CLOSER LOOK

Fourth NIH AP Workshop: Testing and Adoption of Current and Emerging Technologies

July 6-7, 2016; Bethesda, MD; Day #2 Highlights - Draft

Executive Highlights

Greetings from Bethesda, Maryland, where the humidity made us feel like we were back in NOLA and where the Fourth Artificial Pancreas Workshop at NIH has come to a close. These two days flew by, but not without giving us plenty to think about. While our Day #1 report focused more on big picture themes in the field and what is needed, Day #2 focused on technical issues such as the FDA's role, device interoperability/ standardization, cybersecurity, new sensing and hormone technologies, and implantable devices.

Overall, this valuable meeting's focus was slightly longer-term (next-gen and next-next-gen) than we would have expected, probably reflecting the horizon of academic research and NIH funding. By the next time this meeting comes around, at least one and probably more than one commercial AID system will be available. What would be a disappointment in gen one? What must the field do in the next 12-24 months to set this field up for success? What can be learned from CGM's commercialization? Who is going to educate providers? What research questions remain that we must answer as soon as possible? And what will be learned in gen one to drive further improvement?

We give HUGE congrats to JDRF, NIH, FDA, Helmsley Charitable Trust, DTS, and so many dedicated researchers for putting this fantastic meeting together, following iterations in 2013 (where industry still had to be convinced to do AID), 2008, and 2005. Catch our top 12 highlights from Day #2 below, and read our Day #1 coverage if you missed it.

Top 12 Highlights

1. FDA's Dr. Courtney Lias gave her strongest support yet for diabetes device interoperability, asking in Q&A "how can the FDA incentivize manufacturers? … This should benefit everyone regardless of business model." Her optimism was striking and gave us hope that more manufacturers will adopt standards, even if FDA cannot mandate it.

2. Tidepool CEO Howard Look persuasively argued that interoperability will enable an "artificial pancreas ecosystem" that brings products to market faster; praised the diabetes DIY community for leading innovation; and busted some of the biggest concerns over opening up data and device communication. See his slides here.

3. Ms. Melanie Yeung (University of Toronto) shared an update on work to develop open data standards for diabetes devices: four BGMs have now adopted the Bluetooth BGM profile (Roche Accu-Chek Connect, Ascensia Contour Next One, AgaMatrix Jazz Wireless, Trividia [Nipro] True Metrix Air); there are "high hopes" that CGMs will adopt the standardized Bluetooth profile "in the near future" (Dexcom's G5 doesn't have it); and command and control standards for pumps are under discussion.

4. An insightful closing panel gathered a spectrum of views on the big questions leaving this meeting: What does the AID field need? What will accelerate adoption? What are the big barriers? Comments touched on access, provider education, FDA's openness, type 2, and more.

5. Dr. David Klonoff's presentation on DTS' cybersecurity standard was followed by some broader debate in Q&A: what are the absolute cybersecurity risks with pumps and AID, and what are the potential unintended consequences of too much attention on this topic (unnecessary worry, slower uptake, less interoperability)?

6. Dr. Ken Ward revealed that AgaMatrix now owns the iSense/Bayer needle-free CGM. He also shared promising data from Pacific Diabetes Technologies' (PDT) efforts to combine CGM sensing/inulin infusion in a single catheter (human studies in first part of 2017).

7. Bigfoot Biomedical's Lane Desborough shared how the power of feedback and customer demands for automation interoperability eventually propelled innovation, efficiency, and safety in highly complex, hazardous continuous process plants. Lots of learning here for diabetes.

8. Harvard's Dr. Eyal Dassau shared a succinct list of pros and cons on one of the toughest questions in AID: should a commercialized control algorithm reside in the pump or on a smartphone?

9. Thermalin's Dr. Bruce Frank, co-inventor of Humalog, discussed the company's preclinical insulin analogs (faster onset, shorter duration, ultra stable), including an ultra-concentrated U1000 in development for miniaturized artificial pancreas systems.

10. What's Gen 2.0 or 3.0 of artificial pancreas? Many expressed hope for implantable CGM and insulin delivery, and six companies were present today, including two we hadn't heard of: Theranova (intraperitoneal AP) and PhysioLogic Devices (intraperitoneal AP with U1000 insulin). Early-stage implantable CGM developers Biorasis and Capillary Biomedical were present, along with later stage GlySens and Senseonics.

11. Xeris' Dr. Steve Prestrelski gave an overview of the glucagon field for bihormonal artificial pancreas use, asserting that Xeris' approach to stabilization has lower development risk than others in the field.

12. Take a look at the agenda from the inaugural NIH AP Workshop in 2005, and boy, it is crystal clear how far the field has come, particularly CGM.

Table of Contents

Executive Highlights

Top 12 Highlights

Detailed Discussion and Commentary

What Is Needed To Facilitate The Development Of A Viable Commercial Platform And To Deliver Artificial Pancreas Systems To People With T1D In The Near, Medium And Long Term?

Panel Discussion - Quotable Quotes

Regulatory Considerations for Component AP Systems

Current Challenges | *Howard Look (CEO, Tidepool, San Francisco, CA)*

Top 12 Highlights

1. FDA's Dr. Courtney Lias gave her strongest support yet for diabetes device interoperability, asking in Q&A "how can the FDA incentivize manufacturers?" NICE! She likened the Agency to curlers (yes, those athletes in the Olympics who sweep ice), paving the way for artificial pancreas component manufacturers to succeed by *encouraging* interoperability and standardized communication among component devices (pumps, CGMs, algorithms) - "This should benefit everyone regardless of business model." This level of optimism was striking and gives us real hope it will encourage companies to adopt the already-published communication standards. Dr. Lias gave a similar talk at last month's ADA DiabetesMine D-Data Exchange, and today, she continued to dissect the current regulatory process, which requires an onerous separate approval for every combination of devices (i.e. sensor A + algorithm A vs. sensor A + algorithm B require separate PMA approvals) - in her view, this is "quite cumbersome" and "destined to fail" from a rapid innovation perspective. She again lamented the cautionary cases of Tandem and Animas, who both, after months of navigating liability and contract issues, submitted full PMAs to operate with Dexcom's G4 only to see the G5 come out. With standardization, which she emphasized does *not* equate to "squashed innovation", there can be a straightforward way to link all component devices both within and between companies, saving everyone time. However, with such a component artificial pancreas model (swapping devices in and out without needing a separate PMA for each permutation) there are still regulatory challenges: If a device fails, who is responsible? Currently, it is the PMA holder, but who would it be if there were no

official partnerships? "What we don't want is patients falling through the cracks," neglected because no company feels liable. She also expressed concern over component device modifications: "How can devices be modified and remain safe in a system when developers are not working together?" Still, device communication standards that everyone adopts would be a big step forward in the field, and it was highly notable to hear Dr. Lias' strongest enthusiasm yet. The FDA cannot mandate device makers adopt a standard, so it will be up to companies to decide if the benefits are worth it.

- **Dr. Lias: "We need to define how we're going to deal with intended uses of products."** This is a concern when it comes to standardization and plug-and-play component system, as ensuring that every pump/algorithm/sensor/insulin combo works together would be impossible. We'll be interested to see what the FDA does here. Questions we hadn't thought of before arose. The insulin point came up a few times in Q&A, for example - if an artificial pancreas system is approved for lispro and aspart, but a patient puts in regular insulin or ultra fast aspart, are there concerns? What must companies show on the use of insulin in different systems? Dr. Lias wasn't too concerned about this near-term, noting we may need to address it down the road.
- **What are the interoperability barriers in industry? No one from a company spoke up, but David Panzirer suggested it's a competitive advantage issue** - companies believe keeping their device communication propriety gives them a market advantage (e.g., a closed system that have complete control over). Conversely Howard Look and Melanie Yeung argued that that there are competitive *advantages* to opening up, though this will be a big change for many historically closed companies - if a device can connect to any other standards-compliant device or app, companies may worry about the risks or liability associated with that, or competitors learning their IP (unfounded worries, according to Mr. Look and Ms. Yeung).

2. Tidepool CEO Howard Look persuasively argued that interoperability will enable an "artificial pancreas ecosystem" that brings products to market faster; praised the diabetes DIY community for leading innovation; and busted some of the biggest concerns over opening up data and device communication. See his slides here. As he has done in the past, Mr. Look argued that when device makers expose their data and control protocols, many valuable things can happen: "we enable interoperability, we catalyze an ecosystem, we foster innovation, we get products to market faster, and we help more people more quickly, safely, and effectively." He addressed many of the common concerns about opening up data and interoperability (e.g., safety, liability, security risks, competition), highlighting some of the upsides too: combining data together from different companies' products (e.g., Medtronic pump, Dexcom CGM) will result in more patient safety to analyze data; interoperability enables a faster process to get products to market for partnered companies ("Clearly, if you are Animas or Tandem, and you just shipped a pump with G4 under a full PMA, and G5 came out, you wish you could do this faster. This saves time as a device maker"); and likely a broader spectrum of apps and devices that can help personalize therapy (i.e., companies can't possibly think of all the device innovations or software combinations that could benefit patients). Mr. Look proposed an "enable the ecosystem switch" in devices to manage liability concerns; such a setting would enable users to toggle ON/OFF interoperability features, but with a warning message. He concluded by addressing the OpenAPS DIY community, arguing it is at "the leading edge of the artificial pancreas ecosystem." He shared his personal experience building the system for his daughter ("not easy," even as a "geek dad"), which he said has had a gamechanging impact on his family's quality of life. He encouraged the entire room to embrace the DIY community and learn from their experiences. More details from this talk are below!

3. Ms. Melanie Yeung (University of Toronto) delivered an update on work to develop open data standards in diabetes devices: four BGMs have now adopted the Bluetooth BGM profile (Roche Accu-Chek Connect, Ascensia Contour Next One, AgaMatrix Jazz Wireless, and Trividia [Nipro] True Metrix Air); there are "high hopes" that CGMs will adopt the standardized Bluetooth profile "in the near future" (Dexcom's G5 does not have it); and command and control standards for pumps are under discussion. The BGM news was very encouraging, as Roche and Ascensia (formerly Bayer Diabetes Care) are big players, and by adopting the standardized Bluetooth glucose profile, their meters can communicate seamlessly with apps and other devices

- no proprietary agreements needed. Ms. Yeung hopes to see the CGM Bluetooth standard adopted in the near future, though no product currently has it. She was careful to point out that, while Dexcom's G4 Share and G5 transmit to a phone through Bluetooth, they are not using the official CGM standard, and any device communication would still need separate proprietary agreements. She added, "We need a tipping point from large companies to see innovation change," perhaps referring to Medtronic. Looking forward, standards are still in development for command and control of insulin pumps, and work is ongoing to develop authorization and authentication procedures and address cybersecurity. All of these efforts to standardize, she remarked, crucially prevent what would otherwise be redundant and wasteful effort. In addition, communication standardization represents a competitive advantage, encouraging new researchers and companies to enter the "innovation ecosystem" and opening up resources so that they can be put toward improving, not decoding, systems. Ms. Yeung concluded on an optimistic note, reporting that there are many open-sourced libraries and tools available (e.g., PCHA/Continua has a whole suite of tools to verify and test that protocols have been developed correctly), and her team is ready and willing to help any device maker incorporate standards.

- **Ms. Yeung argued that using standards is not a security threat and does not hamper innovation**. She emphasized that "with a consensus (profile), we can actually improve the level of security." As for lost innovation, she quelled concerns by reminding manufacturers that they could still have a "secret sauce" and have a little piece of the market that is special to them.
- **Europe has taken a big step forward on open standards and interoperability**, **as six countries** (Austria, Norway, Denmark, Finland, Sweden, and Catalonia) have committed to using Continua Design guidelines in telehealth programs, which enable open, interoperable health data exchange. This move at the nation level should push more device makers to adopt interoperable standards, or their devices won't be used.

4. An insightful closing panel gathered a spectrum of views on the big questions leaving this meeting: What does the AID field need? What will accelerate adoption? What are the big barriers? The panel combined perspectives from patients (JDRF advocate Alecia Wesner and our own Adam Brown), FDA, industry (Medtronic, Mode AGC), payer experts (Amanda Bartelme, Dominic Galante), funders/associations (JDRF, HCT, DTS), and investigators (Jaeb, T1D Exchange), and many interesting themes arose: patient cost-sharing and exclusion criteria will be the biggest reimbursement concerns with AID; the FDA highly supports studies in a wide range of A1c's and patient populations (otherwise, it may need to restrict product labels); endocrinologist and PCP education will be a major barrier to adoption; payers are still making it difficult to access CGM (paperwork, pre-authorizations, cost-sharing), and some patients with type 1 still get just three strips per day; moving AID to a phone will be key for expanding adoption, and FDA is supportive (though some concerns need to be worked out); for patients and families, closed loop systems are truly gamechanging overnight (but some patients will *only* use them at night); patients are not involved nearly enough in the device design process, and pumps have the most room to improve; will fewer MDIs switch over to AID now that better basal insulins are available?; type 2s can benefit from AID, though payers are highly concerned about the cost exposure in this population (however, if expensive oral/injectable drugs are removed, it could be cost-saving or neutral). See a snapshot of quotable quotes in the detailed discussion below. We especially enjoyed remarks from AID study participant Alecia Wesner, the always-insightful Dr. Stayce Beck (Chief, Diabetes Diagnostics Devices Branch, FDA), and the under-the-radar but influential Dr. Yiduo Wu (Artificial Pancreas Team Lead, FDA).

5. Dr. David Klonoff's presentation on DTS' cybersecurity standard was followed by some broader debate in Q&A: what are the *absolute* cybersecurity risks with pumps and AID, and what are the potential unintended consequences of too much attention on this topic (unnecessary worry, slower uptake, less interoperability)? Dr. Klonoff gave a few examples of medical device hacking, including malicious hacking of one insulin pump in 2011, and more recently, the patient-led DIY Nightscout and #OpenAPS movements ("A cat and mouse game" between patients and device makers). DTS convened a consensus group and released a diabetes device cybersecurity standard in May (DTSec). Now, companies can submit to have their product tested by a certified lab to prove they have adequate cybersecurity in their devices. The FDA will apparently recognize this soon, though it will not be mandatory. The presentation sparked a broader debate on cybersecurity. While standards are a good thing to

speed product testing and review, how much should we alarm the diabetes community about this topic, and what are the unintended consequences? We include some of the Q&A views below from our own Adam Brown, Bigfoot's Lane Desborough, Dr. Klonoff, and Tidepool's Howard Look.

- **Adam Brown: "My big worry about cybersecurity is the noise factor and the absolute risk patients *actually* face.** As someone living with diabetes, what is my *real* risk of getting my pump hacked, and what are the unintended consequences of focusing too much public attention on cybersecurity as a key issue? For example, people may not go on pumps or AID for worry their device may be hacked, when in reality, the risk is incredibly low. Additionally, we might make devices ultra secure, but will that add burden to enter passwords or make devices less usable? These design changes can reduce quality of life. Last, I'm concerned that overly worrying about cybersecurity may even prevent device companies from being interoperable and open, a trend that will hurt innovation that could help promote patient safety. I live with diabetes and certainly support rock solid cybersecurity, but I just want to caution the room: let's be really, really careful not to blow this out of proportion in the public when the real risk is incredibly low, and there might be a downside of too much focus." See Dr. Klonoff's response below.
- **Dr. Klonoff: "We talked with Homeland Security and FDA - we can either do this too early or too late, and they said we're not too early. Obviously nothing should be overblown.** We're trying to avoid scaring people - we're not out there giving interviews like that. Regarding device design, we looked at the idea of using a code/fingerprint to authenticate, but rejected it, because it would add burden."
- **Howard Look: "We have to balance actual risk with getting devices out quickly.** For a thought experiment, consider the older gen Medtronic pump that is the pump of choice for OpenAPS. In order to hack the pump, you'd have to go through many, many laborious steps and know the serial number of the pump. If someone wants to kill my daughter by going through all that trouble, well, let's just say there are easier ways to kill my daughter. God forbid, but I'm just being honest here. It is actually very low risk vs. high benefit that has occurred with OpenAPS because people can now have closed loop and not go too high or low. We should think through things like that. But of course, we should make sure communication between devices is secure."
- **Lane Desborough: "Two words: technical debt. It is very difficult to retrofit cybersecurity into an existing system.** You have to architect cybersecurity in from the ground up. You cannot bolt an escape hatch onto the Space Shuttle. There is an advantage to starting fresh and architecting cybersecurity in when kicking off a project."
- **Howard Look: "The big keys with cybersecurity are the ability to do rapid iteration**, continuous integration, and the ability to improve software very quickly. The most secure software in the world is open source - "many eyes make all bugs shallow."

6. Dr. Ken Ward revealed that AgaMatrix now owns the iSense/Bayer needle-free CGM. He also shared promising data from Pacific Diabetes Technologies' (PDT - this is Dr. Ward's company) efforts to combine CGM sensing/inulin infusion in a single catheter (human studies in first part of 2017). The former was new news to us, as we were not aware Bayer had sold off the sensor (presumably before the divestment to Panasonic [now Ascensia], though we're not sure). We cannot find anything on AgaMatrix's website, but look forward to seeing if the company pursues commercialization - they have very smart manufacturing and strategy in particular. The review of PDT's progress highlighted the team's efforts to wrap a sensor electrode around the insulin infusion cannula. Interestingly, PDT has discovered that phenol (insulin preservative) interferes with accurate CGM sensing ~30% of the time, driving an alarmingly high false peak and subsequent sensor poisoning. The team has changed its sensor to an osmium-based chemistry biased at 180 mV, and no longer sees this effect. Animal studies are ongoing and the hope is to move into human studies in the first part of 2017. There is another group in Graz, Austria (SPIDIMAN) also working on this challenge, but using optical sensing. A single-port for CGM and insulin could go a long way in reducing burden and we hope these efforts are fruitful! We assume PDT would eventually license its technology to a CGM or infusion set player.

- **On CGM accuracy, Dr. Ward looks at large sensor errors (30%/30 mg/dl) and noted his preference for using *mean* ARD (not median).** Mean ARD takes into account outliers, more accurately reflecting a sensor's full range of performance - particularly critical for closed-loop systems, where large sensor errors can lead to dangerous outcomes. Median ARD, on the other hand, often inflates a sensor's performance, and is sometimes misleadingly used by companies when still called "MARD." Dr. Ward said it is fine to present median ARD, but it should *always* come alongside mean ARD.

7. Bigfoot Biomedical's Lane Desborough gave an outside-the-diabetes-box talk on interoperability in industrial automation, sharing three key takeaways for AID: (i) automation is pervasive in over 20,000 continuous process industry facilities like power plants, oil refineries, and paper mills, where far more complexity exists (1,000-10,000 control loops per facility, all unique); (ii) interoperability standards enable safe, cost-effective automation of complex, hazardous processes (with much bigger stakes than in diabetes, as plants cost billions of dollars and operate over a multidecade life); and (iii) automation performs well because of the power of feedback. Mr. Desborough shared stories from his time working at Nova Chemicals, Honeywell, and General Electric, noting that from ~1960-2000, processing plants were shackled to closed, proprietary automated systems. A single supplier (e.g., Honeywell, ABB, Foxboro, Siemens) was responsible for all aspects of automating a plant's process for a 15-year contract, a great deal, but with a caveat for the customer: "a closed ecosystem with high switching costs and low innovation." Vendors like Honeywell were overcharging customers and offering less value relative to new technology at the time (e.g., high-performance computers that were 1/10 the cost). Mr. Desborough said that customers like Exxon Mobil complained - vendor lock-in was expensive, not innovative - and drove the field to embrace open, interoperable, plug-and-play automation systems. Interoperability has been that way ever since, and the key enablers are pretty relevant to our field: devices that were smart enough to self- configure and self-diagnose; standards for virtually all kinds of wired and wireless interfaces in these plants; and customer-driven innovation. In addition, the move to interoperable, open platform automation opened Pandora's Box, forcing industrial automation to confront issues such as cybersecurity, patching, updating, and human factors - this industry has decades of experience with topics which are only now starting to receive attention in diabetes devices. We found this talk most valuable and particularly appreciated the learnings from other fields with which we aren't familiar. Impressively, Mr. Desborough did not mention the word "diabetes" once! He has often quipped that "the future is already here, it just hasn't been evenly distributed yet," and his skills from industrial automation will be an asset as Bigfoot moves to commercialize its AID system.

8. Harvard's Dr. Eyal Dassau shared a succinct list of pros and cons on one of the most challenging questions in AID: should a commercialized control algorithm reside in the pump or on a smartphone? The FDA has historically been viewed as the bottleneck to a commercial, smartphone-based AID system, though today's comments from Drs. Lias and Beck echoed recent views: the Agency is open to using a phone, though some things have to be figured out (e.g., What if the phone battery dies? What if it is on silent?). These sound addressable to us. Still, Dr. Dassau's list below illustrated the tough tradeoffs companies may need to make on this question. The critical drivers, of course, are what patients will like better, what's better for usability, and what will drive diabetes engagement - these remain unclear, though many (but not all) love now getting CGM data on their phones. This reminds us of the overnight-only vs. 24/7 use of AID systems - which will different patients prefer? UVA is investigating this question in its ongoing 11-month Project Nightlight study (we first heard about this study at ATTD 2015), and we wonder if a similar efficacy/preference study could be applied to smartphone vs. integrated algorithm AID systems.

	Pros	**Cons**
Algorithm in Smartphone	- App implementation: cool factor - Large display - Powerful processor	- Where did I leave my phone? - Battery life? - May not work for everyone - Operating system updates and

	- Sizeable memory - Cloud connectivity	upgrades - Cybersecurity - Privacy
Algorithm in Pump	- No moving parts - Dedicated battery - Secure communication, - On body ecosystem - Never leave home without it - Robust design as a medical device	- Limited processors - Limited memory, size - May require a remote device for display, activation, and cloud services

- **Dr. Dassau noted that the AID field will hit a wall in performance and technology with subcutaneous-based systems, and moving the pump, sensor, or both to the intraperitoneal space would improve performance** - faster insulin kinetics and less variability ("amazing results" in simulations). The challenge to date has been the size of devices and site issues with systems like Roche's DiaPort. Dr. Dassau mentioned a fully integrated, implanted AID system in development at Physiologic Devices (ThinPump), which is smaller than the original MiniMed implantable pump, would use Thermalin U1000 insulin, and perform CGM sensing and delivery in the intraperitoneal space.
- **Regarding pump miniaturization,** Dr. Dassau covered potential for "embedded control" that places the algorithm on a chip to minimize power consumption (as far as we understood it). He highlighted significant progress in miniaturizing pacemakers - ~50% of the size every ten years - and hoped that similar progress could be made in pumps, which has not nearly happened in the last 20 years.

9. Thermalin's Dr. Bruce Frank, co-inventor of Humalog, discussed the company's preclinical insulin analogs (faster onset, shorter duration, ultra stable), including an ultra-concentrated U1000 in development for miniaturized artificial pancreas systems. Dr. Frank explained that there has always been a trade-off between speed and stability - "If we want speed, we want monomers. If we want stability, we want hexamers." Thermalin has developed three proprietary technologies - a monomeric insulin analog, active excipient, and shorter insulin analog action - with the goal of developing rapid on/off, concentrated, and stable therapies. Based on data that Dr. Frank presented, the company has made progress: (i) Thermalin has monomeric analogs that don't appear to form fibrils in a realistic time scale (> 50 days fibril-free); (ii) A euglycemic clamp study in swine showed that a U1000 (!) monomeric analog has an even faster onset than Lispro at U100, and lasts about the same amount of time as Lispro, ~4-5 hours; (iii) A screening program conducted in STZ rats has identified 14 modified analogs that shorten the duration of action by up to 25% of the standard. The data is encouraging for AID, though we'd note that Thermalin still has not moved into humans. Dr. Frank said that he expects more rapid insulins to reach market within the next eight years, though it wasn't clear if he meant Thermalin's candidates or any company's candidates. Dr. Frank acknowledged that it is unclear how much bandwidth should be poured into developing even faster insulins; how fast is fast enough for the artificial pancreas? What is the minimum improvement required to make a difference? Will there be diminishing returns to additional speed? This has the biggest implications for fully automated systems responsive to meals, and those insulins will need to be quite fast indeed to prevent any postprandial spike.

10. What's Gen 2.0 or 3.0 of artificial pancreas? Many expressed hope for implantable CGM and insulin delivery, and six companies were present today, including two we hadn't heard of: Theranova (intraperitoneal AP) and PhysioLogic Devices (intraperitoneal AP). Early-stage implantable CGM developers Biorasis and Capillary Biomedical were present, along with later stage GlySens and Senseonics. Several speakers saw intraperitoneal or subcutaneous implantation of pumps and CGM as a possible next step to minimize hassle and improve efficacy, compliance, and patient

satisfaction. Still, there are challenges to overcome on the size, cost, battery life, reliability, and usability fronts. It's hard to know how far these products are out, but we hadn't realized how many companies are working on implantable approaches; six were represented on one of the discussion panels alone.

Company	Product in development
Theranova	Intraperitoneal AP
Biorasis	Implantable CGM
PhysioLogic Devices (Peter Lord)	Implantable, intraperitoneal AP utilizing U1000 insulin and Dr. Dassau's IP algorithm
Capillary Biomedical (Dr. Jeffrey Joseph)	Long-term implantable CGM, insulin pump, artificial pancreas algorithm
Senseonics	180-day Implantable CGM
GlysSens	Long term implantable CGM

- **"The diaPort system works for years because it is put in a cavity, not a wound. I think the shift needs to be away from sub-cutaneous, away from 3.5 inch floppy and toward thumb drive."** There is no wound or immune response to worry about when dealing with implantables. In addition, such systems confer more rapid insulin uptake and diminished CGM delay. This next-gen trajectory definitely holds water, in our view.
- **Dr. Joseph Lucisano (GlySens): "The most appealing configuration is some kind of fully implanted system...we have data from 1300 respondents confirming that this is the configuration people want and they would prefer it to anything they would have to deal with."** The beauty of a fully implanted system is that it eliminates altogether the need to wear anything on the body. Not only does this make patients happy, but, as Dr. Jeffrey Joseph pointed out, guarantees 100% compliance. Dr. Joseph also mentioned that skilled surgeons could perform the requisite procedures without leaving scars, theoretically a barrier to uptake, and that he believes a safe and accurate fully implantable system could be in place in 5-10 years.
- **Most panelists asserted that there is no evidence to suggest that infection risk is a concern for implantables.** Some said they were hesitant to consider implantables because skin infections are (usually) benign, while peritonitis can be deadly. However, one speaker cited a 380-patient-year Harvard study in which ~2% of patients implanted with pumps got pocket infections, but there were no cases of peritonitis. This suggested that the risk for infection from an implanted pump may not greater than that in the case of a pacemaker.

11. Xeris' Dr. Steve Prestrelski gave an overview of the glucagon field for bihormonal artificial pancreas use, emphasizing that Xeris' approach to stabilization has lower development risk than others in the field. He broke down glucagon development into three broad areas - see table below - and highlighted Xeris' very strong stability up to two years. The company is in phase 3 with its rescue pen, phase 2 for pump applications, and toxicology studies are ongoing. Dr. Prestrelski did not give an NDA submission timing on either product, nor did he mention the use of DSMO, which has come up as a concern with Xeris' formulation in pump infusion sets. He also did not address the Bionic Pancreas team's move to use Zealand's glucagon in its upcoming studies. However, he did note that Zealand is the leader in developing a glucagon analog for pumps (phase 2), and has shown "reasonably good stability," but only at 5 degrees Celsius (still needing refrigeration). We're glad to see such a variety of approaches to pursue glucagon for pump indications, since there could be upside in certain populations desiring tighter control or more spontaneity.

Approach	Players	Notes

Glucagon reformulation *Lowest Development Risk*	Xeris Biodel Arecor Latitude	- Takes native glucagon, common excipients, and optimizes the stability. - Glucagon's safety and effectiveness has been demonstrated. - Lowest regulatory and development risk: 505(b)2 pathway. - Excipients in FDA active ingredients guide
Glucagon formulation with novel excipients *Higher Development Risk*	Dr. Ken Ward - Curcumin Adocia Biochaperone (preclinical)	- Native glucagon, safety demonstrated - Excipient not present in approved pharmaceutical product, may need to be demonstrated independently
Glucagon analogs *Highest Development Risk*	Zealand Lilly Sanofi	- Non-native glucagon analogs. Changes to primary sequence of glucagon designed to improve efficacy, safety-tolerability, and/or stability. - NDA, - Immunogenicity and off-target effects possible - Analog safety and potency and efficacy has to demonstrated

12. Take a look at the agenda from the inaugural NIH AP Workshop in 2005, and it is crystal clear how far the field has come. That meeting was only a day long, and the first word in the title was "Obstacles" - a far cry from this year's two-day meeting focused on broader testing and adoption. CGM was in its infancy and the big barrier to improving the field - two of the four presentations on obstacles focused on CGM (design factors and biological issues). There was no FDA guidance on artificial pancreas devices at the time, and the field was really just a concept. The progress been incredible, and tremendous kudos go to JDRF and NIH and so many researchers for moving the field forward. We would be nowhere without them, and we're glad the ball is now moving into companies' courts to bring systems to market - there is still so much to make happen and we hope the funding will continue to move multiple players in the field, since the first-gen products are only the tip of the iceberg.

Detailed Discussion and Commentary

What Is Needed To Facilitate The Development Of A Viable Commercial Platform And To Deliver Artificial Pancreas Systems To People With T1D In The Near, Medium And Long Term?

PANEL DISCUSSION - QUOTABLE QUOTES

- **Dr. Stayce Beck (FDA): "For people to want to adopt these things, going to a phone is probably key, and we'd like to see that. I do think that there are some technical challenges that probably need to be addressed - I'm not the person to do that, I think the stakeholders are.** For example, you need a way to get alerts on your phone if you're going low, running out of insulin, pump battery is dying, etc. If your phone is on silent, you won't be able to hear that. You shouldn't have to decide between getting a good night's sleep with a phone on silent and being able to hear alerts."
- **Dr. Beck: "We will suggest that manufacturers look at broad variety of people (high A1c, comorbidities, hypo unawareness).** We encourage it by saying the label may be limited if they're not looked at. We're very, very supportive of groups looking at the devices in many diverse populations."

- **Dr. Yiduo Wu (Artificial Pancreas Team Lead, FDA): "We know first-gen devices cannot and will not be perfect. Most patients seem appreciative.** We hope that first-gen will have a much larger patient base than we've had in trials so we can identify issues faster once they're in the market."
- **Amanda Bartelme (Volunteer, JDRF): "The biggest challenge with payers isn't a coverage issue. If we have data showing efficacy, that won't be an issue.** It's, 'What are the hurdles that are put up to the patients that have access?' That is how you narrow cost. How much cost is passed to patient?"
- **Ms. Alecia Wesner (T1D, New York City): "I have been in two artificial pancreas trials, and I shouldn't say this, but I wish I had stolen the systems.** In my first trial with UVA, I would wake up in the morning to see my perfect overnight blood sugars and it was so great. I'm athletic and live in New York City - it's a tough environment, and nights are tough. Artificial pancreas made it easier. It was so hard to give it back at the end of the trial. Knowing that it's out there and not available is a hard pill to swallow."
- **Adam Brown (Close Concerns, San Francisco, CA): I was in the six-month JDRF CTR study of DiAs - it had a 24/7 and overnight component, but I decided to only wear it overnight during the extension phase, because during the day, it was just too much burden. I learned that patients are going to use these systems in very different ways** - some people are only going to use this overnight, or if you don't mind additional alarms, some are going to wear it 24/7 (especially if they're missing boluses, it's going to be such a gamechanger). The other thing is that the connectivity, the alarms, and carrying stuff around in this research trial was a big burden, and we often undervalue that. For me, the burden outweighed the glycemic benefit I got from it during the day. We should think carefully in the community about the benefits that we're giving people with these devices in terms of glucose efficacy, and also the tradeoffs that we're asking them to make." We'd add that studies should position things to patients very honestly upfront - "This is not a commercial product, it is far from ready, we need your feedback to improve it, etc." - which can manage expectations and drive to better commercial form factors.
- **Dr. Henry Anhalt (T1D Exchange): "Many endocrinologists are not familiar with insulin pump therapy - so the question is who will go on them? Tough question.** The user interface issue is critical; the form factor is critical. There is a lot to be learned after the first systems come in, there's going to be a lot of iteration. It's hard to imagine what kind of combinations of buttons people will push and what will happen. There will be an iterative component, not only on the sensor accuracy, but also on the user interface."
- **Dr. Bob Vigersky (Medtronic Diabetes): "I was really struck by your comment about wanting to steal the device. In the 670G trial, 80% of individuals requested to stay on it.** Thanks to FDA, they are. This says that (1) people felt like you and the benefit outweighed the burdens and (2) we're getting a lot of extra data out of these ~100 patients who continue to be on it. Relating to cost and availability - this is probably the biggest barrier. We as a community have to work with payers, health ministries around the world, and the only way they will respond is if we show, with credible evidence, that this has benefits on A1c and benefits in the psychosocial realm. If we can do that, then payers will have to pay, I think."
- **Dr. Jen Schneider (parent; Mode AGC Co-founder): "I'm the parent of a child who has been pumping for 13 years. Relief of the nights is something we talk about a lot here.** The issues around sleep, I think it's probably the number one issue that parents have - waking at night to act as a child's pancreas. These artificial pancreas systems can restore normalcy to families."
- **Mr. Brown: "What percentage of people with T1D will ultimately want to wear an AP device? 50%? 75%?** I have no idea. But the two concerns I always hear from people on injections and fingersticks are: I don't want to wear something on my body, and it's too expensive. To me, if this technology is going to make it beyond current pump and CGM users, it has to address those two questions, or give enough bang for the buck in other aspects to outweigh those concerns."

- **Dominic Galante (Precision for Value): "Payers are concerned with the application of AID systems in type 2 diabetes.** You need strong healtheconomics data that this is a better treatment."
- **Dr. Bob Vigersky (Medtronic Diabetes): "I want to push back on type 2. Many patients with T2D are not well-managed** - they're on SGLT-2, GLP-1, long acting insulins, etc ... the cost of those will be more than offset if they are put on closed loop, plus they'll have better control.
- **Dr. Steven Russell (MGH): "This makes sense in the subpopulation of type 2s on insulin. Few have A1c's less than 7%.** We have a pilot study that enrolls people with type 2 diabetes that use MDI. In those, it looks like insulin only works pretty well. It's simpler. And preliminary data suggests we can target a set point of 100 with insulin alone, which we can't do in type 1s."
- **Ms. Wesner: "I don't work in diabetes - I'm an industrial designer, I design products - but I've had type 1 diabetes for 37 years. I've been in three clinical trials, two for AP. I have rarely been asked about the user interface or product development.** I question, and I hope, that manufacturers are using industrial designers for this, especially for the interface design. This patient voice is never heard in the product design cycle - let it be."
- **Mr. Vincent Crabtree (JDRF): "We need to think about what it is that will make people switch from current therapies to AP,** especially because the burden of MDI will also be reduced with longer-acting basal insulins coming out."
- **Mr. Brown: One thing that frustrates me about pumps is that you can't actually test drive them before you buy.** It's "one-and-done" - you get a pump and you have it for four years. It's ridiculous, because it's way more important than a car, and we could go test drive any car we want right now. I wish the business model of pumps would change so that there would be some way for a patient to test it." [Editor's Note: Following the conference, we've learned that Medtronic does have a free MiniMed 530G six-week trial program, though insurance is billed upfront and refunded if pump therapy is not continued. We wish pumps could be tried with no strings attached, just like test driving a car.]

Regulatory Considerations for Component AP Systems

CURRENT CHALLENGES

Howard Look (CEO, Tidepool, San Francisco, CA)

Tidepool CEO Howard Look persuasively argued that interoperability will enable an "artificial pancreas ecosystem" that brings products to market faster; praised the diabetes DIY community for leading innovation; and busted some of the biggest concerns over opening up data and device communication. See his slides here. As he has done in the past, Mr. Look argued that when device makers expose their data and control protocols, many valuable things can happen: "we enable interoperability, we catalyze an ecosystem, we foster innovation, we get products to market faster, and we help more people more quickly, safely, and effectively." He addressed many of the common concerns about opening up data and interoperability (e.g., safety, liability, security risks, competition), highlighting some of the upsides too: combining data together from different companies' products (e.g., Medtronic pump, Dexcom CGM) will result in more patient safety to analyze data; interoperability enables a faster process to get products to market for partnered companies ("Clearly, if you are Animas or Tandem, and you just shipped a pump with G4 under a full PMA, and G5 came out, you wish you could do this faster. This saves time as a device maker"); and likely a broader spectrum of apps and devices that can help personalize therapy (i.e., companies can't possibly think of all the device innovations or software combinations that could benefit patients). Mr. Look proposed an "enable the ecosystem switch" in devices to manage liability concerns; such a setting would enable users to toggle ON/OFF interoperability features, but with a warning message. He concluded by addressing the OpenAPS DIY community, arguing it is at "the leading edge of the artificial pancreas ecosystem." He shared his personal experience building the system for his daughter ("not easy," even as a "geek dad"), which he said

has had a gamechanging impact on his family's quality of life. He encouraged the entire room to embrace the DIY community and learn from their experiences.

- **What if the artificial pancreas ecosystem were based on interoperable components? What would it look like?** Mr. Look shared a vision of CGM sensors, pumps, and paired helper apps that all talk to each other seamlessly, allowing patients to swap in and out the components that meet their specific needs. The table below highlights the list of parameters on Mr. Look's slide, and he noted near-infinite permutations are possible - the athlete with type 1 may want a waterproof pump that is shockproof and pairs with an exercise app, while a toddler may need a patch pump with a small reservoir, remote monitoring capabilities, and the most accurate sensor. The key is all the technologies talking to each other, enabling patients to choose and a much broader ecosystem than any company could develop on its own.

T1D Adult **Toddler** **Honeymoon** **Pregnant mom**	
AP System Component	**Options**
CGM Sensor	Dexcom Medtronic Abbott NewCo
Pump	Single reservoir Dual reservoir Patch pump Waterproof Large/small reservoir Shockproof Disposable
Helper Apps	Remote monitoring Research Athlete training Pump control Telemedicine

- **One by one, Mr. Look addressed some of the biggest perceived challenges to an artificial pancreas ecosystem of interoperable devices** (e.g., "It's hard. I'm scared. It's extra work. They won't let me (regulators or lawyers)"). Below we show the concerns that he presented as myths and how he advised looking at them.
    - **MYTH 1: If we open data or control protocols people might do bad things and blame us. Competitors will misuse our data. We might get sued.** In reality, Mr. Look argued, exposing data makes device safer: it helps people know how the device works, and it allows people to use other products in the vibrant ecosystem. "I couldn't see data from my daughter's pump and CGM together - that made my daughter *less* safe." Letting the ecosystem happen and letting other people write software, he said, gives device makers other ways of achieving outcomes. "If competitors want to misuse data, they will do it anyways. You might get sued, but I would argue that liability is increased if you are not doing everything you can do to expose data and control protocols."

        - **Mr. Look suggested an "Enable the ecosystem switch" to manage liability concerns.** Such a setting would enable users to toggle ON/OFF interoperability features, but with a warning message - e.g., "Do you want to enable external remote device control? Warning: this device is not intended for use with products that have not been FDA approved for use with this device." He urged companies to allow the ecosystem to emerge by putting a switch in products - "If you are worried about liability, you can mitigate it."
    - **Myth 2: It's extra work and will slow us down.** "Clearly, if you are Animas or Tandem, and you just shipped a pump with G4 under a full PMA, and G5 came out, you wish you could do this faster. This saves time as a device maker." For a company like Medtronic, this may not be faster, though it certainly shouldn't be much slower, and could open up more innovation on top of its products. That is speculation on our part.
    - **Myth 3: Opening protocols is a security vulnerability. It allows hackers to remotely control my devices. I should wait until my protocols are more secure. I should wait until there are standards.** "If you are Insulet, you already had to make your device secure. And Medtronic pumps are not a hack; you need a six digit code to get in. It's like saying I hacked your garage door, but I needed the code. The net benefit of publishing data and control protocols far outweighs the risks."
    - **Myth 4: Regulators will never allow it. We'll never get support for it.** "We just heard from FDA that it's better for everyone: regulators, patients, companies. FDA supports it. In our interactions, the FDA has been fabulous. They and their team are some of the smartest, most well-meaning people; they want this stuff to happen. There is a paragraph at the front of every guidance document. 'You can use an alternative approach; just come talk to us.' I encourage all of you to do it. We built a quality system at Tidepool, and we think it's a good system that delivers safe and effective software. It doesn't look like the guidance document, but it is a great. We showed FDA and they said, "Wow, that is really great, and we'd love for you to go give talks to other startups."

- **Mr. Look has built an OpenAPS DIY automated insulin delivery system for his daughter, and the quality of life and glycemic improvements have been gamechanging**. "To be clear, I'm a geek dad, and not speaking as Tidepool. Tidepool is not shipping class III medical devices. But my daughter has been using OpenAPS. It's not easy to put together, but it does work and it works really well. Look at these charts: on Tuesday night, she had two scary lows that we had to wake up and treat. On Wednesday night, she was high all night and woke up not feeling well. On Thursday night she went on the OpenAPS closed-loop - in-range all night. Every night on OpenAPS looks like this, and she wakes up at 100-110 mg/dl every single morning."
- **Echoing OpenAPS user Mark Wilson's talk at ADA, Mr. Look highlighted that the DIY community is not a bunch of hobbyists trying to turn their devices into hot rods with fancy paint. "Diabetes is not about the car; it's about the drive."** As Mr. Wilson said at ADA, people with diabetes have been handcuffed to their car's steering wheel, with an upside down dashboard that makes it very difficult to drive (i.e., using devices to manage diabetes successfully). What the OpenAPS community has unleashed for its users is a better driving experience: better sleep, more time-in-range, and more convenience to view and interact with data (smartwatches, phones, tablets). DIY users are often portrayed as hobbyist hackers exhilarated by tinkering; in fact, they just want to live better with diabetes, and the lack of interoperability is making it more difficult.
    - **As noted in our ADA report, this is a very tricky regulatory issue, though the challenges of building the OpenAPS system will make it hard to scale. Still, there is always some risk with DIY products**, and certain motivated patients are choosing to accept that risk right now in exchange for better glycemic control, sleep, and quality of life. We like that patients can make the tradeoffs. Dr. Courtney Lias said at ADA that these systems do technically fall under FDA jurisdiction, though there is apparently

some debate about what constitutes distribution, and she openly encouraged the DIY community to talk to FDA. We'd note there is a LOT of setup burden for an OpenAPS (Mr. Look said it took him two full weekends, and he is a "geek dad"), which importantly makes the system far from plug-and-play. What we most hope is that learning from this community can make its way into commercial products that the masses can benefit from.

- **Mr. Look noted three keys for secure, interoperable data transmission between devices: authentication, commands and data, and encryption**. He noted that these are "very well studied" in other fields and "work really well" for enabling safe interoperability and no need for proprietary vendor connections. On the data front, Mr. Look praised JSON, a modern standard for data exchange. His example showed a CGM sending the pump information (e.g., MARD, sampling interval, time units, etc.).
- **His talk urged everyone to read an "incredible" paper from innovation guru Dr. Eric von Hippel (MIT) and Andrew Torrance (University of Kansas): "The Right to Innovate," published in Social Science Research Network in 2013.** Torrance and von Hippel advocate for protecting "The Innovation Wetlands." Mr. Look added, "The wetlands is an ecosystem. We used to say, 'What do we need the wetlands for?' Well, bad things happen when you cover up the wetlands. We protect the wetlands now - what a valuable resource they are for us. We must allow DIY to thrive in an innovation wetlands."

--by Adam Brown, Brian Levine, and Kelly Close