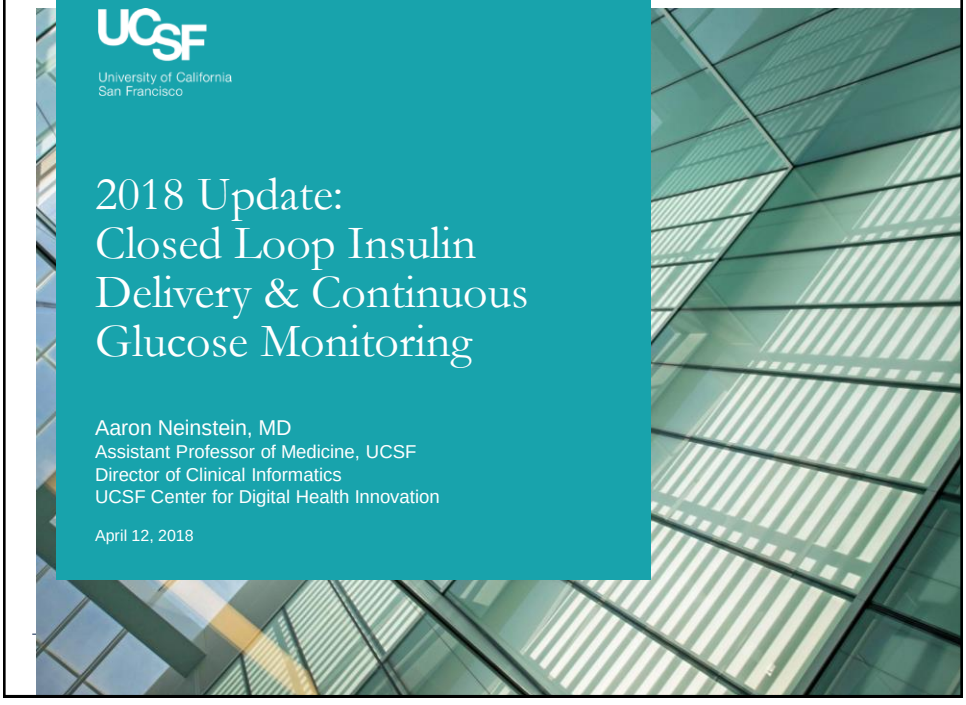


Disclosures

- Advisor
  - Tidepool (no financial relationship)
- Research grant support
  - Cisco Systems Inc

What's new in 2018?

Last year:

- Clinical trials data for Medtronic 670G closed loop system
- Expanded FDA indication for CGM (insulin dosing decisions)

Now:

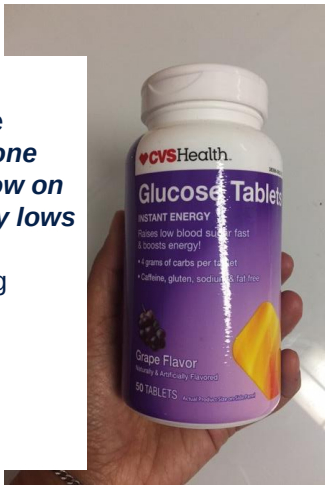
- Real-world experience with Medtronic 670G system
- Expanding CGM options

Closed Loop Insulin Delivery Is Here

"Hi Dr.,

I hope you're well! I have a photo of my glucose tablets attached. ***I used to go through about one bottle per month on the Animas Ping, but now on the 670g it lasts me 3-4x as long because my lows are so infrequent***. I think I bought this bottle sometime in November before the Thanksgiving break, and I still have 1/2 left in January."

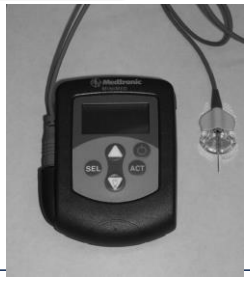
Note: Her A1c is 6.6 %



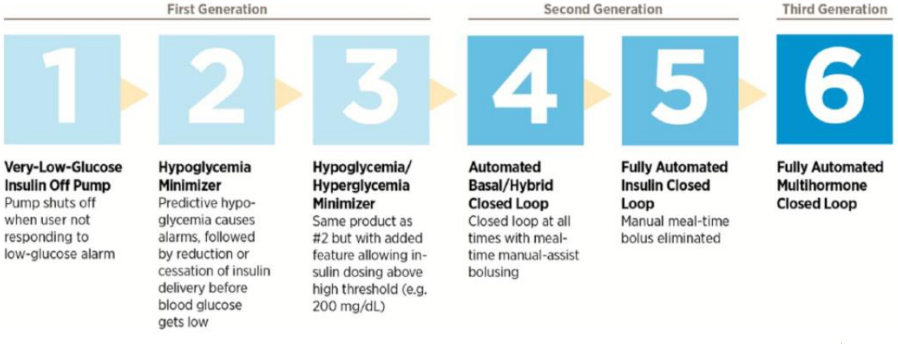
Historical Perspective

1983 – First insulin pump

1999 – First continuous glucose monitor



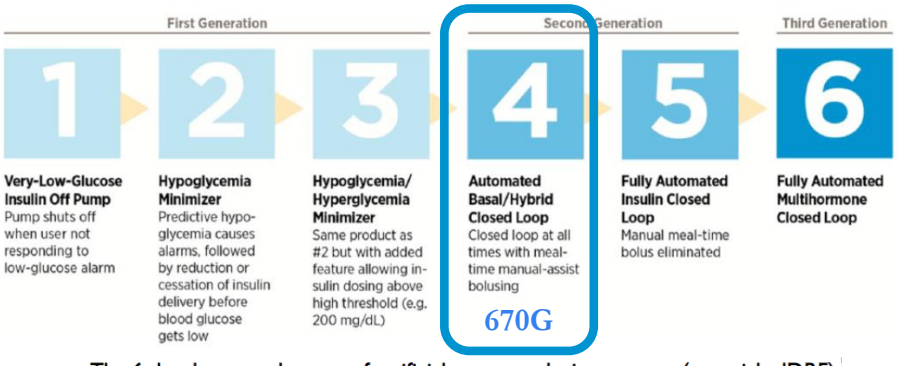
Stages of Artificial Pancreas Development



The 6 developmental stages of artificial pancreas device systems (copyright JDRF).

Trevitt S et al. Artificial Pancreas Device Systems for the Closed-Loop Control of Type 1 Diabetes: What Systems Are in Development? J Diabetes Sci Technol. 2016 May.

Stages of Artificial Pancreas Development



The 6 developmental stages of artificial pancreas device systems (copyright JDRF).

Trevitt S et al. Artificial Pancreas Device Systems for the Closed-Loop Control of Type 1 Diabetes: What Systems Are in Development? J Diabetes Sci Technol. 2016 May.

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Medtronic 670G Pivotal Trial

- 10 sites; 129 subjects (32 teens, 97 adults)
- Incl Criteria: T1D for >2 yr, A1c <10%, Pump for >6 mos +/- CGM
- Protocol
  - 2-week in-home run-in: Manual Mode
  - 3 month in-home study: Auto Mode enabled. Included 6-day/5-night hotel stay with 4 hr/day exercise, i-STAT BG testing q30-60 min over 24 hr period.
  - Subjects asked to calibrate sensor 3-4 times per day, enter carbs for meal boluses, and do fingerstick BG for correction boluses.
- 12,389 patient-days (9412 patient-days for adults) studied.
- Auto Mode enabled by adults a median 88.0% of the time (IQR 77.6%–92.7%) or 21.1 hr/day (IQR 18.6– 22.2 h/day)

Garg SK et al. Glucose Outcomes with the In-Home Use of a Hybrid Closed-Loop Insulin Delivery System in Adolescents and Adults with Type 1 Diabetes. Diabetes Technology & Therapeutics. 2017 Jan 30.

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Medtronic 670G Pivotal Trial Data

	Run-In	Study	P
Percent of Sensor glucose values in range:	Mean ± SD (median, IQR)	Mean ± SD (median, IQR)	
≤ 50 mg/dl	1.1 ± 1.2 (0.6, 0.3-1.3)	0.6 ± 0.6 (0.4, 0.2–0.9)	<0.001
≤ 70 mg/dl	6.4 ± 4.3 (5.7, 3.2-8.2)	3.4 ± 2.1 (3.0, 1.5–4.4)	<0.001
71-180 mg/dl	68.8 ± 11.9 (70.1, 62.6-77.6)	73.8 ± 8.4 (74.9, 70.0–79.1)	<0.001
>180 mg/dl	24.9 ± 13.5 (22.9, 14.8–32.6)	22.8 ± 8.9 (21.8, 16.6–27.4)	0.01045
>300 mg/dl	1.8 ± 4.1 (0.7, 0.1–1.9)	1.3 ± 1.7 (0.7, 0.4–1.6)	0.38836
HbA1c, %	7.3 ± 0.9 (7.2, 6.7–7.8)	6.8 ± 0.6 (6.7, 6.4–7.1)	<0.001
Total Daily Dose, Units	44.9 ± 23.7 (40.1, 30.1–51.8)	47.9 ± 28.0 (41.3, 30.8–53.3)	<0.001
Basal Insulin, as % of TDD	54.1 ± 10.9 (52.7, 46.8–60.9)	46.8 ± 9.4 (46.4, 39.7–54.3)	<0.001
Weight, kg	79.9 ± 18.2 (76.6, 67.7–86.4)	81.3 ± 16.0 (78.1, 68.6–89.5)	<0.001

Garg SK et al. Glucose Outcomes with the In-Home Use of a Hybrid Closed-Loop Insulin Delivery System in Adolescents and Adults with Type 1 Diabetes. Diabetes Technology & Therapeutics. 2017 Jan 30.

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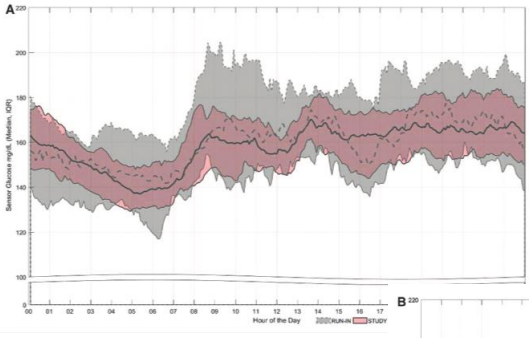
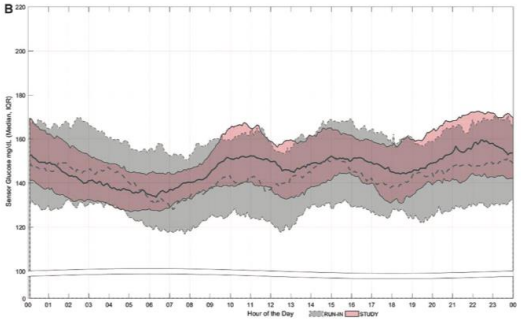


Adolescents

Adults



Median and Interquartile range of sensor glucose values midnight to midnight

Gray and dotted line = Run In

Pink and solid line = Study

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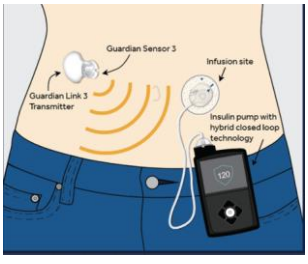
What have we found with the 670G?

- ✓ Greater peace of mind
- ✓ Improved sleep quality
- ✓ Reduced fear of hypoglycemia
- ✓ More time in range
- ✓ Waking up more mornings with on-target BG
- ✓ Less time at extreme high and low

- +/- Less diabetes hassle
- +/- Decreased sense of regimen burden
- +/- Increased freedom to participate in activities



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670G: Who does what?

- Clinician-Set
  - Carb ratio
  - Active insulin time
  - Manual mode settings
- Algorithm-Determined
  - Auto basal
  - Insulin sensitivity factor
  - Auto mode targets
- Patient
  - Fingerstick calibrations
  - Input carbohydrates
  - Announce exercise
  - Input fingersticks for correctional boluses

Yes, the 670G works, but…

1. The algorithm doesn't really "learn" you. It adapts to past 6 days.
2. The system is relatively conservative.
3. You lose a lot of flexibility.
   - No manual boluses
   - No extended boluses
   - No temp basals
4. It chooses sensitivity factors / correction automatically. You only change carb ratios.
5. Sensors can be somewhat unreliable.
6. Some patients may lose a sense of being in control.

Bottom Line on 670G

It still takes a lot of work and patient input, but, most of the time you have to “let go”

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Here is what 670G use looks like…

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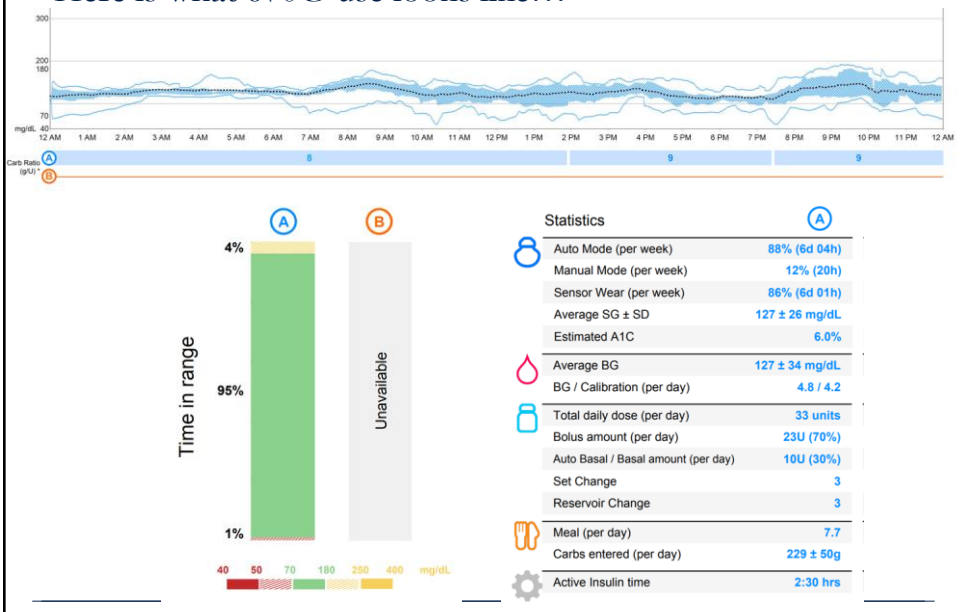
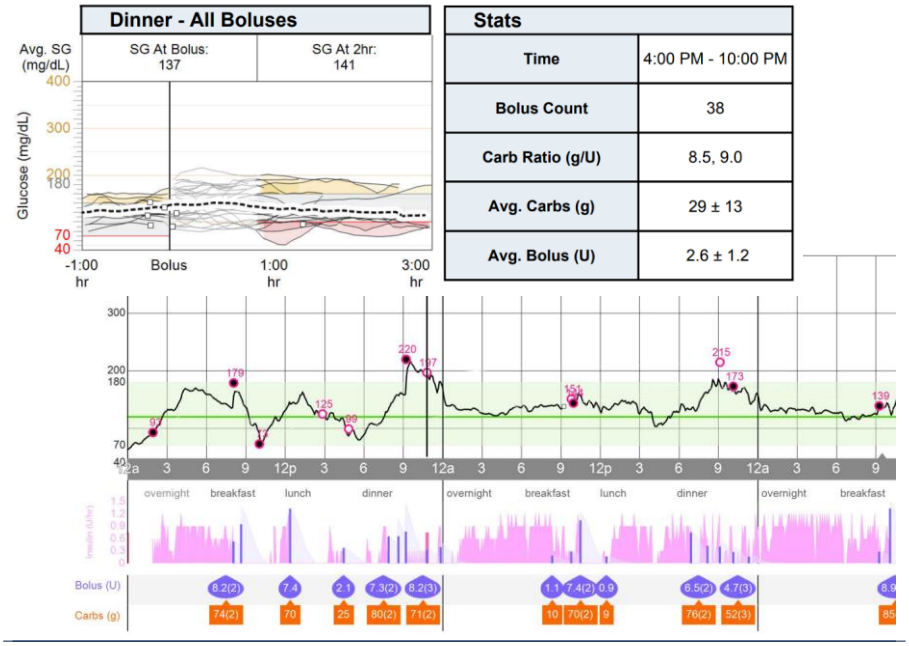
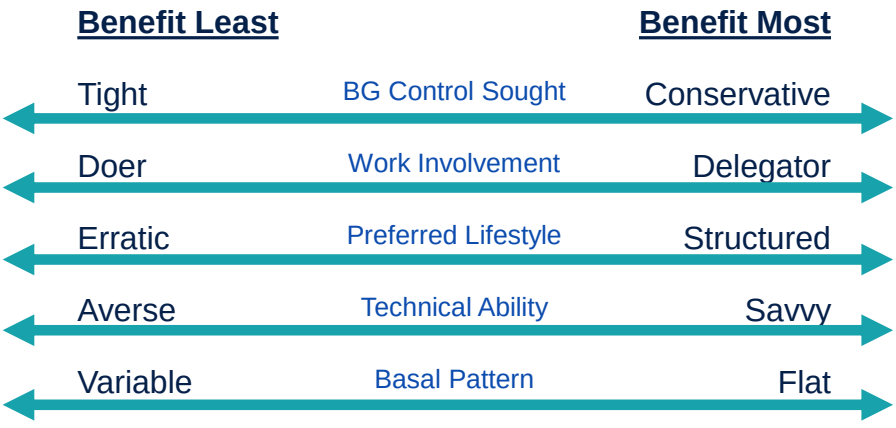
Here is what 670G use looks like…





Choosing the Right Patient for 670G

(adapted from Gary Scheiner)



Gary Scheiner - http://integrateddiabetes.com/670g-and-me-insights-and-incites-on-medtronics-latest-system/

Choosing the Right Patient for 670G

- Newly diagnosed must still learn how to manage T1D.
- Do not start 670G until they've learned the basics.
- Not yet studied in pregnancy.

Assessing 670G Settings at follow-up visits

Auto Mode

- Review Carb Ratios
  - Post-meal highs: Decrease carb ratio 10-20% to give more insulin
  - Post-meal lows: Increase carb ratio 10-20% to give less insulin
- Assess Active Insulin Time (impacts correction dose ONLY)
  - Post-correction high: Shorten active insulin time
  - Post-correction low: Lengthen active insulin time

Manual Mode Settings

- Assess programmed basal rates
  - Compare to total auto basal amount
- BG Targets – 100-150 mg/dL
- Sensitivity using 1800 rule

Patient behaviors

- Exercise
  - Plan ahead – Set temp target 1-2 hours in advance
  - Don't use an "unannounced" pre-exercise snack
  - Leave temp target on for at least 1-2 hours, longer if intense exercise
- Do not give "phantom carbs"
- Ensure that patient's are entering pre-meal BG and giving correction bolus
- Revisit manual basal rates based on auto basal rates

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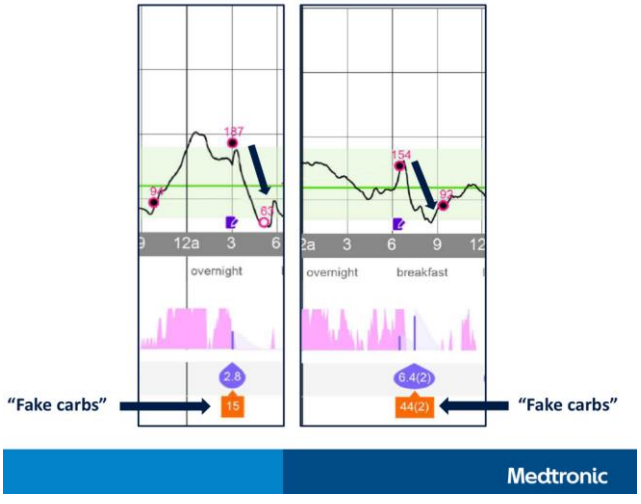
Assessing 670G Settings at follow-up visits

Do not give "Fake Carbs"



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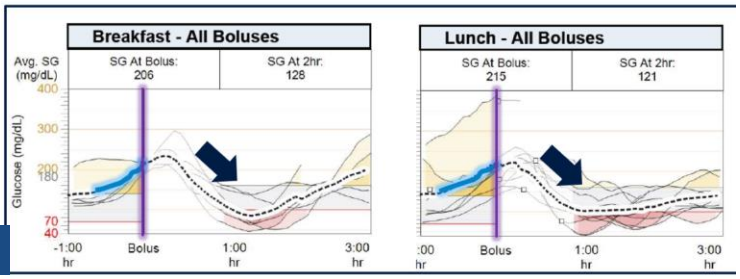
Assessing 670G Settings at follow-up visits

Bolus Pre-Meal, not Post-Meal

Post-prandial lows resulting from post-meal bolusing

Meal Bolus Wizard™ Report



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Tandem – Closed Loop Development

Basal IQ: Predictive Low Glucose Suspend (with Dexcom G5)

Expected later in 2018

Control IQ: Hybrid Closed Loop (with Dexcom G6)

Expected later in 2019

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Tandem – Closed Loop Development

Basal IQ: Predictive Low Glucose Suspend

- Works with Dexcom G5
- Projects 30 min ahead based on last 4 CGM values. Suspends basal insulin when predicting BG <80 mg/dL.
- No alerts when suspending basal before low BG
- Free software update to t:slim x2 pump
- Reduced average time <70 mg/dl by 31% (19 min/day)

Tandem – Closed Loop Development

Control IQ: Hybrid Closed Loop

https://diatribe.org/whats-next-tandem-predictive-low-glucose-suspend-under-fda-review

Other closed loop systems…

Insulet – Omnipod Horizon

Ongoing clinical trial five-day in hotel setting

Bionic Pancreas

Pivotal study testing dual hormone system (insulin & glucagon) expected 2019.

Open Protocol Automated Insulin Delivery (JDRF announced in Oct 2017)

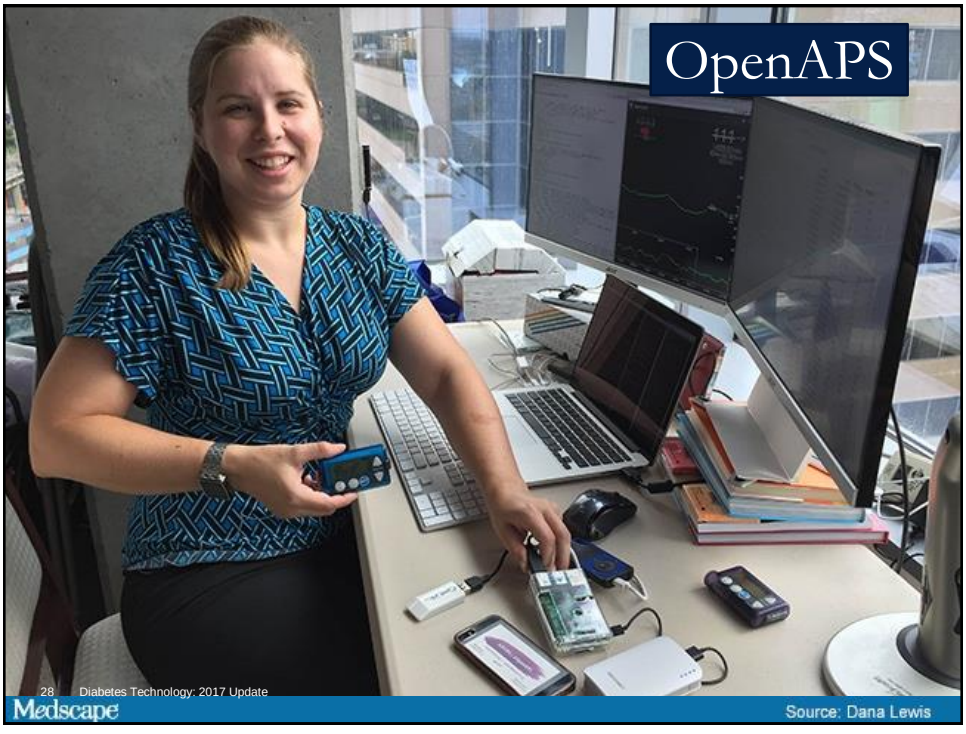
Would allow “mix and match” products – pump, CGM, meter, algorithm – communicating via open protocols

Dexcom G6 received FDA approval in March 2018 as an “interoperable CGM”

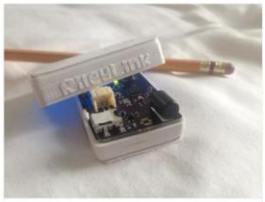
Bigfoot Biomedical

Looking to be a comprehensive “service” rather than a device

Will include CGM (Abbott Libre), pens, pump, meter

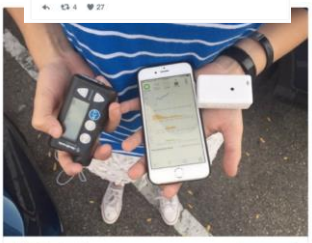


Loop



Howard Look
@howardlook
Follow

Ready for the first day of school with Loop and RileyLink.
Thanks @loudnate @ps2 @OpenAPS
7:48 AM - 15 Aug 2016



Ali Mazaheri
@AliMazaheri
Follow

First day at school with Loop @loudnate @ps2 @bewestisdoing
8:07 AM - 24 Aug 2016

Katie DiSimone
@kdisimone
Follow

Today we started #Loop. Tested it last night with a not-low-carb meal and wow! I could cry happy tears @loudnate @ps2
THANK YOU
5:39 AM - 22 Sep 2016

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Companion InPen

30 2018 Update: Closed Loop Insulin Delivery & Continuous Glucose Monitoring. | Aaron Neinstein, MD

UCSF

UCSF

It's a great system, and it certainly delivers on its promise of bringing many benefits of insulin pumping to pen users: easy carb and dose calculation, dose tracking, data sharing, reminder alerts and more. So it's a powerful tool for insulin users who do not want to wear a pump attached to their body for whatever reason.

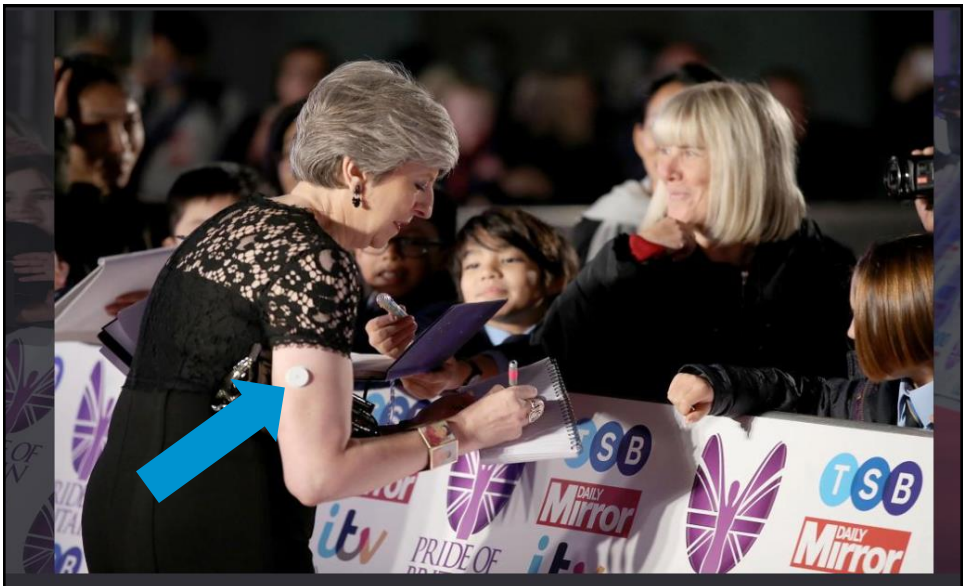
DiabetesMine (Blog)

InPen Availability

- $800 retail price
- Companion says that "70-75% are being covered under pharmacy benefits" and "average copay is $40"
- Coupon available for $549 if patient has to pay cash
- Coverage information available in InPen mobile app
- Mail order pharmacy partner ExpressRx in LA will check coverage and send doctor a prescription to sign
- Not yet available in retail pharmacies
- One-year warranty
- Medicare part D covers it under pharmacy benefit plan

Continuous Glucose Monitoring

The PM wore the patch as she arrived at the Pride of Britain awards last night
IMAGE: GETTY - CONTRIBUTOR



The PM wore the patch as she arrived at the Pride of Britain awards last night

IMAGE: GETTY - CONTRIBUTOR

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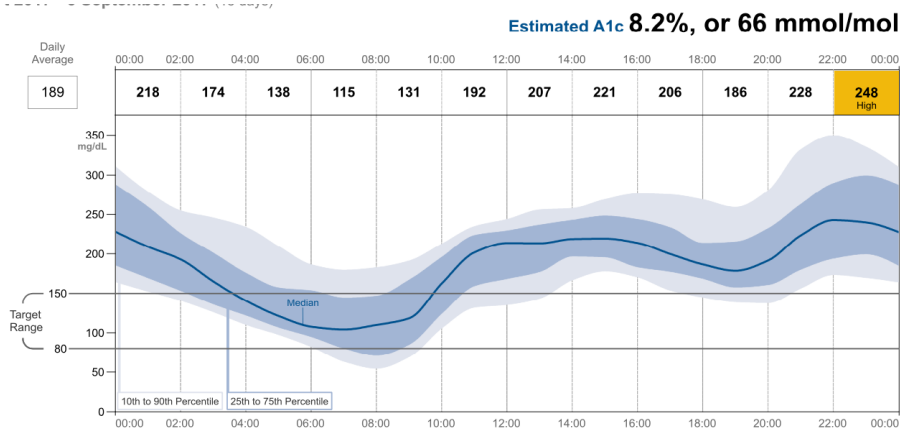
Case 1: 54 yr old man with hx kidney transplant



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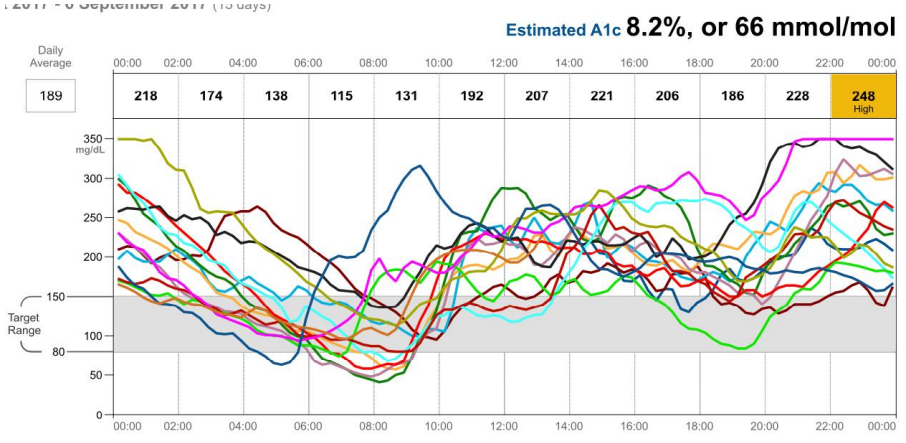
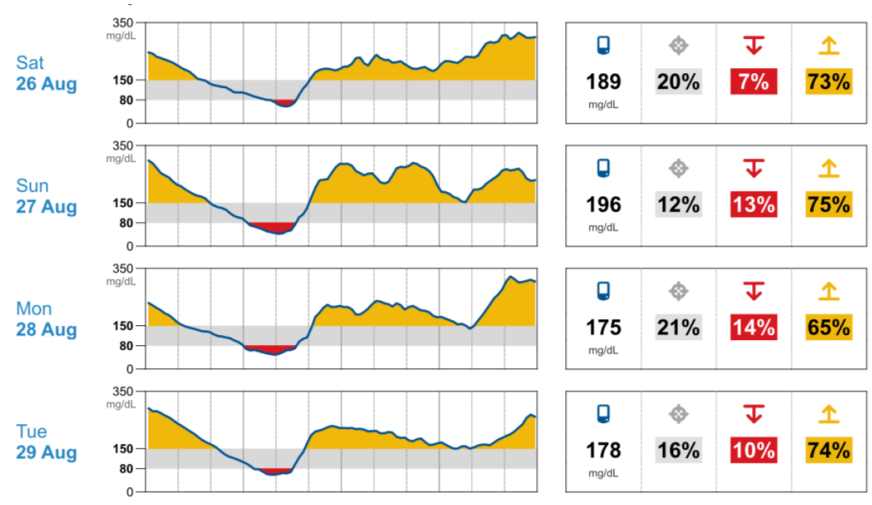
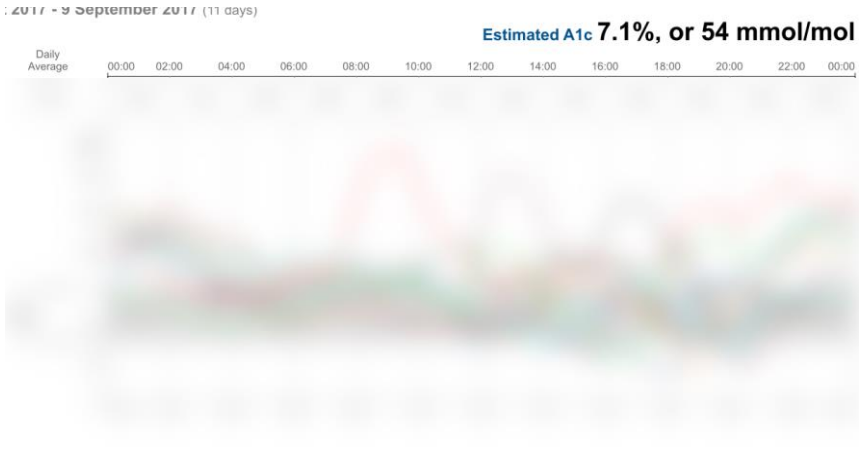

Estimated A1c 8.2%, or 66 mmol/mol
Daily Average
189
00:00 02:00 04:00 06:00 08:00 10:00 12:00 14:00 16:00 18:00 20:00 22:00 00:00
218 174 138 115 131 192 207 221 206 186 228 248 High
350 mg/dL
300
250
200
150
Target Range
100
80
50
0


Sat 26 Aug
189 mg/dL 20% 7% 73%
Sun 27 Aug
196 mg/dL 12% 13% 75%
Mon 28 Aug
175 mg/dL 21% 14% 65%
Tue 29 Aug
178 mg/dL 16% 10% 74%
350 mg/dL
150
80
0

Case 2: 60 yr old woman with chronic pancreatitis

- Basal insulin only
- Repeatedly declines prandial insulin
- Enjoys golfing



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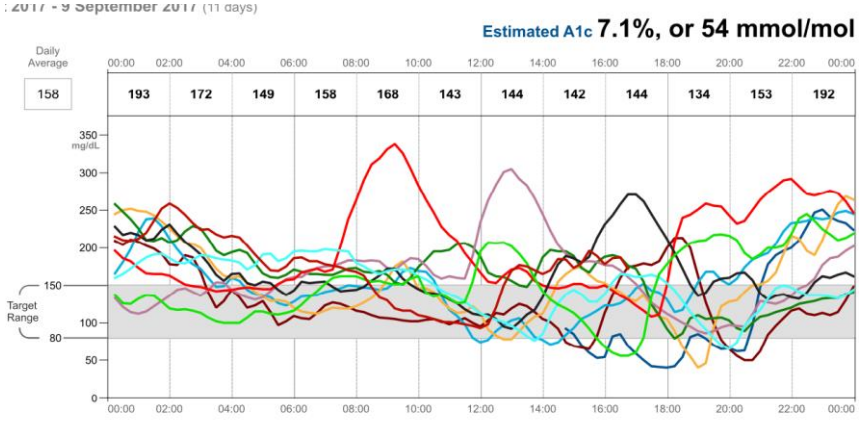
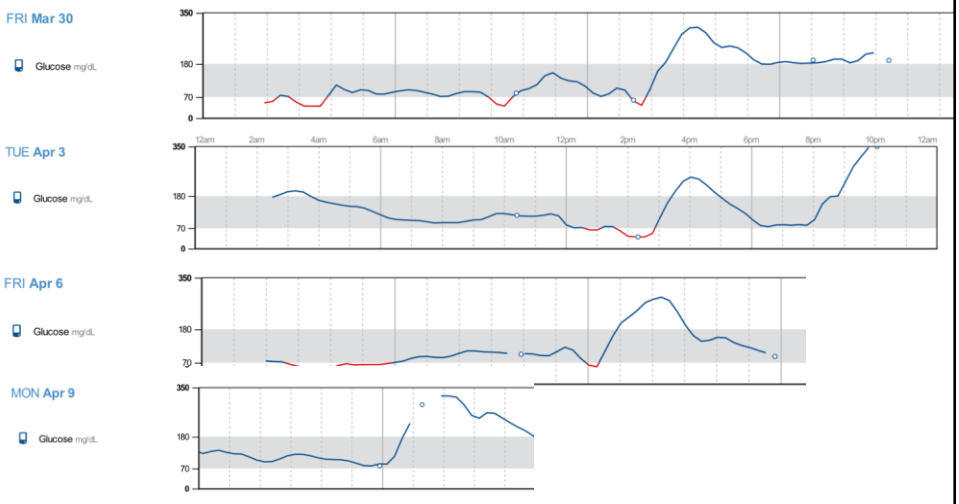


Case 3: 40 yr old woman with CF diabetes

History of poor control (A1c 8-9%)



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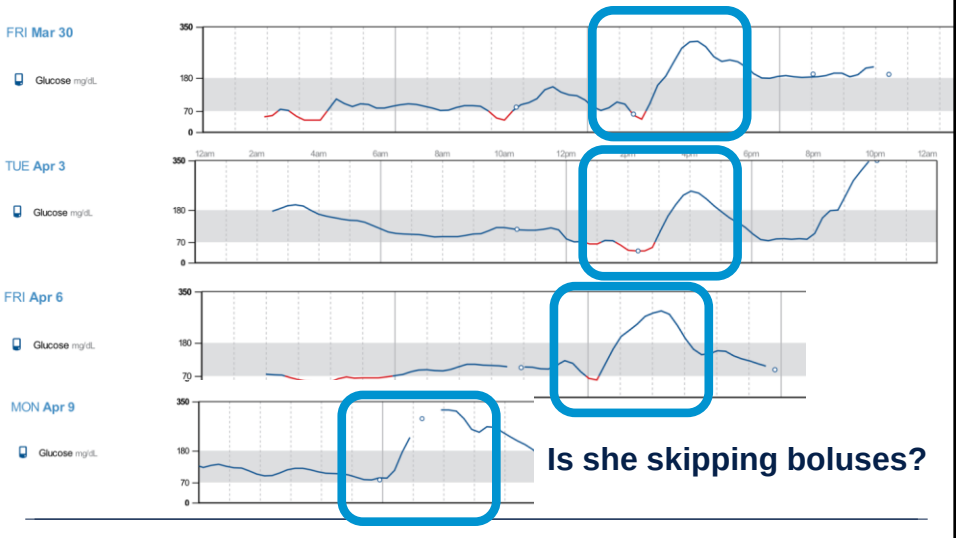

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Case 3: 40 yr old woman with CF diabetes

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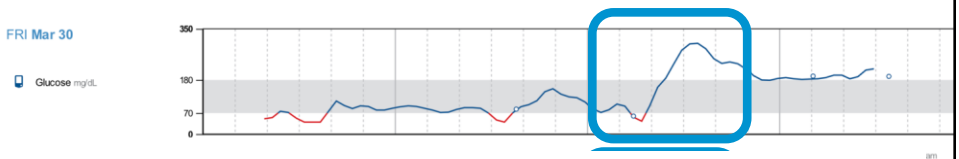

TUE Apr 3

Glucose mg/dL

FRI Apr 6

Glucose mg/dL

MON Apr 9

Glucose mg/dL

BG pre-meal	Starbucks Frappucino (eg Breakfast)	Lunch / Dinner
<80	0	0
80-100	8	6
100-120	8	7
121-150	9	8
151-180	10	9
181-210	11	10
211-240	12	11
241-270	13	12
271-300	14	13
>300	15	14

43 2018 Update: Closed Loop Insulin Delivery & Continuous Glucose Monitoring

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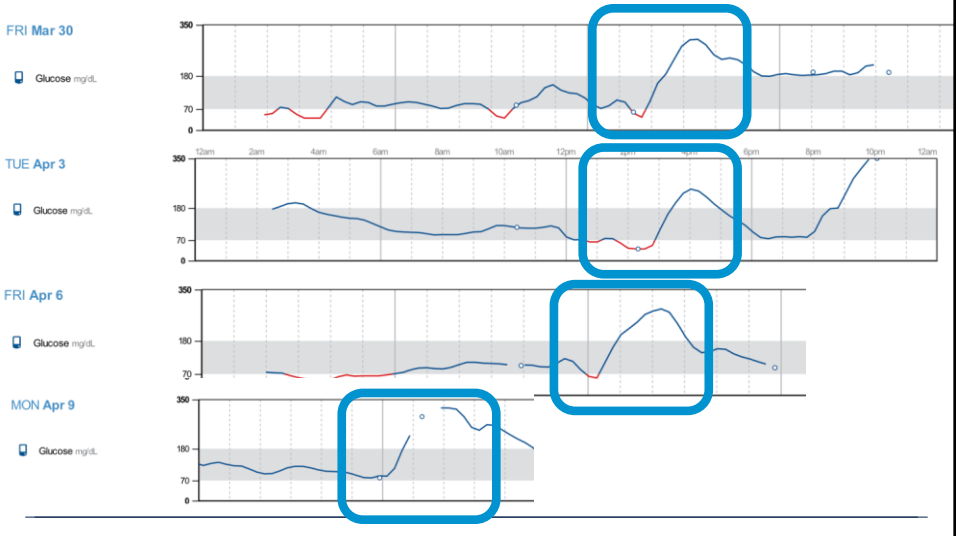
Case 3: 40 yr old woman with CF diabetes

History of poor control (A1c 8-9%)



44 2018 Update: Closed Loop Insulin Delivery & Continuous Glucose Monitoring

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So, should everyone get a Libre?

The good…

- Very convenient
- No fingersticks
- Provides more information
- Gives BG direction/trends
- Cheaper than other CGMs
- Slimmer size profile

The not-so-good…

- No alerts or alarms
- 12 hour warmup per sensor
- Accuracy not as good (but consistent)
- Need to carry a reader device (for now)

Getting A Freestyle Libre

- Medicare coverage
  - Requires 4x fingerstick per day & 4x insulin injections per day
  - Available via Medicare DME suppliers (eg Edgepark Medical Supplies, Byram Healthcare, Solara Medical Supplies, Edwards Health Care Services, Better Living Now, and Mini Pharmacy)
- Private insurance – Available at retail pharmacies
- Cash prices at retail pharmacies (Walgreens, CVS, etc)
  - Reader - $70-100 (one time purchase)
  - 10 day sensor - $30-45 each / $90-150/month

Annals of Internal Medicine ORIGINAL RESEARCH

Continuous Glucose Monitoring Versus Usual Care in Patients With Type 2 Diabetes Receiving Multiple Daily Insulin Injections

A Randomized Trial

Roy W. Beck, MD, PhD; Tonya D. Riddlesworth, PhD; Katrina Ruedy, MSPH; Andrew Ahmann, MD; Stacie Haller, RD, LD, CDE; Davida Kruger, MSN, APN-BC; Janet B. McGill, MD; William Polonsky, PhD; David Price, MD; Stephen Aronoff, MD; Ronnie Aronson, MD; Elena Toschi, MD; Craig Kollman, PhD; and Richard Bergenstal, MD; for the DIAMOND Study Group*

79 subjects per group; mean age 60 years; mean A1c 8.5%

At 24 weeks…

	CGM Group	Control (Blinded CGM) Group	P values
Mean A1c	7.5%	7.9%	0.005
Fingersticks	2.9/day	3.8/day	<0.001
Time per day <70 mg/dL	4 minutes	12 minutes	
QoL metrics	No difference		

Dosing Insulin via Real-Time CGM (rtCGM)

Selection criteria to consider use of rtCGM (Pts meeting one or more)

- Currently treated by intensive insulin therapy
- Experiencing frequent hypoglycemia
- Hypoglycemia unawareness
- Excessive glucose variability
- Varying and/or intensive activity
- Desire to improve glycemic control
- Understands behaviors that influence glycemic control
- Willing and able to use rtCGM on a nearly daily basis
- Willing and able to learn how to use device and receive ongoing education

Aleppo G et al. A Practical Approach to Using Trend Arrows on the Dexcom G5 CGM System for the Management of Adults With Diabetes. J Endocr Soc. 2017 Dec.

Educational skills for rtCGM

At the end of training, prior to rtCGM use, patients and/or caregivers should be able to…

❑ Describe the difference between interstitial fluid and capillary glucose and understand the meaning of lag time.

❑ Recognize the importance of handwashing prior to fingerstick monitoring.
❑ Summarize the calibration procedure and explain when calibration is needed.
❑ Summarize the limitations in rtCGM data accuracy within the first 24 hours following insertion and beyond the manufacturer's recommended wear time.
❑ Demonstrate the procedures for setting alarms/alerts.
❑ Explain the significance of alarms/alerts, glucose trend data, and trend arrows in making treatment decisions.

❑ Explain how to use trend arrows in individualized treatment decisions.
❑ Explain the dangers associated with frequent insulin dosages following meals (i.e., "stacking").
❑ Explain how to use rtCGM during sick days or illness.
❑ Explain individualized monitoring and treatment strategies when exercising (e.g., temporary basal rates, insulin adjustment, carbohydrate adjustment, adjusting for trend arrows).
❑ Demonstrate sensor insertion procedure and list appropriate insertion sites.
❑ Demonstrate the procedure for uploading the rtCGM data

Aleppo G et al. A Practical Approach to Using Trend Arrows on the Dexcom G5 CGM System for the Management of Adults With Diabetes. J Endocr Soc. 2017 Dec.

Adjusting Insulin Doses Using Trend Arrows: Pre-Meal and >4 hr Post-Meal Corrections (*Dexcom G5 only*)

Trend Arrows		Correction Factor* (CF)	Insulin Dose Adjustment (U)
Receiver	App		
⬆⬆		<25 25–<50 50–<75 ≥75	+4.5 +3.5 +2.5 +1.5
⬆		<25 25–<50 50–<75 ≥75	+3.5 +2.5 +1.5 +1.0
↗		<25 25–<50 50–<75 ≥75	+2.5 +1.5 +1.0 +0.5
➡		<25 25–<50 50–<75 ≥75	No adjustment No adjustment No adjustment No adjustment
↘		<25 25–<50 50–<75 ≥75	-2.5 -1.5 -1.0 -0.5
⬇		<25 25–<50 50–<75 ≥75	-3.5 -2.5 -1.5 -1.0
⬇⬇		<25 25–<50 50–<75 ≥75	-4.5 -3.5 -2.5 -1.5

*** Insulin adjustments using trend arrows do not replace standard calculations using ICR and CF. They are dose *increases* or *decreases* from calculated doses.**

Considerations:

For the 4 hours following a meal, avoid adjusting insulin dose using trend arrows. Refer to REPLACE-BG recommendations, summarized in Figure 4, for an approach to minimize hypo- and hyperglycemia during this timeframe.

For frail or older adults, start conservatively to reduce hypoglycemia risk:
- Upward arrows: reduce dose increase by at least 50% (e.g., +1.0 U may become +0.5 U or no insulin increase)
- Downward arrows: increase dose reduction by least 50% (e.g., -1.0 U may become -1.5 or -2.0 U)

For rapidly rising sensor glucose (2 UP arrows; ⬆⬆) at pre-meal, consider administering insulin 15–30 minutes before eating.

For rapidly falling sensor glucose (2 DOWN arrows; ⬇⬇):
- Pre-meal: consider administering insulin closer to the meal
- Near or lower than 150 mg/dL: consider holding pre-meal insulin dose until glucose trends have stabilized

*Correction factor (CF) is in mg/dL and indicates glucose lowering per unit of rapid-acting insulin.

Aleppo G et al. A Practical Approach to Using Trend Arrows on the Dexcom G5 CGM System for the Management of Adults With Diabetes. J Endocr Soc. 2017 Dec.

rtCGM: Up to 4 hour post-meal (*Dexcom G5 only*)

Postprandial Monitoring and Treatment: Using trend arrows for up to 4 hours

Hyperglycemia Prevention
Avoid correcting hyperglycemia for the first 2 hours following a mealtime bolus to prevent insulin stacking.

From 2 to 4 hr Postprandial	Trend Arrow Direction / Recommended Action
150–250 mg/dL	**Arrow Direction:** ↑ or ↑↑ **Action:** ▸ Consider taking a correction bolus using CF. ▸ Monitor for the next 2 hrs. ▸ Avoid additional correction doses for 2 hrs.
>250 mg/dL	**Arrow Direction:** ↑ or ↑↑ **Action:** ▸ Confirm with fingerstick. ▸ Check for ketones if BG is >300 mg/dL. ▸ Take corrective insulin dose by injection (MDI-treated and insulin pump users). ▸ If 2 UP after additional 1 hr: ▷ Confirm with fingerstick. ▷ Take additional corrective insulin. ▷ Change infusion site (if using an insulin pump).

Hypoglycemia Prevention

From 2 to 4 hr Postprandial	Trend Arrow Direction / Recommended Action
Near 150 mg/dL	**Arrow Direction:** ↘ **Action:** ▸ Re-check CGM in 30 min.
	Arrow Direction: ↓ or ↓↓ **Action:** ▸ Re-check CGM in 15 min.
Near 100 mg/dL	**Arrow Direction:** ↘ or ↓ **Action:** ▸ Consider taking 15 g fast-acting carbohydrate. ▸ Re-check CGM in 20 min. If CGM reads <70 mg/dL with arrows still trending down, confirm with fingerstick and take an additional 15 g fast-acting carbohydrate. ▸ If CGM reading continues to drop or CGM level has not begun to rise as expected, confirm with fingerstick and re-check CGM every 15 min.
	Arrow Direction: ↓↓ **Action:** ▸ Follow instructions above but take 30 g of fast-acting carbohydrate.

* Insulin pump users should use established correction factor with pump bolus calculator, which will account for IOB
* MDI-treated pts should give 50% of the calculated insulin during this time (since they cannot account for IOB)

Aleppo G et al. A Practical Approach to Using Trend Arrows on the Dexcom G5 CGM System for the Management of Adults With Diabetes. J Endocr Soc. 2017 Dec.

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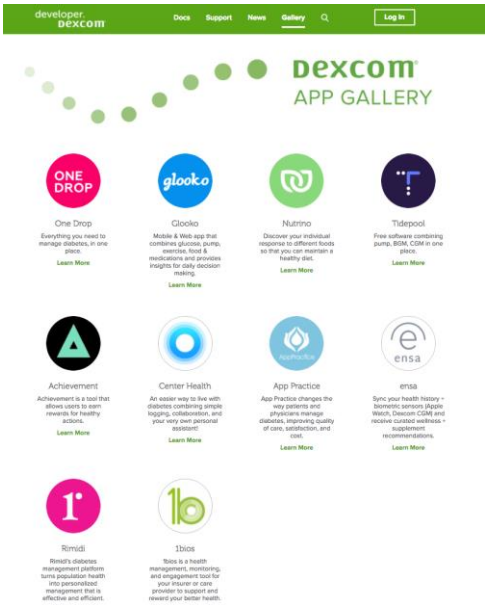
Dexcom API

- Developers use the Dexcom API to create novel applications with Dexcom CGM data, including estimated glucose values, events, statistics, and more.
- Individuals can securely authorize Dexcom CGM data for use by a 3rd party app.
- Enables the creation of an app ecosystem, supporting individual choice in diabetes management.



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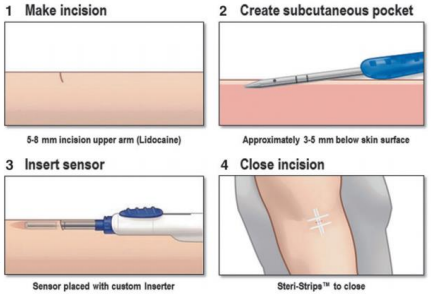
What's coming next in CGM….

Photo Credit: https://asweetlife.org/first-look-at-dexcoms-g6-cgm/

- Dexcom G6 (FDA approved; available mid-2018)
  - No fingerstick calibrations
  - 10 day wear (but… HARD stop)
  - Slimmer transmitter
  - Easier insertion
  - No Tylenol interference
  - Predictive low BG alert
- Abbott Freestyle Libre Gen 2
- Implantable CGM: Eversense



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CGM Comparison

Sensor	G5	FreeStyle Libre	Guardian 3	Eversense
Company	Dexcom	Abbott	Medtronic	Senseonics
Insertion	Applicator	Applicator	Applicator	Surgery
Sensor Life	7 days +	10 days	7 days	90 days
Calibration	2 / day	None	2-4 / day	1 / day
Relative Cost	$$$	$	$$	Unknown
Receiver	Smartphone or Device	Reader Device	Smartphone	
MARD (Accuracy – lower is better)	9%	11.4%	10.5%	8.8%
Choose for…	**Most T1D**	**T2D on insulin; T1D not wanting Dexcom G5**	**TBD**	**TBD**

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Summary: What's coming next?

Last year (2017)

- Clinical trials data for Medtronic 670G closed loop system
- Open source closed loop closed loop systems (OpenAPS, Loop)
- Expanded FDA indication for CGM (insulin dosing decisions)

Now (2018)

- Real-world experience with 1st commercial closed loop system (Medtronic 670G)
- Expanding CGM options

Future

- Calibration-free, accurate CGM
- Multiple hybrid closed-loop commercial competitors
- True closed-loop insulin delivery
- Closed-loop options including "plug and play" and open source