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8th Annual Symposium on Self-Monitoring of Blood Glucose (SMBG): April 16–18, 2015, Republic of Malta

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Abstract

International experts in the fields of diabetes, diabetes technology, endocrinology, mobile health, sport science, and regulatory issues gathered for the 8th Annual Symposium on Self-Monitoring of Blood Glucose (SMBG) with a focus on personalized diabetes management. The aim of this meeting was to facilitate new collaborations and research projects to improve the lives of people with diabetes. The 2015 meeting comprised a comprehensive scientific program, parallel interactive workshops, and two keynote lectures.

Opening Lectures
News from the World of Diabetes

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Prevalence and costs of diabetes. Since 1980, several new medications and devices have been added to the armamentarium for managing diabetes. However, nearly half of individuals with diabetes still do not reach their targets for glycemic control. Among U.S. adults included in the T1D [type 1 diabetes] Exchange Registry (https://t1dexchange.org/pages/clinic-registry), only approximately 20% are reaching their glycated hemoglobin (HbA1c) targets.

Additionally, worldwide prevalence of diabetes continues to increase far beyond expectations. It is estimated that there will be approximately 500 million individuals with diabetes within the next 10 years with resultant increases in costs. The most recent data show that the costs of diagnosed diabetes had risen by 41% between 2007 and 2012; however, the new classes of medications and supplies only account for 12% of medical expenditures.

Although there are trends toward significant reductions in the rates of diabetes-related complications, specifically microvascular disease, mortality in diabetes has significantly increased in both men and women when compared with the control group without diabetes because of the increasing prevalence. Much of the morbidity and mortality seen in diabetes is related to cardiovascular disease, which is highly correlated with fasting plasma glucose. Thus, we may want to consider fasting glucose as the initial target for control, especially in T2D (type 2 diabetes).

Because people with diabetes are living longer—nearly one in four individuals with diabetes is in their seventh or eighth decade of life—the problem of severe hypoglycemia is emerging as a leading health issue in the elderly with diabetes. A recent survey of individuals in their sixth decade of diabetes showed that 25% of respondents felt no symptoms of hypoglycemia until their blood glucose dropped to 40–49 mg/dL (2.2–2.7 mmol/L).

Delay in insulin initiation. In subjects with T2D, there is a significant delay in initiating insulin therapy. Although this delay is likely due to the number of new drugs that provide an alternative to insulin, data from recent studies clearly suggest that early initiation of insulin therapy is beneficial. Interim data from a large prospective Chinese study (ORBIT) of approximately 20,000 individuals with T2D showed a significant decline in HbA1c values in 6 months, and many more patients were able to achieve target HbA1c when insulin therapy was initiated at or below HbA1c of 8.5%. Moreover, a recent study of 552 Asian patients with poorly controlled T2D who were started on once-daily glargine showed that patient-led insulin titration resulted in significantly greater reductions in both HbA1c and fasting plasma glucose compared with physician-led titration.[1] These results reiterate the glycemic benefits of insulin therapy and demonstrate that patients are able to self-manage their basal insulin regimens when guided.

New treatments. New basal insulins may encourage earlier initiation of basal insulin therapy. One new insulin is peglispro, which may have preferential hepatic action due to its reduced

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peripheral effect. Results from a recent study of peglispro showed significantly lower HbA1c values at 26 and 52 weeks compared with glargine treatment in individuals with T1D.

Among new therapies being added to care for people with T2D are the sodium–glucose co-transporter (SGLT)-1 and -2 inhibitors. Although there is growing concern about the increased risk of ketoacidosis with SGLT-2 inhibitor treatment in both T1D (with off-label use) and T2D, use of dual SGLT-1 and -2 inhibitors as an adjunct to insulin therapy may have important benefits. A recent prepivotal pilot study of 30 individuals with T1D treated with sotagliflozin, a dual SGLT-1 and -2 inhibitor, showed significantly positive results, including improved glycemic control, weight loss, and no increase in hypoglycemia.[2] Given the growing number of individuals with T1D who are overweight or obese, medications that lower weight when used in combination with insulin are clearly valuable. The future of non–insulin therapies as adjunctives to insulin treatment will be the target for investigation in the next decade.

Future of closed-loop systems.   The role of devices such as continuous glucose monitoring (CGM) devices and insulin pumps alone or in combination has been clearly showing to reduce hypoglycemia, improve glucose control, and reduce glucose variability. Future systems are likely to be hybrid closed-loop systems where both hypoglycemia reduction and improvement in HbA1c can be expected when automation is implemented. However, challenges remain for developing dual hormone (insulin/glucagon) systems.

Summary.   Although the prevalence of diabetes continues to rise, overall complication rates are decreasing. It is also clear that cardiovascular disease is clearly related to fasting hyperglycemia. Hypoglycemia in the elderly and in people living longer with both T1D and T2D is clearly an issue. Additionally, treatment of T2D needs to be revisited, whether it is with early insulin therapy or early changes in the medications.

In the future, we may see new basal insulins, and for insulin-requiring patients, full or hybrid closed-loop systems may be available.

Accu-Chek® and Personalized Diabetes Management—What Can You Expect?

Matthias Axel-Schweitzer, Roche Diabetes Care, Mannheim, Germany

Background.   Despite the development of new therapies and technologies, many individuals with diabetes are not meeting their diabetes management goals. Achieving optimal glycemic control while minimizing the risk of hypoglycemia remain daily challenges. The core business of Roche Diabetes Care is developing product solutions that enable people with diabetes to meet the challenges of diabetes management but still maintain a high quality of life. These product solutions not only have to be evidence based, with demonstrable clinical efficacy and value, but they must also address the time constraints of clinicians and financial constraints of payers.

Personalized diabetes management.   Fundamental to our business approach is applying these product solutions within the context of personalized diabetes management (PDM). PDM is a formal process that individualizes therapy through a recurring cycle of patient education, structured monitoring, analysis/interpretation of glucose data and other information, therapy adjustment, and assessment of efficacy.

Accu-Chek Connect diabetes management system.   The Accu-Chek Connect diabetes management system is a product solution recently added to the Roche Diabetes Care portfolio that exemplifies how we are applying new technologies to the PDM process. The system combines smartphone and Web-based technologies with proven approaches to diabetes management in a way that facilitates efficient diabetes data collection and analysis and promotes collaboration between patients and their healthcare providers.

Using the system, patients utilize a blood glucose meter (Accu-Chek Aviva or Accu-Chek Performa) to obtain a glucose value. The meter transmits the value and other relevant data to a smartphone application (app), which presents the data in meaningful graphic, actionable formats. The app also includes several management tools, including an automated bolus advisor and preprogrammed monitoring regimens (e.g., 3-day/seven-point profile, testing in pairs) to facilitate structured glucose testing. If the user chooses to share his or her information, the data are automatically uploaded to the cloud where they are accessible through both user and healthcare provider Web portals. For clinicians, the Web portal homepage presents a list of all patients using the system, identifying those patients at greatest risk for hypoglycemia, hyperglycemia, and/or glycemic variability.

In addition to the Accu-Chek Connect diabetes management system, we have a growing portfolio of insulin pump solutions, and we are working to develop a system that allows for automated insulin delivery. Supporting this effort is our CGM program, which is now coming to fruition. The clinical efficacy and feasibility of the technologies and clinical approaches utilized in our product solutions have been demonstrated by robust medical evidence.

Evidence-based technologies.   Regarding proven technologies, a recent study by Pleus et al.[3] showed that the blood glucose meters used by the Accu-Chek Connect diabetes management system achieved high accuracy when criteria of the recently published International Organization for Standardization standard ISO 15197:2013 were applied. The safety, efficacy, and clinical utility of the bolus advisor algorithm have been proven in several studies.[4–6] Additionally, we have shown that use of the computer reports incorporated into the user and healthcare Web portals enables patients, caregivers, and clinicians naive to diabetes data management software to identify and utilize key diabetes information with significantly greater accuracy and efficiency compared with traditional logbook information.[7] As reported by Harrison et al.,[8] patient satisfaction with these types of technologies is high and correlated strongly with ease of use and improved diabetes management.

Evidence-based clinical approaches.   There is also extensive evidence that supports the clinical approaches inherent in our product solutions. We know there is a strong association between frequent blood glucose monitoring and HbA1c. Moreover, the value and utility of Structured Testing, specifically use of 3-day/seven-point glucose profiles, has been demonstrated in numerous studies, such as the STeP study,[9] the PRISMA study,[10] and, most recently, the STeP IT UP study[11] from Australia. As shown in the

recent STENO ABC study (publication pending), carbohydrate (CHO) counting, in combination with use of our bolus advisor (Accu-Chek Aviva Expert) improves glycemic control in individuals naïve to CHO counting who are treated with multiple daily insulin injections (MDI).

We also have two large clinical trials (ProValue studies) underway to evaluate the PDM concept within both specialty and general medical practices. Results from these studies will provide valuable information about the most effective and efficient ways to individualize diabetes management within a defined process of care.

Summary. We now think in terms of product solutions and how they can be used to improve diabetes care and reduce the burden of diabetes management. Our goal is to bring product solutions that are not only patient oriented in individualizing care, but also address the needs and constraints of healthcare providers and payers.

Glucose Monitoring and Diabetes Management Solutions

Implementing "Structured Testing" in an Australian Setting—The STeP IT Up Study

Jane Speight, Deakin University and The Australian Centre for Behavioural Research in Diabetes, Melbourne, Australia

Background. Structured self-monitoring of blood glucose (SMBG) is an approach in which blood glucose data are gathered according to a defined regimen, interpreted, and utilized to make appropriate pharmacologic and/or lifestyle adjustments. Despite the proven clinical and psychosocial benefits of structured SMBG reported in several recent studies,[9,12,13] use of SMBG in individuals with non–insulin-treated T2D remains controversial.

In a recent Cochrane Review, which summarized 12 randomized controlled trials involving over 3,000 participants, the authors reported that although there is a statistically significant, short-term reduction in HbA1c when SMBG is used, the reduction is not clinically significant, nor is it sustained.[14] Nor was there a positive effect on patient satisfaction, well-being, or health-related quality of life, according to the report. From a health economic perspective, the review suggests that costs are higher with SMBG. Given these assessments, the authors concluded that the clinical benefit of SMBG in non–insulin-treated T2D is "limited."

It is noteworthy that the findings from this Cochrane Review[14] were based mostly on studies in which frequency of SMBG was inadequate, regimens were not specified, and/or SMBG data were not used to inform therapeutic change (diet, physical activity, or medication). Nevertheless, because Cochrane Reviews carry significant influence with health policy decision-makers regarding reimbursement, both public and private payers are assessing the value and utility of SMBG in this diabetes population.

It is our position that evidence from recent studies that used "structured" SMBG clearly demonstrates both clinical and psychosocial benefits for people with non–insulin-treated T2D. Although these benefits have been shown in U.S. and European studies, the generalizability of these findings has not yet been shown in Australia.

The Structured Testing Program Implementation Trial (STeP IT UP) assessed the impact of structured SMBG on HbA1c, hypoglycemia, and diabetes-related distress (Diabetes Distress Scale total scores) in 136 adults with non–insulin-treated T2D managed in 22 primary care settings across Australia: mean (SD) HbA1c, 8.7% (1.2%); mean (SD) age, 60.8 (12.2) years; 39.7% women; and mean (SD) body mass index (BMI), 32.1 (6.3) kg/m^2. In this 24-week, multicenter, uncontrolled, observational study, Australian clinicians with structured SMBG experience trained their patients to collect/interpret structured SMBG (seven-point profiles over 3 consecutive days), using the Accu-Chek 360° View 3-day profile tool. Patients completed the tool prior to their visits at Weeks 4, 12, and 24; results were discussed at each visit. At 24 weeks, there was no increase in hypoglycemia but significant improvements in HbA1c and diabetes distress.

Our findings align with earlier studies that use of structured SMBG by adults with non–insulin-treated T2D supported by primary care clinicians is associated with significant improvements in glycemic control (without increasing hypoglycemia) and diabetes-related distress. Furthermore, our study demonstrates the feasibility of implementing structured SMBG in routine primary care in Australia.

GoCARB—An EU-Funded Project to Support People with Diabetes in Counting Carbohydrates and Estimating the Size of the Insulin Bolus

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Background. People being treated with intensive insulin therapy can only estimate their optimal prandial insulin dosage after accurate CHO counting. Studies have shown that an error of $\pm 10\,g$ in CHO estimation does not influence the postprandial glucose profile, whereas an error of $\pm 20\,g$ significantly impacts the postprandial glucose profile.[15,16]

A key feature of most insulin pump systems is the capability to automatically calculate bolus insulin dosages to cover CHO intake and address out-of-range blood glucose levels. This capability has recently been integrated into blood glucose monitoring devices and, more recently, into stand-alone smartphone apps.

As diabetes is becoming increasingly prevalent throughout the world and it has been demonstrated that people with diabetes are inaccurate in calculating the CHO content of their meals, there is an urgent need for automated tools and services that will support diabetes patients with CHO counting.

GoCARB project. The GoCARB project is funded by the European Commission and is a collaboration among the University of Bern (project coordinator), Roche Diabetes Care in Mannheim, and Roche Diabetes Care in Indianapolis. The goal of the project is to develop and evaluate a system that provides automatic and near real-time estimation of meal CHOs for individuals with T1D and that utilizes mobile phone technologies, artificial intelligence, and computer vision.

Computer vision is a scientific field that utilizes methods from artificial intelligence and image analysis for image acquisition, processing analysis, and image understanding. Computer vision includes methods that allow us to detect where an object is in a picture, recognize it, segment it, define the different parts of which it is made up, and reconstruct its three-dimensional model.

Prototype development. In developing our prototype, the first requirement was that the error rate should be less than ± 20 g of CHO. Our assumptions were that the food types should be included in the image and nutritional database, that the plate is circular and shallow, and that the food items are not occluded.

When utilizing the prototype app, the patient places a reference object (the size of a credit card) next to the meal and takes two pictures using a smartphone. One picture is taken from directly above the plate; the other is taken at an angle of $30°$. The captured images are then analyzed.

First, the plate is detected, and the different food items are identified, segmented, and separated from each other. In the next step, the food type of each food item is identified. By using the results of the segmentation step, the second image, and the information from the reference object, each segmented food item is reconstructed in three-dimensional space, which allows us to estimate its volume. By knowing the volume and the food type, we can use the U.S. Department of Agriculture nutritional database to calculate the corresponding amount of CHOs. This information is fed into the bolus calculator, and the patient is presented with the calculated quantity of CHOs and the required insulin dose. The patient can either accept or ignore the result.

Prototype evaluation. We used a two-step procedure to evaluate the system. In the first step, we evaluated the system under controlled laboratory conditions, using 24 real food images. In this assessment, the absolute error was found to be 6 ± 8 g of CHO, with a relative absolute error of $10 \pm 13\%$.

The second step of the evaluation involved 19 adult individuals with T1D who were presented with six different meals. Each person was asked to estimate the CHO content of each meal according to his or her usual method and then to repeat the procedure using the GoCARB system. At the end of the session, each participant was asked to complete a questionnaire.

Results from this evaluation showed significantly lower absolute error (13.3 ± 13 g vs. 28.3 ± 38.5 g) and relative absolute error ($28 \pm 20.5\%$ vs. $56.1 \pm 75.6\%$) with the GoCARB system than with the patients' estimation. More than 80% of the time, the error for GoCARB was less than 20 g. It was striking that the SD associated with GoCARB use was much lower, which indicates that the GoCARB is much more reliable than people with T1D themselves in calculating CHO content.

Results from the questionnaire showed that most patients found the app to be both useful and easy to use. Most patients also indicated that they would use the app regularly. The only criticism was that the app tended to be slow, mainly because of delays with the wireless network (client-server architecture).

Utilization with artificial pancreas. Our next step was to integrate the GoCARB system into the artificial pancreas (AP) framework, using the U.S. Food and Drug Administration (FDA)–accepted T1D simulator and an in-house-developed adaptive control algorithm. Several simulations using open loop (standard treatment) and closed loop have shown that the use of GoCARB results in lower high-glucose concentration and an increased percentage of time spent in the target range, with almost 0% of glucose concentrations above 180 mg/dL.

Future development. The project ends in August 2015; however, we have already submitted a protocol for a larger study to evaluate the third prototype of the system. The primary objective of this study is to investigate the effect of GoCARB use in the glycemic control of individuals with T1D. The trial will start once the protocol has been approved.

Accu-Chek Connect—A Blood Glucose Meter and Diabetes Management System Goes Online

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Background. In Africa, there is a combination of unique factors that conspire to increase the incidence of diabetes. It is anticipated that the rates of diabetes in Africa are going to double over the next 20 years. Moreover, we know that diabetes is poorly controlled; the most recent available data from a site north of Johannesburg show the average HbA1c at 8.8%.

In South Africa, a third of our population is below the age of 30 years, which is exceptionally contrasting with what is seen in more developed countries. Unfortunately, it is the young and economically active population that will bear the brunt of the diabetes epidemic, and we expect our continent will suffer from chronic underfunding of this condition.

Mobile telecom scenario in South Africa. There is widespread access to mobile technology in South Africa. Recent studies are emerging that indicate cell phone penetration is more than 100%.[17] Additionally, the majority connect to the Internet via smartphones rather than desktop computers. It is also interesting that users tend to keep their mobile phones for a very short time due to aggressive incentives offered by the phone companies to upgrade. This strong cell phone penetration created an obvious opportunity for Roche Diabetes Care to launch its Accu-Chek Connect diabetes management system.

Accu-Chek Connect diabetes management system. South Africa was among the first countries in the world to use the new Accu-Chek Connect diabetes management system. The Center for Diabetes and Endocrinology in Johannesburg "connected" our first patient on July 17, 2014.

The Accu-Chek Connect diabetes management system consists of a home blood glucose meter, which connects wirelessly, via low-energy Bluetooth® (Bluetooth SIG, Kirkland, WA), to the users' Accu-Chek Connect diabetes management app on their mobile device. This app contains a multitude of functions, including a bolus advisor embedded in the app, informative graphs and reports that help to identify blood glucose and behavior patterns, a health events log, and a clinically proven 3-day profile Structured Testing tool. The app allows users to tag their meals by means of a photo, which can be added to their diary and viewed by their healthcare practitioner (HCP). If patients choose to share their information with their selected HCP, the data are automatically uploaded to the cloud and transmitted to a secure Web portal. HCPs are then able to assess this information and engage with the patient to improve glycemic outcomes.

Experiences with the system. The early experiences of the Accu-Chek Connect diabetes management system were not always favorable, and it was uncertain as to which

patients would benefit the most. Over time, we identified specific characteristics of patients who we considered ideal candidates for using the system. These include younger patients (<45 years), patients who are ''tech savvy,'' patients who are likely to be less well controlled and have limited success with other skills (CHO counting), and patients transitioning from basal insulin therapy to more intensive insulin regimens. Conversely, we continue to see limited success when caregiver support is inconsistent or inadequate.

From a clinical practice perspective, we found that the system improves office efficiencies. As shown in the AC-CRUES study,[7] use of the software-based reports is significantly better than looking at traditional diaries and paper logbooks. Some of the staff reported that it can take as little as 15 min to get through five patients. Additionally, the system literally keeps the team connected through constant, multidisciplinary feedback among them in the clinic.

Remaining challenges. Although we have refined our ability to identify the most suitable candidates, we recognize that CHO counting remains a challenge for many insulin users. We are currently addressing this issue with our training staff. Additionally, we have had to deal with a condition that we call ''web-based burnout,'' with both staff and patients; the system is only effective when everyone is logging in and utilizing the information.

Summary. The burden of diabetes will continue to increase worldwide. Fortunately, South Africa has a telecom infrastructure with significant smartphone penetration that will enable individuals with diabetes to benefit from the new technologies being developed to assist in diabetes management. The Accu-Chek Connect diabetes management system meets all of the system requirements of a chronic care model as described by the American Diabetes Association in its annual clinical practice recommendations. The system is proactive, lends itself to decision support, and promotes real collaboration between HCPs and their patients.

How Can Healthcare Companies Leverage Patients' Experience to Enhance Diabetes Management?

DAISY—How the Diabetes Association in Support of Youth Is Pushing Patient Self-Management in Malta

Christopher Barbara, Maltese Diabetes Association, Valletta, Republic of Malta

Background. According to the 2013 National Statistics Office Report, the total population of Malta is approximately 420,000. Malta has the second highest percentage of individuals living with diabetes in the Mediterranean, surpassed only by Cyprus. The International Diabetes Federation (www.idf.org) estimates that there are 30,000 adults with diagnosed diabetes in Malta and another 8,000 who are undiagnosed. These figures do not include those who have impaired glucose tolerance or impaired fasting glucose, which can lead to the development of diabetes.

DAISY—Diabetes Association in Support of Youth. Although the Maltese Diabetes Association has been actively working to support individuals with diabetes in Malta, my peers and I—a group of young adults living with diabetes—wanted to start an initiative that addressed the needs and issues of young people with T1D. Collaborating with Ms. Therese Piscopo, who was working at the Diabetes Clinic, we founded DAISY in 2009.

The name is based on three simple words—Diabetes, Support and Youth. The daisy flower was selected as our logo for a variety of reasons. First, the petals represent the various components of effective diabetes management: diet, exercise, monitoring, medication, and education to obtain a healthy lifestyle. Second, although many insects visit the flower each day, the daisy is not bothered by any of them; although persons with diabetes need to recognize the condition and be aware of the complications, one must never be discouraged. Additionally, the daisy represents innocence, simplicity, cheerfulness, and sympathy, virtues that are reflected in the DAISY youth group.

DAISY believes that diabetes care needs to incorporate not only the biological aspects of the condition but the psychosocial aspects as well. This is in accordance with the World Health Organization's definition of health as ''a state of complete physical, mental and social well-being, not just the absence of the disease.'' Because most diabetes costs are due to diabetes complications, the key focus of the group is on prevention. Additionally, DAISY advocates that all individuals with diabetes should be empowered to be self-reliant and provided with ongoing information and support throughout the course of their lives.

Education and support. DAISY organizes community health programs, education boot camps, and other events that target youths around the country to assist them with their diabetes management efforts. The group is also engaged in advocating for allowing students to monitor their glucose at school and administer insulin without interference from school personnel. The group works closely with the Maltese Diabetes Association, in collaboration with their pediatric team, to educate the public and remove the taboo attached to diabetes in order to address social and employment discrimination. We formed a multidisciplinary diabetes team consisting of diabetes nurse specialists, dieticians, pediatrics, podiatrists, and psychologists to hold regular educational sessions.

International collaborations. In addition to its local efforts to raise awareness through social media, DAISY is part of the Diabetes Youth Advocates (DYA) Europe, which is an online community of people from across Europe who come together to leverage their knowledge in and experience with the support of people with T1D. The goal of the community is to share ideas and build a network among other countries to explore synergies, share resources and tools, and think of possible collaborations.

Continuous Glucose Monitoring

How Good Is Good Enough, and Which Metrics Are Appropriate to Describe the Performance of CGM?

Michael Schoemaker, Roche Diabetes Care, Mannheim, Germany

Background. CGM systems are providing more information than traditional systems for SMBG. Because CGM sensor accuracy can impact both the clinical utility and patient

acceptance of CGM use, it is important to consider the performance characteristics seen in the current systems when assessing the clinical value of this technology. Although advances in CGM technology have significantly improved the clinical utility of CGM devices compared with earlier versions, it is often difficult to assess the accuracy and precision of current devices due to differences in assessment protocols and reporting of results.

Key limitations. The challenge in assessing CGM system performance is overcoming some important limitations. The first limitation is that we currently assess accuracy based on a blood glucose comparator. However, this comparison uses only 2–5% of the available CGM values; the remaining values are not considered in the metric. The second limitation is that our assessments are measuring glucose in two different body compartments: blood and interstitial fluid. There is a lag time of approximately 5–10 min (depending on the rate of glucose change) between the appearance of glucose in the blood and interstitial fluid. When CGM and blood glucose readings are paired according to their time stamp, this may be inadequate from a physiological point of view.

Nevertheless, a common metric used for assessment of CGM accuracy is the aggregate mean absolute relative difference (MARD) between all temporally matched sensor data (interstitial glucose) and reference measurements (blood glucose) across all subjects of a study. Reported as a percentage, MARD is the average of the absolute error between all CGM values and matched reference values. A small percentage indicates that the CGM readings are close to the reference glucose value, whereas a larger MARD percentage indicates greater discrepancies between the CGM and reference glucose values.

However, using the overall MARD can sometimes be misleading. For example, when we look at the overall MARD of two different CGM devices—the FreeStyle® Navigator® (Abbott Diabetes Care, Alameda, CA) and the Medtronic (Northridge, CA) Guardian®—the overall MARD values are somewhat equal (12.4% vs. 16.4%, respectively). However, when the MARD is measured in the lower glucose range (<70 mg/dL), the difference is significant (22.6% vs. 32.2%).

It is also necessary to look at differences in MARD during periods when glucose levels are rapidly changing. In a recent head-to-head study between the Dexcom® (San Diego, CA) G4® sensor and the Roche prototype sensor, we again saw fairly close similarities in overall MARD values (10.9% vs. 8.6%, respectively). However, during scheduled periods of induced hyperglycemia and hypoglycemia, the differences in MARD at various rates of glucose change were striking.

Unresolved issues. Although we have seen significant improvements in the accuracy of today's CGM devices compared with earlier generations, we still have some unresolved issues with these systems. A key issue is sensor signal dropout due to compression of the sensor. Compression can occur if, during the night, the patient rolls onto the side where the sensor is attached and thereby causes an increase of local tissue pressure around the sensor, which leads to a decrease of local blood flow. This can eventually lead to a decrease or loss of sensor signal. As soon as the patient rolls back on the other side, the sensor signal recovers again.

Assessment of CGM performance using MARD cannot detect these occurrences. However, an alternative metric could be the calculation of the precision absolute relative difference (PARD). PARD is a metric used to compare glucose readings from two identical CGM sensors working simultaneously in the same patient; a lower percentage indicates greater precision (less variance). Using this metric, all CGM data are considered for performance evaluation. However, there is no correlation to blood glucose concentration. Nevertheless, the comparison of two concurrent CGM sensors provides additional and complementary insights into CGM sensor properties and performance. CGM performance studies that present both MARD and PARD at various glucose ranges facilitate a more reliable assessment of a given CGM sensor's true accuracy and precision characteristics.

Summary. The question "How good is good enough?" can only be answered in relation to the intended use. When used as a stand-alone, adjunctive device for monitoring current and trending glucose levels, with no control over insulin pump infusion, current CGM devices are adequate for their intended use. However, as soon as CGM data are used for therapy decision or the CGM device is to control insulin delivery directly, accuracy and precision become increasingly important depending on the degree of control.

Although the performance of the newer CGM sensors has improved, these systems still show prolonged unstable and unreliable episodes. Clearly, more sophisticated performance parameters and acceptance criteria are needed. Moreover, standardization of the metrics used to assess CGM accuracy and precision is needed to help developers, physicians, and patients to make informed decisions regarding the CGM systems that they are considering to use.

An Update on the Automated Pancreas

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Background. The underlying technologies utilized in AP systems have evolved rapidly. Several different AP development programs are currently underway. Over the past 4 years, engineers at the University of Virginia Center for Diabetes Technology have developed the Diabetes Assistant (DiAs), a smartphone-based AP system.

Development approach. The DiAs system leverages the technological advances we have seen in CGM devices and insulin pumps, mobile personal computing, local and global wireless communications, cloud-based data aggregation, and intelligent algorithms (both real time and retrospective). Today, the system consists of a smartphone loaded with a modified version of the Android™ (Google, Mountain View, CA) operating system (Medical Android), a graphical user interface, and closed-loop insulin dosing software that is wirelessly connected with a CGM system and an insulin pump. With the help of Roche engineering, our team recently added support for the Roche Accu-Chek Spirit Combo insulin pump, which already included wireless communication capabilities.

In designing the DiAs system, our goal was to build a platform that would be suitable for long-term home trials, which meant replacing the laptop computer with a smartphone to control the system. We chose the Android phone because it provides complete control over the operating system, allowing us to incorporate only those apps and

functionalities that are specific to AP operation. The smartphone interface was designed for patient operation, utilizing audible alarms and ''traffic lights'' that indicate patient risk for hypoglycemia and hyperglycemia. Information regarding the status of the various devices (e.g., insulin pump, CGM device) is presented at the top of the screen. The system consists of a network of apps, some of which provide a patient-facing interface and others that run continually in the background. For example, the Safety System application independently calculates the probability of developing hypoglycemia within the next 30 min. If impending hypoglycemia is detected, the system begins to gradually attenuate insulin delivery. This usually results in no hypoglycemia.

Although the system is designed for patient operation, we have also built in several research functionalities that allow us to monitor patient status and archive data for research purposes. The system also features an automated notification function that can inform medical staff as needed.

Human studies.   The DiAs system has been used in a series of long-term home trials in the United States and Europe over the past year, as well as in studies at children's diabetes camps. Our studies have included 302 participants who have used the system for a total of 62,173 h. A weighted meta-analysis of all studies showed that when used 24 h/day, the DiAs system reduced average blood glucose from 153.6 mg/dL to 148 mg/dL, increased time in range from 65.9% to 72.8%, and reduced time below 70 mg/dL by 50% compared with sensor-augmented pump therapy. In overnight use, the results were even more striking: average blood glucose decreased from 153.1 mg/dL to 139.2 mg/dL, time in range increased from 63.7% to 78.1%, and percentage of time below 70 mg/dL was reduced by a factor of 3.

In one recent study of the DiAs system, investigators assessed the safety and performance of the AP in 16 adolescents with T1D following omission of meal insulin, which is common occurrence among teenagers.[18] The DiAs system provided improvements in postprandial glucose control without increases in hypoglycemia.

Another study looked at the system's ability to ''reset'' the patient's glucose to near-normoglycemia (120 mg/dL) each morning.[19] Over the 5 study nights, use of the DiAs significantly improved the percentage of time spent between 80 and 140 mg/dL, mean glucose level, and overnight glucose level compared with sensor-augmented insulin pumps. Tighter overnight glycemic control also resulted in improved daytime control on the following day.

One of the key learnings from the studies is the impact of ''alarm fatigue.'' In our early development efforts, we felt that more alarms would be safer for patients. However, we have found that this is not necessarily the case, and our current system has significantly fewer alarms.

Summary.   We view the AP as a network of services and devices that all communicate with one another. Technological advancements are driving the rapid improvements seen in current AP systems. In its first embodiment, the AP system may involve only one or two devices; however, we believe it will continue to expand as we learn more about what users want and need through ongoing, long-term home studies.

Hot Topic in Diabetes

Why HbA1c Does Not Suffice for Diabetes Management—A Laboratory Perspective

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Background.   HbA1c has been used in routine clinical laboratories for diabetes monitoring since 1977. The utility of the HbA1c test as a predictive measure of diabetes complication risk was demonstrated in the Diabetes Control and Complications Trial (DCCT), which showed that patients were able to reduce the risks of nephropathy, retinopathy, and cardiovascular complications through intensive glycemic control. Efforts have been made worldwide to standardize HbA1c, and with the exception of some point-of-care (POC) systems, it is now among the most highly standardized protein measurements available.

The value of the final glycation end-product reflects the concentration of hemoglobin, the glucose concentration within the red blood cell, the steric accessibility of the different side chain amino acid groups, the lifespan of the glycated protein, and the analytic determination by the laboratory. Although HbA1c remains the best validated, integrated measure for blood glucose currently available, the accuracy and utility of HbA1c measurement can be impacted by several issues.

HbA1c as a monitoring tool.   As a monitoring tool, HbA1c has several limitations. For example, patients often have multiple pathologies. If the pathology reduces the lifespan of the red blood cell (e.g., chronic kidney disease, hemolytic anemia, hypersplenism, major blood loss, blood transfusion) during the previous 3 months, HbA1c values will be falsely lower. Conversely, conditions such as iron deficiency and anemia can produce falsely elevated HbA1c values. There are also situations where there is a genetic effect on the rate of formation of HbA1c; this has been shown in monozygotic twins without diabetes.

Another limitation is that HbA1c primarily reflects those glucose levels from the most recent 2–4 weeks, which can be influenced by changes in patient behaviors prior to testing. It has also been shown that some of the newer therapies, such as sitagliptin, can impact HbA1c values in as little as 20 days.

Additionally, because HbA1c is only an average of the blood glucose over the past 3 months, it cannot detect glycemic variability during that time period, which can affect patient outcomes. Reducing oscillations can decelerate the progression of diabetic vascular disease in T2D; however, this benefit has not been seen in T1D.

HbA1c as a diagnostic tool.   There has been significant discussion regarding the use of HbA1c as a diagnostic tool in which 6.5% (47.5 mmol/mol) would serve as a cutoff point for diabetes. It is important to note, however, that this proposed level is based on its ability to predict the development of microvascular complications; it does not reflect normal glycemia not in diabetes. Therefore, it is possible that an individual with HbA1c <6.5% may, in fact, have impaired glucose tolerance, impaired fasting glucose, or even diabetes. Additionally, one must appreciate that there are different ethnic groups that do not comply with this universal value,

with African Americans being at risk of retinopathy with HbA1c values of <6.5%.

Clinical interface issues. The concept of HbA1c is not intuitive. It is difficult to explain to patients who are more familiar with the relevance of their blood glucose readings. Still, introducing new terminology may be even more confusing for patients. Although use of estimated average glucose (eAG) in lieu of HbA1c may alleviate some of the confusion, this metric also poses challenges to the clinician due to overlapping ranges at each eAG cut point. For example, the range for eAG of 7 mmol/L (6% HbA1c) is 5.6–8.4 mmol/L, 6.8–10.3 mmol/L for eAG of 8.5 mmol/L (7% HbA1c), and 8.2–12.1 mmol/L for eAG of 10.2 mmol/L (8% HbA1c). These overlapping ranges can make it difficult to determine whether a therapy change is needed because an eAG of 8.5 mmol/L could be interpreted as either a higher range of 6% HbA1c or the lower range of 8% HbA1c.

Summary. Although the HbA1c test remains the best integrated marker available, it has significant limitations both as a monitoring tool and as a diagnostic tool. HbA1c neither addresses the issue of glycemic variability nor does it fully address clinical needs at the clinician–patient interface. Physiological and pathological issues can also limit its usefulness. Therefore, use of HbA1c alone as a measure of glycemic control risks oversimplification as a monitoring tool.

Keynote Lecture

Who Is in Control? How the Gut Microbial Ecosystem Influences Our Eating Behavior and Contributes to Obesity and Diabetes

Robert Ratner, American Diabetes Association, Alexandria, Virginia

Background. The microbiome is the population of bacteria, viruses, fungi, and archaea that live in the gut and on the skin. It is a complex ecosystem with a high degree of interindividual variability that provides benefits to the host, including nutrient harvest from food and protection against pathogens. Because the microbiome is dynamically regulated by both genes and environment and, in turn, critically influences both physiology and lifelong health, its role in the development and progression of both T1D and T2D is being investigated.

Microbiome characteristics and mechanisms. There are approximately 100 trillion microbial cells in the human body. When discussing these cells it is important to first define the area of the body that you are focusing on. As you move down the gastrointestinal (GI) tract, the numbers and types of bacteria change because of changes in pH levels. We have identified 57 common species, and they are comparable among all ethnic groups. Looking at associations between these bacteria and health, we know that there is a link between diversity of microbial cells and health: the greater the diversity, the healthier the individual.

Association with T1D. In studies of female non-obese diabetic (NOD) mice, which have a high proclivity for T1D,

it has been shown that when the male NOD mouse colon is colonized with female feces, the risk of T1D is identical to that of the female mice. Conversely, in the wild type, diabetes-prone BioBreeding (BB) rat, if you colonize their colons with *Lactobacillus johnsonii*, the risk of developing diabetes is abrogated.

In a human study,[20] investigators found that children who eventually developed T1D showed a gradual decrease in GI bacteria diversity over time. One specific type of bacteria, the *Bacteroides*, appeared to strongly correlate with autoimmunity. The ratio of *Bacteroides* to firmicutes increased significantly in the children who developed diabetes but decreased in those who did not.

It has been hypothesized that early exposure to antibiotic use changes the microbiome in such a way that it may actually predispose children to autoimmune diseases. The marked increase in T1D tends to be occurring in those with low genetic risk. A second hypothesis involves the mode of infant delivery. When a child is born vaginally, that child is automatically inoculated with maternal bacteria, whereas a child delivered by cesarean section is not inoculated.

Similarly, there are effects of breastfeeding on the microbiome of the offspring. The American Diabetes Association is currently funding a major project that looks at the microbiome of infants of mothers with diabetes compared with controls to see whether there are differences that get transmitted to the child, and then follow the microbiome of the infant.

Association with weight gain. Several recent studies suggest that the microbiome is linked to obesity and CHO intolerance. A study by Ley et al.[21] showed a progressive decrease in firmicutes with a progressive increase in *Bacteroides* in obese individuals who were put on a diet for 52 weeks, indicating that obesity has a microbial component. These changes were independent of meal composition. Conversely, firmicutes increase and *Bacteroides* decrease with weight gain in lean individuals. It is unknown whether changes in weight are the result or cause of changes in the microbiome.

Animal studies have shown that obese-prone rats have differing microbiota compared with obese-resistant rats when both are maintained on the same high-fat diet. When the microbiota from the obese-prone rats is transferred to the obese-resistant rats, those rats exhibit increased food intake, weight gain, and adiposity.

There is also interest in the effects of artificial sweeteners, specifically saccharin. In a recent study,[22] saccharin-fed rats showed increased weight gain compared with rats that were fed glucose. Investigators transferred the feces from the saccharin-fed rats or control feces to germ-free rats. The rats that received the feces from saccharin-fed rats developed significant CHO intolerance. However, the relevance of these findings to humans remains questionable.

Mechanisms of action. Historically, the microbiome was thought to affect metabolism by simply breaking down complex CHOs to provide more useful calories for absorption or, alternatively, burning fuel in the GI tract in a futile manner that does not contribute to caloric intake by the host. However, when the number of ''calories in versus calories out'' is assessed, there appears to be no change as the microbiome changes.

The alternative model is that the microbiome is sending signals across the GI tract to affect overall metabolism

mediated by inflammation. Inflammation, characterized by elevated C-reactive peptide, has long been associated with diabetes, obesity, and cardiovascular disease. It is known that bacterial lipopolysaccharides function as a metabolic endotoxemic that can trigger many of the conditions seen in the metabolic syndrome, starting with low-grade inflammation. It is possible that the microbiota is broken down by the lipopolysaccharides, which, unlike microbiota, can cross the mucosal barrier in the intestinal lumen and induce endotoxemia and inflammation. It is interesting that a recent study showed that *Akkermansia muciniphila* plays a protective role by increasing the mucus layer thickness and allowing or promoting the body to generate antimicrobial peptides—particular bioactive lipids—to reduce metabolic endotoxemia.

Currently, this mechanism is only a hypothesis. According to Koch's postulates for causality—a microorganism must be identified and isolated from a diseased organism—there should be an association of that microorganism with the disease that can be affected by intervention, and the cultured microorganism should reproduce the phenotype when it is introduced into the organ. Animal studies, using *Ralstonia pickettii*, seem to be bringing us closer to establishing causation. One recent study demonstrated that transfer of *R. pickettii* into diet-induced obese mice significantly reduced insulin resistance.

Weight loss. One mechanism by which weight loss is dramatically seen is following Roux-en-Y gastric bypass. Assessments of the ecology of the microbiome in obese individuals have shown an increase in the change in richness and diversity of the microbiome following gastric surgery. The question, now, is whether you can take the microbiome characterized in the post–gastric bypass patient and colonize the GI tract of obese patients who have not had bypass with those bacteria and see the same effect? Unfortunately, this can only be done in animal studies.

Another recent study looked at germ-free mice that were colonized by the feces of animals that had either sham surgery or Roux-en-Y bypass. Investigators found no weight loss in mice that received feces from the sham-surgery mice, but an immediate and profound loss of weight occurred in those animals that received the microbiome from post–Roux-en-Y bypass mice. Moreover, this weight loss occurred with no change in food intake. It has been hypothesized that this occurs due to increased levels of propionate in the GI tract, which results in increased energy expenditure.

Progress in human studies. The FDA has recently approved the first indication for fecal transplant in humans for the treatment of *Clostridium difficile*, the cause of an aggressive infection that carries a >90% mortality. The FDA guidance for doing fecal transplants is now very clear-cut. Today, studies in inflammatory bowel disease are ongoing. However, there are no studies of microbiome transfer or fecal transplants in people with diabetes currently underway.

Summary. Increased gut microbial diversity is healthy. Although altering the gut microbiota is associated with autoimmunity in T1D and obesity, causation has not yet been demonstrated, and the specific pathogens or the specific preventive organisms have not yet been identified. Passive microbiome transfer through fecal transplant, as well as active changes in the microbiome through either prebiotics or

Roux-en-Y bypass, impacts autoimmunity and energy metabolism. Because we are in the infancy of knowing the specific mechanisms behind these effects, controlled trials meeting Koch's postulates are required to prove causation.

Once clear mechanisms by which these microorganisms exert their influence are understood, it may be possible to utilize this knowledge to intentionally change human metabolism. It is important that many of the approaches that could potentially be derived from an understanding of the microbiome, such as probiotics and nutritional therapies, are relatively inexpensive and may be readily accessible for broad populations.

Hot Topics in Diabetes

Mimicking Endogenous Glucose Regulation—Challenges for an Automated Pancreas

Rita Basu, Mayo Clinic Rochester, Minnesota

Background. One of the problems with mimicking physiology for the AP is addressing the knowledge gaps that exist in this field. These gaps are related to several issues, including postprandial physiology (specifically the diurnal pattern and postprandial glucose flux), physical activity, and hepatic glucagon sensitivity.

Postprandial physiology. Glucose metabolism in the postabsorptive state relates mainly to the liver and other tissues. Endogenous glucose production (EGP) relates to how much glucose is produced from glycogenolysis and from indirect pathways, which are from precursors, such as glycerol, lactate, alanine, and glutamine, that can synthesize glucose through gluconeogenesis. The kidneys also produce some amount of glucose. Uptake of glucose then occurs in the muscle, fat, and brain tissues. In the postprandial state, food from the gut contributes additional glucose to the blood.

EGP is primarily regulated by portal insulin concentrations, portal glucagon concentrations, ambient glucose concentrations, free fatty acids, the autonomic nervous system, the hypothalamus, and cortisol. Individuals with T1D have abnormalities of both glycogenolysis and gluconeogenesis.

T1D and insulin resistance. Using triple tracer meal technology, we studied healthy people and people with T1D to assess differences in postprandial glucose, insulin, and glucagon responses following mixed meals over 3 days. As expected, we saw a robust postprandial glucose response, blunted insulin levels, and inappropriately suppressed glucagon levels among the T1D subjects compared with healthy subjects. However, there was no difference in meal appearance. EGP was not as suppressed in the T1D individuals.

We also found that insulin sensitivity patterns during breakfast, lunch, and dinner in the T1D subjects were exactly opposite to those seen in the healthy individuals. Whereas insulin sensitivity was highest at breakfast in the healthy individuals and then dropped down at lunch and dinner, insulin sensitivity in the T1D individuals was lowest at breakfast and gradually improved throughout the day.

In individuals with T1D, we saw greater insulin resistance, lower portal insulin concentrations, and a lack of early suppression of postprandial glucagon concentrations. These findings have important implications for AP development.

Effects of exercise on postprandial CHO metabolism in T1D. Using the same triple tracer technology, we studied the effects of exercise on insulin, glucose, glucagon, EGP, and glucose uptake in individuals with T1D and healthy subjects. Subjects consumed a mixed meal and exercised 2 h later. Our analysis showed that insulin concentrations rose during exercise, which is likely due to mobilization of insulin from subcutaneous fat depots, possibly in response to increased blood flow in abdominal fat. We also saw that glucagon response during exercise was sluggish but with a robust EGP response. In summary, glucose clearance was reduced, implying significant insulin resistance in individuals with T1D during exercise.

In another study, we looked at the effects of "low-grade" activity in people with T1D in order to understand how normal, everyday physical activity impacts postprandial glucose control. We found that even walking after a meal significantly reduces the postprandial excursion.

Glucagon in AP development. We recently conducted some three-step euglycemic and hypoglycemic clamp studies (low dose, medium dose, high dose) in individuals with T1D to determine whether there is a dose–response of EGP to glucagon, whether glucagon sensitivity varies with prevailing glucose concentrations, and whether glucagon clearance changes with glucagon concentrations.

Our analysis showed that there is an ascending dose–response of glucagon on EGP. We also found that hepatic glucagon sensitivity does not increase during hypoglycemia, nor does glucagon affect peripheral glucose uptake. These factors should be considered when we devise the next-generation dual-hormone AP algorithms.

Insulin Pump Therapy

The Accu-Chek Insight Diabetes Therapy System

Til Rendschmidt, Roche Diabetes Care, Mannheim, Germany

Background. The Accu-Chek Insight diabetes therapy system has four major components: (1) insulin pump; (2) hand-held controller; (3) insulin pump cartridge and cartridge filling system; and (4) infusion sets. The pump features a full color display with intuitive user interface, illuminated cartridge compartment, automated detection of plunger position, and an integrated infusion set adapter.

The system is supported by data management software (Accu-Chek 360°, Accu-Chek Smart Pix) and the Accu-Chek 360° configuration software for insulin pump and data management set-up. The configuration software also allows users to copy settings from the Accu-Chek Combo insulin pump system and the Accu-Chek Aviva Expert blood glucose monitoring system to the Accu-Chek Insight diabetes therapy system. Bolus delivery speed and bolus lag time are configurable to optimize therapy. To address pediatric needs, the system features lower minimum basal rates and bolus dosages, smaller basal rate increments, and a higher maximum correction factor setting. Evaluations of the system are ongoing.

User-relevant routine tasks. In a nonclinical study, the Institute for Diabetes Technology, Ulm, Germany, investi-gated the ease of use of the Accu-Chek Insight diabetes therapy system compared with other insulin pump systems currently available in Germany. These systems included Accu-Chek Spirit Combo, Animas® (West Chester, PA) Vibe™, DANA Diabecare R (Advanced Therapeutics, Warwick, United Kingdom), Paradigm™ Veo™ (Medtronic MiniMed), t:slim® (Tandem Diabetes Care, San Diego), and OmniPod® (Insulet Corp., Bedford, MA). Results from the evaluation showed that the Accu-Chek Insight diabetes therapy system required fewer steps and physical "clicks" for changing the insulin cartridge, infusion set, and cannula. Although the steps required for choosing a basal profile were similar across the systems tested, the Accu-Chek Insight diabetes therapy system required significantly fewer physical clicks for this task.

Accu-Chek Insight insulin pump EU study (preliminary findings). The Accu-Chek Insight insulin pump European Union (EU) study was a 6-month, single-arm, prospective, multicenter, multinational trial, enrolling individuals with T1D and T2D who had been treated with intensive insulin therapy (insulin pump [continuous subcutaneous insulin infusion (CSII)] or MDI) for at least 6 months. Coordinating investigators for the study were Prof. Rudy Bilous, United Kingdom, and Prof. Rudolf Prager, Austria.

The purpose of the study was to obtain information regarding the system performance under routine practice conditions, evaluating clinical data, user feedback, and uploads of the device history. Of the 91 patients enrolled in the study, 10 withdrew, leaving 81 patients, all with T1D. These patients were mostly experienced insulin pump users and had moderate glycemic control at baseline ($7.8 \pm 1.0\%$ HbA1c).

At 6 months, only slight HbA1c reductions were seen among those patients with previous insulin pump use, whereas significant reductions were seen among those previously treated with MDI. Not surprisingly, the most significant HbA1c reductions were seen among those patients with the poorest glycemic control at baseline regardless of previous therapy. During the 6-month study period, two episodes of hypoglycemia and two episodes of diabetic ketoacidosis (DKA) were reported. However, one of the DKA events was associated with a dislocated cannula.

A patient questionnaire demonstrated a high level of acceptance of the system. In response to open-ended questions, patients indicated several system features that they favored most, including ease of use, pump size, screen information provided on the pump and hand-held controller, ability of the hand-held controller to communicate with the pump, and discreet operation of the pump.

Based on these findings, we concluded that the Accu-Chek Insight diabetes therapy system was effective and safe to use under routine practice conditions by adults with T1D. Glycemic control improved when switching from MDI therapy and was maintained in previous insulin pump users. User acceptance of the new system was high.

Accu-Chek Insight Kids Study: comparing CSII with MDI to reach HbA1c targets in children and adolescents with T1D. Roche Diabetes Care is currently recruiting patients for a randomized, controlled, Phase 4 study in children (6–17 years of age) with T1D. The purpose of this study is to compare metabolic control, treatment satisfaction, and quality of life during CSII therapy using the Accu-Chek

Insight diabetes therapy system with MDI therapy. The study will be conducted in the United Kingdom, Germany, and Austria, and it is expected to be completed in March 2016.

Little People, Special Needs—Insulin Pump Therapy in the Pediatric Setting

Jesper Johannesen, University of Copenhagen, Copenhagen, Denmark

Background.   Children and adolescents with T1D cannot be regarded as small T1D adults. They have special needs in respect of diabetes treatment because they are physically and mentally growing and dealing with puberty, which heavily influences diabetes treatment and outcome. Unlike adults, they must have a caregiver.

Challenges.   Children face several challenges in managing their diabetes. Their physical activities are more variable than those of adults, resulting in fluctuating blood glucose levels. They often have unpredictable eating habits as both young children and teenagers. Small children can have difficulties recognizing their own hypoglycemia, and the symptoms can be quite subtle. Insulin management can also be difficult because of fear of injections and varying insulin needs. Because small children have high insulin sensitivity, they mostly require fairly small doses. On the other hand, teenagers contend with increased insulin resistance that occurs in the early morning (the dawn phenomenon), which is likely due to the release of growth hormones and cortisol. Apart from all this, the fact that children are not their own caretakers also influences daily family life. The complexity of balancing diabetes management with providing a relatively normal childhood can put significant stress on all family members.

Transitioning responsibility from caregiver to patient.   When children are very young, they require a caregiver to manage all of their daily diabetes management activities. As children grow, they gradually take on more of these activities. It is important to note that patients in their mid-teenage years are still not able to take on full responsibility for self-management because their brains have not yet matured to the point where they can effectively organize and manage all of the necessary tasks. Additionally, teenagers do not want to be viewed as different from their peers. This can lead to poor self-management and resultant hyperglycemia and hypoglycemia. These conditions are not only potentially life threatening, they can be extremely embarrassing, socially. However, I explain to my patients that if they are willing to take only 3–4 min a day to perform their blood glucose measurements and inject their insulin, they are very likely to do all things their peers are doing. Most importantly, I also make it clear to my patients that, principally, all blood glucose values are good (they can be high or low) because they serve as a tool for them to calculate the correct insulin dose.

Glycemic goals.   In my practice, we work to achieve HbA1c values of 7.0–7.5% (53–58 mmol/mol) with fewer than five hypoglycemic events and DKA events per 100 treatment-years. Our fasting and postprandial goals are 4.5–6.5 mmol/L and less than 10–12 mmol/L, respectively. We make the treatment goals as realistic as possible, and we make sure these goals are known to the family.

Indications for CSII in Denmark.   Today, intensified diabetes treatment, including insulin pump therapy, is widely used in the pediatric setting. Insulin pump treatment is used much more frequently compared with its use in adult diabetes care. More than half of the patients in Denmark under the age of 18 years are insulin pump users. The indications for pump treatment in Denmark include >7.5% HbA1c, blood glucose fluctuations, hypoglycemic unawareness, needle phobia, and age <6 years. In the Danish Diabetes registry (in 2013), we found that approximately 37% of our pediatric patients achieved the <7.5% HbA1c goal. We also saw that patients using an insulin pump had a lower risk of hypoglycemia.

We recently conducted a study to identify our pediatric patients who positively responded to insulin pump therapy. Positive response was defined as lowering HbA1c by 1.0% or achieving HbA1c <7.5%. Good adherence was defined as seven or more blood glucose measurements and seven or more insulin boluses per day. At 24 months, only 32% of the patients studied qualified as responders; the highest numbers of responders (45%) were children <6 years of age. Frequent daily self-management of blood glucose and bolusing were significantly higher among responders versus non-responders.

We also looked at use of CGM among pediatric patients and found significant differences among the various age groups: 70% for patients 0–6 years old, 50% for patients 6–12 years old, but only 12% among patients >12 years old. Therefore, although we have seen significant improvements in glycemic control in clinical trials with CGM, those benefits can be hard to obtain in real life for teens.

Summary.   Creating a safe atmosphere in patient consultations is essential for obtaining information, especially when talking with teenage patients. It is also helpful to encourage patients and their caregivers to talk about their successes and challenges with diabetes management. This opens up opportunities for problem-solving, and it provides guidance for determining realistic treatment approaches. Clinicians must also make sure that the current treatment regimen is correct and optimized.

It is important that we, as clinicians, identify where our patients are with their diabetes, what their current needs are, and how we can help them to meet these needs. Moreover, we have to make sure that the advice we give makes sense to them. It is also important to emphasize that all blood glucose measures are good because they allow them to take action when needed. Dedicated interaction among the diabetes team, the patient, and patient's caregivers are of outmost importance to ensure a positive collaboration, which is essential for a positive outcome. In summary, we must make every effort to adjust the treatment to the patient, not the patient to the treatment.

The Unveiling of the DAWN2 Study—Understanding the Psychology of Diabetes Can Help HCPs Better Manage Their Patients and Their Disease

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Background.   Ideal diabetes control requires healthcare providers to understand the psychology of the person living with diabetes in order to establish collaboration to aid in the

translation of medical management into behavioral control. Diabetes is not just about medical management; rather, outcomes are achieved through the control that individuals are able to actualize in their lives. Therefore, we need to become comfortable listening to patients, and then we need to have a plan how to go from listening to communicating to negotiating in a way that motivates the individual to do the work that is necessary for change. Our understanding of the obstacles to communication and collaboration was greatly expanded by the DAWN2 study.

The DAWN2 study—Diabetes Attitudes, Wishes, and Needs.. DAWN2 was a multinational study that assessed psychosocial outcomes in people with diabetes ($n = 8,596$),[23] experiences of family members of people with diabetes ($n = 2,057$),[24] and perceptions of healthcare professionals ($n = 4,785$)[25] in 17 countries. The results of the study were reported in 2013.

Among healthcare providers, approximately 63% reported that their patients need improvement in dealing with emotions associated with diabetes.[25] Most healthcare providers indicated that their success in caring for their diabetes patients depends largely on their ability to understand and manage diabetes-related emotional issues; however, <20% reported receiving training in the management of psychological aspects of diabetes. Assessment of physician attitudes about T2D treatments revealed that although only 26% of primary care/general practice and 20% of diabetes specialists would delay starting oral medication, 62% of primary care/general practice and 50% of diabetes specialists reported that they would delay insulin initiation until it is absolutely necessary.

Assessment of the patient participants revealed that rates of depression were twice that of the general population,[23] and this was associated with reduced well-being. Diabetes-related distress (Problem Areas in Diabetes Scale 5 [PAID-5] score ≥40) was reported by 44.6% of participants, ranging from 34% for individuals with T2D treated with diet and exercise to 53% for individuals with T1D. Fear of hypoglycemia was identified as a significant issue among many patients as well.

We also looked at belief systems and how patients approached their care because these issues need to be understood and aligned. Regarding insulin injections, there was obvious misalignment. Although the percentage of people with T2D who would be willing to take insulin (65%) was relatively high, 52% of patients also reported that starting insulin would mean they had failed in their self-management. Thus, starting insulin is perceived as a negative outcome.

Diabetes has a ripple effect; it not only affects the individual living with diabetes but also impacts on family members.. Among family members of non–insulin-treated patients, 61% reported at least one aspect of life had a slight to very negative impact. The finding was higher (69%) among family members of insulin-treated individuals.[24]

Overall, the DAWN2 study showed a clear "disconnection" in terms of how healthcare providers and patients engage with each other. For example, 76% of healthcare providers reported that they encouraged their patients to ask questions "most of the time" or "always,"[25] whereas only 32% of patients reported that their healthcare providers engaged in this behavior.[23]

Empowering healthcare providers. From a psychological point of view, behavior change is a parallel process. Not only do we have to focus on the change in individuals, but healthcare providers need to change as well. We have identified specific skill sets that can facilitate these behavior changes. First, we need to establish relationships that are based on collaboration and empowerment, not on teaching and telling. Then, we need to get to the behavior we are asking patients to engage in. This involves motivational skills, assessing readiness to change and then working with people regardless of where they are on that readiness scale. When the individual is ready, we can then work on behavior modification skills, taking into consideration the psychosocial issues of the person's life. If the individual is not ready, we need to take expectation of change off the table. This does not mean that we give up. Instead it means that we must understand the reasons why the individual is not ready.

Health Belief Model. The Health Belief Model is the strongest predictor of health behaviors, which include seriousness, personal responsibility, and controllability. When a patient is not ready to change, examining his or her health beliefs can become a valuable source of help. If we can maintain a relationship with patients in which we can help them re-examine their health beliefs in a nonjudgmental way, this can be very helpful (e.g., helping the individual with T2D to see that insulin is not a sign of failure but a pathway to control).

When patients become ready, there is a fairly effective strategy around behavior modification. This involves collaborating with patients to set "first-step goals." These goals must be reasonable and attainable by the patient in the immediate context. The next step is called "shaping," which occurs once the patient becomes confident in achieving the first-step goals. Shaping is a very effective means of increasing patient self-efficacy. We then engage in "stimulus control," which involves identifying the cues in the environment that elicit behavior. The last step is "reinforcement management," which is a powerful way of helping patients use incentives while they transition from external motivation into an internal motivation.

Actively Involving the Patient Outside the Doctor's Office Creates Deeper Relationships with the Patient and Increases Patient Engagement

Egils Bogdanovics, Charlotte Hungerford Hospital, Torrington, Connecticut

Background. People with diabetes are expected to maintain vigorous self-management practices to minimize health complications and improve quality of life. Diabetes self-care is especially time consuming, demanding dietary adherence, systematic glucose monitoring, administration of medications, and exercise. Members of our clinic staff frequently wished that they could "live with our patients" for a few days, realizing that spending a weekend together would be more productive in teaching lifestyle modification than brief clinic visits.

"Diabetes Boot Camp." We have engaged patients in a "real life setting" for 3-day weekend retreats at our "Diabetes Boot Camp." These intensive, highly programmed retreats feature lectures, equipment demonstrations,

interactive group sessions, and the development of individualized exercise and meal plans. Staff and attendees share meals and activities. Spouses of participants are invited to attend an afternoon session to review the challenges of both controlling diabetes and living with a person with diabetes.

Prior to each meal a registered dietician explains what the meal will consist of, and insulin doses are calculated accordingly. Exercise includes group walks, yoga, and rowing. On Friday, all participants begin CGM. Throughout the weekend, CGM data are downloaded, and the results are reviewed by the group.

The pilot program in early 2009 focused on persons with T1D with subsequent 3-, 6-, and 12-month evening ''reunions.'' Sessions have alternated between T1D and T2D participants.

Outcomes. Over the years, we have followed several outcomes, including glycemic control, hypoglycemia frequency, exercise frequency, and self-management practices. We have also assessed changes in patient empowerment, using the Diabetes Empowerment Scale Short Form.

Improvements in HbA1c have been seen among both T1D and T2D patients in the first year after attending the program. Even when HbA1c levels did not change, empowerment improved, mostly because of a decrease in the fear of hypoglycemia and improved self-management skills.

Summary. The teaching of diabetes self-care within the constraints of current clinical practice is often limited for time reasons. A weekend away from home enables patients to concentrate solely on their diabetes self-management. Interactions among patients are critical. The entire group benefits from reviewing each other's CGM tracings. Our patients feel empowered and realize that they are not alone. The interactions among people with diabetes (both those ''seasoned'' and those newly diagnosed with diabetes) and staff have led to continued long-term relationships and have benefitted both patients and providers. As providers we felt our ''batteries recharged'' with a renewed sense of job satisfaction.

What Are the Challenges of Implementing Personalized Diabetes Management in the Pediatric Specialist Center?

Henk Veeze, Diabetes Centre for Children and Youth, Rotterdam, The Netherlands

Background. Diabeter is a large independent diabetes specialist center for pediatric and young adult T1D patients. The center currently manages over 1,500 patients at four sites throughout The Netherlands. The team of 36 people practices personalized medicine, making use of specially developed technologies, such as the Diabeter Dashboard, an electronic system that links patient and physician to encourage self-management with diabetes care team support.

Diabeter strives to create a relaxed environment, featuring round tables in consultation rooms to facilitate collaborative interactions between staff and patients. The centers present three evening programs for patients each year to discuss new technologies and approaches.

VCare Diabetes Management System. The Diabeter centers utilize a ''Cloud Care'' model to monitor and assess patient status. Using the VCare Diabetes Management System created by Dr. Veeze, patients upload data from their blood glucose meters, CGM devices, and insulin pumps into the system and then receive a color-coded report on the Diabeter Dashboard within a few minutes after the upload. The system also features a dosing calculator that is based on collected and published data on parameters influencing the required dose. It provides a dosage advice for regular insulin at breakfast and lunch, for rapid-analog insulin at dinner, and for long-acting insulin analog as basal insulin. In essence, the system creates a circle of data that allows clinicians to quickly review patient status and then provide feedback to patients.

Improvements. Since 2006, Diabeter has shown significant improvement in patient HbA1c levels compared with other centers. This is likely due to the continuous exchange of data instead of the usual four patient visits per year. In 2014, almost 90% of patients using sensor-augmented insulin pumps reached their HbA1c goal of <7.5% (<58 mmol/mol), followed by insulin pump alone (approximately 58%) and patients treated with MDI (approximately 47%). Among 90 Dutch clinics, the center has the lowest annual hospital admission rates (<3%). Additionally, Diabeter center nurses can see almost twice as many patients per day as other centers because all administrative tasks have been eliminated from their consults. Through utilization of diabetes management technologies in conjunction with the VCare system, Diabeter has improved the clinical care of its patients and increased its efficiencies.

Understanding and Promoting Adherence to SMBG and Insulin Therapy in Diabetes—Lessons from Interventions to Promote Adherence to Complex HIV/AIDS Drug Regimens

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Role of adherence in diabetes self-management. Adherence is essential to outcomes at every level of diabetes self-management. Suboptimal adherence to SMBG and insulin therapy represents a challenge to individual glycemic control, patient health outcomes, healthcare personnel resources, and the sustainability of healthcare systems. Adherence to SMBG and insulin therapy, it is to be emphasized, is an ongoing behavioral process that requires performance of a complicated series of actions that must be implemented appropriately on a daily basis and maintained over the lifespan of the individual with diabetes. The challenge is that the embedded behavioral demands of self-management adherence in diabetes are complex and often clinically unaddressed.

From the patient perspective, adherence requires, among other things, acceptance of having a chronic disease and acquisition of actionable SMBG and insulin therapy information. Patients also need to master skilled performance of actions including reliable self-cueing of performance of SMBG at appropriate intervals and administering insulin as prescribed in the context of competing daily demands and distractions. Patients need to become skilled in performing these and related self-monitoring and self-management tasks and knowledgeable about the linkage between SMBG and insulin, and they need to learn to think about self-management in relatively positive as opposed to punishing

terms. Much of diabetes education, however, focuses on the pathophysiology of diabetes (e.g., how the pancreas works), and programs often fail to provide patients with "script-like," easy-to-implement information that they can deploy in their personal lives to effectively engage in SMBG and take appropriate insulin therapy action on the basis of blood glucose readings. On examination, much of the information about diabetes self-management presented to patients is completely irrelevant to the specific behaviors that the individual will have to negotiate across the lifespan, although this can, and should, change.

Another missing piece: motivation. In addition to the need to provide patients with actionable information and to strengthen their skills for performance of self-monitoring and self-management actions, people with diabetes must be well motivated to carry out these complex and demanding practices on an ongoing basis. Motivation is composed of elements of *personal motivation* and *social motivation*. Personal motivation to self-monitor and self-manage is based on the individual's expectations about what will happen if he or she undertakes particular diabetes management actions. Social motivation to self-monitor and self-manage is a function of the individual's perceptions of what people who are important to him or her want the individual to do. It is important to note that adherence to SMBG and insulin therapy requires individuals with diabetes to be well informed, skilled in undertaking self-management tasks and behaviors, and well-motivated—and these individuals need to be coached by equally well-informed, well-motivated, and skilled diabetes clinicians and educators.

Motivational interviewing. Motivational interviewing is inspired by the view that strategies that are more persuasive than coercive, more supportive than argumentative, and, critically, generated by patients themselves are most likely to incline patients to act. The overall goal of motivational interviewing is to increase the patient's intrinsic motivation so that change arises from within rather than being imposed from without. The motivational interviewing approach can move forward in the clinical setting on the basis of two key questions: How *important* does the patient consider specific aspects of his or her self-management—and *what would have to happen to make the self-management action more important*? and How confident does the patient feel in his or her ability to perform each self-management task—and *what would it take to increase his or her confidence about undertaking self-management actions effectively*? These questions can be posed in clinical education conversations to strengthen patient motivation to act and can be supplemented by coaching to provide script-like information and skilled self-management implementation.

LifeWindows is a personalized, interactive, software-based adherence promotion intervention, inspired by motivational interviewing principles, that was designed to strengthen antiretroviral adherence among individuals with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), and looking to the future, it is applicable to diabetes self-management. In its current iteration, the HIV/AIDS patient interacts with the program while he or she is in the clinician's waiting room. In that interaction, the program assesses the patient's information, motivation, and skills with respect to medication adherence. It then guides the patient to interact with one of 21 highly engaging, interactive interventions to strengthen his or her information, motivation, or skill with respect to medication adherence. At the end of the interaction, while the patient is still in the waiting room, he or she and the program mutually agree on a small but—critically—achievable adherence goal. It is further "agreed" that the patient will interact with the program again in 2 months at the return clinician visit. This is an intervention that never ends—and it also works. Over a 2-year interval, LifeWindows was able to strengthen adherence to complex, toxic, antiretroviral medications at ≥90%, whereas other individuals in controlled conditions simply faded. Moving forward, development of software-based information, motivation, and behavioral skills coaching to strengthen adherence to SMBG and appropriate insulin therapy may be an efficient and cost-effective addition to our efforts to empower people with diabetes to manage their condition.

Summary. Adherence to SMBG and insulin therapy requires performance of a complex series of behaviors that must be enacted appropriately and maintained over the lifespan of the individual with diabetes. Script-like information, motivation to act on it, and behavioral skills for acting effectively are essential for adherent self-management. Systematic assessment of adherence to recommended patterns of SMBG and recommended insulin routine should become standard of care as should efforts to ensure that patients are well informed, well motivated, and skilled at implementing these self-management practices. Motivational interviewing, guided by suggested clinical questions, is a practical means of strengthening adherence to diabetes self-management. Motivational interviewing facilitates patient identification of "*what it would take*?" to strengthen adherence. Software-based motivational interviewing methods and other technological developments (meters that inform, motivate, and up-skill patient adherence) are aspirational targets for future development.

Further information can be found in articles by Fisher et al.[26,27]

Smart, Smarter, Smartest—The Increasing Interdependence Between Medical Devices and Consumer Electronics

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Overview. We are experiencing the start of an era where we will use wearables during day-to-day activities on a large scale. New devices to monitor fitness, to provide entertainment, and other applications are moving very quickly from research laboratories to the market.

The history of wearables started at the Massachusetts Institute of Technology in 1955 with the development of the "roulette" computer, a device that predicted roulette wheel behavior in casinos. More recently, we have developed devices that use skin conductance to measure physiological arousal that can be used in several scenarios, ranging from self-feedback for stress management to visualizing mass excitement levels in performance situations. In the future, we can expect the number of wearable devices to grow. This is especially true in the medical space, which is considered to be one of the fastest expanding application domains for wearables.

Medical application. The boundaries between consumer and clinical device markets are becoming leaner every year. This trend is driven by several factors, including consumer demand for ubiquitous and constantly accessible healthcare, increased presence of chronic conditions (such as high blood pressure, diabetes, depression, and obesity) and a corresponding need for preventive healthcare, an increasingly aging global population, availability of cost-effective, wearable technology, and remote access to storage and computation resources. Although this trend facilitates opportunities for providing healthcare services to larger populations at lower cost, it will also pave the way to personalized medicine where prevention, diagnosis, and treatment of a disease can be tailored to individuals' characteristics and behavior.

Issues and concerns. The growth in this transformation has raised several challenges for users, clinicians, regulatory bodies, and device manufacturers. Patients who have difficulties understanding the technical details of their devices can often be misled by wearable providers. This may cause patients frustration and, sometimes, aggravation of their health problems, especially if they continue using the unreliable device for treatment instead of relying on professional health support. An additional issue for the users is lack of data privacy. Very often, startup manufacturers place a low priority on the security of their products. As a result, their products are exposed to risks, such as identity theft, profiling, stalking, embarrassment, extortion, and corporate misuse.

Moreover, clinicians will get questions from patients about the reliability of the wearables, and they will have difficulties finding answers about products. Additionally, it is difficult to evaluate and compare capabilities of different devices as manufacturers often are not providing any scientific proof validating their claims about the medical performance of the wearables. These devices also generate large volumes of around-the-clock-data, which are very often difficult to process and contain artifacts.

From a regulatory perspective, the challenges are also significant. Regulatory bodies such as the FDA and the European Medicines Agency (EMA) will have difficulties defining and classifying the electronic devices that are required to obtain approval prior to commercialization. Although the notion of enforcement discretion provides flexibility to the FDA as it continues to fine-tune its regulatory policy, it also creates uncertainty about what applications might be regulated in the future. This uncertainty has prompted many medical wearable providers to pursue a commercialization path without obtaining FDA approval and often overclaim the capabilities of their products. This, in turn, places the larger, regulated healthcare device manufacturers at a significant disadvantage because they are required to follow a very lengthy approval process. Because the product life cycle is much more dynamic and shorter for the consumer electronic markets, the technology developed by the regulated manufacturers may be out of date by the time they have gained approval.

Ongoing research. Working in collaboration with experts from Harvard University, Massachusetts General Hospital, Brigham and Women's Hospital, and others, we are launching several longitudinal clinical studies. One such study is focused on identifying predictors related to health and well-being and economic performance from daily-life data. In this study, we are monitoring 50 students, 24 h/day, for eight semesters to collect data on their physiological activities, sleep, and contextual data, using wearables from our group and mobile phones.

In another project, we are following more than 300 depression patients treated with medication, psychotherapy, electroconvulsive therapy, or transcranial magnetic stimulation. Over 8 weeks of treatment, we are following several parameters, including physiological signals (using wristbands), sleep characteristics, voice characteristics, phone usage, and questionnaires. Results from this study will be published in the near future.

We Are Not Waiting—How ePatients Can Take Medical Devices (and Health Care) to the Next Level

Doug Kanter, Databetes, New York, New York

Background. I am here, first and foremost, as a patient. I was diagnosed with T1D in 1986. I went on my first insulin pump in 1987, and, in 2010, I went on my first CGM device and immediately loved it. Just having more information was a huge benefit to me. Yet, it was also a time of mixed emotions. Around that time, I had my first diagnosed microaneurysm on my retina. I ended my photography career in Beijing, moved back to New York, and enrolled in the Interactive Telecommunications Program (ITP), a 2-year graduate program at New York University, where I studied interaction design, data visualization, and user experience.

My main focus was Databetes, which started as a personal project exploring my own medical data. ITP is all about prototyping, and I used my data as the basis for several projects. Throughout 2012, I kept track of every diabetes-related data point in my life. I started with all of my different medical devices and scrapped the data, but I also used a variety of different wearables. I kept a Google Docs spreadsheet of every single food I ate, took hundreds of pictures of my food and moved them to Flickr, tracked my location with some open source software, and tracked all my activity with RunKeeper. I believe that what allowed me to improve this much was that I had built a better feedback loop for myself. I also really believe in the power of lifestyle data such as food and exercise in particular.

Databetes is now a commercial software company, and we are applying the lessons learned to try to help other patients as well. Our first app is called Meal Memory, which is designed to be a simple and faster way to record a meal. Users first take a photo of their meal and then enter the CHO count and premeal glucose. Two hours later, they receive an alarm, reminding them to enter a postmeal glucose reading. All of the readings are color-coded as high, in range, or low, and then they're laid on top of the photos. We are now in the process of launching a new version of this software, which is integrated with Apple Health.

One of my biggest frustrations has always been the siloed data, that I could not get my data from different devices together in one place. As a developer working in this space, I became involved with the We Are Not Waiting movement.

We Are Not Waiting. We Are Not Waiting started at a diabetes conference with other developers. Most members either have T1D or are parents of children with T1D. As the name implies, we are frustrated with the delays in the market.

Although we are interested in designing our own solutions, it is difficult to do this without open access to data.

To address this issue, we are leveraging the fact that most of us are patients. As such, we are working to put pressure on device manufacturers to allow us open access to our own medical data. We are also advocating for the development of standards for data formatting and interoperability in order to facilitate our own product development efforts regardless of the device we are using. Additionally, we are pressuring the FDA to reexamine their restrictions on releasing data. The role that We Are Not Waiting imagines is one that replaces the traditional vertical system (where each company builds within its own silo) with a standardized data exchange that allows companies like mine to build on top of those data, and to serve as a pathway that allows other developers to build on top of it.

One of the most well-known examples of the organization's efforts is the "Night Scout" or "CGM in the Cloud" project. The project was developed by parents of a T1D child who figured out how to hack their child's Dexcom CGM system, hook it up to an Android phone, and send the data up into the Cloud. This allowed the parents to remotely monitor the child's glucose throughout the day and night, which gave them greater peace of mind.

We have also seen some response from the FDA. Recently, they announced that they are going to deregulate some of the health data out there, specifically, much of the retrospective data that are a few hours old and cannot be used for real-time decision support. This is very encouraging, especially for start-up companies that may then have a lower regulatory burden and do not have to raise as much money to get user data.

What we see going on in the We Are Not Waiting movement is a reflection of what is occurring across all of health care. The do-it-yourself movement has finally come to health care with so many sensors now being available, all the different wearables, and, obviously, the smartphones.

Two people who saw the potential of where all this was going are Gary Wolf and Kevin Kelly, who are both editors at *Wired Magazine*. In 2007, they proposed a collaboration between users and toolmakers who share an interest in self-knowledge through self-tracking. And this gave birth to the Quantified Self movement, which is organized around meetups where people who have done first-hand experiments in self-tracking discuss their projects, touching on three main points: What did you do? How did you do it? What did you learn?

Each project is very different as are the people who did them. Everyone brings a different set of skills to their project, and I am really excited to see where this movement goes in the future.

SineDie Study—Safety and Effectiveness of a Smart Telecare System for Gestational Diabetes

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Background. Pregnancy is characterized by insulin resistance and hyperinsulinemia, and it may predispose some women to develop diabetes. Several adverse outcomes have been associated with gestational diabetes mellitus (GDM), including fetal macrosomia and neonatal hypoglycemia.

It has been demonstrated that detection and treatment of GDM significantly reduce the risk of these complications. However, convincing institutions to adopt the established guidelines for GDM diagnosis and treatment has been problematic. The expected increase in expenses required for adherence to these guidelines appears to be the major obstacle.

The Endocrinology and Nutrition Department of the Sabadell Hospital, in cooperation with the Polytechnical University of Madrid, has developed a computer-based smart telemedicine system, SineDie, to give support to GDM patients before insulin is required. The system combines a platform for remote monitoring of diabetes-related parameters with an artificial intelligence system based on expert knowledge, which generates automatic feedback to patients.

The SineDie system. The SineDie system performs automated modifications of the prescribed diet to correct hyperglycemia or ketonuria. The system also identifies situations that require the initiation of insulin therapy.

To use the system, the patient downloads data from her blood glucose meter to the computer, which classifies the glucose measurements according to a defined decision tree. Once the patient receives this first classification, she can then relocate some values if the classification has not been accurate. However, this happens with only 1.3% of the values. The patient then inputs the value of ketonuria if it has been positive and if she has eaten a high amount of CHOs. Analysis of this information prompts one of four possible responses via text message: (1) it can be assumed that all information is correct; (2) we do not have enough information for data analysis; (3) diet has to be modified; or (4) insulin is needed.

If the system detects a certain degree of repetitive hyperglycemia or positive ketonuria, an automated proposal for diet modification is sent to the patient without any intervention by an HCP. However, if the system also detects that insulin therapy should be initiated, it then notifies the HCP along with recommendations for the insulin type and insulin dosage. The patient receives a text message explaining the new situation and that a medical appointment has been scheduled. With the system, we can view a list of all the patients with information about their status. We can also see if the patient has seen the change in the treatment and confirm whether she has made the prescribed changes.

System evaluation. We are currently conducting a randomized, controlled study involving 120 women with diagnosed GDM. In the study, patients in the SineDie arm are asked to perform glucose testing four times per day and download their data every 3 days; the control group continues their weekly face-to-face clinic visits (usual care).

Preliminary data from our interim analysis (SineDie, $n = 43$; Control, $n = 26$) showed very positive acceptance and use of the system. SineDie patients performed glucose testing 3.9 ± 0.3 times per day and downloaded their data every 2.9 ± 1 days. The system modified the diet automatically in 18 cases and recommended insulin therapy for 52% of patients. System recommendations were accepted 82% of the time; however, actual initiation of insulin was delayed at 44% of the clinic locations. Neonatal outcomes were similar between the study groups. Patient questionnaires showed high satisfaction with the system.

Summary. Interim analysis showed that the SineDie system allows GDM patients treated with diet therapy to minimize the number of face-to-face visits while being followed in a safe and efficient manner. If these results are confirmed in the final analysis, we assume that these findings will facilitate more widespread implementation of the evidence-based GDM diagnosis criteria.

The Burden of Knowledge—Liability of HCPs in the Field of mHealth

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Background. We have seen significant advancements in mobile technology and connectivity over the last several decades. Smartphones have now eclipsed personal computers (PCs) as the major computer source, and the market is continuing to grow as PCs are flattening out. Today, individuals spend more time looking at a smartphone screen than any other screen available. Although the utilization of mobile telecommunication technologies for the delivery of health care (mobile health [mHealth]) is still in its earliest stages of development, the evidence supporting its potential to impact the delivery of care, to improve outcomes, and to lower costs is apparent.

Currently, there are no guidelines to determine the scope of a physician's liability if he or she causes harm due to faulty or inaccurate information from a mHealth app or device. Similarly, there are no guidelines regarding the standard of care required of healthcare systems that promote certain apps to patients. However, as health apps become more prevalent, standards of care for their use will likely begin to emerge.[28]

Liability. Liability requires proof that a physician owed a duty of care to a patient and deviated from it, with the patient being injured as a result. The first step in limiting liability is the recognition, on the part of both the patient and the provider, of the services being provided and the level of risk of the condition and individual being monitored. Thus, the incorporation of mHealth technology by physicians would not significantly alter the malpractice liability landscape any more than would the adoption of any other types of technology that practitioners have already adopted. For the patient, the traditional physician–patient relationship is based on direct contact and care. If a patient were to provide the physician with inaccurate information, a form of contributory negligence, the liability of the doctor's liability would, or at least should, be substantially limited.

Privacy. Legal protections of privacy have been unable to keep pace with the changing technological landscape. The Health Insurance Portability and Accountability Act privacy rule applies only to "covered entities," which include providers, health plans, and clearinghouses; it does not cover consumers who are using apps outside the healthcare setting. If a consumer voluntarily downloads software, any data extracted are not considered unauthorized and therefore not protected by the Computer Fraud and Abuse Act.[28]

Of the 600 most commonly used mHealth apps, only 183 had privacy policies. Moreover, consumers' understanding of these policies is questionable. The average length of the privacy policy was 1,755 words, ranging from 65 to 6,424, and the average reading grade level was at the college level.

Data security. The greatest current source of security breaches in healthcare data is through lost/stolen devices. With increased use by practitioners of smartphones and tablets for patient care, there will be an increased risk of security breaches.

Licensure. The issue of licensure must also be considered because the use of several different health apps can involve the cross-jurisdictional practice of medicine. Because licensure is left to state governments, there are over 50 different licensure requirements in the United States, making it difficult and often illegal to provide care across state borders.

Summary. Extraordinary advancements in mobile technology and connectivity over the last several decades have provided the foundation needed to dramatically change the way health care is currently practiced. However, in order for mHealth to achieve its potential, users need to be confident that their data are being delivered to a trusted source that will review and respond appropriately as close to real time as possible. How this can be accomplished and what the liability is of the receiving provider are currently unknown. Little or no legal precedent has been established for mHealth technology and its oversight.

Increase in Prevalence of Type 1 Diabetes—New Insights

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Background. The incidence and prevalence of T1D are increasing worldwide. Moreover, T2D is occurring in younger patients. Several hypotheses have been put forward to explain these observations.

"Accelerator hypothesis." One hypothesis that attempts to explain the increasing incidence of T1D is the "accelerator hypothesis," which links the increase in incidence of T1D and T2D to the same cause, namely, the increasing obesity.[29,30] The hypothesis proposes that the increasing BMI of children, as part of the increasing BMI of our entire population, somehow accelerates the immune process of autoimmune destruction of β-cells. This acceleration could be due to the fact that when children are obese, their β-cells are more active, which renders them more susceptible to autoimmune destruction because a higher percentage of β-cells must be recruited from precursor cells.

In a Finnish study, investigators saw a strong correlation (0.87) between BMI and incidence of T1D,[31] and the 1970 British Birth Cohort showed that the BMI at 10 years of age was predictive of future development of T1D.[32] However, data from other countries have not shown this relationship. Therefore, although the "accelerator hypothesis" may have support in some countries, it does not fully explain the increasing incidence of T1D.

Possible relationship with infant diet. Studies have looked at the association between breastfeeding and risk of developing T1D; however, it is difficult to differentiate whether this is due to a potential protective effect of breast milk or detrimental effect of cows' milk. A pooled analysis of a subset of observational studies included in a 2012 meta-analysis suggests

weak protective associations between exclusive breastfeeding for at least 2 weeks and T1D risk.[33] Among the included studies that compared breastfeeding with no breastfeeding, the association was not as significant.

In a recent study in which investigators tested the hypothesis that weaning infants to an extensively hydrolyzed formula decreases the cumulative incidence of diabetes-associated autoantibodies in young children, no reduction in the incidence of diabetes-associated autoantibodies was seen after 7 years.[34]

We know that T1D is associated with celiac disease and that the association is greater than with other autoimmune diseases. Therefore, there is an interest in the possible relationship between early gluten exposure and predisposition to T1D. A recent study showed that delaying gluten exposure until 12 months of age does not substantially reduce the risk for islet autoimmunity in genetically at-risk children[35]; however, an earlier study showed that there may be a window of exposure to cereals in infancy (within the first 4–6 months) outside of which initial exposure increases islet autoimmunity risk in susceptible children.[36] This suggests that the later study, which looked at exposure at 6 months or 12 months, may not have had optimal timing.

Asthma and atopic eczema. We know that both T1D and asthma have an immune component and that the incidence of both is increasing. A study by Fsadni et al.[37] showed that the incidence of T1D had a positive correlation with both wheezing and atopic eczema; however, there was no correlation between the incidence of T1D and the prevalence of rhinitis or rhinoconjunctivitis.

There are several chemicals that are associated with risk of T1D. Among them is ground ozone, which is also associated with asthma. Thus, ozone, which is a pollutant that is increasing in many regions, may explain the relation at the country level between asthma and T1D and why both are increasing.

Bacterial exposure. A recent study found significant negative correlations between the incidence of T1D and mortality for all infectious diseases studied.[38] There were also significant positive correlations between the incidence of T1D and antibiotic susceptibilities of *Streptococcus pneumoniae* (causing pneumococcal disease) but not to those of *Haemophilus influenzae* (causing many kinds of serious infections). Because infectious disease mortality and antibiotic susceptibility are surrogate markers for bacterial exposure, these results provide support for a negative association between bacterial exposure in a community and its incidence of T1D. We also know that antibiotics can play a role because heavy exposure to antibiotics will decrease bacterial exposure and possibly have an effect on the gut microbiota. This effect can be either protective or detrimental, depending on the timing and which antibiotics are used.

Altered gut microbiota. Several factors, such as obesity, ozone, lack of bacterial exposure, and even cesarean section, increase the risk of T1D. Most of these factors are increasing in many parts of the world, and all may result in changes in the gut microbiota. Whether the relationship between these factors and T1D can be explained by altered microbiota is unknown. We have no studies to show a causal effect, but we do know there is an association.

Summary. T1D is caused by an interaction between genetic and poorly identified environmental causes. As genetic factors are relatively stable over time, the increase in T1D can only be explained by environmental changes experienced over the last few decades. However, the environmental factors predisposing to T1D are poorly and incompletely understood, making our quest to determine the mechanisms of the increasing prevalence of T1D more difficult. Epidemiological and ecological studies may help to provide some insight into possible mechanisms.

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