Closer Look

Diabetes Technology Meeting (DTM) 2015 Full Report

October 22-24, 2015; Bethesda, MD - Full Report - Draft

Executive Highlights

In this report, we bring you our full coverage of the 15th annual Diabetes Technology Meeting (DTM) in Bethesda, MD - three days of insights on the artificial pancreas, CGM, apps, next-gen insulin, and more. This was more of a commentary year than a major new data year, as artificial pancreas systems gear up for larger studies, as next-gen CGM systems launch or get close, and as digital health still gets its footing. We share our comprehensive coverage below.

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New Developments in CGM

CGM SYSTEMS

Rebecca Gottlieb, PhD (Director, Advanced Research, Medtronic Diabetes, Northridge, CA)

Dr. Rebecca Gottlieb's presentation emphasized the value of integrated pump-CGM systems. The biggest news came on the MiniMed 670G - patients in the pivotal trial have successfully petitioned the FDA for continued access and use of the hybrid closed loop system. In partnership with the FDA, Medtronic is extending use of the system for two years beyond the pivotal study or until final regulatory approval - the fact that patients wants to keep the system seems like an obvious early sign of its effectiveness. She did not share any new accuracy data for Medtronic's Enlite 3 or Harmony sensors, but to show the benefits of driving insulin automation with CGM, Dr. Gottlieb compared hypoglycemia with Dexcom G4 Platinum (as reported at ADA 2015) to the MiniMed 530G (threshold suspend [TS] off and on) and the MiniMed 640G - while time spent <55 mg/dl was identical with Dexcom G4 and MiniMed 530G/Enlite (threshold suspend OFF), it was halved with threshold suspend turned ON and reduced 75% with the MiniMed 640G's predictive suspend algorithm. Notably, Dr. Gottlieb announced that the non-intensive diabetes therapies business is building a new "super simple" sensor, and this division includes prediabetes. We also saw some early data from Medtronic's Watson partnership, which used the super computer to analyze glucose and insulin data from 100 patients with six months of CareLink data. The cognitive computing system predicted hypoglycemia in the three hours post bolus insulin delivery with 80-90% accuracy. Medtronic is clearly moving much faster than a few years ago and we very much appreciate the way management is thinking far beyond new pump and CGM devices.

- **Notably, patients in Medtronic's MiniMed 670G pivotal study have successfully petitioned the FDA for continued access and use of the hybrid closed loop system.** In partnership with the FDA, Medtronic is extending use of the system for two years beyond the pivotal study or until final regulatory approval (launch is expected by April 2017). This is a certainly a very positive early sign of a system people want to use - "I don't want to give it back" - and we're elated to see Medtronic and the FDA making this possible. Apart from the benefit for these patients, it strongly suggests FDA has become more confident on the real-world safety of closed loop systems. As a reminder, the MiniMed 670G is currently in a pivotal study slated to wrap up *by May 2016*.

- **Dr. Gottlieb showed the benefits of driving insulin automation with CGM sensor, comparing hypoglycemia with Dexcom's G4 (**as reported **at ADA 2015) to the MiniMed 530G (threshold suspend [TS] off and on) and the 640G.** She said the data for the 530G/ Enlite (TS OFF) reported below was identical to the Dexcom poster presented at ADA 2015 ("Regular-Life Use of Patient Real-Time Continuous Glucose Monitoring (RT-CGM) Data"). As always, it's hard to compare across different studies and this was a retrospective analysis, so the results are directionally interesting though hardly the last word. We hope to see future head-to-head studies comparing the efficacy of CGM + MDI vs. automated insulin delivery.

Time Spent <55 mg/ dl at night	**530G/Enlite (TS OFF)**	**530G/Enlite (TS ON)**	**640G/Enlite (PLGM ON)**
Mean hours/night	0.4	0.2	0.1
Standard Deviation (hours per night)	1.0	0.4	0.3
# of Subjects	13,136	34,402	1,387

- **The MiniMed 640G will communicate with MiniMed Connect in the future for viewing data on a nearby phone, remote monitoring, and auto-upload to CareLink.** In what is a missed opportunity, Medtronic has not incorporated Bluetooth into the pump for direct communication with a phone, suggesting that management believes the security risks and potential regulatory concerns are not worth the extra effort at this point in time. It also may be that Medtronic perceives that user experience would not be as positive as it could be in future, and it has elected to wait to provide this additional functionality.
- **Dr. Gottlieb briefly highlighted the partnerships with DreaMed and IBM Watson to build a fully automated closed-loop.** The slide added a "Context" illustration that showed a wearable wristband, presumably to track activity. No timeline has ever been shared for Medtronic's fully automated closed loop, which we assume is 2018+. Both announcements came in April 2015 (DREAM closed-loop algorithm, IBM Watson partnership).
- **"Watson can deliver personal hypoglycemia prediction with 80-90% accuracy."** Dr. Gottlieb showed an exploratory IBM Watson analysis that analyzed glucose and insulin data from 100 patients with six months of CareLink data. Notably, the cognitive computing system predicted hypoglycemia in the three hours post bolus insulin delivery. "We can wait for the combination of events to occur," she said, "and alert the individual. This technology can transform insights into personalized recommendations and actions." The idea seems exciting and we look forward to prospective, real-time studies of the notification technology. It would certainly be compelling to receive a notification, "You are likely to go low" several hours before it occurs - particularly one generated by a computer and not requiring a health professional to generate it, which makes scalability far more possible. The regulatory questions of these types of recommendations are likely the key gating factor - we so hope that the FDA sees the potential here, and that companies can prove it.
- **Dr. Gottlieb gave the most detailed breakdown on Medtronic Diabetes' new operating structure, highlighting that the non-intensive diabetes therapies division includes prediabetes and developing a "super simple" CGM sensor.** We assume this would be the order of something like Google/Dexcom are planning, but aren't sure what the output or form factor will look like. The breakdown further specified the healthcare provider groups each segment will target. We first learned in F1Q16 that Medtronic's non-intensive diabetes therapies division saw high 60%-range growth driven by sales of professional CGM (iPro2) and infusion ports for type 2 diabetes (i-Port Advance) - clearly the base would be low, but we are very impressed by the focus.

Intensive Insulin Management	Non-intensive Diabetes Therapy	Diabetes Service and Solutions
Type 1 diabetes and intensive type 2 diabetes	Type 2 diabetes, prediabetes	Diabetes data, connectivity, healthcare delivery
Pumps and CGM, closed-loop*	"Super simple" CGM sensor, iPro2*, i-Port Advance*	MiniMed Connect*, Infusion sets*, Diabeter clinic*
Endocrinologists	Primary Care Physicians	Not specified, but presumably a range of HCPs and patients themselves

* Not mentioned on slide, but added based on what we know from prior reporting and investigation

DEXCOM G5 MOBILE: CGM ON YOUR SMARTPHONE

Apurv Kamath (Senior Director, Research and Development)

Dexcom Senior Director of R&D Apurv Kamath exclusively focused on the recently launched G5 Mobile system in lieu of Dexcom's typical slate of pipeline updates. He ran through the new mobile app, transmitter, updated receiver, and Clarity software (see diaTribe's comprehensive test drive), and said Dexcom is already working on many requested glanceability and compatibility improvements: Apple Watch, a Today widget for the iPhone lock screen, and Android compatibility. Mr. Kamath emphasized collaboration throughout his talk: (i) work with Dr. Claudio Cobelli's team to develop Software 505 (G4AP algorithm); (ii) a partnership with Upstream Thinking to design the G5 app ("to cross from the early adopters to the majority requires a change in thinking, reaching outside the organization"); (iii) Meal Memory via Apple HealthKit (see diaTribe's test drive of that app); and (iv) the very exciting collaboration with Stanford and EPIC's EHR leveraging Apple's HealthKit (see Dr. Kumar's talk elsewhere in this report). There was a serious focus on how Dexcom is enabling an ecosystem, which now spans partners across pump/closed-loop (Animas, Tandem, Insulet, Bigfoot, Bionic Pancreas), data management platforms and apps (Apple Health, Diasend, Glooko, Meal Memory, mySugr, Tidepool, Training Peaks), and even EHR goliath EPIC. Mr. Kamath's last slide only said, "Stay tuned..." a clear sign that Dexcom's early forays into connectivity are only in the first innings.

APPLICATION OF A SECOND-GENERATION LONG TERM IMPLANTABLE CONTINUOUS GLUCOSE MONITORING SYSTEM IN HUMAN SUBJECTS

Joseph Lucisano, PhD (GlySens Inc., San Diego, CA)

Dr. Joseph Lucisano shared an update on GlySens' 12-month fully implantable CGM (no external attachments), focusing on big picture takeaways from the recently extended ongoing trial (six months to 12 months) that could support a CE Mark (n=20; primary completion in July 2016). Of the 10 implanted sensors thus far, eight have continued on to months 6-12 - one device was explanted because it did not meet performance criteria (we do not know exactly what that means), and one patient had anti-glucose oxidase antibodies (non-neutralizing). Dr. Lucisano did not share accuracy metrics, but appeared very pleased with the results and patient enthusiasm for the implanted sensor and standalone receiver. He is an intense guy and could not possibly feign enthusiasm in our view for a product in which he didn't strongly believe - we have watched him for many years and it is a pleasure to see this product gain some traction though it goes without saying that the environment for CGM is incredibly competitive. He ran through a few study CGM traces that showed encouraging fidelity to the Dexcom G4 Platinum and measured blood glucose. The device has a sensor time lag of 7.7 minutes, a calibration drift of 1% per week, and is expected to support a multi-week calibration interval. Dr. Lucisano believes the company has "retired significant development risks," and it's notable that nine of nine participants that were asked "were delighted to extend the trial" (only eight of the nine sensors could proceed). GlySens hopes to add additional de-noising techniques to further

improve the algorithm. Plans for a regulatory filing, company financing, and a commercial partner were not disclosed. In the implantable realm, GlySens' key advantages over Senseonics are (i) a sensor that does not require a body-worn device for power and communication (preserving the invisibility advantage of an implanted CGM); (ii) a 12-month expected implant (vs. 3-6 months for Senseonics); and (iii) the potential for a once or twice per month calibration interval. Senseonics' key advantages are (i) a mobile app to view the data (unlike GlySens fairly large-looking standalone receiver) and (ii) a smaller sensor implant. Cost, manufacturing scalability, and real-world accuracy are unanswered questions for both systems.

NEW DEVELOPMENTS IN PROFESSIONAL SENSOR GLUCOSE MONITORING

Scott Harper, BS (Abbott Diabetes Care, Alameda, CA)

Mr. Scott Harper provided valuable insight into how Abbott is thinking about the potential of professional (blinded) sensor glucose monitoring with its FreeStyle Libre Pro system. Mr. Harper opened by acknowledging that professional systems can provide critical information for making therapy decisions that can lead to very actionable behavior change. We appreciate Abbott's goal of drawing in more type 2 patients, particularly those not doing well and in greatest need of therapeutic changes (not all need to wear CGM all the time - in fact, we could see a great deal of progress emerge for those not on insulin by simply wearing the system once and at six month intervals at which A1c wasn't below 7%). At the same time, Mr. Harper spoke to the downsides of current professional offerings, stressing the burden of cost, carrying a receiver, and calibrations along with the hassle for providers of cleaning and disinfecting devices between uses. The perceived (and real) hassle factor has been massive, which is why the systems haven't taken off and we see major opportunity for change with FreeStyle Libre Pro. With this product, Abbott believes it has a device that fits the professional niche well given a number of its advantages: disposable, cheaper than traditional CGM, factory calibrated, 14-day wear, stores data on the on-body component (no receiver/ reader), and very easy to train both HCPs and patients on. We believe this product can grow the professional category markedly (admittedly from a low base), and the regulatory risks seem low. We assume Pro also paves the way for a consumer version of FreeStyle Libre (pivotal study complete, but not submitted to our knowledge). We're not sure at what cadence Abbott will submit the latter to the Agency. We also believe research would benefit enormously from greater use. To date, there has been frustration by many manufacturers who would like to use the product in research but have been stymied by the capacity constraints.

- **Abbott submitted its blinded FreeStyle Libre Pro to FDA in 2Q15.** A US pilot study of the Pro - which began recruiting type 2 participants in April (n=132) - did wrap up in August and results have not yet been posted. Neither the study nor the timeline was mentioned in the presentation, though we assume an approval is still on track for 2016.
- **Abbott is actively seeking global regulatory approval and additional indications for FreeStyle Libre.** While it was not completely clear whether Mr. Harper was referring to the consumer or Pro version, we assume both. As a reminder, Abbott recently completed a study to expand FreeStyle Libre's EU indication to pediatric patients. Study results have not been posted, and there is no official submission timeline in the EU. We assume it is currently possible to buy FreeStyle Libre online (no prescription is needed) and use it in children, which makes it's hard to know if this will enhance uptake.
- **Mr. Harper noted that Abbott will also seek indications for alternative body sites wear.** Of course, many patients wear the system elsewhere on the body in the real-world, though perhaps this claim could help increase uptake for those who say, "I don't want to wear that on my arm." At ATTD 2015, Dr. Iain Cranston (Portsmouth Hospitals NHS Trust, Portsmouth, England) noted: "Most people using Libre have purchased the devices themselves, so will put it where they damn well like. The upper quadrant of the buttocks is a popular place, and it stays on for two weeks. On the abdomen is another popular place, but more likely to fall off."
- **Is there an underpenetrated Professional market?** The market for professional CGM is definitely in need of better products that HCPs will find easier to learn and teach, and we believe

Abbott has major clinical and commercial potential in FreeStyle Libre Pro. We would love to see routine professional CGM become an integrated part of diabetes care in the future - especially for type 2 patients, but also for type 1 patients not at their glycemic target.

- **As a reminder, the Pro is nearly identical to the consumer version.** The key difference is that the on-body component stores data every 15 minutes over a two-week period (~1,340 data points) instead of over eight hours. Patients themselves do not get a reader, but would put the sensor on and come back to the provider in two weeks to have it downloaded. The Pro stands in contrast to the consumer version of Libre, which takes readings more frequently (~once/minute) and comes with a real-time touchscreen reader for scanning the data and obtaining the current value.

TIME DELAY OF CGM SENSORS: CAUSES AND COUNTERMEASURES

Guenther Schmelzeisen-Rekeker, PhD (Roche Diabetes Care GmbH, Mannheim, Germany)

Dr. Guenther Schmelzeisen-Rekeker presented the findings of a recently published Roche study (Schmelzeisen-Redeker et al., JDST 2015) that investigated the extent of time delays with the company's prototype CGM. The clinical trial enrolled 37 patients with type 1 diabetes, who wore two or four prototype sensors simultaneously (overall 108 qualified data tests) during experimentation. Study protocol involved inducing glucose swings in patients during in-clinic visits while taking SMBG values every 15 minutes. Findings indicated that the "raw signal" time delay of the Roche prototype sensor was nine minutes relative to BGM measurements, though this was reduced to four minutes with a predictive correction algorithm. Analysis of time delays observed in the same patients during two separate visits (separated by eight months) further suggests a patient dependent delay (e.g., longer and shorter delay times are unique to patients). Indeed, Dr. Schmelzeisen-Rekeker estimated that 40-50% of individual time delay is explained by patients, leading him speculate that personalized time delays in future algorithms might help to improve accuracy of CGM systems. This is certainly an intriguing idea, though we wonder about the clinical added value on the list of things to worry about for CGM uptake. Dr. Schmelzeisen-Rekeker did not share any update on the commercial progress - we wonder if the device is still on track to launch in the next ~15 months, per remarks at the 2Q15 Analyst Day.

- **As a reminder, we saw data from the Roche prototype CGM in a poster presented at ADA 2014.** The study compared Roche's CGM to the Dexcom G4 Platinum. The mean seven-day MARD was 10.9% for the G4 Platinum and 8.6% for the Roche prototype.

ACCURACY AND LONGEVITY OF AN IMPLANTABLE CONTINUOUS GLUCOSE SENSOR IN THE PRECISE STUDY: A PROSPECTIVE MULTI-CENTER PIVOTAL TRIAL

Jort Kropff, MD (Academic Medical Centre, Netherlands)

Dr. Jort Kropff presented interim three-month data from Senseonics' 180-day EU pivotal trial of its implantable CGM system (fluorescence-based subcutaneous sensor, body-worn transmitter with Bluetooth connectivity, and a mobile smartphone app). The single-arm, multicenter investigation enrolled 81 patients with type 1 diabetes, who had two sensors inserted bilaterally into their upper arm (Clinical Trials Identifier: NCT02154126). Sensor accuracy was compared to YSI at ten in-clinic visits. Preliminary data was encouraging - overall MARD in a subset of patients (n=44) was 11.4%. Accuracy diminished in the hypoglycemic range, where overall MARD was 19.2%. The Clarke Error Grid showed 84% of measurements in Zone A and 15% in Zone B (# of paired points unreported). There was no degradation in accuracy over time, and 88% of sensors successfully reported continuous glucose data over the 90-day period. Ultimately, the accuracy and durability are fairly encouraging for a first-gen product, though the outstanding question is what this data will look like at six months and in the full cohort of patients. That data that should be available "at the beginning of 2016." Dr. Kropff did not confirm or deny plans to launch the implantable CGM in Sweden and Norway by the end of 2015, the expectation we heard when the device was submitted for a CE Mark in August (expected in "late fall"). We also continue to wonder if the on-body transmitter negates the advantage of an invisible implantable sensor.

- **Overall MARD vs. YSI was 11.4%, and it did not degrade over time.** This is in line with the company's ADA 2014 pilot data (MARD of 11%). The Clarke Error Grid showed 84% of points in Zone A and 15% in Zone B. The sensor's ability was evaluated over a typical range seen in type 1 diabetes (~40-400 mg/dl). Accuracy diminished in the hypoglycemic range, where overall MARD was 19.2%. In hyperglycemia, MARD was 9.9%.
    - **For comparison, the accuracy is slightly worse than Dexcom's G4 Platinum** (MARD: 9.0% with updated software 505), comparable to Abbott's FreeStyle Libre (an impressive 11% MARD on factory calibration), and better than Medtronic's Enlite (MARD: 14-15%).
- **The sensor reported 17% missed alarms and 25% false alarms at the hypoglycemic threshold (<70 mg/dl).** This is certainly not ideal, though to be expected given the 19% MARD in hypoglycemia. We can imagine that patients would be frustrated with one in four false positive hypoglycemic alarms. Performance in the hyperglycemic range (> 180 mg/dl) was stronger, with only 12% missed alarms and 8% false alarms.
- **Patients wearing Senseonics' CGM experienced significant improvements in glycemic control (baseline A1c = 7.8%) - average A1c reduction was 0.5% over 90 days.** We note that this could be the impact of the clinical trial (since there was no control group), though it's still impressive considering that patients were in good control at baseline.
- **There were no serious adverse events, though 17 adverse events were reported in 12 of the 81 patients.** Skin reactions (five) that mostly resolved after a couple days and site infections (three) were the most common adverse events.
- **We were impressed to see that transmitter wear compliance was very good.** Median wear time was 23.5 hours/day over the 3-month period. Of course, it will be interesting to see whether compliance remains high through 180 days, and what this compliance looks like in the real world vs. other devices like FreeStyle Libre and Dexcom G5.
- **Dr. Kropff did not discuss the timeline or pathway for US approval for the sensor.** Earlier this year, management suggested that discussions with the FDA were ongoing and, that if things moved as planned, Senseonics could start enrollment in a 90-day pivotal study by the end of 2015. This was on par with previous expectations and presumably puts a US commercialization in 2017 timeframe. Just as they already have in the EU (with Rubin Medical), we assume Senseonics will find a partner in the US to commercialize the technology.
- **As we have detailed previously, the Senseonics CGM system has three main components:** a subcutaneous implantable sensor (3 x 15 mm) inserted into the upper arm, a body worn transmitter, and a mobile medical app running on a smartphone. Once the sensor is implanted, a user only deals with the body worn transmitter and mobile app. The on-body transmitter powers the sensor through near-field communication and relays sensor glucose information to the smartphone app through a Bluetooth LE link. The transmitter vibrates when either a hypoglycemic or hyperglycemic threshold level is reached, is attached via an armband or replaceable adhesive, and measures 1.4 cm x 4 cm x 4 cm (0.55 in x 1.6 in x 1.6 in). It can be taken off at any time and put back on without doing anything on the app. The app provides full access to glycemic levels, allows event logging, and permits cloud communication with care providers. We continue to wonder if the on-body transmitter negates the advantage of an invisible implantable sensor. Senseonics has not seen this in studies, but the real test will come when the system is commercialized.

A NOVEL CGM SENSING TECHNOLOGY

Shinjiro Sekimoto, MS (Arkray Inc., Kyoto, Japan)

After emerging onto the CGM scene at DTM 2014, Arkray's Mr. Shinjiro Sekimoto returned to the stage to provide another look at the company's 14-day CGM that employs a novel glucose sensing technology. This

"direct electron transfer principle" (DiET) relies on the enzyme glucose dehydrogenase to mediate the faithful and reliable detection of glucose. At least based on what they disclosed publically, Arkray has only moved slightly past the in-vivo studies that were presented last year, though we imagine there is some work that hasn't been made public. This year's results again came from volunteers without diabetes, in which the device demonstrated a mean MARD of 10.9%, ranging from a low of 5.4% to a high of 20.3%. The Clarke Error Grid showed 84% of measurements in Zone A and 15.0% in Zone B (n=3,125 paired points). Again, there was no mention of sensor performance in the hypo- and hyperglycemic ranges, and we would strongly temper enthusiasm regarding the prototype - it's not hard to show an excellent MARD when glucose is in range for most of the day. However, the key element in Arkray's CGM is the sensing technology, which operates at a lower electric potential (0.15 V) vs. typical CGMs (0.6 V) and evidently confers the ability to overcome acetaminophen interference. As evidence, Dr. Sekimoto shared data investigating Arkray's CGM operating at voltages of 0.15 V and 0.6 V, demonstrating that acetaminophen bias only occurs at the higher potential. The challenge, according to Dr. Sekimoto is ensuring reliable signal detection at that lower potential (though Arkray seems to have addressed this obstacle). If true, this capability would be a plus for the system - as a reminder, FreeStyle Libre does not have interference with acetaminophen (though it is contraindicated for use with high doses of aspirin) and Dexcom has mentioned a similar goal for its Gen 6 product.

- **As a reminder, Arkray's system involves two components: an on-body component (sensor + transmitter) worn on the abdomen and a mobile medical app running on a smartphone.** The app stores glucose readings and provides real-time glucose trend information and, notably, can receive sensor glucose readings wirelessly from the on-body component. The electrode itself measures 0.25 mm in diameter (with an estimated 3 cm length) and is designed to penetrate the skin at an angle (~30 degrees from perpendicular).
- **The key element in Arkray's implantable CGM is the company's novel sensor chemistry that employs a novel Direct Electron Transfer (DiET) technology.** For background, sensing technology involves the reduction of an enzyme via the receipt of an electron from glucose. This electron eventually gets oxidized onto the sensor electrode, which is interpreted to indicate the presence of glucose. Typical sensing technologies have required the presence of an intermediate complex in this process to mediate the transfer of electrons from glucose to the sensor. However, Arkray's approach is unique in that it eliminates the need for this intermediary complex by using the enzyme glucose dehydrogenase. This enzyme consists of an FDA-dependent complex that enables the direct transfer of electrons from the enzyme to the sensor electrode. Because of this "direct electron transfer" (from which the technology gets its name), DiET decreases the number of redox reactions required to detect glucose, (reportedly) improves the reliability and sensitivity of glucose sensing, and requires a simpler manufacturing process.

PANEL DISCUSSION

Dr. Beck: Dr. Lucisano, your data was very impressive. What's the feedback you've gotten from patients on having it under the skin?

Dr. Lucisano: One of the best ways to answer that is to remark that when we reached the part in the trial where subjects were asked to volunteer to extend the trial, all 9 were delighted to extend. A lot said they don't feel it, they don't know it's there. It's being well tolerated.

Dr. Howard Zisser (Insulet, Billerica, MA): In the Watson partnership, why did you use the six different groups?

Dr. Gottlieb: There was a training set of data to see if Watson could predict hypoglycemia in the three hours after bolus delivery. There were correlations within those groupings.

Q: My first question is for Dexcom. Have you thought about collaborating with Nightscout?

Dr. Kamath: The short answer is that we collaborate with them and discuss technologies with them already. However, we live in two different worlds: one that is a member of industry and another that is DIY. We

characterize Nightscout as a lead community that we study in order to understand user innovation. What user innovation points to is the value that needs to be created responsibly by industry.

Q: How do you account for calibration drift with FreeStyle Libre?

Dr. Harper: The simple answer is that you build a sensor that doesn't drift. The more complex answer is that you have to have tight manufacturing and control. You need to make sure the sensor is stable over its shelf life. You also need to establish that the sensor will perform the same across patients. We've demonstrated all of this in *in vivo* and *in vitro* experiments.

Jim Petisce (BD): In your clinical study, your had 81 subjects, 162 sensors. Did any of those 162 sensors need to be redeployed because they didn't work?

Dr. Kropff: No.

Adam Brown, (Close Concerns, San Francisco, CA): Aside from Dexcom and Abbott, who have clear pathways to lower cost (pharmacy distribution, FreeStyle Libre), how are companies on the panel thinking about cost, especially those working on implantable systems?

Dr. Kropff: Unfortunately I'm not capable of answering that question since I'm only a researcher.

Dr. Gottlieb: I'll answer for Medtronic. We are thinking about cost. We are thinking about balancing accuracy for closed-loop systems with a type 2 product. That latter group is looking for a lower cost and super simple sensor.

Dr. Lucisano: I can just add that from our perspective, having a longer lived device will give us some more latitude over the operating cost.

How Good Does CGM Need to be for a Primary Indication to Replace SMBG?

REGULATORY CONSIDERATIONS FOR NON-ADJUNCTIVE CGM INDICATIONS

Alain Silk, PhD (FDA, Silver Spring, MD)

FDA scientific reviewer and type 1 patient Dr. Alain Silk gave a highly optimistic talk on the non-adjunctive use of CGM in diabetes management. Dr. Silk clearly appreciated that CGM can provide critical information for making therapy decision (continuous data, alarms, trend information). However, he also noted that using CGM directly for treatment decisions represents a significant "paradigm shift in diabetes treatment," since the complexity of CGM introduces new risks. As such, it was refreshing to hear the FDA's perspective that non-adjunctive use of CGM is about more than point or average accuracy - said Dr. Silk, "focusing on point accuracy is too narrow … We DON'T think there is a single number [e.g., MARD] that is going to describe this." Dr. Silk instead impressed upon attendees the importance of taking a broader, human factors approach, noting that the challenge for industry will be convincing the FDA that the sum of the benefits of non-adjunctive CGM outweigh the sum of the risks. Hard to argue with that stance, though what that proof looks like is unclear to us. Most interesting were Dr. Silk's specifics comments that the FDA would consider approving non-adjunctive use for a CGM that is less accurate than a meter but has appropriate fail-safes built in (labeling, training, design to facilitate safety) in light of the convenience benefit. We felt this was an extremely forward-thinking and practical approach given the many advantages of CGM vs. SMBG and was perhaps best summarized by Dr. Silk's closing words: "CGM is more than point glucose values … it is a tradeoff of risks and benefits." As a reminder, Dexcom believes it is in sync with the FDA on an insulin dosing claim and expects to have one sometime in 2016.

- **Dr. Silk opened by acknowledging that continuous glucose monitoring brings the potential for much smarter therapeutic decision-making.** Continuous measurements bring more information and clarity (especially through trend arrows and alarms). As Dr. Silk noted, CGM informs very treatment decisions compared to blood glucose monitoring - e.g., a blood glucose value of 200 mg/dl with two down arrows requires different action from a value of 200 mg/dl on a meter.
- **"The idea that CGM can be used directly for treatment decision represents a paradigm shift in diabetes treatment," said Dr. Silk.** Non-adjunctive CGM will require adjustments on

the part of users and providers to account for the different type of information that CGMs bring. After all, while treating with CGM has benefits, FDA believes that it introduces new risks: (i) it will bring an additional level of complexity in insulin dosing (e.g., factoring in rate of change); (ii) it could lead patients to overreact to alarms; and (iii) it could lead patients to neglect insulin on board (especially for patients on MDI). We think these are fair points, and people will gain comfort dosing insulin off CGMs as they gain more experience. Proper education and training can also help avoid adverse outcomes.

- **The FDA clearly appreciates the benefits of non-adjunctive CGM, and this label claim seems to be on the near-term horizon.** This was best captured by Dr. Silk himself: "The message that I want to get across is that focusing on point accuracy is too narrow. We understand that using CGM for treatment has certain risks. It puts glucose information into context with rates of change. We believe that if the benefits of using CGM for treatment outweigh the risks, then it would be appropriate for CGM to be used as primary indication."
    - **Human factors will have to be top of mind.** Below are just a few of the questions we think companies will have to answer:
        - How will CGM actually be used non-adjunctively in the real world?
        - How will CGM be used by different user populations?
        - What kinds of errors can be expected?
        - What calibration frequency is ideal and what are the associated risks and benefits?
        - What kind of labeling and training will prepare users and providers for non-adjunctive CGM?
        - What will happen when a user does not properly calibrate a system, and then relies on it to dose insulin?
- **"It's important to note that CGM technology has progressed and has addressed many early limitations," concluded Dr. Silk.** We found it valuable to hear the Agency's broad confidence in CGM as a technology along with its faith that many issues related to performance have been addressed. See below for a reproduction of Dr. Silk's comparison of "CGM then vs. CGM Now." Indeed, there is clear belief that improvements in CGM have enhanced diabetes management and that the ability of CGM alarms to inform hypo- and hyperglycemia stand as a significant benefit to patients. We heartily agree the field has moved a long way since even five years ago.
    - Limited accuracy à Improved accuracy
    - Sensor dropouts à Sensor quality
    - Large sensor errors, noisy signals à Technological improvements
    - Time lag, interferences, calibration à Algorithm changes

NON-ADJUNCTIVE USE OF CGM: FUTURE DIRECTIONS

Jessica Castle, MD (Oregon Health and Science University, Portland, OR)

Dr. Jessica Castle opened her discussion of the utility of non-adjunctive CGM with a message for regulators and industry alike: "Guess what? Patients are already using non-adjunctive CGM." She shared data from a recently published survey in type 1 patients (n=74), documenting the significant drop in SMBG following a year of CGM use: 6.8 SMBG/day to 3.2 SMBG/day. The findings are not surprising, though came as a testament to the real-world use of the technology … and the fact that non-adjunctive CGM is not merely a convenience. As Dr. Castle noted, it's a way of life. Dr. Castle discussed the hassles involved in dosing insulin using SMBG, running through the gamut of appreciated and underappreciated challenges: lancing fingers, obtaining a "good drop," washing hands clean (often forgotten), drying hands cleanly (forgotten even more often!). The infrequency of SMBG came through loud and clear in the T1D Exchange data (some of the most motivated patients at the best centers): 80% do not test their blood glucose the recommended 6-10 times per

day. If the majority of engaged patients aren't testing, Dr. Castle's data posed a compelling question: Is it regulator's duty to rethink non-adjunctive testing? After all, regulators are not simply responsible for safety in principle, but safety in practice. The implicit message seemed to be very "WeAreNotWaiting-esque" [our words], and while the commentary did not at all read as a criticism of regulatory efforts to date, we absolutely salute Dr. Castle for prompting an insulin-dosing claim for CGM.

Importance of Hypoglycemia as an Endpoint in Clinical Trials

ALGORITHMS TO PREDICT THE LIKELIHOOD OF LOW GLUCOSE

Timothy Dunn, PhD (Abbott Diabetes Care, Alameda, CA)

Dr. Tim Dunn discussed Abbott's ambulatory glucose profile (AGP) report, highlighting the likelihood of low glucose indicator (red, yellow, green light) that appears below the modal day plot. This is part of the software that accompanies FreeStyle Libre, was published last year, and was a key part of the SIGN study presented at EASD 2014. Abbott's reimbursement studies for FreeStyle Libre - REPLACE and IMPACT - are utilizing AGP, and Dr. Dunn highlighted the use of hypoglycemia endpoints in both studies (a primary endpoint in IMPACT and a secondary endpoint in REPLACE). We like FreeStyle Libre's reporting software and agree that it can meaningfully change patient-clinician conversations to prompt faster and more accurate therapeutic change.

IMPORTANCE OF HYPOGLYCEMIA AS AN ENDPOINT IN CLINICAL TRIALS

Boris Kovatchev, PhD (UVA, Charlottesville, VA)

Dr. Boris Kovatchev emphasized that diabetes treatments need to prove their efficacy in clinical trials balancing two critical endpoints: frequency of hypoglycemia and A1c. He warned against optimizing based on one parameter - A1c - since closed loop systems and other interventions need upper and lower limits of control. Dr. Kovatchev and colleagues have developed a blood glucose risk function, which reflects this tradeoff and increasingly penalizes hypoglycemic values as they become more dangerous. The function has been in use for 17 years, including in decision support system (2005-2010) and in the design of closed loop control algorithms. Dr. Kovatchev's risk of hypoglycemia function has also been incorporated into Dexcom's new Clarity software.

JDRF PERSPECTIVE

Campbell Hutton, MSPH (JDRF, New York, NY)

Ms. Campbell Hutton opened her lecture with a call to action - "Hypoglycemia is the number one barrier to patients with diabetes achieving tight glycemic control." She asserted that hypoglycemia is problematic in all its forms, drawing specific attention to the underappreciated consequences of mild and moderate hypoglycemia that can be "very impactful" for people with type 1. Noting, too, that fear of hypoglycemia leads to poor glycemic control, she stressed there is broad agreement that hypoglycemia matters; the real question is establishing a definition for clinical studies that can allows us to compare hypoglycemia across trials. She drew persuasively from artificial pancreas studies, stressing that trials to date have had different ways of measuring hypoglycemia (area under the curve vs. time-in-range vs. time < 70 mg/dl) that make it challenging to evaluate the relative efficacy of various systems. As such, JDRF hopes to move toward a standard set of outcome metrics for artificial pancreas (and other) studies moving forward through a new initiative - the Type 1 Diabetes Outcomes program. A key goal is to develop a consensus for the definition of hypoglycemia. The program will bring together patients, providers, clinicians, researchers, and policymakers in a steering committee of sorts to create a proposal. We're excited to hear about this program, since an accepted definition of hypoglycemia would be clinically valuable, help with payment decisions, identify gaps in research, and inform policy.

PANEL DISCUSSION

Timothy Dunn, PhD (Abbott Diabetes Care, Alameda, CA); Alexander Fleming, MD (Kinexum, Harpers Ferry, WV); Campbell Hutton, MSPH (JDRF, New York, NY); Boris Kovatchev, PhD

(University of Virginia, Charlottesville, VA); John Pickup, MD, PhD (King's College London, London, UK)

Dr. Gottlieb: If we come up with a measure for clinical studies, should we be putting CGM on every trial?

Dr. Kovatchev: It depends on how long the trial is. The frequency and extent of hypoglycemia can be assessed without CGM in sufficiently long-term studies. We have shown that with metrics out there. If the study is shorter, yes, CGM is very valuable tool to assess hypoglycemia. However, I want to get very technical for a second. For the warning and measurement of hypoglycemia, the devil is in the details. In what Tim Dunn from Abbott just said, the hypoglycemia predictor assumes the distribution of values below a certain level is gamma. That's wrong. The distribution is normal. If you base it on that, the predictive power of this metric based on outliers is diminished. If you have time, fix it.

Dr. David Klonoff: I wanted to make a statement about why we organized this important session. It's because at the Diabetes Technology Society we believe that developing hypoglycemia endpoints are very important. We are also introducing a new initiative today to address type 2 hypoglycemia and how to develop appropriate labels for drugs. Some of this overlaps with the type 1 conversation. We see oral agents affecting the incidence of hypoglycemia in patients with type 2 diabetes. If we look at a new definition for clinical trials, we can identify a particular event that is harmful for patients and an event that can be quantified for many thousands of patients. What we also need is a proper metric for hypoglycemia. There are ways of looking at this. I hope that JDRF and DTS can work together, and I think there will be some overlap between type 1 and type 2 outcomes.

Ms. Hutton: Thank you Dr. Klonoff. I think there will be a lot of collaborative effort and we look forward to it.

Q: A few points about terminology and definitions. Firstly, I wonder whether non-severe and severe hypoglycemia terminology can be useful to take forward. I'd like to encourage us to think about terminology. Also, I always try to get through to patients that hypoglycemia is a complication of diabetes. Even if it's not an endo complication, it's clearly a complication. Lack of hypoglycemia awareness hasn't been defined internationally at this stage, and I suggest we make a definition for this. Next, I've found it very difficult to adequately analyze clusters within individuals, when conducting studies. Who to enroll and outcomes are also difficult.

Dr. Fleming: Those are all great points. First, I agree that terminology is important. As a heritage of the DCCT, our gold standard for assessing hypoglycemia today is assisted hypoglycemia episodes. It was the only thing they could use back then because there was no reliable glucose home monitoring. All that has changed now. We should be using CGM as one tool to pick up nocturnal hypoglycemia. I do think that we've got to look at practical ways to define endpoints that have event rates that are sufficient to allow exercisable trials. We just can't do these mega trials like we've done in the cardiovascular field.

Q: Is there a composite scoring system that takes into account hypoglycemia rates, time-in-range, variability, and hyperglycemia? That way we can score out different controllers as to how they perform.

Dr. Kovatchev: The curve has been introduced many years ago. Since then, there has been entire development of risk analysis of blood glucose data. It covers both hypoglycemia and hyperglycemia. We published a control variability analysis to assess closed loop control algorithms. It's a colored plot mapping out hypoglycemia and hyperglycemia. There's also average daily risk range (ADRR), tailored for SMBG data, which gives one number for the risk of hypoglycemia and hyperglycemia. There are tools out there.

Q: Are there any that take all four into account, given the non-linearity?

Dr. Kovatchev: The function that I showed turns the non-linearity into a linear scale. That's a key feature of that function. All of these tools account for the non-linearity.

Jeff Joseph: John, you brought up a good point that the risk of hypoglycemia is related to cardiovascular mortality. There are also clinical trials that show that hypoglycemia is related to myocardial infarctions and other cardiovascular events. I think it's the increased autonomic

response that's related to cardiovascular risk. That's what I think. So that's what I recommend.

Dr. Pickup: I think it's interesting that there isn't a lot of information on cardiac arrhythmias in practice. That is one of the things we've failed to look at: Why is it that hypoglycemia is associated with morality? I think that's one of the things we should be looking more at.

Q: This is a technology question. I've noticed that when I get hypoglycemia just as a person without diabetes, I get cold. It seems like all these wrist sensors are coming out such as the apple watch and Fitbit. Are there any sensors that we can put on the skin that would just tell people that they're going down and alarm them?

Dr. Price: It is a marker for some people, but it's not a consistent marker. People have looked at physiologic factors and it's just not there yet. I'm not aware of subgroups in which it's a reliable marker.

Dr. Pickup: We looked at this in the 1980s and these devices were popularized and commercialized at that time. There are patients where you can detect hypoglycemia by changes in skin conductance, sweat response, stress response, etcetera. But for some patients, you're almost in coma by the time these effects take place. It's extremely variable.

Dr. Fleming: It comes down to semantics when we talk about endpoints. Say some kind of measure of skin response would be reliable. To a regulator it would be a surrogate, indirect end point, which is less persuasive. On the other hand, hypoglycemia is an event, and it's been difficult to define it but it's not a surrogate. Some people say A1c is a surrogate, which I disagree with but it doesn't tell you directly where a patient is going to end up exactly in terms of micro vascular complications.

Dr. Kovatchev: The point that you made is very important in the following sense. We now have sensors that make additional signals available: Fitbit, you name it. These additional signals have been tested in isolation some years ago, and they weren't sufficiently specific by themselves to distinguish hypoglycemia all the time. But, added to glucose values and glucose trends they can have tremendous value in improving the detection of hypoglycemia.

Q: I think we should abandon the term "mild hypoglycemia." The implication is that it doesn't matter. But if you're at 51 mg/dl, which is not les than 50 mg/dl, the outcome could still be catastrophic if you're driving a car. The implication of mild is it doesn't matter. But it could under the right circumstances. Is there data on hypoglycemia's effect on our most important organ - brain and long-term CNS problems? People that get glucoses of 50 mg/dl thousands of times over decades, cannot be good for your brain. Is there any information on that?

Dr. Pickup: It is terribly important in the developing brain of children, where it has been studied. The influence of repetitive hypoglycemia in adults is less important. It's more important in the child for obvious reasons. You only have to drop blood glucose a tiny amount, to 4 mmol/l, down from 5 or 6 mmol/l before you get some kind of behavioral change. So just subtle changes in lowering blood glucose are important. I'm with you there.

Ms. Hutton: Part of the process that our group is going to go through for the T1D outcomes program is looking at and evaluating all the evidence that exists for hypoglycemia and other outcomes. We will identify if there are gaps, and the effects of hypoglycemia on CNS may be a gap that needs to be explored as a subsequent step of this program.

Q: Do you know any articles on patient preferences and fear around nighttime hypoglycemia?

Ms. Hutton: I'm not aware of any specific data on that topic, but as part of our program we are including people with type 1 diabetes. We do think that there needs to be robust data collection on patient preferences. Nocturnal hypoglycemia would certainly be part of that.

Dr. Pickup: We did a qualitative analysis of patient responses to nocturnal hypoglycemia when they were on CGM. One of the most important themes that emerged from the analysis was how much patients appreciated

that CGM and threshold-suspend can reduce the impact of nocturnal hypoglycemia. So there are quite a number of patient responses on this front.

Dr. Fleming: There are a lot of studies that document the fear of nocturnal hypoglycemia. I think it's a no-brainer. If I had type 1 diabetes, this would be my biggest concern since it's a period when I'm not in control. So yes, I think we need to document it. But I think it is part and parcel of living with type 1 diabetes.

Dr. Price: Novo Nordisk has sponsored a survey on the impact of nocturnal hypoglycemia on quality of life and productivity. We can talk after this session.

Q: In terms of nocturnal hypo and patient perspectives, I know that in the UVA Closed loops studies emphasizing overnight control, several patients have generated blog posts. I see that more and more blog posts are being analyzed. What can this show us?

Dr. Kovatchev: I have the advantage of having the data so I don't need the blog posts. Our long-term study supported by JDRF on nocturnal hypoglycemia is finishing now. Patients' appreciation of the system is being analyzed in a few months, and we are supposed to crunch the data by the end of January. We will have more contemporary data on long-term studies soon.

Q: What sort of data should we be gathering with regard to hypoglycemia? I think we have seen that clinical hypoglycemia self report from patients underestimates the problem. So if you have the same question for a care partner, you'll have a much more accurate event reporting from the care partner rather than the patient. This is never systematically evaluated in the context of randomized trials as a secondary measure. I think that it's important to keep in mind. It makes sense to use CGM as a main endpoint.

Dr. Pickup: there are lots of issues. One is when designing the trial, it's important not to exclude patients with severe hypoglycemia. That's one mistake that we've made. We also need to do the trial long enough to get an accurate measure of hypoglycemia which you need at least six months duration to do. So measuring hypo at all in a clinical trial would be a major step forward. You have to educate patients what your definition of hypoglycemia is before the trial starts so everyone knows what everybody is talking about. I agree there's general confusion on the subject.

Dr. Yogish Kudva (Mayo Clinic, Rochester, MN): On the issue of using CGM to measure hypoglycemia - is a MARD of 10% critical even in the hypoglycemia range?

Dr. Kovatchev: I don't know. 10% was the relationship between sensor deviation and outcome. What we found out is that when insulin dosing on a sensor with MARD <10%, the outcome does not change if you go further down; 5% is not much better than 10%. Whether that is sufficiently accurate to measure hypoglycemia - I don't know. I can speculate. Over a certain period of time, 10% would be sufficient. We have to decide how long is that period of time. If you want to assess hypoglycemia over a few hours, probably not. But if you carry on over a week, probably yes.

Dr. Kudva: With G5, is it accurate enough to use an endpoint?

Dr. Price: Yes.

Dr. Dunn: Just an addition. Sensors are not perfect, but nor are other systems. SMBG requires such a large study size. The first big step is to start measuring hypoglycemia consistently, and we can use sensors to start collecting data.

Dr. Gottlieb: CGM provides objective documentation of what's going on throughout a study.

Dr. David Rodbard (Biomedical Informatics Consultants LLC, Potomac, MD): One thing that will help patients and researchers is approximating glucose on a logarithmic scale. Hypoglycemia will be more evident this way. Once you utilize the log of glucose, then using the mean and standard deviation, we can calculate the probability of glucose being under any threshold very easily. Closely related to that, because severe hypoglycemia is so rare, we don't have the number of events we need. The thing we can do is correlate the frequency of hypoglycemia above 80 mg/dl with the frequency of hypoglycemia above 50 mg/dl. Then you

can use a level of 80 mg/dl as a surrogate for lower hypoglycemia cutoffs. I think we need to make things easier for patients.

Dr. Dunn: I agree with you from a technical point of view. We need to make it clear to patients that hypoglycemia is something that needs to be on the priority list. With the broader use of sensors, this is becoming a better-appreciated priority. I think we need to take smaller steps into it though.

Dr. Rodbard: The only place I've seen hypoglycemia described on a log scale is Nightscout. Lane Desborough stretched out the hypoglycemic range. I think it improves our subjective ability to improve what happens in the closed-loop range.

Dr. David Klonoff: The way we at DTS have been looking at the type 2 diabetes population is quite in line with what David said. Mild and severe hypoglycemia are not two separate diseases. The way we see it, there is a continuum and that mild hypo occurs at one frequency, severe at lower frequency, extremely severe at even lower. The more data we have to support that the better. We can work with pharma companies to look at end points from their data of products that lower blood sugar. Does the data go down progressively? We agree that David's approach is good. Currently what's happening is that the extreme end of the continuum has been sliced off - you're so bad that you are in a coma or need hospitalization. There are a lot of problems with that. Even though we are looking for hypoglycemic reduction we can't show it. One might say that we're in a situation now where mild hypo at 70 may not be clinically relevant. At around 70 you get counterregulatory, you get autonomic around 60, cognitive around 50. It's arbitrary what the clinicians say is relevant and meaningful. We need this number to be more practical in clinical trials as an end point.

Dr. Kovatchev: I can relate to that in the sense that the pattern from 70 to 60 to 50 is called tail of distribution It's important to take the tail to extrapolate to higher or lower frequency in time. I can pull a hundred thousand data points right now to show how that tail looks.

Dr. Klonoff: I think the problem is similar for both type 1 and type 2. There are products that could be helpful, but we are not identifying the right tools for those products.

Dr. Patricia Beaston: What's important are the rules for designing a trial. If companies or investigators pick their own method of doing it, the question is, "What did they really study?" Imagine if you have pump A system and pump B system, pump B is only different because of one new functionality. But they used all of the alarms, four point calibrations, and a much more accurate glucose meter. Then you have a control group on sensor-augmented pump therapy, with no alarms, and a different quality glucose meter - you're not actually looking at the new functionality of that one pump. We need to make sure that we capture the information and that it is explained very clearly. And then there are the expectations of subjects in the study. This is a rare-ified group. We have to explain to colleagues if we expect them to choose the system for the correct patient.

[Comment]: I just want to remind everyone that what we care about with hypoglycemia is the delivery of glucose to the tissues. There are very few studies where we look at this. Ultimately, the glucose level and the rate of blood flow both matter, because you can have a low glucose but be asymptomatic because of a high blood flow rate. I don't know how to measure this in a clinical trial, but the delivery of glucose to the tissues is what we really care about.

Mobile Apps

REGULATION OF MOBILE APPS

Bakul Patel (Associate Director for Digital Health, FDA, Silver Spring, MD)

FDA's Associate Director of Digital Health Mr. Bakul Patel lived up to our high expectations, delivering a remarkably forward-thinking talk on how the Agency plans to regulate this rapidly moving, nuanced area. The Agency is taking a risk-based approach to digital health that is platform independent (apps today, but

what in the future?) and intended to promote innovation, patient engagement, and safety. Hard to argue with that, though the devil is always in the details. FDA is focused on functionality (what an app does, not where it lives) and is narrowly tailoring its regulation to those devices of "higher risk" - what defines "higher risk," of course, is a matter of interpretation. Mr. Patel briefly highlighted four key guidance documents: mobile medical apps (final), medical device data systems (final; MDDS), general wellness (draft), and medical device accessories (draft). It was excellent to hear him use words like "ecosystem," and he clearly understands the need not to overregulate this field. He did not talk specifics about diabetes, though we have seen this area moving in the direction with approvals of Dexcom's G5, MiniMed Connect, and the down-classification of retrospective CGM data. Mr. Patel urged visiting the FDA website for examples of regulated and non-regulated mobile medical apps, admitting "we are not answering" all questions (email digitalhealth@fda.hhs.gov or Bakul.Patel@fda.hhs.gov), and said its his goal to make sure policies are clearly articulated. Our biggest question relates to wellness CGMs (Sano, Echo Therapeutics) - will these be exempt from regulation through the wellness guidance?

- **Based on the Mobile Medical Apps final guidance, FDA's regulatory oversight applies to mobile apps that are either intended:** to be used as an accessory to an already regulated medical device, or to transform a mobile platform into a regulated medical device. For instance, things like Dexcom's G5, MiniMed Connect, and smartphone-connected meters. Our impression is that bolus calculator apps ARE subject to regulatory oversight, since they provide specific treatment suggestions (see below).
    - **The following diabetes apps are listed on the cleared/approved mobile medical apps page (last updated on February 17, 2015, so it doesn't include recent Dexcom, Medtronic, and Roche approvals):** Diasend, WellDoc Diabetes Manager, FreeStyle Tracker (cleared way back in 2002), Infopia Glucophone BGM, Sanofi/ AgaMatrix's iBGStar BGM, PositiveID's iGlucose data hub, Ideal Life BGM, iHealth Align BGM, MyGlucoHealth BGM, Symcare Diabetes Management Program, **and WaveSense Diabetes Manager.**
    - **Lower risk mobile health apps are exempt from regulation.** These apps are not considered "mobile medical apps" - patient self-management apps, tools to organize and track health information (not for treating or adjusting medications), tools to access health information documents and communicate with healthcare providers, tools that automate simple healthcare provider tasks.

Mobile apps (NOT focus of oversight)
▪ Help patients self-manage their disease or conditions without providing specific treatment or treatment suggestions ▪ Provide patients with simple tools to organize and track their health information ▪ Provide easy access to information related to patients' health conditions or treatments ▪ Help patients document, show, or communicate potential medical conditions to healthcare providers ▪ Automate supple tasks for healthcare providers ▪ Enable patients or providers to interact with personal health record (PHR) or electronic health record (EHR) systems

- **FDA has released a draft general wellness guidance, and a final version is expected in the next few months.** This guidance exempts products that inherently present a very low risk to users' safety. There is some nuance to the label claims here: products can be marked without any reference to disease or conditions, OR with a disease-related general wellness claims that contain

reference where it is well understand that healthy lifestyle choices may reduce the risk or impact of a chronic disease or medical condition.

    - **The big question is whether wellness CGMs (e.g., Sano, Echo Therapeutics) will meet these criteria.** It's somewhat hard to believe such products will fit "wellness claims," as these CGMs could be used in the real world to manage diabetes. Perhaps companies can get around regulation if they claim the device is for general wellness - "Monitoring of blood sugar for general wellness purposes" - rather than for the "management of diabetes." Another method around regulation could be to show broad indicators of blood sugar (red, green) instead of specific glucose values. Of all the digital health regulatory nuances, this area of wellness CGMs is definitely one to watch.

- **FDA has released a draft medical device accessories guidance that narrowly defines accessories and parent devices.** FDA is defining accessories narrowly, and the level of risk stems from the *accessory*, as opposed to just because it is connected to a parent device. For instance, the MiniMed Connect relay device is actually a 510(k), even though it connects to a CGM-integrated pump (PMA device). We see this as a major positive for innovation in connectivity and the useful extension of medical devices going forward.

    - **An accessory** is a device that is intended to support, supplement, and/or augment the performance of one or more parent devices.
    - **The parent device** is a finished device whose performance is supported, supplemented, and/or augmented by one or more accessories.

LINKING CGM DATA WITH AN ELECTRONIC HEALTH RECORD

Rajiv Kumar, MD (Stanford University, CA)

Dr. Rajiv Kumar summarized Stanford's digital health solution - the "Diabetes Triage Report" - for directly integrating Dexcom CGM data into the electronic health record, EPIC. Dr. Kumar spoke from experience as a pediatric endocrinologist, demonstrating a solid understanding of the practical obstacles to clinical care - too few resources, too little time with patients, manual uploading of data, silo'd data. He ran through how Stanford has worked with Dexcom and EPIC to passively and automatically send data from someone wearing a Dexcom CGM (G4 and G5) to the Epic EHR: (i) user wears Dexcom CGM and runs Share 2 app (G4) or G5 app; (ii) data is posted to Apple HealthKit with a three-hour delay; (iii) EPIC MyChart app pulls data from HealthKit and sends directly to the EHR. The result is the kind of population health that diabetes care needs to move to. Dr. Kumar stressed that a flowchart consisting of 288 blood glucose values/day would undermine the purpose of the seamless workflow - instead, his group has devised algorithms that run analytics and identify high-risk patients (those with A1c > 9.0%, those with lots of hypoglycemia, etc.). They are flagged in red, making it easy to see who needs follow-up. This is exactly what the field needs - bringing together connected devices and software solutions to inform therapeutic decision-making and reduce the burden on providers. Indeed, the benefits of the system were perhaps best summarized by Dr. Kumar himself: "No increase in workflow; increase in improved care." Judging from the way Dr. Kumar was swarmed by clinicians following his lecture, we were not alone in our enthusiasm for his work.

- **The Stanford team has built algorithms into the Diabetes Triage Report to perform basic trend analysis and pattern recognition.** It kind of looks like Microsoft Excel running within EPIC, so it definitely needs some work on the usability. Still, even the basic functionality sorts patients by age and medical information, identifies high-risk patients, gives estimated A1c's, and shows the number of readings per day. Even more impressively, Dr. Kumar stressed that it does not burden providers with alerts either; the software in its current iteration only interacts with providers when they open the program (i.e., avoiding real-time alerts that can be overwhelming).

    - **It strikes us that this software framework could easily be extended to other Bluetooth-connected devices (meters, pumps, pens, etc.).** We hope that this is the next step as the software would be even more powerful if insulin, carbohydrate, activity, and pump data could be integrated into the EHR as well.

- **Impressively, Dr. Kumar's group has made his software publically available (gluvue.stanfordchildrens.org).** He acknowledged that a lack of impetus is the primary reason why there has not been more change in this ecosystem to date. Now, as he noted, "that is no longer an excuse."
- **What are the additional benefits of the Diabetes Triage Report?** There is no need to open separate software programs; no wasting valuable in-clinic time downloading devices; less documentation required at visits; tighter feedback loops with patients; the workflow is simpler; communication with patients is more streamlined; enables remote care; etc.
- **Notably, Dr. Kumar shared that there is actually a revenue model now in place for telehealth** - "95251" is a code that can be used once a month for the review of 72 hours of CGM data. The pay is not very high ($44 for Medicare, $85 for private payers), but Dr. Kumar suggested one person in the clinics that reviews many patients' data at regular intervals.

MOBILE APPS IN DIABETES: QUANTITY VS. QUALITY

Ellie Strock, ANP-BC, CDE (Voluntis, Inc., Plymouth, MN)

Ms. Strock, the Director of Medical Affairs at Voluntis, devoted her presentation to assessing available mobile apps and sharing trial results on Voluntis's Diabeo/Insulia therapeutic companion software. Diabeo/Insulia involves two components: a prescribed, patient-facing smartphone application that provides individualized insulin dosing guidance and coaching with healthcare providers, and a clinician-facing web portal that delivers remote monitoring capabilities and notifications. The software was CE-marked in 2013 and has shown promise in early clinical trials. Notably, an RCT (TELEDIAB-1) of patients with type 1 diabetes (n = 180) showed a 0.9% A1c reduction in the group using Diabeo/Insulia combined with telemedicine support compared to control. A follow-up study (TELEDIAB-2) showed similar results for patients with type 2 diabetes using basal insulin therapy. The software's third trial, TELESAGE (NCT02287532) is currently recruiting participants and will evaluate the effectiveness of Diabeo of type 1 and type 2 individuals using basal/bolus or pumps; the goal is to show efficacy and obtain reimbursement. A key question is whether the telemedicine component is scalable. According to Ms. Strock, users have incredibly positive feedback about Diabeo/Insulin, success that she attributes to the software's real-time connection with a healthcare team on a digital platform.

- **Currently, there are over 650,000 mobile health apps on the market, but only 103 are FDA approved.** In a study published in 2015 by Huckvale K et al on 46 mobile insulin calculators, 67% overall carried a risk of "inappropriate output dose recommendations that violated basic clinical assumptions" - pretty frightening given their widespread availability through personal smartphones, and the fact that most of them are offered for free. She was, however, enthusiastic about two FDA-cleared mobile apps, WellDoc's BlueStar and Roche's Accu-Check Aviva Connect, that have both shown A1c improvement compared to control in clinical studies

A MEAL DETECTION AND CARBOHYDRATE ESTIMATIO ALGORITHM BASED ON CGM DATA FOR USE IN AP SYSTEMS

Sediqeh Samadi (Illinois Institute of Technology, Chicago, IL)

Diabetes Technology Society Student Research Award winner Ms. Sediqeh Samadi provided an overview of her research examining meal detection in artificial pancreas systems. As she noted, a primary problem in the development of closed-loop systems is the accurate detection and estimation of meal carbohydrates that can necessitate meal announcements for accurate control. To overcome this burden, her work investigated the ability of Qualitative Trend Analysis (a meal detection technique) to identify consumed meals and meal sizes in five patients using CGM readings. Preliminary findings indicated that the technique was able to detect 92% of meals with just seven false detections. The results did come in a relatively small sample (61 meals), though ultimately offer hope that meal prediction algorithms can offer an avenue to move toward fully closed-loop systems in the future. Ms. Samadi acknowledged that hybrid systems will remain the status quo in the near term and echoed commentary - which we've heard from many others in the past year - that

fully closed systems will be challenging to achieve in the absence of faster-acting insulins or the addition of glucagon.

PANEL DISCUSSION

Kyle Rose (mySugr, Vienna, Austria): Given the rapid growth, we need a better understand of this intimidating labyrinth of choices for both patients and healthcare providers. Is it realistic to think that rating organizations like App Script can do this without being influenced by sponsors? They need this sponsorship to survive.

Ms. Strock: It definitely is something to look at. I'm not aware of anything in the consumer area to help assess that. You go into the app store and you look at a list and you have to download everything to see if they are going to work. Many apps are downloaded and never used again. We need to look at ways to support that because it can be costly.

Dr. Patel: There are a thousand apps coming up every month, and almost that many die every month. Keeping up with that evolution and keeping that tracked in some way is challenging and I think that's a different way of thinking.

Dr. Barry Ginsberg: I have mostly a rant. Dr. Kumar, what you did was very nice. But we don't look at what we've already done. We had interoperability standards in the mid 1980s for one EMR talks to another EMR, or how does one EMR talk to a lab or external devices. There are standards for all those things, which everyone has ignored. When you look at the graph you put up of Dexcom data, that was developed in 1984, 1985 by Roger Mazze and David Rodbard. And they did it nicer than the modal plot you showed. We ignore things we've developed at our own peril.

Dr. Kumar: Point taken. The point was not the modal day visualization. The point was the passive data collection. I wish I had power over the data sharing and interoperability. I don't know who to blame. There are certainly weaknesses to overcome.

Dr. Ginsberg: I know who to blame. It's CMS - they decided to pay for EMRs and didn't set any standards.

Dr. Kumar: No comment.

Q: Dr. Kumar, I want to compliment you on passively getting so much information into the EHR. I work in the type 2 world and I hope you're thinking about bringing that data into the EHR in a similar fashion?

Dr. Kumar: The challenge is getting the information into Epic's chart. They only collaborate with people who are in every hospital. It's tough when not everyone has an Apple phone.

[Comment]: I think we need other people with meters that send data into HealthKit more easily. What you've set up seems like it would work well for any Bluetooth BGM.

Dr. Kumar: Yes. There are Bluetooth meters out there and that's the quickest way into the EHR.

Dr. Strock: Another thing I'd point out is that the Ambulatory Glucose Profile was published many years ago. As part of that project, we did some piloting with Epic and we did that before HealthKit was there. We connected the data into Epic and had interactive PDF and it worked. Taking that from technically making it happen to actually putting it into practice has been a challenge. However, having that accessibility within the EHR is really critical because that data is just gone otherwise.

Dennis Harris (The Endocrine Society, Washington, DC): You mentioned that with the automatic upload of CGM data to EHR, you wouldn't be micromanaging and calling someone up if they hit 30 or 500. Wouldn't it be great if you could do that? Is there a problem with having that data in your records and not doing anything about it? Is there a liability for clinicians using mobile apps? Could this limit use?

Dr. Kumar: Our *long-term intent* is to micromanage. We aren't set up for that right now, as it requires a lot of manpower and reimbursement. We can't be responsible for every BG as it comes in the chart. This is the first step towards that goal. My timeline is 3-5 years to provide that real time support. With regards to liability, I don't know the answer. I've talked to lawyers and HHS, and it's really hard to know. Do I stop because we don't know? I don't feel anymore dangerous now than when someone texted me during this talk with a question.

Ms. Strock: The field is so new and it's one of those questions that we need to address in detail. Having 24/7 data does bring the question of what is your responsibility as a clinician, what is your responsibility as a patient. How can we define it in these systems?

Dr. Patricia Beaston (FDA, Silver Spring, MD): Dr. Kumar, I'm impressed about the amount of data you can go through. You have the advantage of using one system and a process you are familiar with. Ms. Strock, you said you ask patients what they like. How much interaction have you had with HCPs? We see a number of devices of different quality and format, and I cannot imagine a PCP treating a lot of people with type 2 diabetes, who all pick their own app and expect me to be familiar with it. It's barraging me with information. When you're working on this, have you talked to HCPs about their wish list and what they're willing to accept or not accept?

Ms. Strock: Diabeo has 75-80% satisfaction. The majority of patients want to continue on it. On a larger scale of apps in general, patients bring them to providers with no experience - it's something we are all bombarded with. There is no standard, and that needs to be addressed in the general health and wellness area. App Script is helpful in that context, "Here are apps I would recommend to my patients." Having some tools like that would be helpful.

New Treatment Paradigms

REGULATORY ASPECTS

Courtney Lias, PhD (FDA, Silver Spring, MD)

FDA's forward-thinking Dr. Courtney Lias framed her regulatory presentation with a scenario: "A private citizen creates a "Do-It-Yourself" device (e.g., artificial pancreas device) and shares that device with others (e.g., sharing code, specifications, etc.)." How would the FDA regulate such efforts (e.g., Nightscout, #DIYPS, and Bigfoot Bryan Mazlish)? Dr. Lias openly discussed the requirements that DIY devices have to fulfill, which seemed reasonable, though definitely challenging for those hacking away in their garage: (i) Responsible party; (ii) Design control; (iii) Transparency, adequate instructions, and human factors; (iv) Safety mitigations; (v) Surveillance, recall, and corrective actions. Her comments on "distribution" were fascinating - it's not just mailing out physical devices, but includes specifications, code on the Internet, or even a server that gives results to people. She concluded with a lot of empathy for the #WeAreNotWaiting movement, and said FDA is "trying to push companies" to bring these innovations to market. Dr. Lias specifically noted that a phone can now be used instead of a CGM receiver (referring to Dexcom's G5) and artificial pancreas devices have improved by "leaps and bounds." "We recognize the need for smooth and efficient pathways for technology, and efficient clinical trials." Three cheers to that.

- **Responsible party:** This is key to assuring all bases are covered and minimizes problems falling through the cracks. A responsible party provides an outlet for feedback, complaints, and relief. Dr. Lias said responsibility is a key question when problems arise for artificial pancreas devices - is the algorithm, pump, or CGM developer liable? When devices go through the FDA process, it is very clear who is responsible.
- **Design control:** Devices need clearly stated specifications that must be tracked over time. When modifications or changes are made, there must be thoughtful consideration of potential risks and the impact on related systems.
    - **Example:** modified AP software code that is incompatible with a rarely used pump setting causes the bolus calculator to use the incorrect value for insulin-on-board.

- **Transparency, adequate instructions, and human factors:** These requirements help users know what to expect from a device. There must also be clear communication of device limitations. "If possible to mess it up, someone will do it, no matter how "stupid" it seems to the developer." Devices need clarity surrounding the data (or lack of) collected in clinical studies.
    - **Example:** an artificial pancreas app designed so that users may inadvertently hit the bolus button when intending to input meal data.
- **Safety mitigations.** Dr. Lias emphasized, "ALL devices that contain software have bugs," and unanticipated software bugs can have "devastating effects." Certain clinical scenarios cannot be modeled or predicted, and clinical studies with safety mitigations in place allow for discovery of significant device failure modes. Dr. Lias was adamant that "this is not theoretical" - multiple times in artificial pancreas studies, the safety mitigations in place (e.g., caregiver) were the only reason a patient wasn't harmed. In those cases, software bugs or device failures would have resulted in severe patient overdoses.
    - **Example:** Software that incorrectly calculates small insulin doses required for children is not discovered until a serious adverse event occurs (outside of a clinical trial with monitors).
- **Surveillance, recall, and corrective actions.** If an issue is identified, the responsible party must ensure that risks to other users are mitigated. Corrective actions must be implemented for all affected parties, and corrective actions must be verified for effectiveness. Issues arise when there is no one responsible for tracking adverse events or complaints to detect device problems.
    - **Example:** Artificial pancreas users report problems on #APtwitterhandle, but due to the high volume of tweets, it is not seen, tracked, or dealt with.
- **"Distribution" has many forms - it's not just mailing out physical devices, but can be specifications, code on the Internet, or a server that gives results to people.** FDA takes enforcement based on public risk - as more people are affected and risk increases, the likelihood of enforcement rises. The whole issue of Nightscout/CGM in the Cloud was thorny from a regulatory perspective, since the open source effort (no clear responsible party) was sharing software on the Internet. This comment suggested that Nightscout/CGM in the Cloud qualifies as "distribution," and thus, would be a regulated medical device (our speculation). We assume FDA did not take enforcement action against Nightscout because of low perceived risk (e.g., small number using it, parents wouldn't put their kids on it unless it worked). And of course, Dexcom got Share and the Share receiver approved relatively quickly - perhaps the Agency accelerated those efforts instead of shutting Nightscout down.

ARTIFICIAL PANCREAS: FROM TWO TO MANY

Bryan Mazlish (CTO, Bigfoot Biomedical, Milpitas, CA)

With just a Bigfoot title slide on display (nice!), Bryan Mazlish shared his compelling story developing an automated insulin delivery system for his wife (Dr. Sarah Mazlish) and son, culminating in the founding of Bigfoot Biomedical. His 15 minutes of remarks detailed the remarkable journey, starting from his son's diagnosis (lots of sleepless nights), using his finance background to develop several software configurations (remote monitoring to intelligent prediction algorithms to a full automated insulin delivery), building hardware (Mazlish Box), rapid closed-loop algorithm iteration with his wife Sarah (a new version every week), not being able to share the system with other patients, unsuccessfully shopping the technology to device companies (no sense of urgency), founding a company with Jeffrey Brewer and Lane Desborough, acquiring Asante's assets, and signing an agreement with Dexcom. Whew! In new news to us, he did mention that Bigfoot is in FDA discussions to start a clinical trial "very soon" - we assume this is an early feasibility study, as the company has previously said it would be in a pivotal trial by the end of 2016 (otherwise, it is a massive acceleration in timing). Bigfoot has now grown to more than 30 people, and expects to be near 50 by the end of the year (!). Bryan concluded in brilliant fashion: "I'm determined not to waste my opportunity to contribute. The technology is ready. FDA is a partner. The community of people

with type 1 diabetes is eager. There is no reason to delay. We are not waiting." See below for our favorite quotes from this talk.

- **"Automated insulin delivery is not just one feature. It's a totally different experience. It's not something layered on top of existing pump therapy. It's a total change in the paradigm of care."**
    - **Mr. Mazlish attributed the lack of industry partner traction to three factors in Q&A:** (i) The traditional business model is tough ("this is a service, not just a device"); (ii) lack of understanding that automation is not just "a better feature ... it's different therapy" (we love that); and (iii) a hesitation to being the first (" ... companies were ready to be fast followers once Medtronic does it").
- **"The results were almost indescribable - life on the system was so much easier. Type 1 diabetes is now a different disease.** But that's when it started to get complicated. As a family, we accepted our own risks. What about everyone else? The hardest part was not being able to share it. Sarah and I went to FDA to get feedback on what we had done. The FDA is okay with us using it, but they rightfully said, 'If you want to distribute, even for free, you'll need to go through a process that ensures safety.' Creating a class III medical device was never on my radar."
- **"So I looked for a commercial partner. For two years, I shopped the technology to relevant players.** I was essentially willing to give it away. Some discussions got far. One company even licensed it. But I was disappointed by the lack of urgency. Months turned into a year, and there was little action."
- **"This May, we announced the acquisition of Asante. We have a formal relationship with Dexcom. We're on our way. We've grown from three founders to over 30 people.** We expect to be near 50 by end of year. We're hackers and entrepreneurs with and without type 1 diabetes. The FDA is a strong partner. What started out as a sleep deprived sprout has turned into a garden, and we hope it becomes a forest."
- **"Bigfoot is doing more than automated insulin delivery.** We're going from two to many, and integrating automation into daily lives with regulatory requirements and reimbursement realities. We want to increase sleep. Reduce fear. Improve quality of life. Reduce the burden. And improve math for the healthcare system. So far, so good."
- **"In the right context, machines can do better than humans.** They never tire and they never get distracted."

Questions and Answers

Dr. Patricia Salber (Health Tech Hatch, Larkspur, CA): Bryan, how are you funded?

Mr. Mazlish: Bigfoot has been funded by a number of sources, including high net worth individuals and families with a connection to the disease. We're actively raising a round of financing if anyone is interested. [Laughter]

Dr. Yogish Kudva (Mayo Clinic, Rochester, MN): Is there a first product you're looking at?

Mr. Mazlish: We are developing a type 1 diabetes management system for the holistic aspects of living with type 1 diabetes - all the touch points that one has to manage day to day. It's not just how do I deliver my insulin or manage my glucose. It's all aspects. It will include an automated delivery component and a number of other aspects. This is a service, not just a device.

Dr. Kudva: Will you submit to the FDA?

Mr. Mazlish: Yes. We're in discussions with the FDA to start a clinical trial very soon.

Dr. Courtney Lias: Your story is very compelling. We understand the frustrations companies have. Sometimes the FDA has a bit of influence in certain areas. Are there areas FDA could try to change things for companies that have innovative technologies?

Mr. Mazlish: FDA continues to do a tremendous job facilitating. We know that FDA has constraints it has to work in. And like all of us, there are limited resources. I don't think there is any one thing. Had I been as steeped in the artificial pancreas guidance when it was up for review, I might have made some comments. Maybe there is an opportunity to discuss that.

Dr. Lias: Guidance you can always comment on. One other thing - we are starting to throw our support in interoperability. For products like yours, where separate products are put together, there are some challenges with combining things that weren't designed to be put together. It HAS to be solved. People have good ideas to facilitate and speed up interoperability.

Dr. Roman Hovorka: Bryan, you tried to communicate with industry, but didn't receive too much open hand. Why? What is driving the slowness of industry?

Mr. Mazlish: It's an excellent question I still ask myself. There are a number of issues. The business model. It's challenging to consider going through the path and following the same reimbursement model that exists for devices. We're taking a different tack. There is a fundamental lack of understanding that this isn't just a better feature. It's different therapy. It's going to bring value to the market. Maybe I shouldn't be giving that away at this point. There's still a hesitation to being the first. The sense I got was companies were ready to be fast followers once Medtronic does it. [Laughter]

Dr. Hovorka: Where tech is moving, is there a future of using phones for driving closed loop?

Dr. Lias: It's obvious we should move that way. It's ridiculous to require people to carry around multiple computers. There are things to think about, but they are solvable, and people are going ahead with it. With insulin delivery from a phone, there are definitely things to think about, especially with cybersecurity. But we can do that.

Dr. Hovorka: Is that a Class III device?

Dr. Lias: With medical mobile apps, we don't consider the phone a medical device. The app may be. For instance, when we talk to companies about Android, they have to figure out how to handle updates. Or what if someone doesn't update? Those discussions have been going on for a few years. The Agency is comfortable with where things are going. We will deal with it - not stand in way - and make it as safe as possible.

Dr. Hovorka: What about an artificial pancreas app?

Lias: It always depends on what the app is. Some apps are class III medical devices.

Q: I've been seeing patients for quite a while. There is quite a diversity of people with type 1 diabetes in terms of intelligence and resources. One of my stock phrases of the year is, "You've got to be smart to take care of yourself with diabetes." With some of these innovations, are we at the point where they can be adopted to a broad spectrum? Or are these for the smart person with diabetes.

Dr. Salber: Omada Health is a good example of a tech company you don't have to be super sophisticated to use. They have telephone calls, health coaches, and a web-based platform to get information. We know older people are getting online and using tools in ways we never thought. There are text based programs you can use without being really sophisticated. And then there are various patients who go to PubMed and subscribe to medical journals.

Dr. Lias: I talked about transparency and human factors. When a company is studying a product, they should understand it and include information so the healthcare provider can decide who it is appropriate for. Will the features of this device create a risk for my patient?

Dr. Salber: In telemedicine areas, we're all over the place. There are text programs to telephones to kiosks to incorporating artificial intelligence. I had a specialty consultation over the telephone and it was one of the best encounters I've had. The real challenge is how do we know who should get what type of care delivery for what kind of problem at what point in course of care? Right now, we're defaulting to, "It's the consumer's choice."

Dr. Richard Kravitz: There are more good questions than answers here. The digital divide is closing. In some cases, ownership of cellular devices is beginning to approach natural averages among minorities and less educated groups. But a gap still exists. We found that a significant percentage of patients interested in our PREEMPT study were unable to participate because they didn't have access to smartphone.

Mr. Mazlish: The onus is on the developer - the company - to make the device accessible. That might mean tradeoffs. It doesn't do everything that it can do, but it makes it more acceptable. Examples are devices like CeQur and V-Go. There is a great opportunity to attune these technologies to make them more accessible.

Dr. Salber: Companies need to do a much better job of incorporating real users into the development process.

Dr. David Klonoff: With cybersecurity and phone controllers for the artificial pancreas, I think we'll see two separate phones in one package. We'll have current phones and then some other controller that is walled off. Samsung and Blackberry are going that direction. My question - healthcare is being managed in a corporate way, where physicians and providers have to follow algorithms. But we're also seeing empowered patients that want certain types of care. How does that tension affect healthcare? Payers may not want to see that type of care, and there may be pressure on HCPs to ignore it if it goes against algorithms.

Dr. Salber: With reimbursement, we're in a tough transition period. When we get to a value-based system those issues will smooth out.

Novel Markers

A MULTI-DIMENSIONAL COMBINED ENDPOINT FOR UNDERSTANDING GLYCEMIC CONTROL

Robert Vigersky, MD (Medical Director, Non-Intensive Therapies, Medtronic Diabetes, Washington, DC)

Medtronic Diabetes' Dr. Bob Vigersky gave an outstanding talk on novel visual and numerical representations that capture composite diabetes outcomes (A1c, hypoglycemia, weight). His favorite representation is called the glucose pentagon (DT&T 2009 and JDST 2012), a single graph and number combining five elements of glycemia (A1c; SD; time >160 mg/dl; AUC > 160 mg/dl; and mean glucose). Dr. Vigersky called it a "beauty" and would only improve the metric by adding hypoglycemia (AUC <70 mg/dl). He reviewed his own novel approach published earlier this year in JDST, combining A1c, hypoglycemia, and weight change in a single score out of 100. His example scores using actual clinical trial results were highly compelling. For instance, a study comparing canagliflozin to glimepiride (Lancet 2013) showed no difference in A1c, but a dramatic difference in the composite scores (accounting for hypoglycemia and weight differences): 95 points for canagliflozin vs. 40 points for glimepiride. Composite scores from the ASPIRE in-home and DAFNE HART studies illuminated similar takeaways: no difference in A1c, but very strong composite scores of 80 for the treatments. Dr. Vigersky was highly realistic in his remarks, assuming it will take "10-20 years" for the diabetes community to get used to a composite outcome (similar to how long it took A1c to gain credibility). He called for professional organizations, clinicians, and industry to agree on a composite metric to better describe overall glycemic control - this is particularly essential for many next-gen therapies that may not show improvements in A1c but do reduce hypoglycemia and improve time-in-range.

- **Dr. Vigersky covered a few other composite visual and numerical representations:** Liebl et al., *JDST* 2013 (visual plot for A1c + hypoglycemia); Damiano *NEJM* 2013 (visual plots with A1c and hypoglycemia); Rodbard *JDST* 2015 (visual plot of time-in-range and mean glucose); and Augstein et al., *BMC Endocrinologist Diab* 2015 (Q score).

Selected Questions and Answers

Q: What tradeoff between hypoglycemia and hyperglycemia is appropriate?

Dr. Vigersky: We need to get the stakeholders together to agree upon what metrics would be appropriate to include in a composite. It could be a set. And then we need to subject that to prospective research, or data sets

that we already have like the JDRF CGM study and DCCT. We need to look at how these composites would compare to the standard outcome, A1c. Are they better predictors? Do they capture some events better and not others? We need everyone to agree what metric it should be in terms of hypoglycemia and hyperglycemia. Is it AUC? Duration? Number of hypoglycemia episodes? Is it per patient per 100 years? Is it a threshold? Not everyone can agree, but if we lock the professional societies and FDA and industry in a room for a day or two, we can come out with something they would agree on. At least that would be a start, subjected to some objective research. Does this translate into something meaningful to predict outcomes? We need to do the hard work of collecting that data. And we may fall back on A1c as still the best predictor. Or, if you weight against hypoglycemia and sacrifice a bit of A1c, maybe outcomes are better. But until we test it, we'll never know.

Q: You may have difficulty getting people to agree. From patients you've seen, and patients I've seen, you weight these things differently. Can you argue for a flexible methodology to those different clinical scenarios, rather than a single set of standards?

Dr. Vigersky: We're doing this with A1c already. Setting goals based on individual needs. I see no reason why we cannot do the same thing with a composite metric.

Q: I applaud you. We should also include what's important to patients.

Dr. Vigersky: Agreed. It could be other things too like blood pressure, lipids, and other co-morbid issues. Those may be weighted more importantly.

Is There a Role for Blinded CGM in Addition to Real Time CGM?

NO

Steve Edelman, MD (University of California San Diego, CA)

The charismatic Dr. Edelman made the case that there is no role for blinded CGM in 2015 and beyond, emphasizing that patients with diabetes have the right to un-blinded CGM to cope with the high variability of insulin therapy. He acknowledged circumstances in which he believes blinded CGM to be acceptable: clinical research settings, certain patients with type 2 diabetes, and cases where education for un-blinded CGM is not possible. He then launched into a strong, passionate argument for un-blinded CGM. "CGM is the single most important advance for people with type 1 diabetes since the discovery of insulin." He noted that insulin itself remains highly imperfect due its narrow therapeutic window and inevitable unpredictability, and that real-time CGM can help patients tread the fine line between complications and hypoglycemia more safely. Further, it can shed light on the glycemic variability that A1c doesn't account for, revealing those at risk of significant oxidative stress, cardiac arrhythmias, and other complications. Dr. Edelman also presented data from a 2012 study on the iPro2 blinded CGM, showing that blinded CGM has no significant effect on glycemic control, presumably because it only allows for retrospective calibration and analysis. According to Dr. Edelman, un-blinded CGM will bridge the gap until a "real cure" for type 1 diabetes is discovered, and there is no role for blinded CGM in diabetes care.

- **Dr. Edelman shared multiple devastating stores of his patients who, despite optimal management with an insulin pump, died in their sleep from severe hypoglycemia.** He also provided examples of patients suffering from severe hypoglycemia while driving, killing passengers in other cars. These tragedies served as testament that un-blinded CGM can be truly life saving, especially when Bluetooth-enabled devices allows parents and loved ones to have access to the real-time data. Dr. Edelman also showed an image of a Medtronic CGM on a dashboard display (the actual Ford/Medtronic prototype was announced four years ago) that could do wonders for preventing severe hypoglycemia while behind the wheel.

YES

Ian Blumer, MD, FRCPC (University of Toronto, Ontario, Canada)

Dr. Blumer's engaging argument for blinded CGM centered on the fact that (i) it works; (ii) it's cost effective; and (iii) it is an excellent alternative for patients who do not want real-time (RT) CGM. According

to Dr. Blumer, blinded CGM can be more effective than un-blinded because it allows for clinician-directed recommendations and therapeutic changes. Further, it is more affordable than RT-CGM. In his opinion, it is also an excellent teaching tool, and he keeps ten systems in his office to loan out to patients for weeks at a time. In addition, Dr. Blumer believes that blinded CGM has a role for patients who have abandoned RT-CGM; approximately 40% of RT-CGM users abandon the technology due to cost, adhesive issues, alarm fatigue, data overload, skin reactions, and burden of another device. [We assume that is old data and look forward to seeing how it changes with next-gen technologies coming out or coming soon.] Blinded intermittent use of CGM might also be helpful in convincing non-users to go on CGM via a "trial" period.

Novel Insulins

SYNTHETIC GLUCOSE-RESPONSIVE INSULIN

Matthew Webber, PhD (Massachusetts Institute of Technology, Cambridge, MA)

Dr. Matthew Webber delivered a fascinating presentation on the Langer Lab's glucose-responsive insulin, which relies on covalent modification with stabilized, negatively charged phenylboronic acid (PBA) for its glucose-induced solubility. He presented results from early mouse model studies, in which the PBA-containing insulins all demonstrated responsiveness to glucose. Notably, the insulin derivative with a fluoro-containing PBA (Ins-PBA-F) displayed the strongest and quickest response to elevated blood glucose levels. Results from a mouse dose-escalation study showed that the PBA-modified insulin was more responsive than insulin detemir in hyperglycemia, and induced less hypoglycemia in a non-diabetic mouse. The lab also conducted a study using CGM to establish kinetics, confirming that the response kinetics of the PBA-modified insulin mirror those of a healthy functioning pancreas, with no significant difference between the two. Dr. Webber noted that his team is currently thinking of new ways to refine the "off-switch" of the PBA-modified insulin to prevent low blood glucose. The lab is also investigating routes of "excipient-only" control; engineering molecules that aren't connected to the insulin itself but control its properties. The research is still super early but looks promising. As a reminder, Merck is still in phase 1 (n=74) with its glucose responsive insulin, with primary completion expected in December 2015 This was one of the most impressive talks of DTM, as glucose-responsive insulin represents one of the few "near-cures" that has moved from theory to science. We are very excited about the Langer Lab's work on this front.

- **According to the paper published by Dr. Webber's lab in December 2014, the glucose-responsive insulin was prepared by covalent conjugation to synthesized molecules containing an aliphatic moiety and a phenylboronic acid (PBA) moiety.** This was achieved by direct amidation of PBAs or phenyl bromides to an aliphatic domain, followed by a Suzuki coupling reaction. The use of aliphatic chains offers an extended circulation half-life (as seen in Insulin detemir), while PBA provides a glucose-sensing element. Specifically, PBAs bind reversibly to cis-1,2 and cis-1,3 diols such as glucose, stabilizing the negative charge on boronic acid.
- **To induce glucose-binding of the PBA moieties at physiologic pH, Dr. Webber's lab used fluoro-, nitro- and sulfo-contaning PBAs, thereby providing electron-withdrawing character to lower their pKa.** These conjugates were attached to insulin at the B29 lysine residue, resulting in four PBA-containing insulin derivatives: amido-modified (Ins-PBA-A), fluoro-modified (Ins-PBA-F), nitro-modified (Ins-PBA-N), and sulfo-modified (Ins-PBA-S). All four were responsive to elevated glucose concentrations.
- **In a mouse model of insulin-deficient diabetes, glucose-tolerance tests (GTT) performed at four, seven, and ten hours after PBA-modified insulin administration revealed that Ins-PBA-F was the most potent in reversing blood glucose levels and was still effective at the ten-hour GTT.** All four PBA modified insulins were effective at restoring blood glucose to a normoglycemic (< 200 mg/dl) level at the four-hour GTT, whereas only Ins-PBA-S, Ins-PBA-F, and Ins-PBA-N were effective after the seven-hour GTT. Ins-PBA-F and Ins-PBA-N were still able to restore normoglycemia after the third GTT at ten hours following insulin administration, with Ins-PBA-F showing the strongest response.

- **Dosing studies comparing Ins-PBA-F with the active ingredient in Insulin detemir (Ins-LA-C14) established glucose-sensitivity of the PBA-modified insulin, with reduced hypoglycemia when administered in a normoglycemic state.** At a GTT performed three hours after 1.0 and 3.0 IU/kg doses were administered in insulin-deficient diabetic mice, Ins-PBA-F was significantly ($P < 0.05$) more responsive than either Ins-LA-C14 or native insulin. At 5 IU/kg, there was no significant difference between the responsiveness of Ins-PBA-F and Ins-LA-C14. In healthy (non-diabetic) mice, the hypoglycemia index for Ins-PBA-F was significantly less ($P < 0.05$) than that of Ins-LA-C14 and native insulin at 3.0 and 5.0 IU/kg doses.
- **CGM studies showed the slope of decrease in blood glucose level to be significantly steeper (faster) for Ins-PBA-F than for Ins-LA-C14.** This slope was similar to that observed in a healthy mouse with no insulin deficiency. Further, the area under the curve (calculated from the beginning of the GTT at three hours after insulin administration until the six-hour end point) showed that the responsiveness of Ins-PBA-F was comparable to that of a healthy pancreas, whereas Ins-LA-C14 had a much larger area.
- **The Langer Lab was unable to confirm glucose-mediated binding to serum albumin in Ins-PBA-F, the reported mechanism of action for Ins-LA-C14.** Though this may still be the underlying mechanism, Dr. Webber note that it is also possible that PBA-modified insulin binds to immobilized diols such as those on glycosylated proteins (which are greater in number in those with diabetes).
- **In Q&A, audience members raised the question of the speed of absorption of the PBA-modified insulin, to which Dr. Webber responded that it would be the same as other insulins administered via subcutaneous injection.** This, of course, is the major limitation of insulin administered by this route, as there will likely always be a lag time while it is absorbed from the adipose tissue into the bloodstream. But perhaps if it could be packaged in an ultra long-acting degludec-like PK/PD, there is good potential for a once-daily product.

DANCE 501, A NEW NOVEL INHALED INSULIN DELIVERY SYSTEM

John Patton, PhD (Dance Biopharm, Brisbane, CA)

Dance Biopharm's Dr. John Patton gave a valuable post-mortem on Pfizer's Exubera, highlighting lessons learned and how the company's inhaled insulin (Dance 501) will overcome them. Most notable were updated regulatory timelines: the company plans to start a phase 2b study in 2016, four phase 3 studies in 2017 (two in type 2, two in type 1), submit to EMA and FDA in 2019, and secure approval in 2020. These are well behind the previous timeline to begin phase 3 in 2015. Dr. Patton did not give an update on Dance's financing plans - the company postponed its IPO in October 2014 (originally filed in April 2014). Most of his presentation ran through reasons for Exubera's failure (he blamed Pfizer's failed launch, impatience, and management: "Pfizer CEO Jeff Kindler Killed Exubera"), followed by Dance 501's key advantages: a small electronic inhaler that looks like a consumer device (and could allow for connectivity in a second-gen device); a multi-dose dispenser; guided breath control lights to ensure it is inhaled properly; low excipient content that minimizes cough; and a clear, reasonable regulatory pathway in both Europe and the US. Dr. Patton talked about Afrezza very objectively ("we're rooting for them"), noting that the high excipient content causes cough, and the short tail of action does not fully cover meals. He implied that Dance's lower excipient content and different PK/PD profile - slower than Afrezza up front and with a longer tail - makes it a "very different product" from Sanofi/MannKind's offering. Dr. Patton acknowledged in Q&A that the lack of spirometry equipment in endocrinologist offices is a challenge for uptake, but he hopes Sanofi/MannKind will pave the way.

- **Dr. Patton shared the EMA and FDA regulatory requirements for Dance 501.** It sounded like Dance will pursue a harmonized FDA and EU filing, so the clinical program will fulfill the more robust FDA requirements.
    - **We'd note these are more onerous than implied in Dance's S-1 filing to go public last year.** Last April the company planned to conduct a single global phase 3 non-

inferiority trial in early 2015 to support approval in type 2 diabetes in the EU, US, and China.

	EMA	FDA
Toxicology	1 month dog	6 months dog
# of Phase 3 Trials for Approval	2 in type 2 adults (type 1 in Europe post-approval)	2 in Type 2 Adults 2 in Type 1 Adults
Total # of Patients	500 inhaled, 500 comparator	1,000 inhaled, 1,000 comparator
Contraindicate	Severe asthma and COPD, smokers	Severe asthma and COPD, smokers
Post-Market Studies	Yes	Yes

- **The Dance 501 electronic Aerogen inhaler "looks like consumer electronic device."** It is designed to deliver a liquid recombinant human insulin formulation ("mist"). Lights on the Aerogen inhaler guide the user, and if the inhale is too fast, it turns off. Cough is less likely with the device than other inhaled insulins. The proprietary vibrating mesh technology (120,000 times per second) is used in intensive care ventilators; 85% of what comes out of the inhaler goes to the lungs. The inhaler is loaded with an eye dropper (2U and 6U strengths), and the hope is a second-gen version can load prefilled cartridges directly in.
    - **Dance 501 appears to have a time to peak around 60-90 minutes (by our estimate) and a tail of action that lasts at least eight hours.** The profile is slower and longer than MannKind's Afrezza, though Dance 501 does appear to peak as fast or faster than Humalog, depending on the dose size. Given the PK/PD differences, Dr. Patton called Afrezza "a very different product" from what Dance 501.
- **"New insulins take time." Dr. Patton showed a graph of Lantus sales, which didn't start taking off until six years post launch.** It was a compelling chart to counter inhaled insulin naysayers, and evidence to criticize the Pfizer management team, who didn't give Exubera enough time to gain traction.
- **"Things went wrong at Pfizer."** Dr. Patton criticized Pfizer's management team, who didn't think Exubera was making money fast enough. The product was pulled off the market, though Dr. Patton emphasized it wasn't a product recall and there was no safety or efficacy signal. A quote from Goldman analyst Jami Rubin filled one slide, "Pfizer felt the drug would sell itself, samples were sparse, TV ads were late, too benign and not exciting. They did not court the nurses or the certified diabetic educators, who play an even bigger role than physicians in putting patients on insulin. They ignored them."
- **Dr. Patton made a case that inhaled insulin is safe, headlined by suggestion of long-term improved lung function.** He acknowledged short-term, "very small declines (1-2%)" in lung function (reversible), but long-term (eight years) improved (>50%) lung function. Dr. Patton further noted potentially better hypoglycemia vs. injections. All inhaled insulin programs, he said, have shown higher antibodies, but these have been of the same type as injections, decline over time, and have "no clinical effect." Inhaled insulin has a "very small signal" for lung cancer in former heavy smokers, but it is "not known if real."
- **We certainly believe that Afrezza is a product that could improve patient outcomes** - while it has been easy to disparage a new product launch that faces significant commercial challenges, as we've taken to saying, if we're all happy with the state of health for people with diabetes in the US and globally, "We can all just go home!" In the US alone, only 27% of patients are on insulin of any of kind and 45% are not at their glycemic targets. While insulin use is higher in

many parts of the EU, glycemic control numbers don't appear to be much better, and with patients living longer, the healthcare system does need alternatives that can help patients reach their goals - or needs different approaches to products that can help them do the same. While obviously not everyone struggling belongs on insulin or would benefit from Afrezza, we believe there is a clear mismatch between patients not at goal and those who would benefit from more intensive therapy - and we believe this group will only expand in the future, fueled merely by the epidemic numbers of those at risk for and developing diabetes.

- **In 1985, there were roughly 30 million people globally with diabetes and probably at least 15 million not at their glycemic targets, today, less than 30 years later, there are approximately 400 million people globally with diabetes and likely at least 200 million people not at their glycemic targets.** Particularly on the type 2 front, the sheer number in the population with diabetes who are not reaching their glycemic targets - many at great expense to the system - prompts important questions as to whether the system will be able to sustain the expenses of so many people not at their glycemic or cardiovascular targets. There have been key challenges like spirometry that have created a more challenging environment for Afrezza, but there are clearly patients and HCPs that have benefited from it, and likely many millions more who could.
- **In our short-sighted system that is focused on reducing payments today, we worry about system costs tomorrow and today!** We do think that public/private partnerships to look at how to help patients reach targets would be illuminating, as would clear goals to reach a better status quo. Specifically, we also think FDA could be more reasonable about what post-marketing trials that it is asking for - asking, for example, for studies to be done in patients that smoke heavily seems nearly unethical? We also would like to see Sanofi market Afrezza alongside Toujeo, its new long-acting basal - there is real education needed not among HCPs on how to help patients reach their glycemic targets, but about various new products in the market - these two seem logical bedfellows. Ultimately, because statistics have not improved in the past decades and because the onslaught of new patients poses such challenges along the public health continuum, we'd like to see a more concerted effort focused on helping patients who have chosen not to take or intensify insulin. Human factors work suggests that patients will benefit from a range of options, especially options that are easier for patients and healthcare providers to use. While a range of barriers have prevented many from accessing Afrezza, we do not believe we are at the point where options that work can be closed off - we'd much prefer to see what can be done to make various options work for patients beyond traditional MDI, which has been challenging for multiple generations.
- **We would like to get more information on Dance in terms of what it would bring the market that Afrezza has not** - it will be interesting to see comparisons between the two if those come to pass, although the very challenging and misunderstood commercial environment will certainly pose challenges. Since there are not obvious other solutions that are helping patients intensify insulin, we welcome approaches that are innovative - they will all also need to prove that they have the support of regulators (beyond approval), payers, and manufacturers.

STABILITY OF INSULIN AND GLOBAL WARMING

Andreas Pfu¨tzner, MD, PhD (Pfu¨tzner Science & Health Institute, Mainz, Germany)

Dr. Pfutzner provided an overview of the scope of global warming, emphasizing that the crisis represents a true concern for individuals on insulin therapy. To prevent denaturing of insulin during heat waves and power outages, he is working with a company called Tempromed, a reusable thermoregulatory device for vials and injection pens. Tempromed comes as a case or pen cap, and provides temperature protection at a comfortable injection temperature for an extended period of time. In both cooling and heating tests of Tempromed, it was possible to maintain water at a specified temperature while only spending 330 mW (provided by a small rechargeable battery). According to Dr. Pfutzner, this technology represents an easy way to increase insulin stability over a longer time, and may also help protect against insulin supply deficits after power outages in extreme weather conditions. We appreciate Dr. Pfutzner's forward thinking, and see

Tempromed as a simple and useful device; not only in heat waves and severe storms, but also during travel, camping, and other settings in which refrigeration may not be an option.

- **Dr. Pfu¨tzner noted that extreme weather conditions are already presenting serious risks to people with diabetes such as hurricane Katrina, where many lacked sufficient insulin due to power outages that prevented refrigeration of insulin for days on end.** Insulin and insulin analogs require storage at 40-50 degrees Fahrenheit (4-8 degrees Celsius), and have approximately 30 days of stability. Higher temperatures denature insulin through a variety of chemical changes to the primary and secondary structure and lead to loss of function, a growing concern in the face of climate change.
- **According to Dr. Pfu¨tzner, only a limited number of companies are working on pharmacological solutions that will allow insulin to remain stable for longer at higher temperatures (e.g., Thermalin).** He did not sound too optimistic on this front, given the chemistry challenges and long time to market.

Best Approach to Type 1 Diabetes - Biological or Bioengineered?

BIOLOGICAL APPROACH

Matthias Hebrok, PhD (UCSF, San Francisco, CA)

Opening with an entertaining analogy to comics, Dr. Matthias Hebrok compared the sophistication of artificial pancreas technology (Iron Man) to the potential of biological cell therapy (The Hulk). His presentation provided an optimistic take on biological cures, best summarized by his closing words: "We are entering a new era of human beta/islet cell biology." His confidence stems from both recent literature and his lab's recent work indicating that human embryonic and fibroblast-derived stem cells can relatively closely mimic true beta cells in function. He shared a host of data describing the generation of ß-cells from adult progenitor cells, noting that cells become glucose-responsive, insulin producing, and functional upon transplantation into mice. Dr. Hebrok noted that he is "the first to admit we have a ways to go" before a biological cure for type 1 diabetes is achieved, though at the same time, he emphasized how far we have come. For context, he noted that work has accelerated in an incredible way since embryonic stem cells were first discovered in 1997 (less than 20 years ago!). He pointed to ViaCyte's VC-01 cell encapsulation device as the most concrete evidence of how far these projects have moved while cautioning that results from the ongoing phase 1/2 trial are unlikely to meet sky-high expectations. He was hesitant overall to provide a timeline for biological cures, echoing recent speakers - including Dr. Alexander Fleming (Kinexum, Harpers Ferry, WV) at GTC Bio and Dr. Irl Hirsch (University of Washington, Seattle, WA) at AACE - in suggesting that such adventures should be considered successful even if they do not lead to complete insulin independence. This will be an important message to continue communicating as such therapies move closer to reaching patients, as we imagine there is plenty of room for disappointment given the enormous hype and high expectations in this area. Even therapies that allow for taking 50% less insulin per day would be a win in our book.

BIOENGINEERED APPROACH

Roman Hovorka, PhD (University of Cambridge, UK)

In responding to Dr. Matthias Hebrok's discussion of biological cures for type 1 diabetes, Dr. Roman Hovorka suggested that closed-loop systems are the natural progression of what has been done so far. He contrasted the clinical findings of artificial pancreas technologies with the limited success of immune interventions in humans, echoing commentary we have heard time and again that closed-loop systems offer a bridge to the cure. We felt that Dr. Hovorka took a very practical approach to the question ... as was expected! After all, the question of which approach is more feasible in the short term is relatively straightforward: closed loop by a landslide. While immune interventions are stuck trying to translate success in mice to humans, those in closed-loop development are already moving towards commercial products in pivotal studies. In affirming just how far the closed loop community has come, Dr. Hovorka presented his group's impressive three-month, at-home, unsupervised closed-loop studies that were

published in September in the NEJM - see our complete coverage from EASD 2015. He concluded that technology provides the "revolution that might change the lives of people with type 1 diabetes" in the short term, though acknowledged that the debate between closed loop and a cure really isn't a question of either/or given the dissimilar time horizons. He reiterated Medtronic's goal of commercializing its MiniMed 670G hybrid closed-loop system by mid-2017, while remaining silent about his own group's commercialization plans (though they just received $6 million in funding, as discussed in the highlights section above).

PANEL DISCUSSION

Dr. John Pickup (King's College London, UK): Dr. Hovorka, can you talk about the patients in your trials? Are they the ones that have failed pump therapy?

Dr. Hovorka: We haven't gone into these groups, because we don't necessarily want to go to patients that will be more challenging initially. For closed-loop to work, you have to wear CGM and the pump. You have to have patients who are going to be compliant. It needs to be hands-on still. There is reasonable payback overnight. There is a need to maintain the system to work. I'm very open about it.

Dr. Pickup: How far away are we from testing in groups with hypoglycemia unawareness?

Dr. Hovorka: One of the impositions of the data safety monitoring board was that we don't test in these groups. We could do it right now if they let us. I don't think it is a problem.

Dr. Pickup: You touched on cost-effectiveness during your presentation. What's your feeling about how it's going to go in the first few years following commercialization?

Dr. Hovorka: There are a number of scenarios. Optimally, closed-loop will not come with a premium over pumps considering the benefit. However, I think it will be unique selling point. I think the less optimistic take is that there will be a premium. It is interesting what's happening with 640G. It has the same price as pumps because many patients use it without the CGM. We will see.

Q: On biological cures, nothing is approaching human work in transplanted cells ... Is that true? Is anyone looking at the kinetics of insulin secretion? We've got beautiful molecular biology but it seems to me that we don't have that much in humans.

Dr. Hebrok: There is company in San Diego called ViaCyte that is putting embryonic stem cells device into patients. I don't think the outcome has been derived yet. But in terms of testing in humans, this has happened already. We actually have done the dynamic glucose-stimulated inulin secretion testing for kinetics that you are talking about and we do see responses as we expected. The beta cells are getting better and better. It's just that they are not quite ready for prime time.

Q: Where you place the cells in the body to protect them?

Dr. Hebrok: This is challenging. One thing is that you have to encapsulate them to protect the cells. However, the device has to allow glucose and oxygen to come in. That is really hard. The last iteration of our cells we very close to beta cells. One reason we thought this is that they were very fragile.

Dr. Pickup: Can you talk about the safety of this approach?

Dr. Hebrok: With embryonic stem cells, there is the possibility of a cell creating a benign cancer. I think this can be solved in a number of different ways. You can put suicide genes into cells and trigger them if the need arises. I think this can work.

Q: Are we trying to achieve normal glucose tolerance with closed-loop systems? How close is your system to being fully closed?

Dr. Hovorka: People do carb counting and manual bolusing in our trials. However, not everybody does it all the time. We've noticed that if they do carb counting, they get better outcomes. I think we need faster insulin before we get to fully closed-loop systems. We are certainly trying to get to normal glucose tolerance. However, closed loop is no different than regular treatment in the sense that the risk of hypoglycemic still goes up when glucose comes down.

Q: With regard to cells, are you thinking about developing a product around embryonic stem cell-derived islets or pluripotent cells?

Dr. Hebrok: I still think the human embryonic stem cell is ideal. Pluripotent cells can have mutations. Right now, the embryonic cell is the best option.

Q: What would be the effectiveness and cost tradeoff of a biological cure? What do you think the timeline looks like?

Dr. Hebrok: The research is accelerating at a pace that is unmatched. We had insulin in 1922. Embryonic cells were identified in 1997. We've been at it for less than 10 years and the advances have been mind-boggling. I think it's really going to happen but I really cannot tell you when. Right now, the costs are exceedingly expensive because it is small scale. This has to happen at a larger scale and we have to get companies involved. I think at some point this will be cost effective.

Q: What do you think is the one thing that would lead to really rapid progress in the next five years?

Dr. Hovorka: Very fast insulin. I think we have enough CGM effectiveness with MARD below 10%. I think what we have is good enough for commercialization.

Dr. Hebrok: Money [laughter]. We know where we are and where we have to go. The hundreds of million of dollars that have gone into these devices have been very well spent.

Big Data and Precision Medicine for Diabetes

PRECISION MEDICINE DRIVEN BY BIG DATA, GENOMICS AND PERSONALIZED DIGITAL HEALTH TRACKING: OVERPROMISED HYPE OR IMPENDING NEW ERA FOR HEALTH, WELLNESS AND PREVENTIVE MEDICINE?

Robert Cuddihy, MD (Janssen Pharmaceuticals, Raritan, NJ)

Dr. Robert Cuddihy opened with a very pertinent question for those interested in precision medicine in diabetes: Is this field all hype? His answer was a resounding "No," though he did put the field's enthusiasm into context. As he noted, the ability to classify individuals into subpopulations that differ in their susceptibility to diabetes is inspiring, though far away in practice. Many challenges remain, though these obstacles - in his view - are certainly not a prescription for failure. Dr. Cuddihy positioned our current sky-high expectations as a natural step in "The Hype Cycle" for new technologies, expressing confidence that our excitement will translate into mainstream adoption down the road. He turned to genetics for an analogy, noting the unrealistic expectations and even disillusionment that existed for the potential of precision medicine decades ago and that is only now paying off (e.g., with the emergence of CRISPR, etc.). "We are going to get to much more personalized and individualized medicine recommendations [in diabetes care]," Dr. Cuddihy noted in conclusion. The big question is not "if" but "when."

PERSONALIZING DIABETES CARE

Rodney Hayward, MD (University of Michigan, Ann Arbor, MI)

Dr. Rodney Hayward provided a reproach of current clinical decision-making in diabetes, noting that current guidelines do not do enough to support the individualization of care. He called out widely employed treat-to-target strategies - e.g., targeting an A1c<7.0% for a broad swath of patients - arguing that such broad, single-metric approaches to care do not weigh individual benefits against harm. No debate there, and something the ADA/EASD called for back in 2012. Dr. Hayward pointed to the results of ACCORD, ADVANCE, VADT, and UKPDS as examples that the benefits of tight glycemic control are nuanced - certainly not something to be generalized to entire populations (and with the caveat that the metric - A1c - does not capture hypoglycemia). Dr. Hayward asserted that selecting a glycemic target is perhaps one of the most difficult and controversial aspects of diabetes care - something that depends on age, microvascular complications, macrovascular complications, patient desire for tight control, financial capabilities, etc. - and thus posed an important question: Do providers truly take all these factors into account when making

treatment decisions? He argued no, noting that the majority of diabetes complications and costs are borne by a minority of patients - "Five to ten percent of type 2 patients suffer the majority of complications. It's not doing the public any good to get everyone to tight control." That unsurprising 80/20 description of the data seemed like an odd way to criticize providers' decision making. Dr. Hayward's talk was not a critique of tight control in itself (certainly beneficial for some patients) but rather a call to individualize therapy. In our view, recognizing the importance of personalized therapy is not the challenge - scaling it in short, infrequent office visits is the hard part, and something Dr. Hayward did not address.

MOBILE TECHNOLOGIES TO COLLECT DATA FOR PRECISION MEDICINE FOR DIABETES

William Riley, PhD (National Institutes of Health, Bethesda, MD)

Dr. William Riley discussed the NIH's Precision Medicine Initiative (PMI) for diabetes, which will comprise a striking 100+ million US volunteers and cost the government $215 million. The PMI will rely heavily on electronic health records (EHR) to collect information on participants; genomics, data science, and health technologies will also be central. Dr. Riley reminded the audience that the concept of precision medicine is not new (e.g., prescription eyeglasses and blood transfusions have been around for decades), but a 2011 National Research Council report has driven the recent push. He emphasized that the PMI will derive success by embracing change via the adoption of new devices for measuring glucose, diet, activity, etc., and serving as a "test bed" for these technologies. Dr. Riley was optimistic for boundless future possibilities in mobile diabetes technologies, and hopes to go beyond collecting glucose and A1c to characterize glucose measurements much more intensively. It is intriguing to consider how far we've come in the past decade alone - the iPhone was only introduced eight years ago, and CGM has improved by leaps and bounds since then - which gives us high hopes for the next decade of data collection.

Business Opportunities in Diabetes Technology

21ST CENTURY TECHNOLOGY AND EARLY 20TH CENTURY REIMBURSEMENT

Bruce Quinn, MD, PhD (FaegreBD Consulting, Washington, DC)

Dr. Bruce Quinn contrasted the fast-changing diabetes technology landscape with the slow-moving reimbursement landscape. He opened with a quick review of the "huge advances" we have seen in diabetes technology in the past five years (from the artificial pancreas to next-gen CGMs to mobile health), noting that these advances have not yet been mirrored by changes in the way the FDA and payers perform device assessments. He noted that value-based care is more feasible than ever before - especially with current remote monitoring capabilities - though the transition away from entrenched fee-for-service models is proving difficult. Indeed, he acknowledged that the FDA and payers tend to be stuck in the "1960s and 1970s" in their thinking on healthcare and that creativity is needed to shake up this space. He expressed confidence that the field will get there, but also suggested that patience is warranted as payers and government adjust from the slow, cautious world of healthcare to the fast, iterative world of technology.

- **Notably, Dr. Quinn drew attention to an editorial from Senator Ms. Susan Collins (R-ME) discussing Medicare's failure to cover CGM - see the editorial in *AJMC* here.** We love seeing leading voices - especially in Congress - putting the spotlight on diabetes, and Dr. Quinn shared his perspective that politicians are beginning to take note. As a reminder, the US Senate and House of Representatives re-introduced bi-partisan legislation earlier this year that would establish Medicare coverage of CGM.

INVESTING IN DIABETES

Karen Drexler (Hygieia, Los Altos, CA)

Former diabetes industry executive and now angel investor Ms. Karen Drexler provided an overview and her thoughts on present-day enthusiasm for digital health. She began by putting in context how very real this enthusiasm is, noting that digital health venture funding actually broke $4 billion in 2014 and that it projects to exceed this level in 2015. Driving this enthusiasm is the potential for digital solutions to help with many of the scale challenges our industry faces - too many patients, too few providers, infrequent contact,

inconsistent data, slow feedback loops, growing spending, and outcomes that are not improving. At the same time, there is much to prove and Ms. Drexler stressed that a lot has to improve to make digital health relevant and meaningful in the medical system. In this vein, she concluded her presentation by summarizing a number of challenges that lie ahead for companies attempting to commercialize digital healthcare solutions and provided her thoughts on "what it takes to win" in this field:

- **Ms. Drexler provided three big keys for what diabetes investors are looking for in digital health: patient adoption, proof of outcomes, and a reliable business model.**
    - **Patient adoption:** Companies have to create digital tools that patients are going to want to use and are going to enjoy using. Digital solutions cannot be something that patients are going to use once or twice and lose interest in. She noted that patients have higher expectations than ever before. Digital health products need to offer user experiences that compare to iPhones and levels of customer experience that rival Amazon's. Many patients are underwhelmed with consumer experience of digital solutions currently available. The question is whether digital health products in diabetes can meet the increasingly high bar set by consumer products.
    - **Proof of outcomes:** Ms. Drexler emphasized the need to show improvements in clinical outcomes and tying those outcomes to economic benefits. She noted that technology will not be paid for just because it is new, even though the hypothesis is that digital health can improve efficiency and save costs. The real challenge is proving it.
    - **A reliable business model:** Ms. Drexler stressed that consumer pay models will not work in digital health. Patients, she noted, are used to getting apps for free, meaning that those that rely on consumer financial investment "are not going anywhere." She said the competition for digital health is in the consumer market, and with patients (consumers) feeling increasingly like partners in healthcare, it's up to digital health companies to treat them as such. On that note, we aren't sure this is sustainable and believe subscription models would be possible for incredible value - consumer play for plenty of things like music, coffee, phones, and we would suggest that perhaps they should start to think about paying for things that help not just entertain or nourish but also improve their health.

Glucose Measurement Errors and Insulin Dosing Errors

VARIABILITY OF INSULIN ABSORPTION

Profil's Dr. Tim Heise delivered an engaging presentation on the top three reasons for insulin absorption variability: (i) injection technique/technology; (ii) physiology of the subcutaneous tissue; and (iii) insulin type. According to Dr. Heise, there is virtually no acceptable data explaining the effect of injection technique on insulin absorption variability, a surprising fact given the strong connection between the two. He did, however, present data from multiple studies on subcutaneous physiology and absorption of insulin. Notably, histological cross sections from rats showed that NPH precipitates in crystals in the subcutaneous tissue when injected. This prevents spreading of the insulin, and also creates variability in the time that the crystals are dissolved and absorbed by the body. It was a great reminder of why NPH is so notoriously unstable and unpredictable. Dr. Heise also presented 3D images of insulin injections in pigs, showing that some of the insulin had actually leaked back to the surface of the skin, while the remaining insulin diffused substantially in the adipose tissue. Diffusion itself is affected by subcutaneous blood flow, which has a variation of ± 50% under physiological conditions. Exercise, temperature changes, injection volume, injection technique, and tissue composition (lipohypertrophy) also play a role. Most patients do not appreciate these nuances - many of which are uncontrollable - and we think education on this front could help inform and relieve many insulin users ("That high blood sugar is not your fault - look how many factors you have to account for!"). Dr. Heise stated that NPH has the highest variability of all insulin types, followed by insulin glargine and insulin detemir. Prandial insulins show less variability than basal insulins.

- **The pig study also showed that the insulin concentration near an injection center is close to 100%. As the distance increases from the injection site, the insulin becomes**

beneficially diluted with interstitial fluid, resulting in faster absorption. The faster absorption relates to insulin's oligomeric state (the number of dimers and monomers of insulin), which increases with increasing dilution of the insulin. Therefore, diffusion of insulin along the subcutaneous tissue plays a positive role in enhancing absorption, but is of course not always reproducible in the body due to variation in subcutaneous composition and injection location. Dr. Heise emphasized lipohypertrophy in particular, which causes reduced absorption of injected insulin and very high variability in absorption.

METRICS OF BGM & CGM ACCURACY

David Rodbard, MD (Biomedical Informatics Consultants LLC, Potomac, MD), Luigi Del Re, PhD (Johannes Kepler University Linz, Austria), Rolf Hinzmann, MD, PhD (Roche Diagnostics, Mannheim, Germany), Marc Breton, PhD (University of Virginia, Charlottesville, VA)

Multiple speakers debating the merits of MARD acknowledged the metric's utility as an indicator of CGM accuracy, but as one that does not capture "the whole story." While a low MARD is a requisite for a satisfactory device (most say <10% is needed for insulin dosing), we heard time and again that the measure by itself is insufficient to describe a sensor's full accuracy and reliability. Presentations provided a look at well-appreciated ways in which this metric falsely reports glycemia (e.g., physiological lag) before running through underappreciated circumstances that also interfere with the accuracy of CGM. Most intriguingly, Dr. Luigi Del Re argued that MARD is not a true measure of continuous accuracy since reference readings are taken at specific time points (e.g., every five minutes) and lead to a loss of data between measurements. He argued that the number of paired points and study design can have a significant impact on accuracy results (no argument there), which led audience members to ask why a standard protocol had yet to be developed that might allow for valid comparisons across devices. [All the panelists were just as stumped on this point. Dexcom has really raised the conversation in recent years on all the factors affecting CGM accuracy studies (reference device, points in hypoglycemia, frequency of calibration, excluded data), and yet we continue to see startup CGM companies manipulate the data.] Ultimately, speakers advocated for using MARD, but for using it cautiously - "a sensible metric to summarize the accuracy of a CGM that does not capture the whole story." Encouragingly, Q&A acknowledged that current CGM accuracy is NOT a limiting factor in artificial pancreas development. Panelists said that CGM point accuracy is just one factor that closed-loop algorithms use in determining insulin/glucagon doses (alongside trend indicators, previous experience in achieving control).

Live Demonstrations

THE MYSUGR ECOSYSTEM - CONSISTENT ALL-ROUND CARE VIA MOBILE TOOLS, EDUCATION, MOTIVATION AND COACHING

Fredik Debong (Co-founder, mySugr, Vienna, Austria)

mySugr co-founder Fredrik Debong closed the meeting with a passionate live demonstration of the company's diabetes data logging app. He announced plans for a bolus calculator (launching in next few weeks in Europe) and a new Dexcom integration. mySugr's newest addition - a bolus calculator - has received class 2B approval in Europe and will be launching within a few weeks. The company will embark on the FDA process in the US soon after. We see an app-based bolus calculator (not connected to a meter per se) as a serious market need for MDI users and are very enthusiastic to see the company going down this route. Other newly announced plans include an integration with Dexcom (we assume via Apple HealthKit to import CGM data automatically), integration with iHealth devices (BGM, blood pressure), and a collaboration with Beurer (a Germany-based digital healthcare brand). Though mySugr has been criticized for the "manual entry" burden it effectively puts on patients to log their diabetes data, the list of integrated devices is quickly growing, resulting in less and less manual input required. The app has the most user-friendly interface of any diabetes logging app we've tried, and patients seem to like it: mySugr has 435,273 cumulative users worldwide, and a strong 150,000 active users every month. It is among just a handful of apps in the dQ&A patient panel that more than 50% of its type 1 users consider "indispensable"; contact

CEO of the diabetes market research company Richard Wood. The user base is also 48% type 1 and 52% type 2, representing stronger penetration in type 2 than many other apps we have seen or heard about. What struck us as powerful about the latest version of the mySugr app is the Search feature (allowing a quick find of the last log when you ate a particular food (e.g., lentils), or were at the current location, or at this time of day), and the new analysis features (laying out key metrics in an easy swipe interface). There is a lot to like about what mySugr is doing on the education front - a quiz app, a video academy for type 2 - and we think highly of the team and expect big things in the future.

- ***In a rarity for a digital health company,* mySugr also has a revenue model** - the app is free, though paying $2.99 per month gives access to a slew of Pro features. The company has not disclosed how many users pay this subscription fee but we imagine this will grow over time and that it would be a logical benefit for payers to cover. mySugr has established commercial agreements for bulk licensing, communication, and advertising, and select payer and provider reimbursement (Austria only). The company has followed strict CE, FDA, and ISO13485 clinical guidelines (also rare for an app), raised $4.8 million in March 2015, and has hired industry veteran Kyle Rose (formerly of TheraSense) to lead operations in North America. He is very well liked and regarded and as a patient with diabetes himself, and will be able to bond with the ecosystem very well.

DTS Cybersecurity Standard for Connected Diabetes Devices Project

PANEL DISCUSSION

Seth Carmody, PhD (FDA, Silver Spring, MD), Bryan Cunningham (Levy LLP, Los Angeles, CA), Barry Ginsberg, MD, PhD (Diabetes Technology Consultants, Wyckoff, NJ), David Kleidermacher (BlackBerry Limited, Santa Barbara, CA), Jeffery Reynolds, PhD (Bayer Diabetes Care, Tarrytown, NY), and Margie Zuk (The MITRE Corporation, Boston, MA)

DTM 2015's opening session shared the Diabetes Technology Society's progress on a "cybersecurity standard" for diabetes devices (first introduced by Dr. David Klonoff at ATTD 2015). The steering committee has drafted three documents to date that together seek to describe the scope of the cybersecurity challenge, provide a generic framework for how devices need to be protected, and create an assurance plan for how to get there (e.g., accrediting labs to test devices). The committee is targeting a finalized document in nine months and intends to send out the document for public review in the near future. We certainly agree that cybersecurity is an important safety issue as connected diabetes devices and apps are becoming more common. However, our biggest worry with this program continues to be the "noise" factor - DTS made a big deal in 2013 (May and September) with its BGM accuracy meetings, though nothing substantial has come out of the proposed surveillance program apart from a lot of diabetes community funding spent on travel and meeting together several times - in all, literally hundreds, probably thousands of collective hours of otherwise valuable time. Dr. Klonoff shared that the BGM Surveillance steering committee is still waiting on funding and has yet to move onto the actual testing of BGMs. Nothing has changed meaningfully on this since its start. We continue to wonder whether this cybersecurity standard will run up against similar obstacles? Is it necessary? Will it gain traction among manufacturers and regulators? Is DTS the best organization to spearhead it? And, of course, who will fund it if it is decided that it is needed? We believe that Abbott was one of the funders of the BGM program at one point - and that made us wonder a bit about Abbott's motives since we believe it is moving away from blood glucose monitoring, if slowly, while it waits for FreeStyle Libre capacity to ramp. While we do not believe it will likely stop manufacturing blood glucose strips anytime soon, clearly the innovative work it is doing is outside BGM.

Artificial Pancreas - What is Needed?

PANEL DISCUSSION

Dr. Jeffrey Joseph: What do you think is the most important thing moving forward for better glycemic control with an artificial pancreas? If you had a wish, would it be faster onset of insulin, faster offset of insulin, or more precise PK/PD from day to day?

Dr. Cobelli: Faster onset. Something faster that more closely resembles the function of a normal beta cell.

Dr. Phillip: Would you like it to disappear faster too?

Dr. Cobelli: Sure.

Dr. Phillip: It would be both for me.

Dr. Steil: I can't disagree. It's faster onset. You can always put more insulin in. The problem is getting rid of it all. But the two are going to go together.

Q: What simulator did you guys use for the IP simulations?

Dr. Dassau: We used the famous UVA/Padova simulator with some adjustments.

Q: What's going on around reimbursement for closed-loop with DreaMed?

Dr. Phillip: I don't have that information for you.

Q: Is there any work being done on notifying a patient in real-time of faults?

Dr. Cobelli: For the moment, no. We do have some work going on in telemedicine. We are doing some work on that.

Q: What do you think about pump accuracy? Does that present a problem around glycemic control?

Dr. Phillip: The next generation is coming. Yes, there is room for better sensors and better pumps. There is room for improvement all around. But we are able to do it with current technology.

Q: Does accuracy in the future matter?

Dr. Phillip: As a clinician, I think what we have is accurate enough. The problems are technical issues but not with accuracy.

Dr. Haidar: I think the variability of insulin absorption outweighs the accuracy. If you look at the variability of insulin absorption, I think this is more important to tackle.

Dr. Dassau: I think it's accurate enough right now from a clinical point of view. I think the pharmacokinetics are important to understand. Making it more accurate will make it more complex and prone to error.

Dr. Cobelli: In our experience, I think it is important to distinguish between the pump and insulin. We are happy with the pump; we are not happy with the molecule. We have started playing with inhaled insulin.

Dr. Steil: If you're talking about accuracy, the algorithms need to be accurate enough to deal with those errors. When you talk about absorption, you run into problems. I think we mistake "insulin not working" for "insulin not getting into plasma." I think that's what we need to pay attention to. The question is whether it's a catheter problem, a PK problem, or a PD problem.

Q: Infusion sets only work for 2-3 days. CGMs last almost up to two weeks, 7-10 days depending on the system.

Dr. Phillip: We want a better pump that can last forever if possible, or at least a week or two. We're talking about artificial pancreas - can we create an artificial pancreas out of what we have now? The answer is yes. But we want better insulin, better sensors, better pumps.

Dr. Jeffrey Joseph: We're examining the failure modes through a JDRF grant. We actually see faster absorption at Day 5, day 6, day 7. It's the variability we're trying to understand. It has to do with the variable trauma at insertion. Bleeding around the catheter. There is a huge need for better catheters. JDRF has open RFA to extend catheter wear to 7-14 days.

[Comment]: I think infusion sets are underappreciated.

Q: One of the factors that seem to get less attention is patients' activity level. So in terms of the algorithms, do you think it is going to be essential to incorporate activity in closed-loop systems?

Dr. Steil: I would point out that when we use PID in the ICU, we are working with patients who use 100 units at the beginning and almost nothing at the end. So the algorithm has to be robust to big changes in insulin. We use the same algorithm on everyone, so it's robust to activity and any other dramatic changes in insulin needs.

Dr. Roman Hovorka: I want to ask about commercial uptake. We're seeing progress, and in 2-4 years the first closed loop systems will be in the hands of patients. There are risks and limitations for uptake of these technologies. CGM is still not used very extensively. Pumps have about 40% penetration. What are the risks for closed loop systems not being used? Can we do something right now?

Dr. Phillip: The risk has to do with convenience of use - fewer devices. Having it on a PDA has less chances of being accepted vs. a pump. The less burden on the patients' shoulders, the higher the chances of acceptance.

Dr. Hovorka: So does usability trump efficacy?

Dr. Phillip: I think they are connected. You mentioned patients who stopped using device because it was too complicated and too many devices. Did that affect efficacy?

Hovorka: They didn't stop using, but it was a limitation. I'm not sure it affected efficacy. But it did impact compliance.

Dr. Phillip: I hope it affected efficacy, because you didn't show a hypoglycemia improvement at night.

Dr. Hovorka: We can talk about that offline. Are there views of the panel on whether a risk exists? What can we do about it?

Dr. Dassau: If you don't use it, you don't get a benefit. If we can combine it into something appealing, you don't need a utility belt anymore. I need to be something they can interact with, partner with, and less to think about. That will lead to more efficacy and better results.

[Comment]: I think this is an interesting and important issue. I think we can learn from other fields. How many patients are getting the right treatments? This may become more applicable in the future. I think every medical system has such a plethora of opinion and type 1 diabetes solutions can still be a hunt for sorts.

Q: Have you always used the same supplier? Have you looked at human factors?

Dr. Haidar: We've used different suppliers in different studies. We are planning to do a human factors test. One of the questions we are going to ask is about the burden for patients two pumps.

Q: For two-chambered users, has the experienced been positive?

Dr. Haidar: I was just saying that having two pumps might affect the user experience.

Mr. Manny Hernandez (Livongo, Mountain View, CA): Living with type 1, LADA, two different pumps. Had about three pump failures, one of which could have been deadly. The only reason caught it, was because loop went through me. For time site is on, you as patients are out of the loop. What kind of thinking are your groups giving to fail safe mechanisms to alert to catastrophic conditions?

Dr. Cobelli: What I presented in terms of fault detection is going along this direction. Having information on the glucose sensor and the delivery. You can predict if something is going wrong. Obviously this needs to be tested clinically. The algorithm we have developed has been tested in silico. Your point is well taken. Fault detection is very critical, and having it implemented in artificial pancreas is absolutely a need for long, unsupervised trials.

Dr. Steil: I'm still not a particularly big supporter of MPC, but it's a wonderful strategy for fault detection. Model predictions, if they are accurate, should be able to predict any type of fault and detect it. Rather than giving more insulin, it will just sound an alarm. Model prediction can really do fault detection quite well.

Dr. Dassau: Model prediction is key. Safety of delivery requires a multi-layer approach. One layer is fault detection. One is inherent safe design. There are different limitations on how you design the controller and whether it is geared towards safety. On top of that, you could have additional auxiliary systems. For instance, when alerting users, if they don't respond, maybe it generates an alert to a contact person or to a call center. Different alarms have been tried in different studies, and it's a balance act. How many alarms is the key.

Q: We see very small incremental improvements instead of big changes with these studies. Why? Shouldn't we see a bigger change as we go from patient control to automated control? We should set targets for what control algorithms should achieve.

Dr. Steil: I'm going to disagree that we haven't shown dramatic changes. We used to be targeting 120 mg/dl, and we were able to get patients into normal glucose tolerance. In fairness, it's probably the way science works. That is going to become what the JDRF wants. Let's start with achieving 170 and 180 mg/dl. Then we're making incremental steps forward. We are making the patient do everything. But this is the way we get into the market and then make incremental steps. Maybe it's just patience. Or maybe we have to go back and rethink the whole thing.

Dr. Cobelli: Do you think that reducing hypoglycemic events by five times is a small deal? Do you think that improving the time in target by 30% is a small change? If you have a better idea, you should come on board.

Dr. Steil: This is going to be a small iterative process.

Dr. Phillip: Clinically, it is a significant improvement. That is how we look at it. Another issue is the fact that the experiments we are running now are usually choosing the best patient. We don't choose patients with A1c of 9% or 10% which is one of the reason why the effect is not that dramatic. If we were to enroll all the patients in our clinics, you would see exactly what you want to see.

Nutrition & the Microbiome

THE DIABETES BREAKTHROUGH FOR SUCCESSFUL WEIGHT LOSS

Osama Handy, MD, PhD (Joslin Diabetes Center, Boston, MA)

Dr. Osama Hamdy presented an overview of various interventions for weight loss, focusing on the success his group has seen implementing behavioral strategies. He presented the widely heralded results of Joslin's Why Wait program - presented at ADA 2015 - impressing upon the audience that lifestyle intervention can offer some of the most effective weight loss we see in practice. Implicitly, his message seemed to be that medications and surgery may not be necessary. As a reminder, Why Wait was Joslin's 12-week intensive lifestyle intervention program, in which patients lost an average of 24 lbs (11 kg) (-9.7%) and maintained 16 lbs (7 kg) weight loss (-6.4%) at five years. The study had a focus on strength training that differentiated it from the Look AHEAD program, and that Dr. Hamdy suggested was in large part responsible for the impressive results. We agree that strength training is a tremendously underutilized focus of weight loss programs that emphasize "activity," but don't increase participants' long-term caloric burn enough (e.g., walking vs. building muscle). Joslin is in the process of turning Why Wait into user-friendly software (for children and adults) with the help of HealthyMation, a company aiming to create digital health apps that leverage Hollywood-style animation - essentially combining gamification with behavioral science. Though he did not delve into detail, we were impressed to hear Dr. Hamdy's confidence in the marriage of technology and health as a solution to the obesity epidemic - there is a lot to look forward to at that intersection.

ALTERING THE MICROBIOME TO TREAT DIABETES

Frank Greenway, MD (Louisiana State University Baton Rouge, LA)

Dr. Frank Greenway opened by attributing our ongoing type 2 diabetes and obesity epidemics in part to a loss of dietary diversity. Noting that 75% of the world's food now comes from 12 plants and five animals species, he suggested that the modulation of the gut microbiome holds vast potential to modify this energy imbalance. The connection to type 2 diabetes and obesity has generally received lots of attention in mainstream reporting on the microbiome so the hypothesis was not particularly surprising - what was

notable was Dr. Greenway's discussion of the latest human models and bioinformatic tools used to study the microbiome and how they can help the field move from association studies to causal experiments. He noted that two strategies in particular can be used to correct the microbiome diversity deficit in practice: (i) replacing the diversity that has been lost (e.g., through dietary supplements); or (ii) simulating the gut to produce a greater variety of microbiota. He shared data from Microbiome Therapeutics - a company developing pharmaceutical products that aim to improve health by interacting with the microbiome in specific ways - showing that both approaches are feasible and that both offer the promise of "drug-like effects" with a microbiome mechanism of action. Indeed, drawing from an ongoing clinical trial (n=28), Dr. Greenway presented data indicating the NM504 (a medical food designed to replace the dysbiota reported in type 2 diabetes) significant reduces postprandial glucose control without any adverse effects. A second study, too, (n=10) has shown that a microbiome modulator (i.e., the second approach) can ameliorate the GI symptoms associated with metformin treatment and reduce mean fasting glucose levels. The studies were small, though both offered proof in principle that the microbiome holds potential for diabetes treatment in humans. As always seems to be the takeaway during microbiome talks, we're staying tuned...

Industry Updates

FROM THE NIH

In hallway chatter with NIH's Dr. Guillermo Arreaza-Rubin, we learned the winners of the major UC4 grant for Advanced Clinical Trials to test artificial pancreas systems: Cambridge ($6.4 million), the DREAM consortium ($2.0 million), and Boston University ($1.5 million). More details on the award winners are in the table below. The respective grant winner pages are listed here (Cambridge, Dr. Roman Hovorka et al.), here (DREAM, Drs. Richard Bergenstal, Moshe Phillip), and here (BU, Dr. Ed Damiano et al.). This $10 million in funding accounts for half of the original "up to $20 million," and notably, the UC4 grant for advanced artificial pancreas studies has been reissued here. It is again for "up to $20 million for 1-3 awards; letter of intent deadline is February 9, 2016, for an earliest start date of December 2016". Those not awarded a grant were not specified, but we believe it includes the UVA team.

- **What is unclear from these posts is whether the Cambridge and DREAM groups will use these studies to support a regulatory submission.** Cambridge is using Medtronic devices and a phone running the algorithm, and the language "facilitate pivotal studies" suggests this trial does not directly involve a pivotal study to support a PMA application. DREAM is also a somewhat ambiguous case, as the group licensed the MD Logic algorithm to Medtronic in April. It's hard to know if actual commercialized products will result from this $10 million in funding, though our fingers are crossed. The ambiguity reflects the academic-commercial chasm in closed loop development - the two options pursued thus far are licensing (e.g., Medtronic/MD Logic) and starting a company (e.g., Type Zero).
- **In speaking to BU/MGH's bionic pancreas team, we learned that this funding will go towards a bridging study to start in 4Q16 and examining the dual-chambered iLet device vs. the previous iPhone driven system.** This will be the first test of the fully integrated bionic pancreas iLet device, including a new dual-lumen infusion set. The bridging study will include both insulin-only and bi-hormonal components. The team expects to submit another proposal for its pivotal study in March (the reissued UC4), which would include an FDA PMA application. MGH/BU now hope to begin the pivotal trial in early 2017, slightly behind the AADE timeline to begin in late 2016.

	Grant Size	Proposed Trial Length, Design	Device	Key Purpose
Cambridge	$6.4 million	12 months n=130, 6-18 years 24/7 closed loop (n=65) vs. sensor-	Medtronic MiniMed 640G/ Enlite 3 + Android phone	"The project will provide information to facilitate pivot[a]l studies leading to REGULATORY APPROVAL,

		augmented pump (n=65) Primary endpoint: A1c	running Cambridge MPC	COMMERCIALISATION, AND REIMBURSEMENT of 24/7 closed-loop control"
DREAM	$2.0 million	Six Months n=240, ages 12-21 years 24/7 closed-loop vs. vs. sensor-augmented pump Primary outcomes: % in 70-180, %<70	Not specified, though we assume Medtronic devices based on its licensing of MD Logic in April	"The study design incorporates features needed for an approvable study by the U.S. Food and Drug Administration (FDA) as determined from several pre-submission FDA meetings"
Boston University/ MGH	$1.5 million	n=50, four sites, Phase 1: 2 weeks at MGH Phase 2: 6 weeks at Stanford, Barbara Davis, Nemours Includes both insulin-only and bi-hormonal arms	Bridging study to compare iLet dual-chamber pump with integrated algorithm and Dexcom CGM to iPhone/Tandem t:slim mobile system	MGH/BU will reapply in the next round to fund a pivotal trial to support a PMA application

--by Adam Brown, Varun Iyengar, Ava Runge, and Kelly Close