Closer Look

Diabetes Technology Meeting (DTM) 2015

October 22-24, 2015; Bethesda, MD - Day #1 Highlights - Draft

Executive Highlights

Greetings from Bethesda and Day #1 of the 15th annual Diabetes Technology Meeting. Today, we joined 400+ conference attendees for a packed day of workshops on do-it-yourself diabetes devices, composite outcome metrics, glucose monitoring accuracy, insulin errors, and investing in diabetes technology. See below for our top five highlights, followed by selected full write-ups and panels. Our DTM 2015 preview details what we're looking forward to tomorrow and Saturday.

1. Bigfoot CTO Bryan Mazlish shared his story of developing an automated insulin delivery system for his wife and son, including plans to enter a clinical trial "very soon" and why device companies weren't interested in commercializing his system. Meanwhile, FDA's Dr. Courtney Lias remarked on the requirements for do-it-yourself (DIY) devices and shared high optimism about running closed-loop on a phone.

2. Medtronic Diabetes' Dr. Bob Vigersky gave a most valuable talk on novel visual and numerical representations that capture composite diabetes outcomes (A1c, hypoglycemia, weight).

3. 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." Q&A acknowledged that current CGM accuracy is NOT a limiting factor in artificial pancreas development.

4. Profil's renowned Dr. Tim Heise delivered an engaging presentation on the top three reasons for variability in insulin absorption: (i) injection technique/technology; (ii) physiology of the subcutaneous tissue; and (iii) insulin type.

5. Who is digital health companies' biggest competition? Angel investor and former LifeScan and Amira Medical executive Ms. Karen Drexler argued it's the consumer marketplace - patients are used to getting world-class digital tools for free, and expectations have never been higher.

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Top Five Highlights

1. Bigfoot CTO Bryan Mazlish shared his story developing an automated insulin delivery system for his wife and son, including plans to enter a clinical trial "very soon" and why device companies weren't interested in commercializing his system. Meanwhile, FDA's Dr. Courtney Lias remarked on the requirements for do-it-yourself (DIY) devices and shared high optimism about running closed-loop on a phone. Mr. Mazlish said in Q&A 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. With just a single Bigfoot title slide, Mr. Mazlish took a riveted audience through his 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), 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. Bigfoot has now grown to more than 30 people and expects to be near 50 by the end of the year. Meanwhile, Dr. Lias shared FDA's perspective on the regulatory aspects of DIY devices, which must meet requirements like any other device (e.g., responsible party, design controls, human factors, safety mitigations, surveillance). She was positively empathetic on the patient-led innovation movement, "We understand where people are coming from and the underlying point from #WeAreNotWaiting community. We are trying to push companies to bring these products to market." But her remarks also shed light on how the FDA thinks about "distribution," which broadly includes sharing device specifications, code on the Internet, or even a server that gives results to people. See the detailed commentary below for more from these talks and the most valuable panel discussion.

- **In Q&A, Dr. Lias was very optimistic about running artificial pancreas algorithms on a smartphone:** "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, cybersecurity is a concern. But we can do that ... 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."

2. Medtronic Diabetes' Dr. Bob Vigersky gave a valuable 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.

3. 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 (Johannes Kepler University Linz, Austria) 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).

4. 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.

5. Former LifeScan and Amira Medical executive (now angel investor) Ms. Karen Drexler emphasized that digital health companies have to compete with consumer markets where high expectations and free products are the norm. The commentary came during Ms. Drexler's summary of some of the biggest challenges that lie ahead for digital health players - showing improved outcomes, proving a reliable business model, and exceeding patient expectations. She noted that most patients and payers will not pay for technology just because it is new or because of a "hypothesis" that it improves outcomes. The

challenge, of course, is proving those outcomes and running clinical trials that are typically outside the expertise of technology startups (not to mention, getting them done at a cadence that reflects tech's speed of innovation). Ms. Drexler also advised entrepreneurs to stay away from consumer pay models in digital health, since patients are used to getting digital tools and apps for free - we wonder whether that is reasonable from a profitability perspective. From our view, consumers certainly pay for phones, coffee, and music, and we would instead wonder whether advocacy could persuade consumers to pay for valuable assets that could improve health - while we certainly see the challenge, we don't think it's sustainable for companies to plan to give away everything free - and we don't think consumers should expect it. We do agree from a business model perspective if "someone else" can pay, that will be positive for demand. Companies that rely on a consumer pay model face an uphill battle, Ms. Drexler said, and that is obviously true. At the same time, as we have written many times, patients have higher expectations than ever before**,** and digital health software and devices are expected to bring comparable user experiences to those offered at Apple and Google and Amazon. Unfortunately, the realities of healthcare require tradeoffs (usability, design for safety, cost), and patients are often underwhelmed with the consumer experience in digital health. For Ms. Drexler, the question is not whether digital health products in diabetes can meet the high bar set by diabetes products - the question is whether they can *exceed* the *increasingly* high bar set by *consumer* products. We felt this was well put and framed the challenge well - we do still think it's also about exceeding the high bar of the best diabetes products - we look at Abbott Freestyle Libre, Dexcom 5, Lantus, Januvia, etc. That seems pretty challenging, but perhaps the merging of the two fields (increasingly leveraging consumer products for diabetes applications) holds potential.

Detailed Discussion and Commentary

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.

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.

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