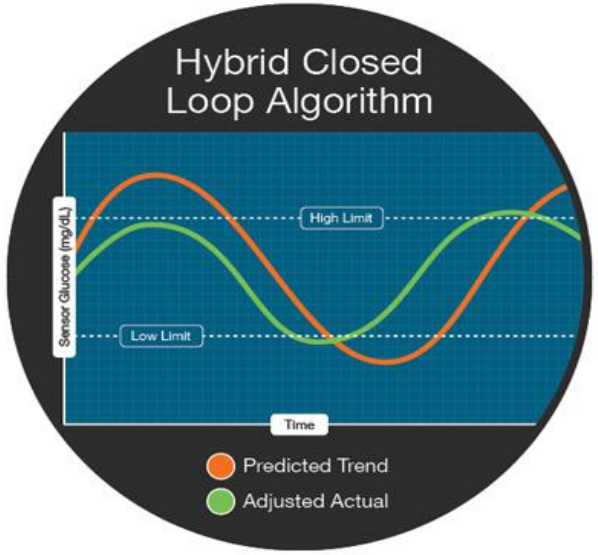
PLGS vs Hybrid Closed Loop System

- Hybrid Closed loop system to be collaborative effort with DEXOM (CGM) and Typezero Technologies to develop algorithms for glucose control

- Will be using DEXCOM G-6 Technology

- Possible launch 2019





TANDEM DIABETES CARE

dexcom

typezero

Medtronic 670G

Closed Loop Hybrid System

First available System of its Type

Only available in US at present

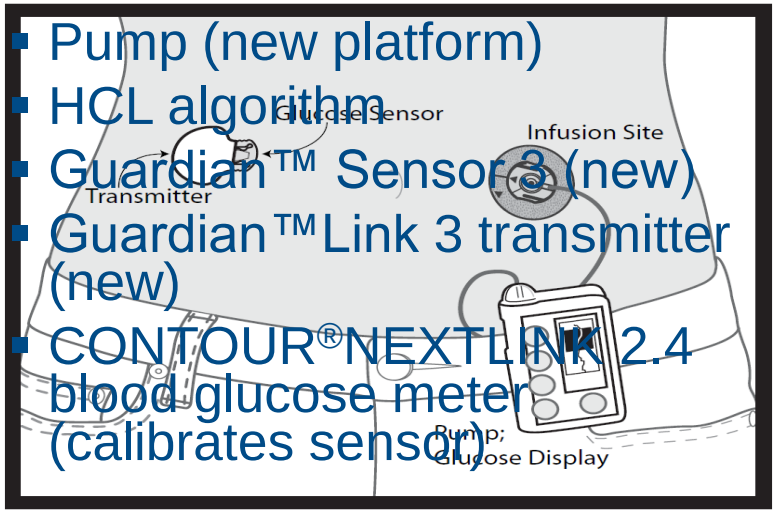
Approved by FDA in late 2016

HYBRID CLOSED LOOP (HCL) SYSTEM
LOOKS SIMILAR TO SENSOR AUGMENTED PUMP

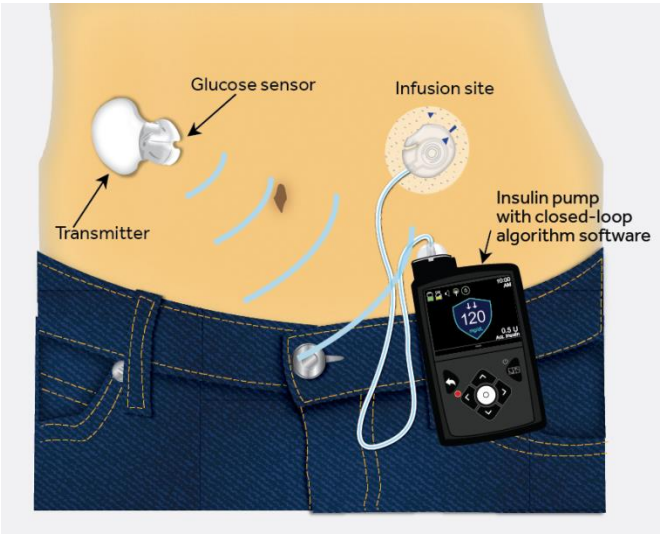
Sensor Augmented Pump (SAP)[1]

MiniMed 670G system includes:

- Pump (new platform)
- HCL algorithm
- Guardian™ Sensor 3 (new)
- Guardian™ Link 3 transmitter (new)
- CONTOUR®NEXT LINK 2.4 blood glucose meter (calibrates sensor)



Hybrid Closed-Loop Technology[2]



WARNING: Medtronic performed an evaluation of the MiniMed 670G closed loop system and determined that it may not be safe for use in children under the age of 7 because of the way that the system is designed and the daily insulin requirements. Therefore, this device should not be used in anyone under the age of 7 years old. This device should also not be used in patients who require less than a total daily insulin dose of 8 units per day because the device requires a minimum of 8 units per day to operate safely.

1. Bergenstal RM, et al. *N Engl J Med*. 2010;363:311-320. 2. Bergenstal R, et al. Poster presented at the 76th Scientific Sessions of the American Diabetes Association, June 10-14, 2016, New Orleans. LA. P-99.

SENSOR AND TRANSMITTER ENHANCEMENTS

Sensor & transmitter have same external design as previous versions but improved internal technology.

MARD	
9.64%	3-4 calibrations/day
10.55%	2 calibrations/day

Guardian™ Sensor 3 and Guardian™ Link 3 transmitter

- **Enhanced accuracy and performance**
- **New diagnostic technology that monitors sensor health**
- **Longer life – 7 day wear**

THE MINIMED 670G SYSTEM
INCREASING LEVELS OF AUTOMATION

Suspend <u>on</u> low*

Suspends insulin delivery ***when*** sensor glucose (SG) reaches a pre-set low limit

Suspend <u>before</u> low*

Suspends insulin delivery ***before*** SG reaches a pre-set low limit

Auto Mode

Automatically adjusts basal insulin delivery based on SG

*Insulin delivery resumes when: 1)Insulin has been suspended at least 30 minutes, AND 2) SG is ≥ 20 mg/dL above low limit, AND 3) SG is predicted to be ≥ 40 mg/dL above low limit

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AUTO MODE BASICS

AUTO BASAL / CORRECTION / MEAL BOLUSES

Basal insulin delivers every 5 minutes

- Algorithm and current SG determine 5-minute basal dose
  - Targets SG of 120 mg/dL
  - Temp target of 150 mg/dL may be used for up to 12 hours

Correction bolus initiated when finger stick BG > 150 mg/dL

- Algorithm determines sensitivity factor
  - Uses finger stick value and targets 150 mg/dL
  - Considers active insulin

Meal bolus initiated by patient entering carbs

- Carb ratio and number of carbs determine amount

Note: Carb Ratio and Active Insulin Time must be programmed

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CLINICAL EVIDENCE

PIVOTAL TRIAL OF A HYBRID CLOSED-LOOP SYSTEM IN TYPE 1 DIABETES

PIVOTAL TRIAL DATA MINIMED 670G SYSTEM (2016)

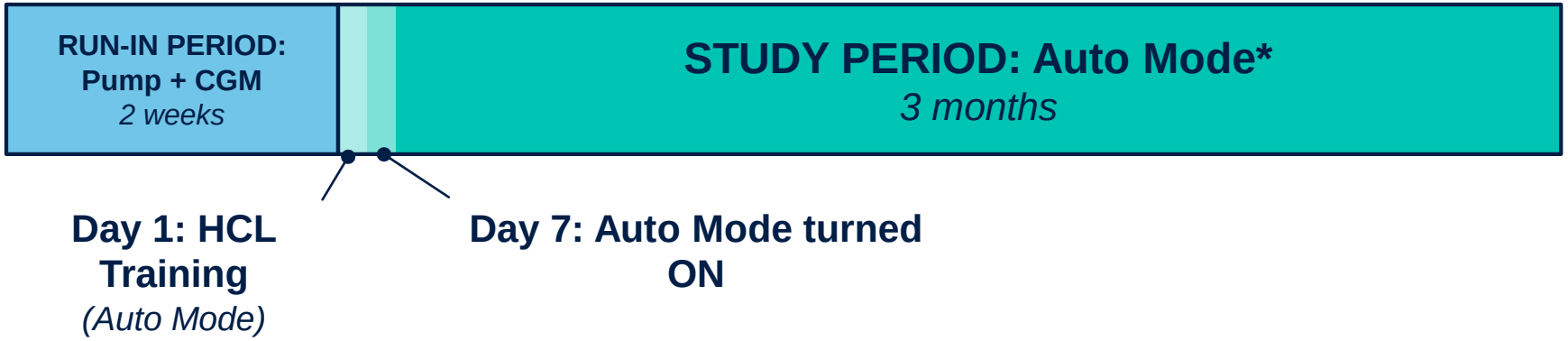
JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

Single-arm, Non-Randomized Study

- Type 1 diabetes > 2yrs
- A1C <10%
- Adolescent: 14-21 yrs
- Adult: 22-75 yrs

- 10 sites (9 US, 1 Israel)
- Pump therapy ≥6 months
  - With or without CGM

Study Protocol



*Included supervised hotel stay for 6 days/5 nights with frequent venous BG measurements using reference instrument (i-STAT)

Due to inherent study limitations, caution is advised when attempting to extrapolate these results to new patients. There could be significant differences.

Bergenstal RM, et al. *JAMA*. 2016;316(13):1407-1408.
Garg SK, et al. *Diabetes Technol Ther*. 2017;19(3):155-163.

PIVOTAL TRIAL STUDY COHORTS
BASELINE CHARACTISTICS

	Adolescents (n=30)	Adults (n=94)
Sex	16F / 14M	53F / 41M
Age (years)	16.5 ± 2.3	44.6 ± 12.8
Weight (kg)	67.4 ± 13.0	79.9 ± 18.2
BMI (kg/m^2)	23.7 ± 3.8	27.1 ± 5.4
Duration of diabetes (years)	7.7 ± 4.2	26.4 ± 12.4
Total daily dose of insulin (units/kg/day)	0.8 ± 0.2	0.6 ± 0.2
A1C at screening (%)	7.7 ± 0.8	7.3 ± 0.9

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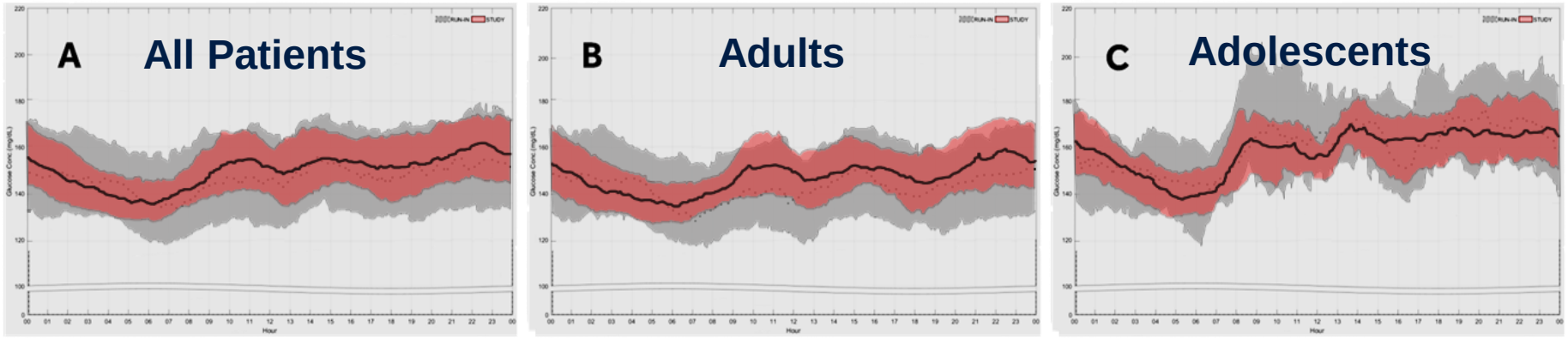
REDUCED GLYCEMIC VARIABILITY
MODAL DAY SENSOR GLUCOSE TRACINGS

Median and Interquartile Range of SG Values / Day & Night



Hybrid closed loop resulted in:

- Increased time in range
- Reduced time spent low and high
- Reduced variability
- Less post-prandial excursion

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*Data as measured by device sensor. Range defined as 71-180mg/dL during study period. Study of 124 adults and adolescents (ages 14-20) with type 1 diabetes. Diagrams rounded for illustrative purposes only.

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MOVING BEYOND A1C
TIME IN RANGE

Day and Night
($p < 0.001$)

Sensor Glucose	Run-in % Time in Range	Study % Time in Range
> 300 mg/dL	2.3	1.7
> 180 mg/dL	27.4	24.5
71 – 180 mg/dL	66.7	72.2
≤ 70 mg/dL	5.9	3.3
≤ 50 mg/dL	1.0	0.6

Night Time Only
(data on file)

Sensor Glucose	Run-in % Time in Range	Study % Time in Range
> 300 mg/dL*	2.1	1.4
> 180 mg/dL	26.8	21.6
71 – 180 mg/dL	66.8	75.3
≤ 70 mg/dL	6.4	3.1
≤ 50 mg/dL*	1.1	0.6

*Data on file

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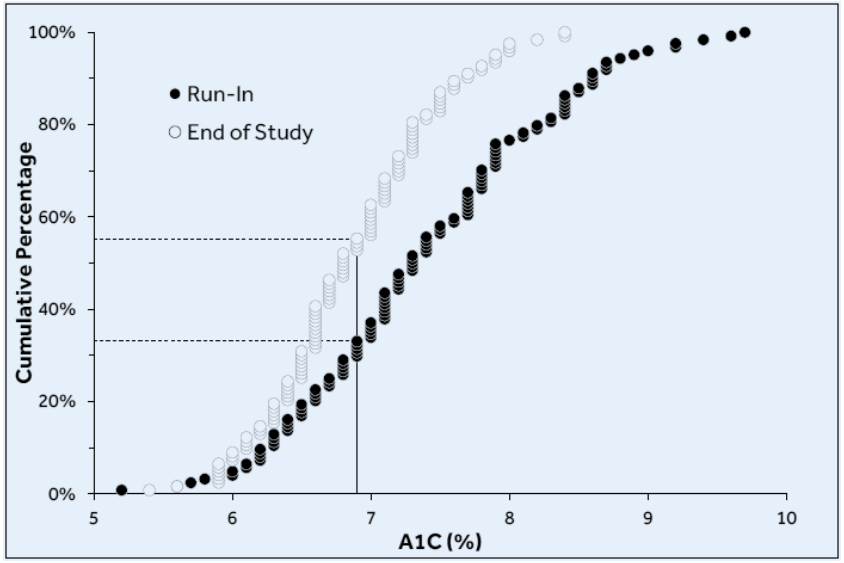
A1C LOWERING ACROSS BROAD GLYCEMIC RANGE
DISTRIBUTION OF A1C VALUES

Pivotal Trial A1C Results

- A1C baseline run-in = 7.4±0.9%
- A1C at study end = 6.9±0.6%
- A1C change = -0.5% (p<0.001)



A1C range	Run-in: *n* (%)	Study end: *n* (%)	Mean Δ A1C
< 7.0%	41 (33.1%)	68 (55.3%)	-0.1%
7.0 to 7.5%	31 (25.0%)	39 (31.7%)	-0.3%
> 7.5%	52 (41.9%)	16 (13.0%)	-1.0%

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RESULTS
KEY ENDPOINTS: TOTAL DAILY DOSE AND HCL UTILIZATION

Parameter	All Subjects			Adolescents			Adults		
	Run-in	**Study**	*p*	Run-in	**Study**	*p*	Run-in	**Study**	*p*
TDD	47.5±22.7	**50.9±26.7**	<0.001	55.6±17.1	60.2±19.9	<0.01	44.9±23.7	47.9±28.0	<0.01
Basal insulin as a % of TDD	53.0±11.3	**46.7±9.1**	<0.001	49.7±12.0	46.4±8.5	0.02	54.1±10.9	46.8±9.4	<0.001
Weight (kg)	76.9±17.9	**77.6±16.1**	<0.001	67.4±13.0	68.4±12.5	0.07	79.9±18.2	81.3±16.0	<0.001

Values = mean ± SD
TDD = total daily dose of insulin (units/kg/day)
Basal insulin = Basal + microbolus

HCL Utilization (% of time)**:**
All Subjects = 87.2%, Adolescents = 75.8%, Adults = 88.0%

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SAFETY OF HCL

DEVICE RELATED ADVERSE EVENTS 12,389 PATIENT-DAYS

	Run-in 2 wks.	Study 12 wks.
Total	**8**	**21**
Severe hypoglycemia	0	**0**
DKA	0	**0**
Severe hyperglycemia* *(BG>300 mg/dL w/ symptoms)*		
▪ Infusion set	5	6
▪ Software or hardware issues	0	5
▪ Sensor issues	0	1
Hyperglycemia† *(BG>300 mg/dL no symptoms)*	0	6
Skin irritation	3	1
Rash	0	1
Pruritus	0	1

Primary Outcomes

* = With ketones <0.6mmol/L, nausea, vomiting, or abdominal pain
† = Without ketones >0.6mmol/L or GI symptoms

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PIVOTAL TRIAL OF A HYBRID CLOSED LOOP SYSTEM
MINIMED 670G SYSTEM

Study Strengths:

- Multicenter design to evaluate safety
- Large number of subjects
- Cohorts included adults and adolescents
- Three months of unsupervised home use of system
- System used 24 hours/day
- Sensor accuracy confirmed by i-STAT reference BG measurements during hotel stay

Due to inherent study limitations, caution is advised when attempting to extrapolate these results to new patients. There could be significant differences.

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PIVOTAL TRIAL OF A HYBRID CLOSED LOOP SYSTEM
MINIMED 670G SYSTEM

Study Limitations:

- Single-arm, nonrandomized, pre-post design with no pre-specified efficacy endpoints or control group[1,2,3]
- Data quantity imbalance between run-in and study phases[1,2]
- Exclusion of subjects with A1C > 10%, recent episodes of severe hypoglycemia or recent DKA[1,2]
- Results of clinical trial must be interpreted with caution.
  - Individual results may be significantly different from those of subjects in trial.[3]

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PIVOTAL TRIAL OF A HYBRID CLOSED LOOP SYSTEM
SUMMARY

- Proven safety with no severe hypoglycemia or DKA during study phase
- Study phase vs. run-in results
  - Increased time in target range
  - Decreased glycemic variability (lows and highs)
  - Reduction in A1C

Due to inherent study limitations, caution is advised when attempting to extrapolate these results to new patients. There could be significant differences.

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Issues with AP Systems

- Algorithm is not customizable
- Need to utilize 2 separate devices on body
  - No combined catheter and sensor at present-being developed
  - Sensor may last 5-7 days
  - Catheters are generally lasting only 3-4 days
- Patient needs to “trust” AP system and not micromanage
- Will individuals continuously wear system
- Governmental regulations may slow progressive of advances
- Stability of Additional hormones in pump systems: Glucagon, Symlin, etc.

Open APS-DIY Closed Loop System

- **NOT APPROVED OR SANCTIONED BY FDA OR OTHER REGULATORY AGENCIES**
- **Open Sourced System- community of individuals**
- Requires a modicum of technical acumen to implement
- Still requires patient involvement with meal bolus and correction
- Additional upgrades are being released frequently
- Utilizes older insulin pumps – ability to unlock
- Work is proceeding to facilitate use of newer pump technology
- ? Utility with Hybrid Closed Loop Systems now available – different more individualized algorithms????
- http://www.openaps.org
- http://dx.doi.org/10.1016/S2213-8587(16)30397-7

Open APS Example

Another example

https://clyde.fode.org:1337/

Patient data to be shown is in real time

This is DIY system which has been modified consistently

Utilizes older pump but technology is cutting edge

Continuous Glucose Monitoring - CGM

Current CGM Systems Available in US

- DEXCOM
  - G4 system – integrated in several pumps
  - G5 system – stand alone at present; utilizes Bluetooth technology
  - G6 system – next generation; will be able to be utilized for 10 days
- MEDTRONIC
  - Guardian Series
  - Enlite Series
  - Integrated systems for hybrid closed loop
- Free Style Libre
  - Professional – 2 week usage
  - Personal

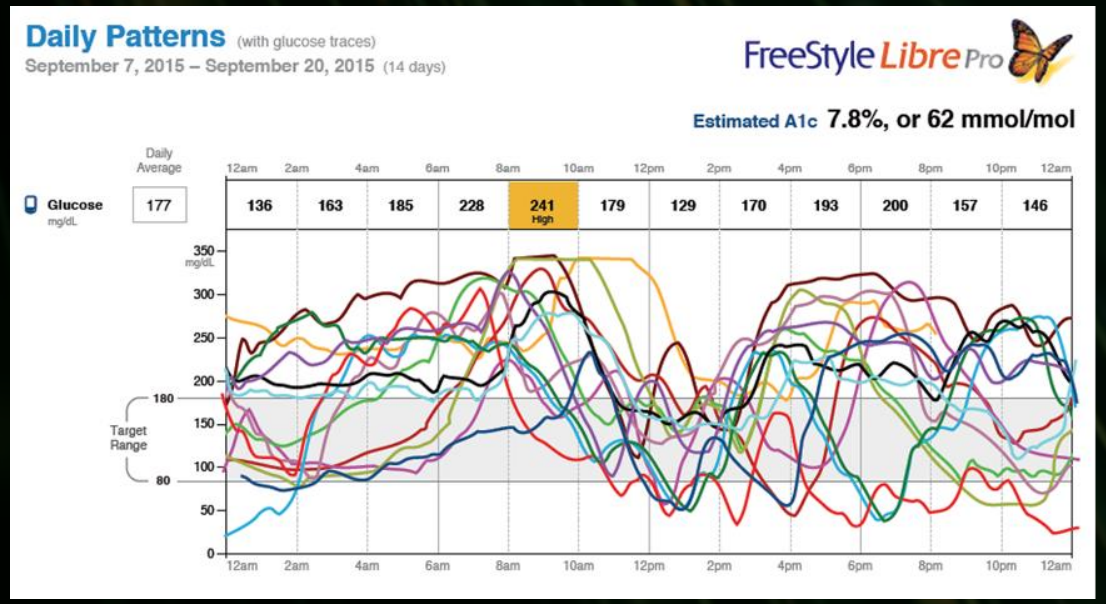
FreeStyle Libre System

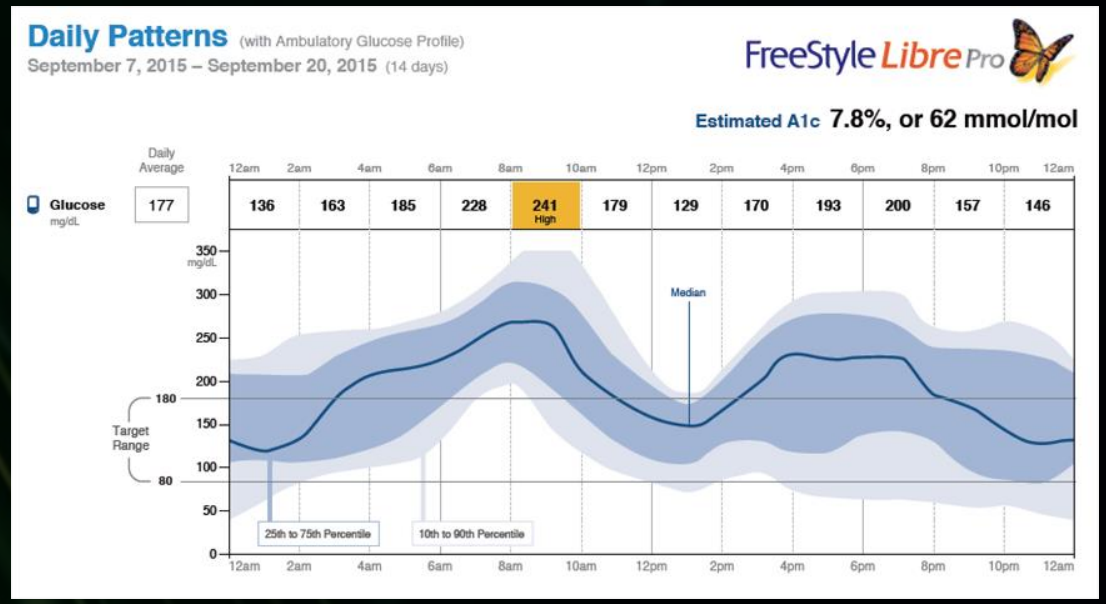
Personal System- not available yet in US – hopefully in 2018

Professional System – available 2 weeks of data can be downloaded and reviewed

Uses similar sensor – easy to apply

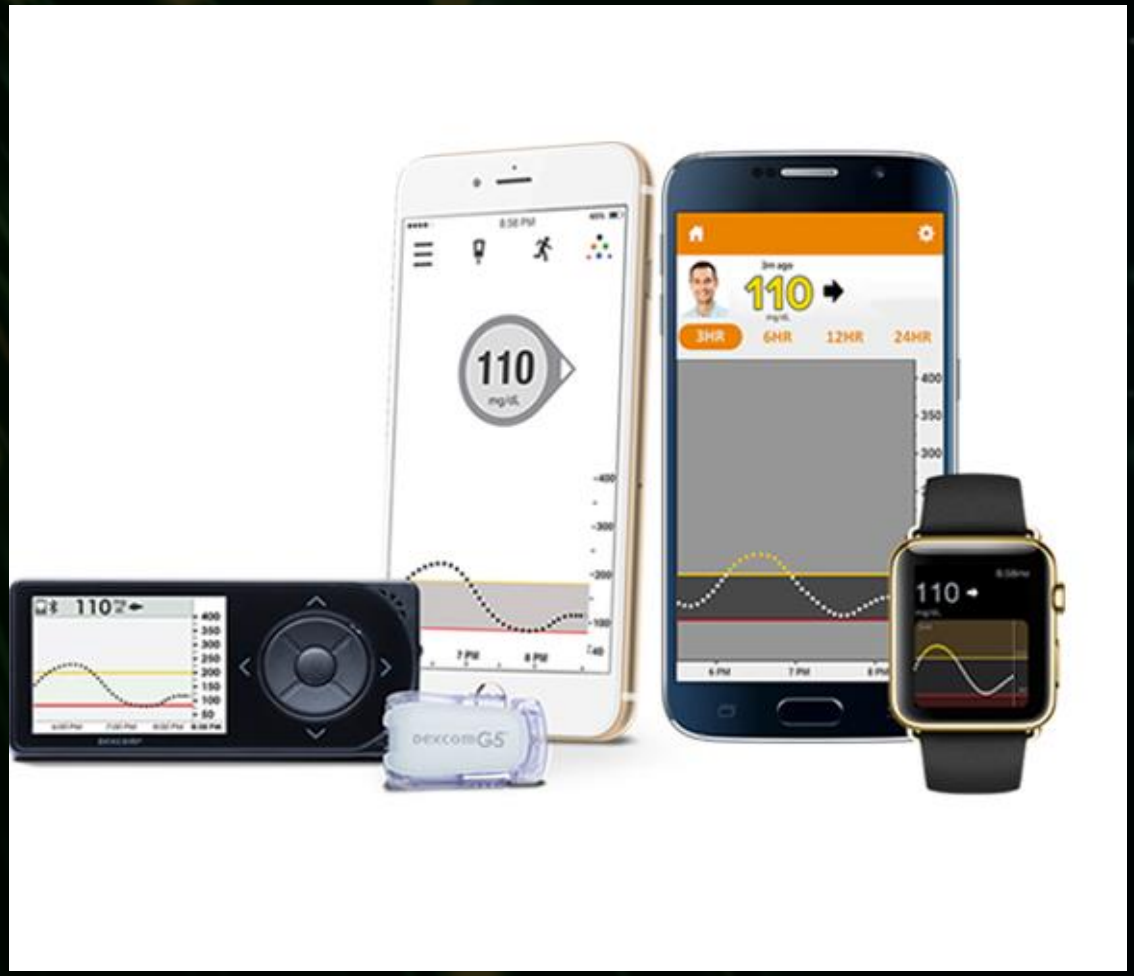
Reports from FreeStyle Libre System





Additional reports available. Can customize to individual patient.

DEXCOM G5 System



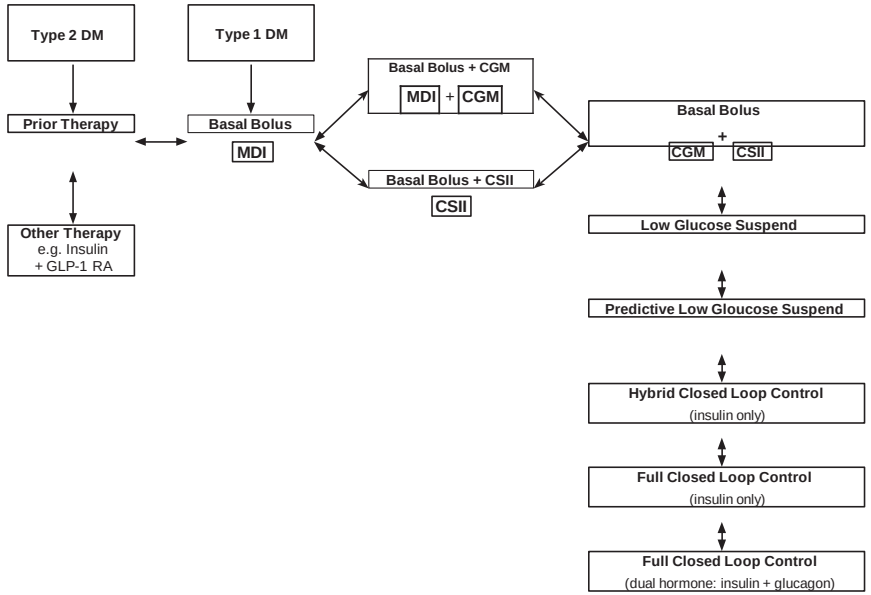


FIG. 1. Flowchart of current and potential future options for management of patients receiving basal–bolus therapy. The first clinical decision is whether to add CGM, to add CSII, or introduce both CGM and CSII. CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion.