MEETING REPORT

5th Annual Symposium on Self-Monitoring of Blood Glucose (SMBG) Applications and Beyond, May 3–5, 2012, Dublin, Ireland

Hilary Hoey, M.A., M.D., FRCPI, FRCPCH UK,^{1,2,*} Anita Mlinac,³ Cam-Tuan Tran, M.D.,⁴ and Christof Schlaeger, Ph.D.⁴

INTERNATIONAL EXPERTS in the fields of diabetes, diabetes technology, endocrinology, and pediatrics gathered for the 5th Annual Symposium on Self-Monitoring of Blood Glucose (SMBG) Applications and Beyond. The aim of this meeting was to continue setting up a global network of experts in this field and provide an international platform for exchange of ideas to improve life for people with diabetes. In line with previous editions, the 2012 meeting comprised a comprehensive scientific program, parallel interactive workshops, pros and cons debates, and a keynote. All these discussions were intended to help identifying gaps and areas where further scientific work and clinical studies are needed.

Opening Lecture: News from the World of Diabetes

Satish K. Garg, University of Colorado Denver, Aurora, CO

In his opening lecture, Satish Garg focused on some of the perspectives on tomorrow's technologies and how they might shape diabetes care in the upcoming years. Diabetes prevalence is rapidly rising. Although it was expected in 2009 that by the year 2030 there will be 300 million people with the disease, today's expectations estimate more than half a billion people will suffer from diabetes by 2030, accounting for a significant increase in both type 1 (T1D) and type 2 (T2D) diabetes. Accordingly, Garg sees a "need to predict for the next 3–5 years rather than decades." Most of the increase involves new cases of T2D, which may increase up to 5% per year. Nevertheless, the International Diabetes Federation (IDF) reports there is also a significant increase in T1D. We don't know if this increase is a cause of unrecognized type 1 entity or some changes in the genetics and the autoimmune milieu, Garg stated. Undoubtedly, these increases in prevalence go along with increasing healthcare costs. Ninety percent of today's cost of diabetes care goes toward caring for compli-

cations of the disease, not really caring for the disease itself. It should be the goal to spend 90% of the cost in caring for the disease today so that we can save to care for the complications.

The Type 1 Diabetes Exchange is an ongoing observational study in the United States that has been sponsored by the Leona Helmsley Trust. The purpose of this network is to improve outcomes for adults and children with T1D by providing a launching point for new clinical research and improving clinical management of the disease. Up to now 25,000 people with T1D have been enrolled. An analysis of the incidence of severe hypoglycemia per 100 patient-years revealed that that severe hypoglycemia has become significantly less frequent in the younger T1D population (up to 25 years) compared with the rates of severe hypoglycemic episodes that were reported 30 years ago in the Diabetes Control and Complications Trial (DCCT) study. However, it appears that we still have a long way to go, in particular when focusing on older patients with T1D who are living much longer nowadays, which implies a relation to hypoglycemia unawareness that is significantly more frequent in the older age groups (≥ 50 years). It is interesting that the Type 1 Diabetes Exchange did not make any association between overall glycemic control in terms of glycated hemoglobin (HbA1c) values and rate of severe hypoglycemia, which is in contrast to the learning from the DCCT trial.

Do these people check their SMBG at home, and does it matter whether they check? Data from 67 leading centers in the United States indicate that the majority of enrolled people with T1D performed three to six SMBG tests per day. Irrespective of the age group or the kind of therapy, a higher SMBG testing frequency was consistently associated with a lower mean HbA1c concentration.

Fasting plasma glucose and early treatment. Early initiation of treatment still appears to be the key to an effective

¹Diabetes Ireland, Dublin, Ireland.

²Faculty of Paediatrics, Royal College of Physicians of Ireland, Dublin, Ireland.

³Adecco Human Resources GmbH, Mannheim, Germany.

⁴Roche Diagnostics GmbH, Mannheim, Germany.

*President Elect, European Society for Paediatric Endocrinology.

treatment of T2D. Recent data¹ from the research group of Matthew Riddle published in *Diabetes Care* show that if treated early enough, the majority of people with T2D can reach a target HbA1c $\leq 7\%$. If basal insulin therapy with insulin glargine was initiated in people with T2D and oral anti-diabetes therapy at an HbA1c concentration of 8%, 75% of the patients reach the target HbA1c $\leq 7\%$ after 24 weeks. In contrast, if basal insulin initiation is initiated later at HbA1c concentrations of 9.5% or larger, only 34% of the patients reach target HbA1c. Although baseline HbA1c did not affect incidence of severe hypoglycemia, it appears that patient behavior is more relevant in this respect.

ORIGIN is a large global trial study investigating whether the provision of sufficient basal insulin to normalize fasting plasma glucose levels may reduce cardiovascular events compared with standard care. The study population of 12,537 people (mean age, 63.5 years) with cardiovascular risk factors plus impaired fasting glucose, impaired glucose tolerance, or T2D have been randomized to receive insulin glargine (with a target fasting blood glucose [BG] level of ≤ 95 mg/dL [5.3 mmol/L]) or standard care and to receive ω -3 fatty acids or placebo with the use of a 2 $\times$ 2 factorial design. Garg highlighted that the baseline HbA1c of 6.5% in ORIGIN is remarkable lower than in the last recent cardiovascular outcome trials Action to Control Cardiovascular Risk in Diabetes (ACCORD), Veterans Affairs Diabetes Trial (VADT), and Action in Diabetes and Vascular Disease: Preterax and Diamicon-MR Controlled Evaluation (ADVANCE); however, the baseline rate of macrovascular complications was highest in ORIGIN. This underlines that this trial focuses on early stages of diabetes associated with a high cardiovascular risk. The final results were presented at the 72nd Scientific Sessions of the American Diabetes Association (ADA) in Philadelphia, PA.²

Glucose variability. Are there any new data that support the importance of glycemic variability as a cardiovascular risk factor? Garg recalled a recently published analysis of the A1c Derived Average Glucose (ADAG) study suggesting that mean glycemia and HbA1c show consistent and stronger associations with cardiovascular risk factors than fasting glucose, postprandial glucose levels, or various measures of glucose variability in people with diabetes.³ It is important to note that we have powerful options to reduce glycemic variability. By analysis of data from continuous glucose monitoring (CGM) devices in insulin-treated adolescents with T1D, it could be shown that insulin glargine reduced glycemic variability, measured as the mean amplitude of glycemic excursion (MAGE), significantly better than NPH/lente insulin over a 24-week period. Garg stated that unblinded or real-time (RT)-CGM has the potential to significantly reduce glycemic variability and therefore can be seen as "behavior changers." Is there a link to oxidative stress markers? The only available data on this topic from Louis Monnier and co-workers⁴ argue that MAGE may be directly related to markers of oxidative stress, a relationship that is particularly seen in T2D. The ongoing Flat Sugar study in the United States is aiming to further investigate these associations in the short term in T2D.

CGM. Data from the Type 1 Diabetes Exchange network have shown that the percentage of CGM users among these insulin-requiring patients is still low, particularly in the pediatric age group. In fact, there are a lot of supporting data

today showing that, irrespective of the age group and how often the devices are used, if they are used more frequently, a beneficial effect on HbA1c is observed: "We are at a crossroads right now, just like we used to be with the SMBG." According to Garg, CGM provides similar benefits in glucose control for people with T1D using multiple daily injection (MDI) or continuous subcutaneous insulin infusion (CSII) therapy. He presented results from a small prospective study he and co-workers did in Denver for which 60 people with diabetes (30 on MDI and 30 on CSII therapy) were instructed to use CGM over a period of 6 months. Without any significant therapy change, the HbA1c decrease at 12 weeks was similar in both groups. Although evidence for CGM use in T2D is still scarce, intermittent use of CGM has been proven to be beneficial over conventional SMBG in a large study performed by Bob Vigersky and co-workers.⁵

Discontinuation of CSII therapy within the first year is a severe challenge. The Type 1 Diabetes Exchange network told us that about 55% of the enrolled population was using an insulin pump. This distribution is most probably not representative of the general U.S. T1D population, in which Garg assumes one out of five people to be an insulin pump user. He expressed his concern that on average one-third of the patients actually reported sending their pumps back to the manufacturer in the very first year after initiating pump therapy.

Sensor-augmented pump therapy in T1D. The STAR-3 trial is one of the most prominent trials investigating the use of sensor-augmented pump (SAP) therapy in people with T1D. For this trial, study subjects were randomized into two groups receiving either MDI therapy or SAP. The main outcome of STAR-3 was that over the duration of 1 year and of all age groups analyzed, the SAP group experienced significantly better glycemic control in terms of HbA1c compared with the MDI group.

Low glucose suspend (LGS) is a safety feature that has been approved in Europe. Food and Drug Administration (FDA) approval in the United States is still pending. That's why the In-clinic Automation to Simulate Pancreatic Insulin Response (ASPIRE) study was performed, the first and largest trial investigating the safety and efficacy of LGS in the United States. ASPIRE provided proof that the use of LGS is effective in terms of reducing duration and severity of induced hypoglycemia and safe as no significant rebound hyperglycemia was observed, stated Garg, who is the first author of one of the articles that have been published⁶ on this trial.

Nocturnal hypoglycemia remains a significant problem in people with T1D. Several studies have investigated experimental overnight closed-loop systems to address this medical need. Currently available data indicate that these systems can potentially reduce the risk of nocturnal hypoglycemia compared with state-of-the-art open-loop therapy in people with T1D.

New basal insulin is awaiting approval. Insulin degludec remains a promising new basal insulin that has been submitted for FDA approval. It is noteworthy that insulin degludec with once-daily dosing provides glycemic control comparable to that with insulin glargine; however, it appears to be consistently associated with less hypoglycemia in people with T2D as well as T1D. In particular, nocturnal

hypoglycemia is significantly less frequent with insulin degludec therapy.

Garg concluded his talk with the notion that, despite all advanced technologies and therapies available, high rates of suboptimal glycemic control as well as severe hypoglycemia remain the biggest challenge. It is his hope that treatments, in particular the closed-loop system, will help us to reduce the rates of hypoglycemia in the future. Reviewing data from studies like the Type 1 Diabetes Exchange and many other studies, it appears to him that using insulin pumps and CGM effectively lowers HbA1c levels, decreases hypoglycemia, lowers glucose variability, and may be weight neutral, and thus early closed-loop trials that are ongoing are the right path to go, at least regarding people with insulin-requiring diabetes.

Demonstrating the Clinical Value—Summary of Important Studies Around Structured Testing

Matthias Axel Schweitzer, Roche Diabetes Care, Mannheim, Germany

What is the mode of action of BG meters? BG meters obviously do not have a direct mode of action (MoA) but simply provide information on BG concentrations. This glucose information consequently needs to be transferred into a medically meaningful therapy decision and action. Taken together, glucose information and medically meaningful therapy decision and action, it is hoped resulting in improved glycemic control—that is the MoA of BG meters.

There is a positive correlation between BG testing frequency and glycemic control. “How do MoA of BG monitoring and correlation between BG testing frequency and glycemic control fit together?” Schweitzer asked the audience. In his view, the element of automation is a key area where manufacturers of medical devices can support the successful use of glucose information and contribute to a more successful disease management. He referred to the example of implementing an automatic bolus advisor in a BG meter that turned out to improve glycemic control in people with diabetes not achieving optimal glycemic control on MDI therapy. The concept of automated bolus calculation was first tested in a “proof-of-concept” study using a separate medical device, not yet embedded in a BG meter or an insulin pump. Later, when the concept was proven to be of value for the patient, the automated bolus calculator was implemented in a BG meter. A large study with more than 200 enrolled people with diabetes, the so-called ABACUS study, is currently ongoing in Germany and the United Kingdom, aiming at analyzing the efficacy and usability of this product. First data from the ABACUS study will be presented at the European Association for the Study of Diabetes (EASD) later this year.

To be most effective, SMBG should be performed in a structured format. Having introduced the concept of automation in terms of bolus calculation, Schweitzer asked how glucose information could be used to manage non-insulin-treated T2D. To provide an answer, Roche Diabetes Care (Mannheim, Germany) has introduced the concept of Structured Testing, which intends to guide people with diabetes and their treating physicians to attain the best glucose information possible by providing the testing algorithm, having the correct analysis of the data from glucose information, the correct diagnosis, and finally support to take the appropriate

action. The IDF also recommends a kind of Structured Testing in their 2009 “Guideline on Self-Monitoring of Blood Glucose in Non-Insulin treated T2D.”⁷ Although the IDF recommends various daily profiles, like testing in pairs, Roche Diabetes Care developed a comprehensive Structured Testing approach with a seven-point BG profile on three consecutive days, the Accu-Chek® 360° View 3-day Profiling Tool. Since 2009, significant numbers of Structured Testing studies have been performed, for example, the STeP Study in the United States and the PRISMA Study in Italy. Although the testing algorithms used differ in terms of the BG measurements taken per day, the principle of structured rather than random testing is what they all have in common. As a consequence, all these studies reported significantly improved diabetes outcomes and improved care of patients.

SMBG is an established practice for patients with T2D and to be most effective, it should be performed in a structured format. That is the conclusion of a recent review on the current role of SMBG in non-insulin-treated T2D published⁸ in the *Journal of Diabetes Science and Technology* last year. Talking about MoA, it is important that we are able to explain the observed added medical value of Structured Testing. The Structured Testing Protocol (STeP) Study proved that people in the Structured Testing arm of the study had significantly more medication or lifestyle changes at any clinical visit. Consequently, more people in the Structured Testing arm started a therapy with insulin compared with the control arm. A very similar picture can be drawn from the Prospective, Randomized Trial on Intensive Self-Monitoring Blood Glucose Management Added Value in Non-Insulin Treated Type 2 Diabetes Mellitus Patients (PRISMA) Study.

Schweitzer closed his talk by concluding that regarding the role of SMBG in current diabetes management, today there is substantial evidence to support that

- the MoA of SMBG is well understood and is to transfer glucose information into a medically meaningful therapy decision and action.
- SMBG is mandatory to achieve and maintain good glycemic control.
- SMBG testing frequency is positively associated with improvement in glycemic control.
- Structured Testing provides added medical value compared with random BG testing without increasing the frequency of testing.
- Structured Testing makes SMBG cost efficient.
- Different Structured Testing algorithms can be applied according to local medical practices and individual patient preferences.
- Structured Testing can be applied to all people with diabetes, T1D and T2D, non-insulin- as well as insulin-treated.

How Would You Decide? Results of the DECIDE Study and Interactive Case Studies

Helena Wachslicht Rodbard, Endocrine and Metabolic Consultants, Rockville, MD Oliver Schnell, Diabetes Research Institute of the Diabetes Research Group, Helmholtz Center Munich, Munich, Germany

In this interactive session, Helena Rodbard and Oliver Schnell presented the results of the DECIDE study as well as a

selection of case examples. Attendants of the meeting had the opportunity to interact via a TED system at certain points of the presentation.

"Collecting data can be very frustrating from a patient's point of view, especially if the physician or clinician does not act upon the numbers. Obviously as it becomes frustrating, patients give up monitoring the blood glucose levels, and eventually their control deteriorates and that all contributes to inertia," Rodbard described one of the key obstacles for patients to stay compliant with common SMBG recommendations. However, there are ways to change this paradigm and empower patients as well as their physicians to use SMBG appropriately and consistently.

Clinical inertia or "treat to failure" is very common among clinicians. Today, mixed data regarding the benefits of SMBG exist from a variety of studies. Although some studies have shown SMBG to be an important component of diabetes management, others showed little or no benefit. According to Rodbard, this is not much of a surprise—when people with diabetes and their treating physicians do not act or are not able to act upon BG information, it's not going to be of any benefit. More recent studies have shown benefits in glycemic control, improving and changing health behaviors, and more timely and persistent treatment intensification. The STeP Study was one of these studies. Beneficial effects on glycemic control were achieved just by a simple paper tool: monitoring BG levels on three consecutive days. At the end of a year, there was a 0.5% reduction in HbA1c in favor of the Structured Testing algorithm, as a result of treatment intensification. It happened very early, even in the first month, Rodbard explained.

The purpose of the virtual, online DECIDE study was to evaluate the impact of an automated decision support tool (DST) on clinicians' ability to identify glycemic abnormalities in structured SMBG data and make the appropriate therapeutic changes based on the glycemic patterns observed. Therefore, 288 U.S. healthcare professionals (HCPs) (approximately 40% primary care physicians, 40% family practitioners, and about 20% nurse practitioners and/or physician's assistants) were equally randomized into four groups receiving either

- structured BG monitoring data from the Accu-Chek 360° View paper tool (Structured Testing Group [STG])
- structured BG data from the 360° View paper tool together with printed reports from the DST (DST group)
- structured BG data from the 360° View paper tool together with the an educational DVD how to interpret the structured BG data (DVD group)
- structured BG data from the 360° View paper tool together with a combination of DST reports and educational DVD (DST + DVD group).

The cases depicted different BG patterns, fasting hyperglycemia, preprandial hyperglycemia, bedtime hyperglycemia, hypoglycemia, postprandial excursions, and normoglycemia. HCPs were asked to identify the primary glycemic abnormality and choose an appropriate therapy based on presented BG information. Responses were compared with the correct answers, which derived from an endocrinologist expert panel.

Overall, 51% of HCPs who used data only from the 360° View paper tool identified the primary glycemic abnormality

correctly, whereas for use of DST, DVD, and DST + DVD, the percentage increased to 77%, 72%, and 82% of the HCPs, respectively. So, what percentage of the clinicians identified the primary glycemic abnormality and selected the appropriate therapy correctly? Significantly more HCPs in the DST, DVD, and DST + DVD groups (49%, 51%, and 55%, respectively) did versus HCPs in the STG (33%).

The positive aspect about this intervention is that it did not afford much time, stated Rodbard: "We all know how pressed clinicians are when seeing their patients, and fortunately we can see here with all of that, the average case only took about 2–2.5 minutes for analysis and recommendation of appropriate action."

She concluded that the clinicians enrolled in the DECIDE study did relatively well when using the structured SMBG form alone. However, use of DVD training, a DST, or both substantially improved clinician performance. And, both the DVD training program and DST provide time-efficient approaches to diabetes management and can potentially play an important role in providing education and clinical support. "It would be very important to do a real-life study with real patients, showing that diabetes management actually improves and that hopefully also the complications of diabetes can be reduced."

Subsequently, Oliver Schnell presented three case examples from the DECIDE study. Participants of the symposium were asked to identify the primary glycemic abnormalities and the treatment of choice from preselected answers via a TED voting system.

Adherence and Nonadherence to Structured Testing: Implications for Intervention from the STeP Study

Lawrence Fisher, Department of Family and Community Medicine, University of California, San Francisco, San Francisco, CA

How do we bring the data from the STeP Study into the real world of clinical care? That was the question Lawrence Fisher raised, and he anticipated that the findings from the STeP Study may lead to some hypotheses about what we can do to translate at least some of the data into what we do on a day-to-day basis. In his view, it is worth to have a closer look at adherence to the testing protocol for the subjects in the STG. STG adherence qualifying for the per protocol (PP) analysis of the STeP Study was defined by the requirements to bring in the filled Accu-Chek 360° View paper tool at four of five visits and having completed at least 80% of requested tests at each visit. Because of this strict criterion, only 51% of all STG patients were included in PP analyses (STG/A), whereas 49% did not follow protocol (STG/NA). Although these patients tested, they did not do so at a rate that conformed to the study criterion. Of the STG/NA patients, 17% dropped out before 12 months, and 32% did not follow the STG protocol. According to PP analysis, the STG/A patients experienced a 0.5% improvement in HbA1c versus patients in the active control group (ACG). STG/NA patients, in fact, showed no improvement versus ACG patients at the end of the study.

For him, the key factor that made the STeP Study work was that poorly controlled, obese people with T2D suddenly and surprisingly began and continued to test their BG. Given the fact that all subjects randomized to the STG received the same training but not all of them tested over the duration of the

study as required, Fisher hypothesized that comparing these two groups at baseline might provide some clues about what made the STeP Study work or not work for these patients.

Substantive differences between STG/A and STG/NA patients at baseline and during the course of study. When comparing STG/A and STG/NA patients, Fisher and co-workers identified significant baseline differences. The STG/NA patient group comprised significantly more minorities, showed significantly lower diabetes self-efficacy (SE), had significantly more co-morbidities, and marginally lower “autonomy motivation” (AM) versus STG/A patients. It is remarkable that both STG/A and STG/NA had relatively similar patterns in change in HbA1c, diabetes distress, SE, and AM over the first 3 months of the study. At Month 3, however, the STG/NA group diverged from the STG/A group and demonstrated poorer scores on HbA1c, SE, diabetes distress, and AM. Over the remaining months of the study, their performance on these measures decreased further, and by 12 months, their scores on these measures met the level of control patients (ACG).

STG/A patients enter a positive motivational hypothesis. Fisher proposed that a mutually reinforcing, reciprocal sequence of behavioral, biological, and psychological change over time enabled STG/A patients to sustain ongoing SMBG behavior. In their case, initial SMBG behavior leads to improvement of control parameters, like HbA1c, and to improved psychology changes in distress, SE, and AM. In contrast, STG/NA patients, who entered the study with poorer initial skills, enter a negative, de-motivational process. At first, there is a positive process, but it is not sustained. These people begin with low motivation and need help at the outset to sustain the SMBG sequence over time (behavior, biology, psychology).

“What do we know about improving engagement that will help patients shift from an initial de-motivational to a positive motivational experience to help initiate and sustain SMBG behavior over time?” Fisher asked. According to him, it is most important to keep in mind that motivation for disease management behavior is driven primarily by feelings, beliefs, and expectations. He appeals for striving to bring covert feelings, beliefs, and expectations that drive SMBG behavior into an overt conversation in a structured way.

The AASAP model targets de-motivational feeling, beliefs, and expectations. Fisher introduced his newly developed five-step program for intervention—the Anticipate, Acknowledge, Standardize, Accept, and Plan (AASAP) program.⁹ This brief, highly structured, and evidenced-based model is derived from motivational interviewing and social exchange theory and targets the de-motivational feelings, beliefs, and expectations that derail SMBG behavior, aiming to label, acknowledge, and normalize them.

“Adherent patients tested because of a positive, engaged, motivational experience, which I suggest is an integrated sequence of behavior, biology and psychology,” Fisher wound up his talk. One result of the study was that SMBG training alone does not assure effective SMBG and Accu-Chek 360° View paper tool use for STG/NA patients—and these make up about 50% of the sample. Therefore,

Structured Testing training is necessary but not sufficient for 50% of non-insulin-using adults with T2D. A “comprehensive” Structured Testing program needs to include the SMBG behavioral component (e.g., Accu-Chek 360° View paper tool) and the SMBG engagement/motivational component (i.e., beliefs, feelings, and expectations about SMBG in a structured conversation).

The presentation of Larry Fisher was followed by an interactive discussion with the audience—What can we do to identify patients that are initially motivated to adhere, and how can we commit the remaining ones?—led by Fisher and Frank Snoek.

Are the New Social Media (Facebook, Twitter, etc.) the Key to a More Efficient and Effective Diabetes Education?

Jill Weissberg-Benchell, Children's Memorial Hospital, Chicago, IL

Jill Weissberg-Benchell opened the session by talking about the role of new social media in diabetes education. The presentation focused on what social media have to offer and concluded with possible concerns that might be raised with them:

There are more people using Facebook today than the number of people that lived on this entire planet 200 years ago. As of September 2009, 93% of teens in the US and 74% of adults were online. 73% of wired teenagers in the U.S. use social networking sites, which is up from 55% just three years before. 72% of young adults (aged 18–29) use social networking sites, as do 47% of wired adults. In the year 2011, the average monthly traffic of unique visitors to top websites and social networking sites exceeded 2 billion.¹⁰

Weissberg-Benchell described the current progress of information technology that provides the basis for the opportunity to implement such tools into diabetes education as well. Given this progress, social networking allows people with diabetes to interact and share their experiences and concerns among themselves.

What can social media and social networking offer? Weissberg-Benchell outlined different positive aspects about social media and their impact on diabetes education:

- **Knowledge.** Social networking sites, to a high degree, are used to gain information on and learn more about diabetes and its treatment. People with diabetes make use of the opportunity of sharing experiences and management strategies in a more personal and unfiltered manner than they might do when talking to their HCP. Social media and social networking sites are more patient-controlled than clinic visits; therefore, much of the information provided is more patient-focused. On the other hand, caregivers can also gain insights into the lives of individuals living with diabetes.
- **Psychosocial support.** Weissberg-Benchell stressed the significance of experiencing support from others that share similar (negative) experiences as it helps patients to cope with their situation. People with diabetes experience a level of understanding among themselves and feel less isolated because they are being reassured that their situations are typical. For adolescents and

young adults, the diagnosis and management of diabetes place substantial burdens on them and their families. This burden may disrupt normal developmental processes and can have a major impact on psychosocial adjustment and successful disease. Social networking may help patients feel better about their gained experiences with diabetes.

- *Improvement of self-care and activation and empowerment.* Another significant factor of successful diabetes management is the involvement of individuals with diabetes in planning and evaluating their own care. Social networking is one method of keeping individuals with diabetes motivated to move from being passive recipients of information to active participants in their own care. Social media can have the property of encouraging and empowering them to pay more attention to self-care and get the (professional) help they might need.
- *Improvement of advocacy.* This aspect addresses effective advocacy goals that can be applied to various fields. From a political perspective, certain campaigns that promote safety at schools or increase funding for diabetes research have already been implemented. Social media can also be helpful to advocate for financing through the Juvenile Diabetes Foundation and the ADA programs.

Do social networking sites cater to the most emotionally vulnerable people? Weissberg-Benchell raised this question to address concerns that are associated with social media and diabetes, namely, that social networking sites may attract individuals who do not understand or who discount their privacy rights because of their desire for information and support. She cited a safety assessment by Lenhart et al.¹¹ that gave specific recommendations for social networking sites: (1) medical disclaimers or reminders that all changes in care plans should be discussed with medical providers should be given, (2) sites should have a formal mechanism for auditing content accuracy, (3) privacy policies should be clearly displayed, and (4) sites should consistently flag commercial content.

Weissberg-Benchell concluded her talk with the optimistic finding that only 3% of the diabetes-specific Facebook pages had posts that promoted non-approved therapies. The concerns about a flood of misinformation on social networking sites are not unreasonable, yet it might be overrated.

LifeMap: An Initiative to Support Alternate Patterns of Support for Patient Self-Care

Lisa Huse, Roche Diabetes Care, Indianapolis, IN

Lisa Huse began her talk by pointing out that with the epidemic growth in healthcare spending on diabetes treatment in the United States, society cannot pay for specialty intervention across the population. Today, diabetes care is largely reliant on the success of the HCP. As time goes on, most U.S. healthcare systems will look for alternative means to get people with diabetes to goal with better self-activation, recognizing that people can no longer function as passive recipients of health care. Employers, health plans, and providers are looking for proactive wellness solutions to increase patient activation.

Before introducing LifeMap, a coaching program to engage people with diabetes, Huse first explained why it is of importance to increase their engagement. She presented data gained from an U.S. supermarket health care plan¹² as an example to successfully reduce healthcare costs by implementing a reward system for healthy behavior. The results proved that 70% of all healthcare costs are the direct result of behavior and that 74% of all costs are confined to four chronic conditions (cardiovascular disease, cancer, diabetes, and obesity). Out of these conditions, modifiable self-management behaviors drive health the most in diabetes.

Trends in health care that point toward the need for increased patient engagement. Huse has included two current trends in U.S. health care in her talk as an example how patient engagement could be encouraged. One of them is the accountable care organization (ACO), defined as a local healthcare organization and its related providers that come together and are held accountable for both the cost and quality of care delivery. By 2014, for ACOs to accomplish meaningful use for electronic medical records, HCPs are going to have to offer patient access to a patient portal where they can access their own healthcare records. ACOs will have to make that connection between their own systems and the patients themselves. Additionally, ACOs are going to look at measurement, measuring 33 parameters for success. Two of those 33 parameters are tied to patient engagement: understanding how well our physicians are communicating and the effectiveness of health promotion and education. At the end of this ACO trial, reimbursement will be tied to those patient engagement parameters.

Another trend in the United States is the value-based benefit design that looks at how employers incent employees to take greater ownership over their own self-care. This involves incenting and rewarding for adoption of healthy lifestyles, such as smoking cessation or increased physical activity activities, appropriate use of services, including certain prescription drugs, and use of providers who adhere to evidence-based treatment guidelines. Incentives can include rewards, reduced premium costs, adjustments to deductible and co-pay levels, and contributions toward their health saving accounts.

Phone- and Web-based coaching—a solution to support resource-constrained healthcare providers and increase patient activation? Huse introduced the creation and implementation of Roche's new venture, LifeMap, a phone- and Web-based coaching initiative, to facilitate alternative patterns of support for patient self-care. The focus of the program is to provide personalized support oriented to the individual's level of health activation. So how does this program work? Coaches, called LifeGuides, interface with people with diabetes through phone or Web contact. However, they don't practice medicine and don't suggest or change medication; they rather focus their attention on encouraging an open dialog where they discuss critical answers to questions, such as "Why isn't a patient compliant with their health care provider's recommendations?" "Why aren't they testing as prescribed?" "What is getting in the way of them understanding their diabetes at a different level?"

One crucial step that helps LifeGuides personalizing people's experience is understanding where those individuals are

in their knowledge, skill, and confidence level with their health. One of the assessments built into the LifeMap is called the Patient Activation Measure (PAM), developed by Dr. Judith Hibbard at the University of Oregon. It consists of 10 questions assessing knowledge, skill, and confidence and is conducted at the beginning of the LifeMap experience and every 10–12 weeks throughout their experience, enabling the LifeGuide to tailor his or her interaction with the individual. The PAM differentiates between four levels, with Level 1 indicating people with diabetes who need to start at the very basics in understanding terms and terminology and evaluating first steps in disease understanding; at Level 4, the individual is at a really high level of knowledge, skill, and confidence but struggles with maintaining and sustaining his or her behavior.

The single greatest contributor to the PAM score is the relationship between people with diabetes and their healthcare team. In this matter, LifeMap offers an alternative use for the Accu-Chek 360° View tool and has therefore implemented the use of structured testing to encourage individuals with diabetes to collaborate with their HCPs. They can learn how to structure their engagement by identifying critical questions and concerns with their LifeGuide before they are going to bring them in to their next office visit.

The next steps of the LifeMap program. Roche is conducting a behavioral observation study to evaluate the effectiveness of the LifeMap program to increase activation, improve health outcomes, and decrease healthcare costs for participating members versus non-participating individuals. Members will be enrolled through employer-based promotions from October 2011 through January 2013 with an enrollment target of 2,500 members. In addition to patient self-reported metrics, health claims data will be analyzed 12 months before and after to identify changes in emergency room visits, hospital inpatient admit days, medication adherence, and HbA1c values. Huse concluded her talk with proposing to share results from this observational study that will be gained in the coming months.

The Use of Smartphone Apps, Telemedicine, and Decision Support Tools for Diabetes Management?

Suzanne Sysko Clough, WellDoc, Inc., Baltimore, MD

The diabetes epidemic has resulted in an overwhelming number of patients needing access to health care. However, the healthcare system has yet to fully operationalize more efficient and effective care models for better chronic disease management. In her talk, Suzanne Clough has split her talk into two parts: identifying areas in the traditional healthcare system that need to be innovated and the role of a technology-driven clinical decision support with a strong focus on the patient in that innovation.

A great demand and opportunity for innovation of diabetes care delivery models. Clough picked one example: the current paradigm of diabetes care and patient education. In the traditional models, the majority of diabetes information and care provided and available to patients occurs mainly within the four walls of the healthcare system. This—coupled with the fact that patients in the United States spend an average of only 1 h a year with their primary care doctor—

creates a great demand and opportunity for innovation of diabetes care delivery models.

A Task Force, jointly convened by the American Association of Diabetes Educators, the ADA, and several additional organizations, identified overriding principles for diabetes self-management education and training (DSME/T) standards,¹³ including:

- DSME/T is effective for improving clinical outcomes and quality of life.
- There is no one “best” education program or approach; however, programs incorporating behavioral and psychosocial strategies and culturally and age-appropriate programs improve outcomes.
- Behavioral goal-setting is an effective strategy to support self-management.
- Ongoing support is critical to sustain progress.

Although DSME/T can indeed improve clinical outcomes and the quality of life, it is estimated that only up to 40% of people with diabetes receive formal diabetes education¹⁴: “While there is no gold standard for what a DSME/T program should look like, we do know that the more personalized the content, the better. Programs that deliver culturally, age, and psychosocially relevant content, work with patients to set goals and provide on-going support are the ones that work.” Clough identified a lack of individualized programming as another concern with the healthcare system.

Technology as a platform to virtually extend diabetes care and education beyond the clinic walls. Clough continued her talk by providing some definitions that help differentiating current technology-driven approaches for a patient-focused decision support:

- Telemedicine: use of technology to provide or enable the delivery of medical care (and information and education remotely)
- Telehealth: interchangeable with telemedicine for some; a broader term for some to mean more than just medical care, but also information and education
- e-health: Internet-based health care delivery; covers a wide range of electronic healthcare services and products from HCPs and non-HCPs
- mHealth: delivery of healthcare services via mobile communication devices

In 2011, diabetes self-management training became one of the reimbursable services added to telehealth in the United States. However, the legislation has determined a few restrictions for this reimbursement. First, the patient has to receive this benefit at an “originating site,” which is defined by the Federal government (e.g., at either the physician’s office or the hospital). The patient must be present for the encounter, which involves interactive, two-way audio and video telecommunications and provides RT exchanges between the practitioner and the individual beneficiary. Thus, care/services must be conducted by an approved HCP. This excludes diabetes educators because they have not been approved.

Clough went on in her talk arguing that traditional medical care and modern technology alone are not the answers. Rather, fundamental to any successful behavior change intervention is the understanding of what occurs when the patient is not with the HCP. How do the life, barriers, beliefs, and

motivators of the “person” part of the patient influence treatment plan adherence and self-management skills? In this regard, Clough cited the results of a randomized controlled trial¹⁵ as an example to demonstrate that non-contextually relevant computer-generated messaging failed to lower HbA1c because it wasn’t relevant and contextual to the individuals with diabetes.

What do patients want from e-health services?. In her conclusion, Clough discussed some answers that have been obtained from patients. One was they wanted RT assistance with daily behavior decision-making. The other was that they wanted it tailored in order to make sense to them. Individualization and tailoring of content are considered powerful because people are more likely to actively and thoughtfully process information if they perceive it to be personally relevant. In two studies,^{16,17} people with diabetes have successfully lowered their HbA1c through a mobile phone personalized behavioral intervention for BG control. The personal and psychometric data that a mobile device can aggregate about the patient when outside the clinic can be the drivers of algorithms that deliver highly tailored and personalized decision support and content to both HCPs and patients.

How Technology Can Leverage Patient Motivation and Improve the Interaction Between Patients and Healthcare Providers

Paul Ciechanowski, Samepage, Inc., Seattle, WA

According to the widely adopted Chronic Care Model by Wagner et al.,¹⁸ health outcomes are optimized when individuals with chronic conditions are activated and informed and engage in productive interactions with a prepared, proactive healthcare team. Between health visits (i.e., the majority of the time), the success of disease self-management and health behavior change is largely dependent on an individual’s unflagging motivation, which may be negatively impacted by task complexity, lack of feedback or support, or life stress. With advances in digital and interactive technology, this new digital landscape offers unprecedented opportunities for motivating individuals in health goal setting/attainment and healthcare engagement.

Paul Ciechanowski concluded this session by focusing on the evidence that Web-based interventions do work. Although the adoption of health-related technology continues to increase with a vast range of offerings in the market, further evidence is needed to prove what features and attributes make such technologies successful both with regard to outcomes and with regard to capacity to engage users over the long-term.

Factors influencing the use of a Web-based application for supporting the self-care of patients. In a Web-based intervention review on the management of T2D,¹⁹ the progress of patients, goal setting, personalized coaching, and some diabetes educational materials have been tracked. There were significant outcomes in self-monitoring, physical activity, nutrition, and diabetes risk factors. Success depended on whether there was a strong theoretical background as well as whether the technology integrated with other commonly used technologies (e.g., mobile phone, short message service messages, or e-mail messages).

Ciechanowski presented data from a Dutch long-term study that looked at something called Diabetes Coach where they had personal data monitoring e-mail, calendars, a life-style coach, and printed features.²⁰ The first interesting outcome was that on average people logged on 49 times over 2 years with a progressively declining rate of engagement. The study observed that common barriers to sustainable engagement were:

- Ceiling effect (i.e., people got bored with the program once they achieved their goal and if it didn’t offer any more challenges)
- Poor user-friendliness
- Lack of reminder features or push factors
- Lack of notification on posted messages
- Lack of integration with traditional care

Factors leading to the success of a Web-based application for supporting the self-care of patients. Subsequently, Ciechanowski talked about the ingredients of successful health-related applications and specifically focused on gamification, defined as the use of features and concepts from games (e.g., points, levels, leader boards) in non-game environments, such as Web sites and applications, in order to attract users to engage with the product.

Whereas gamification is implemented in a lot of areas, health care is lagging a bit behind. Ciechanowski presented some examples, however, showing how gamification is applied in a medical context to promote behavioral change (e.g., for smoking cessation or losing weight). People can learn about coping strategies and may be more likely to stay engaged with the use of game mechanics, including points, levels, challenges, virtual goods, leader boards, gifting, and charity, all of which tap into human motivation and desires (for reward, status, achievement, self-expression, competition, and altruism). They also have the opportunity to share their experiences and their status with their social group, allowing them to encourage, support, and motivate each other. Other examples included, among others, social network communities and/or gameful design, which slightly differs from gamification by using data visualization to make it more appealing.

Successful health visit preparation for the promotion of patient participation. Before concluding his talk, Ciechanowski referred to the limited amount of time an HCP can spend with the patient: “If, as a clinician, you are starting to be rated on your communication, and if you want to feel like you’re doing the right thing for your patient, it might help to have some kind of a prompt so that you don’t miss some of those things.” In a randomized controlled trial by Brown et al.,²¹ they were able to shorten visits with the help of point-of-service prompt sheets. When patients used the prompt sheet (i.e., when they prepared their visit systematically), they asked more questions, and clinicians provided more prognostic information. When both used these prompt sheets, anxiety was reduced, total visit duration was decreased by 11%, and recall was significantly improved. Such a tool allows patients to participate actively in their own primary care visit and enables them to discuss their greatest concerns with their HCP. Ciechanowski presented examples of VisitPrep, which is an online visit preparation prompt sheet offered by Samepage, Inc.

In summary, the Web- and mobile-based interventions help patients engage in care. The collection of multiple modes of entry of data and point-of-service prompt sheets and recommender technologies are all of importance. This is where the trend is going, and health care should stay on top of the state of the art with these tools with which people are engaging.

Pros & Cons Debate—Is Bariatric Surgery Becoming the Preferred Option to Treat Obese Diabetes Patients?

Pro

Donal O'Shea, St. Vincents University Hospital, Dublin, Ireland

It is now clear that when standard lifestyle changes and conventional therapy are not achieving good glycemic control, then upper gastrointestinal surgery should be considered. Complete remission of diabetes can be achieved in 40–75% of gastric bypass patients and 37% in sleeve gastrectomy patients compared with up to 10% in the medically managed group. There is, in addition, the longer-term support of the Swedish Obesity Subjects study showing a longer-term benefit in terms of cardiovascular outcomes.

What we have known until recently is that diabetes is getting worse and that bariatric surgery has a role in glycemia, cardiovascular disease management, and mortality, but we have no Level 1 evidence, and these days, Level 1 evidence is what it is all about.

Gastric band should now be considered negligent in people with T2D. If you're going for a surgical option in someone with T2D, a gastric band is not the appropriate option, O'Shea stated: "I really think it has a very limited role." Any respectable bariatric surgical unit will be doing 80% bypass or sleeve and 20% band. The gastric band is an inflatable cuff that restricts the upper end of the stomach. In general, gastric bands require a lot of follow-up. If someone is having a band put in, one needs to make sure it is a good-quality band and that the surgeon puts in a couple of sutures because people who do a gastric band quickly won't suture it into position, and the chance of slippage is higher. Therefore, it is crucial to know what one is asking for and who is actually doing it. According to O'Shea, the human body is incredible at defending its weight if no surgical options are undertaken. With the gastric band, people lose about 20% of their starting body weight within the first 2 years after surgery and then gradually trend up again over time. Gastric bypass surgeries produce better results, with 30% excess weight lost and a modest trend back up, stopping at about 25% of excess weight lost on average. Recently, results from an Italian randomized, controlled trial have been published in the *New England Journal of Medicine*.²² For this trial, 60 people with T2D, a body mass index of ≥ 35 kg/m², and an HbA1c of $\geq 7\%$ have been randomized in a 1:1:1 ratio to Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion (BPD), or conventional medical treatment. The primary end point was the rate of diabetes remission at 2 years (defined as a fasting glucose level of <100 mg/dL [5.6 mmol/L] and an HbA1c of $<6.5\%$). At 2 years, diabetes remission had occurred in no patients in the medical-therapy group versus 75% in the RYGB and 95% in the BPD group.²² Another randomized study evaluated the efficacy of intensive medical therapy alone versus medical

therapy plus RYGB or sleeve gastrectomy in 150 obese patients with uncontrolled T2D.¹⁰ The primary end point of this trial was the proportion of patients with an HbA1c of $\leq 6.0\%$ 12 months after treatment. The proportion of patients meeting the primary end point was 12% for the medically treated group, 42% for the bypass group, and 37% for the sleeve gastrectomy group, respectively.¹⁰

Success with lifestyle is difficult to achieve, pharmacological intervention is required, and still we are not getting to our therapeutic targets with 50% of our patients even when they are adherent in a clinical trial setting, stated O'Shea: "We are not going to get there with any single oral hypoglycemic agent or any combination of agents."

The question whether gastric surgery should be considered and available for obese people with T2D is now resolved. Although the role of bariatric surgery in T2D has been controversial, for the first time we now have something people thought we would never have, which is randomized and controlled trial evidence indicating that RYGB or BPD will provide better outcome for people with diabetes compared with conventional medical treatment. Certainly, the most appropriate patient selection has to be teased out, and follow-up will have to show that better glycemic control will finally also result in fewer diabetes-related complications and, most importantly, fewer cardiovascular events. In O'Shea's opinion, bariatric surgery will ultimately prove to result in fewer complications in obese T2D, and hence it is becoming the preferred option for obese patients with T2D.

Contra

Guntram Schernthaner, Rudolfstiftung Hospital-Vienna, Vienna, Austria

Guntram Schernthaner started his talk with an attempt to balance positive and negative findings in patients with T2D following bariatric surgery: "Of course, there is weight reduction and effective HbA1c lowering after bariatric surgery." However, at least the later one can also be achieved with a number of drugs (e.g., with a once-weekly glucagon-like peptide-1 agonist). Blood pressure lowering, lipid lowering, reduction of inflammation, reduction of atherothrombotic state, and hormonal changes are other positive effects that have been observed after bariatric surgery. On the negative side, Schernthaner argues that there is no real "cure" for diabetes, a term that is often used by surgeons in this context. The percentage of diabetes remission is widely overestimated. It is important to be aware of the definition of "remission" in this respect. Complete remission according to the 2009 ADA consensus conference²³ is defined as a return to normal measures of glucose metabolism—an HbA1c $<6.0\%$ and fasting BG <100 mg/dL of at least 1 year's duration in the absence of active pharmacologic therapy or ongoing procedures—whereas partial remission is defined as subdiabetic hyperglycemia with an HbA1c $<6.5\%$ and fasting glucose 100–125 mg/dL of at least 1 year's duration in the absence of active pharmacologic therapy or ongoing procedures. Although a meta-analysis from 2009 of primarily uncontrolled studies reported remarkably high complete remission rates of up to 78.1% and partial remission rates of 86.6%,²⁴ it has to be stressed that more recent and controlled studies showed significantly lower remission rates (i.e., a recent randomized trial

published by Schauer et al.¹⁰ observed complete remission rates in patients after gastric bypass and sleeve gastrectomy of 42% and 27%, respectively), which is in line with a retrospective review by Pournaras et al.²⁵ that revealed complete remission rates of 41% and 26%, respectively.

A fact that further argues against a potential “cure” for diabetes by bariatric surgery is that in most published studies an increase in insulin secretion has not been observed, but a decrease after weight loss was observed.

Fifty percent of all bariatric surgery patients are not coming to the follow-up investigations. It is remarkable that about 50% of bariatric surgery patients are not coming to the scheduled follow-up investigations. According to Schernthaner, a comparable rate of loss to follow-up would be unacceptable for any drug.

What do we know about nutritional deficiencies after bariatric surgery? Certainly, nutritional deficiencies after bariatric surgery are common complications. The major macronutrient deficiency after bariatric surgery is protein malnutrition, defined as albumin <3.5 mg/dL. Intolerance of protein-rich foods is common after surgery, and thus many patients do not meet their recommended daily intake. Both reduced intake and poor absorption of protein after bariatric surgery can be related to anemia, zinc, and thiamine deficiencies based on the vitamin and mineral content in protein-rich foods. Common deficiencies in micronutrients include trace elements, essential minerals, and water-soluble and fat-soluble vitamins, which often persist postoperatively, despite universal recommendations on multivitamin and mineral supplement.

Postoperative complications in the long-term are much higher than previously reported. A recently published 5-year analysis of clinical outcomes of 22,693 patients from seven U.S. states who underwent bariatric surgery revealed that although bariatric surgery is associated with substantially decreased obesity-related co-morbidities, it is associated with a higher risk of serious adverse clinical outcomes compared with controls at 1 year after surgery.²⁶ This risk remained elevated until 4 years after surgery. Although many of the serious outcomes were uncommon (<1%), a few of them deserve further mention, including deep venous thrombosis and pulmonary embolism, risk of abscess or peritonitis during hospital admission, need for lysis of adhesions postoperatively, marginal ulcers, hemorrhagic complications, ventral/incisional hernia repair with complications, bacterial or aspiration pneumonia, and acute renal failure during hospital admission.

Furthermore, despite the reductions in body weight, psychopathology persists; many patients have depressions or eating disorders and are at increased risk for committing suicide.

The risk for severe hypoglycemia is significantly increased after bariatric surgery, in particular after gastric bypass. Bariatric surgery might also affect the rate of severe hypoglycemia, Schernthaner suggested. A nationwide cohort study of post-gastric bypass hypoglycemia including more than 5,000 patients undergoing surgery for obesity in Sweden²⁷ revealed that after gastric bypass surgery, the risk for hypoglycemia was significantly elevated, and so was the rate of hospitalization for severe hypoglycemia.

It is important that to date no cardiovascular outcome studies have been performed, and accordingly no evidence-based conclusion can be drawn regarding a potential reduction of cardiovascular events.

Schernthaner commented that it would be unrealistic to assume that bariatric surgery could become a preferred option to treat obese people with diabetes. About 49.2% of all patients with T2D in the United States (approximately 10 million) are obese (body mass index >30 kg/m²), and 24.7% (approximately 5 million) are morbidly obese (body mass index >35 kg/m²). At present about 200,000 interventions with bariatric surgery are performed in the United States per year. About 20% of these are morbidly obese patients with T2D (approximately 40,000 patients). Thus, from the morbidly obese patients with T2D, fewer than 1% has had a bariatric surgery today. If bariatric surgery should be the preferred option to treat these obese patients with T2D, then 4,980,000 or 2,560,000 additional surgeries would be needed if a body mass index of >35 kg/m² or >40 kg/m², respectively, would be the criterion for an operation.

Insulin Pump Therapy in the Management of Type 1 Diabetes—Current Practice and Challenges

Moshe Phillip, National Center for Childhood Diabetes, Petah Tikva, Israel

Insulin delivery via an insulin pump is the best way to mimic the physiology of the pancreatic activity that is available nowadays. Insulin pumps proved to lower HbA1c levels of people with suboptimal metabolic control without an associated increase in the risk of hypoglycemia. Insulin pumps were especially proven to be effective in treating “brittle” diabetes and the “dawn” phenomenon and in coping with unplanned intensive exercise. The use of the pump helps users to regain some of the spontaneity to their daily life.

Status quo of MDI therapy. Moshe Phillip began his lecture with an introduction about the current status of treating pediatric patients with MDI. Currently, despite the fact that new analogs and different kinds of insulin are available, the “pediatric definition of the target of HbA1c below 7.5 according to ISPAD [International Society for Pediatric and Adolescent Diabetes]” guidelines has widely not been achieved yet, stated Phillip, as shown by HbA1c results from 21 centers of excellence, the Hvidøre study group,²⁸ a Scottish survey of 24,750 people with T1D,²⁹ and an Australian survey.³⁰ Phillip said, “Most of the patients are treated by the MDI approach associated with swings in glucose level, changing from hyper- to hypoglycemia during the day, some unpredicted hypoglycemia, and some uncontrolled hyperglycemia.”

The pump is supposed to be, theoretically at least, an answer to several of the different issues that MDI cannot answer. The pumps help to deal with the “dawn” phenomenon and the “dusk” phenomenon, and the pump also helps to deal with the fact that some patients don’t like to inject themselves in between meals. Phillip shared his own experiences with the audience, summarizing that “over the years we tried to look at what was the impact of using insulin pumps on the lives of patients in our clinic, not in a clinical study with two arms, control and intensive intervention, just in the clinic.” He and his team accumulated a lot of experience with the different age

groups "studying" pumps in toddlers, children, prepubertal children, and children during puberty and in those with advanced puberty, meaning young adults. Their publication³¹ showed that switching children and young adults from MDI to a pump has a long-lasting effect. "Those with higher HbA1c showed the maximum effect of the pump on their diabetes control without penalty in severe hypoglycemia," Phillip said.

In the latest issue of the *New England Journal of Medicine*, John Pickup's review³² about the use of the insulin pump summarized that glycemic control as measured by HbA1c is significantly better with the use of insulin pumps than with MDI, that the HbA1c difference is about 0.6%, and the frequency of severe hypoglycemia is actually going down. The worst-controlled patients under MDI improved the best, similar to the observations made by Phillip in the National Center for Childhood Diabetes in Petah Tikva, Israel.

Risk factors that lead to a cessation of pump use. "All pediatric patients with T1D are potential candidates for an insulin pump, and there is no lower age limit for initiating the pump," said Phillip. But, there are certain risk factors associated with pediatric patients who decided to stop the use of their pumps. A study conducted by de Vries et al.³³ revealed that female gender, age above 10 years, and poor metabolic control at pump initiation were associated with an increased risk for pump discontinuation.

Moshe Phillip concluded that currently, there are "great pumps and we have better ways of glucose monitoring, but eventually the patient is the one who has to make all the decisions." The currently available insulin pumps are designed to cope with previously most commonly reported problems, such as pump malfunction, insulin leakage, battery issues, and skin complication. Most pumps also have a well-designed user interface. Yet, comprehensive pump advisors such as the "MD-Logic Pump Advisor Analysis & Report" developed at the National Center for Childhood Diabetes with a correction factor, carb ratio, some activity time, and basal plan are still needed to help people with diabetes to navigate their BG control between hyper- and hypoglycemia.

Insulin Pump Therapy in the Management of Type 2 Diabetes—Current Roles, Future Opportunities

Ian Blumer, Charles H. Best Diabetes Centre, Ajax, Canada

Status quo of MDI in people with T2D. Insulin pump therapy is a relatively seldom-used option in the management of T2D. At present, less than 1% of individuals with T2D living in the United States administer insulin via CSII compared with over 30% of people living with T1D.

There is a paucity of studies looking at the use of CSII in people with T2D. In particular, there are very few randomized clinical trials. Of the available studies comparing CSII with MDI for people with T2D, conflicting results have been observed. This is aggravated by the fact that "the number of patients involved in these studies" is indeed very small. "Clinicians, day to day, are being forced to make decisions about pump therapy based on a handful of patients," said Ian Blumer. The studies from Berthe et al.³⁴ and Wainstein et al.³⁵ found a statistically significant improvement in HbA1c with insulin pump therapy compared with use of MDI. "The two studies with the largest numbers of patients, although the

numbers aren't really large," said Blumer, are those published by Raskin et al.³⁶ and Herman et al.³⁷ showing no significant HbA1c difference between pump therapy and MDI in people with T2D.

Status quo of CSII in people with T2D. A fairly recent meta-analysis by Monami et al.³⁸ concluded that "available data do not justify the use of CSII for basal-bolus insulin therapy in T2D"; however, this was based exclusively on parameters of glycemic control. Some studies looking at quality of life indicators such as treatment satisfaction have shown striking benefits with CSII; however, other studies have shown dissimilar results.

By his own experiences in daily practice, Blumer summarized that people living with T2D who are most suited to CSII therapy are those who are motivated, enthusiastic, accepting of change, wanting greater flexibility in their therapy to suit an active and variable lifestyle, comfortable with technology, willing to do frequent BG testing, and already being treated with MDI in doses that are not inordinate. As newer, simpler pumps become available, the role of CSII in the management of T2D will likely expand, particularly for those patients on multiple daily doses of insulin.

The presentation of Blumer was followed by an interactive discussion with the audience about the question how to identify patients who are most promising candidates, are clearly going to benefit, who are most enthusiastic, and are willing to put in the time and effort. If found as eligible for pump therapy by means of these criteria personally experienced by Blumer, very few patients would stop using the pump therapy.

Continuous Intraperitoneal Insulin Infusion—When? For Whom? How?

Eric Renard, CHU Montpellier, Montpellier, France

Status quo of continuous intraperitoneal insulin infusion. Continuous intraperitoneal insulin infusion (CIPII) has been reported since the 1980s as a mean to deliver insulin with pharmacokinetics and pharmacodynamics closer to physiology compared with subcutaneous delivery. Because CIPII bypasses the subcutaneous space, absorption of intraperitoneal insulin is faster.

Selam et al.³⁹ in Montpellier, France, and other investigators in Italy⁴⁰ compared peritoneal insulin infusion versus the classic CSII and showed differences in terms of rapidity of insulin absorption, earlier peak of insulinemia, quicker return to baseline, and lower peripheral insulin levels. Changes of the rate of infusion lead to quicker changes in insulin action, and, after a bolus of insulin, plasma insulin levels increase more rapidly and also come back sooner to initial levels. Schaepeynck-Bélicar et al.⁴¹ demonstrated "the very good reproducibility of insulin absorption" with "exactly the same insulinemia following the bolus on repeated occasions." Thanks to predominant portal insulin diffusion, plasma insulin levels in peripheral blood are lower than during CSII and likely play a role in lowering the risk for hypoglycemia.

Interesting, and perhaps less well known, is the fact that when patients are treated with the intraperitoneal insulin infusion route for several months, as it has been done in Sweden and reported lately,⁴² and if hypoglycemia is induced, glucagon secretion in patients who had lost it many years ago can

be restored. This means that in T1D, it is a functional, not organic, deficit of glucagon secretion; it cannot be an alpha-cell defect because it can be restored.

The consequences on BG levels include lower variability, a better control of postmeal peaks, and a reduced risk for late postmeal hypoglycemia. Whether performed using wearable or implanted pumps, CIPII results in better glucose control than CSII in terms of glucose variability and occurrence of severe hypoglycemia, while mean BG and HbA1c levels may be better or similar.

Which patients are suitable for CIPII treatment? Good candidates for CIPII are

- people who cannot tolerate subcutaneous insulin without adverse reactions, such as those developing subcutaneous lipoatrophies with CSII
- people in whom subcutaneous insulin is apparently unreliably absorbed
- people who still experience frequent hypoglycemia when treated by CSII, even if it is not severe

Improved glucose control and the reduced occurrence of severe hypoglycemia under CIPII have also led to consideration of this delivery mode in people with diabetes failing to achieve an HbA1c level below 8% with CSII because of high BG variability or in people with diabetes with recurrent severe hypoglycemia and/or frequent nonsevere hypoglycemia also showing hypoglycemia unawareness in most cases.

Implanted pumps—how is that done? Fully implanted pumps have been mainly used for CIPII since the 1990s in spite of high cost and issues of the physical stability of insulin in these devices. Pumps are implanted under the skin. Insulin is infused through this catheter that is partly in the subcutaneous space and partly in the intraperitoneal space. They “have to be refilled with insulin; this is done in hospital every 45–60 days using a specific needle granting access to the central port and can be used for 8 years or even sometimes 10 years without any change,” Renard stated.

A randomized clinical trial has been done in people with T2D with an implantable pump.⁴³ It was shown that using intraperitoneal insulin from an implantable pump significantly lowered the variability of glucose. And, most interestingly, patients do not gain weight when they improve their HbA1c, whereas under MDI they significantly increase weight, showing some benefit when using the intraperitoneal route versus classic subcutaneous treatment.

CIPII with the Accu-Chek DiaPort system. In a randomized clinical trial⁴⁴ with people with T1D, CIPII with the Accu-Chek DiaPort system was compared with CSII. Study results showed that with CIPII with the Accu-Chek DiaPort system, severe hypoglycemia was dramatically reduced in this population selected for high BG instability. “HbA1c was only partially decreased, it was a trend but it was not significant. But the occurrence of severe hypoglycemia was dramatically reduced.”⁴⁴

The most recent development of implanted ports, which allow CIPII through the connection of a wearable pump, may provide an alternative option that is more affordable and solves the insulin stability issue. Current research on closed-loop insulin delivery models supports the interest of CIPII

because reduced delays in insulin action better fit with the tuning of insulin delivery according to the algorithms used.

Pros and Cons Debate: Variable Basal Rate Versus Constant Basal Rate—Which One Is Better?

T1D is associated with complete deficiency of endogenous insulin. A major goal of therapy is to enable the person living with the disease to replace insulin in a manner as physiological as possible. The combination of good self-management skills and modern technology (in the form of pump therapy) can help patients to achieve this goal. Insulin pumps are sophisticated devices and can, if required, provide multiple different rates of insulin infusion in the course of a 24-h period. Whether this level of complexity is necessary remains controversial with advocates on both sides of the argument.

Pro Constant Rate

Sean Dinneen, National University of Ireland Galway, Galway, Ireland

Taking the position pro constant rate basal insulin infusions, Sean Dinneen began his lecture with a description of the anatomy and physiology of a clinical decision: “The components of clinical decision-making should be evidence; of course, we like to think that we practice and do things based on evidence, but actually that’s not the only aspect.”

Dinneen secured the agreement of the audience to remember that “there are patient and physician preferences and influences that go into the clinical decision. There are certainly constraints that influence or impact, usually negatively, on the clinical decision.”

He admitted that “there is certainly no high-quality evidence at the level of randomized control trials, systematic reviews, or meta-analyses to compare constant versus variable basal rate.” There is a huge bias toward patient and particularly physician factors so that when a pump is started, a variable rate infusion is automatically assumed.

Dinneen then discussed some examples of BG profiles “with huge variations in blood sugars” to illustrate that “the key thing” is not the ability to deliver a constant or variable rate of insulin infusion by pump but the skills set. It is the ability to use the technology well, and the key element here is management skills. Pickup, as pointed out in his most recent publication,³² “did of course acknowledge the dawn phenomenon with an increased basal rate here,” but Dinneen was convinced that the point of Pickup was to basically “keep it simple.”

A study conducted and published by Heinemann et al.⁴⁵ found out that at least 2–4 h is required until a new steady state in the metabolic effect is achieved after a significant change in basal insulin infusion. This result argues against multiple and variable intervals in basal insulin. Dinneen summarized his position as a proponent for constant rate infusions with “Let’s keep things simple, at least to begin with. The pharmacodynamics of subcutaneous insulin argues against multiple changes in basal insulin rate. And for certain groups, constant basal rate makes perfect sense.” Another group Dinneen said with which he struggles hugely in his practice is the poorly adherent adolescents, for whom insulin omission is a huge issue: “They just don’t want to have the condition; they just don’t take the insulin. And I think a constant basal rate in that situation may actually help keep them out of hospital.”

Taken together, simplicity is the key to success, and too many variable rates may lead to undesired confusion, among patients and HCPs.

Pro Variable Basal Rate

Hans-Joachim Lüddecke, Diabetic Center, Munich, Germany

As a proponent of variable basal rates, Lüddecke began his lecture with showing his own insulin secretion, illustrating the pulsatile secretion of insulin. With examples to define the basal requirement from clamp studies, experimental studies, epidemiological studies, and CGM-based studies, the underlying phenomena, such as the dawn phenomenon, were discussed. The dawn phenomenon “is defined by a BG increase in the early morning hours of around 10 mg or more, or an increase in insulin of about 20% or more,” said Lüddecke. Lüddecke and colleagues investigated the dusk phenomenon, which is even more controversial than the dawn phenomenon, but they believe that it exists. Furthermore, insulin secretion data showed that very low insulin secretion patterns can be observed at midnight.

Using “a CGM technique, a basal algorithm to define the best insulin requirement,” King and Armstrong⁴⁶ demonstrated the difference between minimum and maximum basal rates. Most of the patients have a difference around 100–150%. But King and Armstrong⁴⁶ even observed patients with up to a 300% difference between lowest and highest basal rate. They found, based on their technique, that the basal rate during the night increases.

In summary, arguments for a variable rate infusion are physiological phenomena like the early morning rise in cortisol and nocturnal surges in growth hormone. These influence insulin action, requiring alterations in insulin secretion, and should mandate alterations in rates of insulin replacement in patients using CSII therapy. Recent evidence from algorithms used in studies of closed-loop insulin infusion systems also supports the view that overnight requirements for insulin are not constant.

Is Interstitial Fluid Glucose Reflecting the Glycemic Status Better than Blood Glucose?

Tadej Battelino, University Medical Center–University Children's Hospital, Ljubljana, Slovenia

Interstitial fluid (ISF) glucose concentration became essential for CGM in the routine management of diabetes. With only a minority of people with diabetes reaching the ADA/EASD target HbA1c, the advantage of CGM in the subcutaneous ISF over SMBG becomes increasingly recognized as clinically meaningful, and first data on long-term projections also indicate that CGM is cost-effective among people with T1D.

Retrospective or professional CGM can help healthcare providers to optimize treatment. Tadej Battelino started his talk with a short view on SMBG, which represents a widely used and commonly accepted technology for monitoring BG today. “SMBG is generously used and accepted and it can be improved with structured education and information technology; however, most patients remain in suboptimal control,” said Battelino. In contrast to SMBG, retrospective CGM offers the possibility to continuously monitor BG levels over a

limited time frame. While almost forgotten for some time, it has been gaining new momentum probably in the last 3 or 4 years, powered by several trials that included glycemic variability as one of their outcome parameters. Retrospective CGM can help healthcare providers to optimize treatment, and it is certainly helpful for education and as a research tool; currently, many pharmaceutical companies use retrospective CGM in almost any study related to glucose control (e.g., in the clinical development of new insulins or when evaluating patients who are particularly vulnerable to hypoglycemia).

What we actually want to use and what our patients want is RT-CGM. Coming back to the initial question, Battelino presented some early study data that were derived from studies with pigs showing that there is an inevitable delay between the blood and the subcutaneous tissue. Following a bolus of intravenous glucose application, the rise of glucose concentration in the subcutaneous tissue was following 15–20 min after the BG concentration change. It is interesting that the BG concentrations in subcutaneous tissue and in brain seem to adjust simultaneously. So one has to keep in mind that when you measure your glucose concentration in the ISF, you will have a physiologic delay in your result, resulting from the distance the glucose has to diffuse within the body compartments. This time delay is not an error of either the sensor or the device and will not be abolished by sensors with improved analytical performance in the future. Given this limitation, it is the trend information of CGM compared with SMBG that delivers most value to the user.

In the course of his talk, Battelino provided a comprehensive overview over the most relevant efficacy data of RT-CGM for different patient populations. He concluded that from an evidence-based point of view, the use of CGM

- is safe within all age groups
- improves metabolic control
- reduces the rate and duration of hypoglycemia
- improves quality of life

Toward the closed loop. Current CGM systems that include an automatic pump-shut-off feature are certainly one step toward a closed-loop or artificial pancreas (AP). These systems have shown to reduce the rate and duration of nocturnal hypoglycemia in those patients at greatest risk without increasing the risk for rebound hyperglycemia. The majority of patients reported feeling more secure at night with these systems, experienced reduced anxiety, and wanted to continue using the systems following the trial. First trials evaluating investigational closed-loop system have already been published. One of them is the MD-Logic Artificial Pancreas System, the subject of a pilot study in adults with T1D.⁴⁷ The MD-Logic Artificial Pancreas System was designed to minimize high glucose peaks while preventing hypoglycemia. Further studies in the broad population under daily-life conditions are certainly to come.

Ten Years of CGM: An Attempt for an Appraisal

Peter Hammond, Harrogate District Hospital, Harrogate, United Kingdom

CGM in the ISF has been used in routine clinical practice for over 10 years now, but despite an increasing evidence base for

potential benefit, its best use in diabetes management remains uncertain, and general funding in the United Kingdom is not available, Peter Hammond summarized.

Evidence for retrospective and blinded CGM is scarce. Initially, CGM was only available as a blinded system, so-called professional CGM. The first approved CGM system was not particularly reliable, and many users were dissuaded from using CGM by poor experiences with this technology. However, the second version of the technology was more reliable and proved a valuable educational tool, demonstrating ways to optimize insulin delivery and adjust lifestyle to improve glycemic control. There is now a significant body of observational literature describing what issues can be identified using blinded CGM in people with both T1D and T2D. However, there is limited and inconsistent evidence for improvement in glycemic control following use of blinded CGM. The exception to this paucity of evidence is the study by Murphy et al.⁴⁸ from East Anglia in the United Kingdom, who showed that intermittent use of blinded CGM throughout pregnancy resulted in a significant decrease in HbA1c in the last few weeks of pregnancy and an associated reduction in macrosomia and more normal birth weight babies compared with women receiving standard care. According to Hammond, this trial revealed that it is the postprandial peaks that are not identified by SMBG but rather by CGM, and it allows women to have some impact on those.

Several meta-analyses have been performed for RT-CGM. The introduction of RT-CGM allowed the user to adjust treatment and lifestyle contemporaneously to address adverse glucose excursions, so-called personal CGM. Studies of RT-CGM, either as a stand-alone intervention with any intensified insulin regimen—particularly the Juvenile Diabetes Research Foundation study⁴⁹—or as part of SAP therapy, have demonstrated that when CGM is used almost continuously, then there are benefits in terms of reduction in HbA1c. However, these are modest; the meta-analysis suggests the average decrease in HbA1c is about 0.3% (0.33 mmol/mol), although the greater the baseline HbA1c, the greater the decrease in HbA1c. There appears to be a problem if you look at hypoglycemia. In clinical practice, CGM is frequently used aiming to protect people against hypoglycemic episodes. “You can reduce the duration of hypoglycemia, as has been shown in a variety of studies, but you don’t really reduce the rate of severe hypoglycemia,” Hammond said. Although RT-CGM can reduce the duration of hypoglycemia, there has been no evidence yet that it can protect against hypoglycemic events. It is important that most of the randomized controlled trials have not been designed or powered to test the effect of CGM on hypoglycemia, and hypoglycemia rates at baseline turned out to be very low. At the moment, we are lacking trials that specifically look at the impact of CGM in those with disabling hypoglycemia or those at particular risk (i.e., those with unawareness), Hammond claimed.

“At least we have got some observational studies,” he added. One Italian survey⁵⁰ looked at data of 129 children and adolescents with T1D on CSII before and after the initiation of CGM therapy. In this population, the frequency of severe hypoglycemia dropped from 11.9 episodes/100 person-years before CGM initiation to 4.1 episodes/100 person-years after

the initiation of CGM. In a subgroup follow-up study⁵¹ of the Juvenile Diabetes Research Foundation trial of those who were randomized to RT-CGM, the incidence rate of severe hypoglycemia was 21.8 and 7.1 events per 100 person-years in the first and last 6 months of follow-up, respectively. So we can conclude there are some hints from observational studies that there is a benefit of RT-CGM in regard to severe hypoglycemia.

Evidence versus practical experience: continuous use is hard to sustain. Available evidence clearly indicates that you have to use CGM practically all the time to gain benefit. However, the practical experience is that those people with diabetes who gain significant benefit from RT-CGM prefer to use it intermittently. Even where the evidence base shows real gain (e.g., during pregnancy), adult users find continuous sensing difficult to sustain. “We try to get all our pregnant women to use CGM at least for a couple of weeks, every 4–6 weeks during the second and third trimesters, but they really don’t like it,” said Hammond. At Harrogate District Hospital, all women with diabetes are offered pump therapy during pregnancy, and, accordingly, the vast majority uses a pump during pregnancy, but they really don’t like that additional bit of kit stuck to them, Hammond explained.

Coming back to the initial task, Hammond summarized his appraisal of CGM as follows:

- It has been in clinical use for more than 10 years now, but
- certainly in the United Kingdom, uptake remains poor,
- best use is uncertain, and
- we do not have general National Health Service funding for RT-CGM.

In his opinion, it still holds true that based on the available evidence, continuous use to achieve target HbA1c levels when intensive insulin therapy apparently needs to be optimized is the main indication of RT-CGM, as recommended by the Association of British Clinical Diabetologists’ consensus from 2010,⁵² although he thinks that on an individual level, a relevant benefit can be achieved regarding the prevention of hypoglycemia.

Finally, Hammond addressed several developmental needs, which include more accurate sensors, hoping that those will contribute to minimize lag time, stand-alone technology for glucose monitoring with no need to calibrate with separate BG meters, a greater user acceptability, which may be related to the design of the CGM sensors, improved data analysis possibilities, enabling patients and HCPs to interpret CGM data more effectively, and a more solid evidence base around hypoglycemia prediction as well as predictive factors of success that enable us to select users more appropriately than can be done today.

The Current Status of CGM Technology and What Improved Sensor Performance May Offer

Dirk Voelkel, Roche Diabetes Care, Mannheim, Germany

The performance of currently available CGM sensors for personal use—inserted in the subcutaneous adipose tissue—is quite limited. The performance is measured by metrics such as the mean absolute relative difference, comparing CGM

sensor data with reference BG concentrations. The decisive element for approximation of BG concentration by interstitial glucose concentration is the signal characteristic of the CGM sensor and the online calibration of CGM sensor signals (i.e., the calculation of ISF glucose concentration from CGM sensor primary signals [e.g., electrical current]).

Tissue compression effects can lead to false hypoglycemia alarms. Dirk Voelkel introduced some major technical challenges that users of CGM systems usually do not see in the clinical data, as those artifacts are usually adjusted by an algorithm. Signal noise, for instance, is present during the day but disappears during the night. It is not an electronic noise but one that comes from wearing the sensor and moving around. "These are artifacts we do not want to see in the visualized data as they are clearly not physiological," Voelkel stated. Second, dropouts during the night can be frequently seen; they are called sensor or tissue compression effects. Basically, these effects lead to a lower signal than the physiological values actually are. As soon as the patient takes a BG measurement, these effects usually disappear, and the sensor data jump back to the normal value. Accordingly, compression effects are hard to detect if only one CGM sensor is used. As they can lead to false hypoglycemia alarms, they have an impact on the quality of life of people with diabetes.

Voelkel presented some sensor data over a period of 7 days (7×24 h) that were derived from a research sensor that is currently under development at Roche Diabetes Care. He pointed out two important aspects: first, datasets are complete, meaning that there are no missing data points, and second, there have hardly been any deviations between the two different sensors over the tested period.

Challenges for an effective calibration are diverse. Thus, as there are obviously very good raw signals, how does one get the data displayed to the user? In order to warrant outstanding CGM performance in terms of the established metrics, several prerequisites for a successful calibration procedure have to be met. Accurate CGM readings obviously depend on adequate calibration of the sensor. Essential challenges for prospective calibration are variable physiologic time lags between blood and ISF glucose, the estimation of in vivo glucose sensitivity (i.e., sensor current per mg/dL glucose) and in vivo offset current (i.e., sensor current for 0 mg/dL glucose), noisy sensor signals requiring filtering without generation of significant filter-induced time lags, and variable in vivo drift of glucose sensitivity over time and in vivo equilibration time after sensor insertion (i.e., "run-in" time), as well as the assessment of suitability of the sensor and BG data for calibration.

The ideal picture is that we have a very short run-in time, stated Voelkel. Yet, in his opinion, a run-in time cannot be completely avoided because of processes that take place in the first hours of the first day of sensor insertion (e.g., healing). Nevertheless, this time can be already used for calibration of the sensor. Another important point is the way and quantity of filtering of raw data as these have a strong impact on the final CGM signal and may induce additional lag times.

Voelkel concluded his presentation stating that there is still some leeway for more accurate and reliable CGM sensors. These sensors have to work not just within the setting of a clinical study, but in fact in real-life situations. Until this is

reached, the user wants to have a reliable and robust sensor performance under all conditions, accurate representation of ISF glucose the whole time, and accurate trend information. By achieving this, the rates of false-positive and false-negative alarms will inevitably decrease.

CGM as an Essential Part of Future Closed-Loop Systems

Lutz Heinemann, Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany

Which CGM system is best for my patient? "This is a standard question," Lutz Heinemann explained at the beginning of his talk, "but I am not aware of a standard answer." There are many factors that come into play that are of relevance: technical performance, of course, but in reality handling, costs, and availability are of critical importance, also for future AP systems. The evaluation of such systems requires adequately designed and performed, head-to-head comparisons in clinical experimental studies. If you screen the available literature trying to find information about which CGM system is best for your patients, it will frequently give you a view of the past in a sense that most often the CGM systems described in these publications are not the ones that are still available on today's market. Thus, it is not only the hardware that is changing; the software implemented in these CGM systems is constantly changing, too. Attempts are being made by the Clinical & Laboratory Standards Institute to impose standardization about how to evaluate the performance of a given CGM system.

The analytical performance of the CGM sensor is the critical component of experimental AP systems. The major reasons why the development of closed-loop systems took so long was that no reliable systems for CGM were available. It was not until recently that needle-type CGM systems were developed and introduced to the market that can be used as an essential part of the three technical devices that are required to close the loop: CGM system, computer with algorithm, and insulin pump. The currently available CGM systems are not approved for usage in closed-loop systems for several reasons. In view of the small therapeutic window of insulin and the danger of the infusion of too much insulin due to an insufficient glucose measurement, the quality of the CGM system is critical. Thus, the demands on the performance of CGM systems in daily life are quite high. In essence, the currently available CGM systems do not fulfill these requirements; however, their performance is improving from generation to generation. Beside the improvement of quality of glucose measurement per se, there are several options to enhance the precision and accuracy of the measured glucose signal by mathematical measures. Reduction of noise, reduction of measurement errors due to delay, etc., are valid options.

By the end of last year, the U.S. FDA issued a draft guidance document that aims to provide adequate guidance and instruction to facilitate the development and marketing of an AP system while, at the same time, adopting a flexible approach. In a nutshell, the FDA wants to see for such studies that the clinical study design matches the indications for use, that study design conditions challenge the system, and that the data clearly demonstrate safety and effectiveness, Heinemann explained.

With these aspects in mind, Heinemann and colleagues established the so-called AP@home Consortium 2 years ago, of which the coordinators are Hans de Vries from the University of Amsterdam and Heinemann himself. The aim of AP@home is to bring the AP system to the patient's home by following two different approaches. The first phase is the so-called two-port approach, which means that AP algorithms will be tested with CGM systems and insulin pumps already available on the market; thus this approach requires two skin punctures to attach the CGM sensor and the insulin pump infusion set. In parallel, in the second phase, innovative AP systems will be developed that combine the insulin pump and CGM system into a single device that uses only one access point through the skin.

One study initiated by the AP@home consortium, the CAT trial, takes particularly care of the FDA considerations. (CAT stands for Comparison of two Artificial pancreas systems for closed loop blood glucose control vs. open control in people with T1D.) "With 48 subjects, the CAT trial to my knowledge is by far the largest AP study that has been performed so far," Heinemann stated. The aim of the CAT trial is to compare the performance of two algorithms used with the same devices versus insulin pump delivery based on SMBG (control arm) in the three main life conditions (rest, meal, and exercise) over 24-h periods. First results of the CAT trial were presented at the ADA annual meeting (intention-to-treat analysis)⁵³ and will be presented at the EASD annual meeting (PP analysis).

CGM systems are available today that allow developing closed-loop systems. Nevertheless, for regulatory approval of such systems, CGM systems with further improved properties are required; however, there are many options for improvement. Heinemann closed his talk with the following conclusions:

- The quality of CGM systems has a significant impact on the quality of AP performance.
- Principal contributors to sensor error are calibration, blood-to-interstitial time lag, and temporary loss of sensitivity.
- Recent studies show that the accuracy of currently available CGM systems is largely comparable, with different devices having advantage on different accuracy metrics.
- Algorithmic strategies exist that could alleviate sensor errors.

Keynote Lecture—Good Bugs or Bad Bugs? The Role of the Gut Microbial Ecosystem in Obesity and Diabetes

*Liping Zhao, Shanghai Jiao Tong University,
Shanghai, China*

As a highlight of the symposium, Liping Zhao presented a keynote lecture on the gut microbial ecosystem and its role in obesity and diabetes. In developed countries like the United States and rapidly developing countries like China and India, people face a devastating epidemic of diet-related chronic diseases, particularly obesity and diabetes. According to Zhao, a paradigm shift in many fronts of medicine is necessary to reverse this epidemic:

The most important [paradigm shift] is the adoption of the supraorganism concept as proposed by the Nobel laureate,

Joshua Lederberg. Basically, human beings are supra-organisms because within our body we have two types of cells. We have 10% human cells and 90% microbial cells, mostly bacterial cells. We have 1% of the genetic information in our body encoded in our human genome, but 99% of the genetic information in our body is actually encoded in our microbiome, particularly our gut microbiome. Our gut microbiome can be regarded as our second genome acquired after birth. But it will be with us for the rest of our life. So anything we take into our system will be co-transformed and co-metabolized by genes and functions encoded in our human genome and our microbiome. And that affects our health.

How much can our gut microbiome affect our health? Gut microbiota, as the second genome for humans, must work in harmonious integration with the first genome to sustain a healthy immunity and metabolism for the host. In animal models, diet has been shown to play a dominating role in shaping gut microbiota. Long-term intake of high-fat diet can override host genetics such that wild-type animals with no known relevant genetic defect can develop severe obesity and insulin resistance.

The relationship between gut microbiota and obesity has become the forefront in this field. Since 2004, publications have shown that gut microbiota can work as an internalized environmental factor to regulate fat storage. Therefore, gut microbiota can ferment otherwise indigestible plant polysaccharides into assorted fatty acids that can be used as an energy source by colon cells. More important is that disrupted gut microbiota can actually deregulate host genes involved in lipid metabolism.

Thus, high-fat diet can disrupt gut microbiota to increase population levels of opportunistic pathogens such as sulfate-reducing bacteria and decrease the levels of gut barrier-protecting bacteria, such as bifidobacteria. This long-term dysbiosis would lead to an increased antigen load in the host's bloodstream to provoke an unresolved chronic inflammation impairing the insulin receptor for development of metabolic diseases.

Is it possible to identify key functional players that are most relevant to obesity and diabetes development? It was this question that has triggered Zhao to propose a strategy called microbiome-wide association studies, which, in some way, is comparable to genome-wide association studies. "The difference is that in addition to a cross-sectional study design, one can also do a longitudinal design or interventional study because the secondary genome is structurally manipulable. Therefore, it is possible to use diet or other nutritional or pharmaceutical agents to change the gut microbiota and see how it changes the host phenotype," Zhao explained. It is interesting that he found out that diet seems to be the most important factor in shaping our gut microbiota structure. He also succeeded in doing a detailed quantitative analysis of the composition of gut microbiota of the animals that had 516 species-level phenotypes and identified 65 key species that are the most relevant to the change of diet, host genotype, or host health phenotype. The analysis showed that the more high-fat diet the animal ate, the higher the population level of the opportunist pathogens, which might explain the finding "that wild type eat the largest amount of the high-fat diet, they have the highest level of this particular bacteria, this pathogen,

and they had the most severe obese and insulin-resistant phenotype."

This new understanding of the key mediating role of gut microbiota between high-fat diet and deranged host metabolism opens vast possibilities for discovering new biomarkers with gut microbiota as a target in preventive management of the epidemic of metabolic diseases. Our animal and human trial data indicate that monitoring structural shifts of gut microbiota, changes of lipopolysaccharide-binding protein, inflammatory cytokines, and fasting insulin levels may constitute a new set of biomarkers for early detection and nutritional prevention of the metabolic syndrome as they reflect the cascades of molecular events from diet-disrupted gut microbiota to increased antigen load to the host to provoked inflammation to insulin resistance. Applications of such gut microbiota-based biomarkers may add new tools in our arsenals for fighting with diabetes in a preventive, predictive, and personalized way.

Acknowledgments

We thank the following presenters for their contribution: Satish K. Garg, Matthias Axel Schweitzer, Helena Wachslicht Rodbard, Oliver Schnell, Lawrence Fisher, Jill Weissberg-Benchell, Lisa Huse, Suzanne Sysko Clough, Paul Ciechanowski, Donal O'Shea, Guntram Scherthaner, Moshe Phillip, Ian Blumer, Eric Renard, Hans-Joachim Lüddecke, Sean Dinneen, Tadej Battelino, Peter Hammond, Dirk Voelkel, Lutz Heinemann, and Liping Zhao.

Author Disclosure Statement

A.M. is an employee of Adecco Human Resources GmbH. C.-T.T. and C.S. are employees of Roche Diagnostics GmbH. H.H. declares no competing financial interests exist.

References

- Riddle M, Umpierrez G, DiGenio A, Zhou R, Rosenstock J: Contributions of basal and postprandial hyperglycemia over a wide range of A1C levels before and after treatment intensification in type 2 diabetes. *Diabetes Care* 2011;34:2508–2514.
- ORIGIN Trial Investigators, Gerstein HC, Bosch J, Dagenais GR, Díaz R, Jung H, Maggioni AP, Pogue J, Probstfield J, Ramachandran A, Riddle MC, Rydén LE, Yusuf S: Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 2012;367:319–328.
- Borg R, Kuenen JC, Carstensen B, Zheng H, Nathan DM, Heine RJ, Nerup J, Borch-Johnsen K, Witte DR; ADAG Study Group: HbA_{1c} and mean blood glucose show stronger associations with cardiovascular disease risk factors than do postprandial glycaemia or glucose variability in persons with diabetes: the A1C-Derived Average Glucose (ADAG) study. *Diabetologia* 2011;54:69–72.
- Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, Colette C: Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA* 2006;295:1681–1687.
- Vigersky RA, Fonda SJ, Chellappa M, Walker MS, Ehrhardt NM: Short- and long-term effects of real-time continuous glucose monitoring in patients with type 2 diabetes. *Diabetes Care* 2012;35:32–38.
- Garg S, Brazg RL, Bailey TS, Buckingham BA, Slover RH, Klonoff DC, Shin J, Welsh JB, Kaufman FR: Reduction in duration of hypoglycemia by automatic suspension of insulin delivery: the in-clinic ASPIRE study. *Diabetes Technol Ther* 2012;14:205–209.
- IDF Clinical Guidelines Taskforce in collaboration with the SMBG International Working Group: Self-monitoring of blood glucose in non-insulin-treated type 2 diabetes. International Diabetes Federation. 2009. www.idf.org/webdata/docs/SMBG_EN2.pdf (accessed October 2, 2012).
- Klonoff DC, Blonde L, Cembrowski G, Chacra AR, Charpentier G, Colagiuri S, Dailey G, Gabbay RA, Heinemann L, Kerr D, Nicolucci A, Polonsky W, Schnell O, Vigersky R, Yale JF; Coalition for Clinical Research-Self-Monitoring of Blood Glucose Scientific Board: Consensus report: the current role of self-monitoring of blood glucose in non-insulin-treated type 2 diabetes. *J Diabetes Sci Technol* 2011;5:1529–1548.
- Fisher L, Hessler D, Naranjo D, Polonsky W: AASAP: a program to increase recruitment and retention in clinical trials. *Patient Educ Couns* 2012;86:372–377.
- Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE, Thomas S, Abood B, Nissen SE, Bhatt DL: Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med* 2012;366:1567–1576.
- Lenhart A, Ling R, Campbell S, Purcell K: Teens and Mobile Phones. April 20, 2010. www.pewinternet.org/Reports/2010/Teens-and-Mobile-Phones.aspx (accessed August 9, 2012).
- Burd SA: How Safeway Is Cutting Health-Care Costs. June 12, 2009. <http://online.wsj.com/article/SB124476804026308603.html> (accessed August 10, 2012).
- Funnell MM, Brown TL, Childs BP, Haas LB, Hoseney GM, Jensen B, Maryniuk M, Peyrot M, Piette JD, Reader D, Siminerio LM, Weinger K, Weiss MA: National standards for diabetes self-management education. *Diabetes Care* 2012;35(Suppl 1):S101–S108.
- Department of Health and Human Services: Healthy People 2010, 2nd ed. With Understanding and Improving Health and Objectives for Improving Health. 2 volumes. Washington, DC: U.S. Government Printing Office, 2000.
- Sherifali D, Greb JL, Amirthavasar G, Hunt D, Haynes RB, Harper W, Holbrook A, Capes S, Goeree R, O'Reilly D, Pullenayegum E, Gerstein HC: Effect of computer-generated tailored feedback on glycemic control in people with diabetes in the community: a randomized controlled trial. *Diabetes Care* 2011;34:1794–1798.
- Quinn CC, Clough SS, Minor JM, Lender D, Okafor MC, Gruber-Baldini A: WellDoc mobile diabetes management randomized controlled trial: change in clinical and behavioral outcomes and patient and physician satisfaction. *Diabetes Technol Ther* 2008;10:160–168.
- Quinn CC, Shardell MD, Terrin ML, Barr EA, Ballew SH, Gruber-Baldini AL: Cluster-randomized trial of a mobile phone personalized behavioral intervention for blood glucose control. *Diabetes Care* 2011;34:1934–1942.
- Wagner EH, Davis C, Schaefer J, Von Korff M, Austin B: A survey of leading chronic disease management programs: are they consistent with the literature? *Manag Care Q* 1999;7:56–66.
- Ramadas A, Quek KF, Chan CK, Oldenburg B: Web-based interventions for the management of type 2 diabetes mellitus:

- a systematic review of recent evidence. *Int J Med Inform* 2011;80:389–405.
20. Nijland N, van Gemert-Pijnen JE, Kelders SM, Brandenburg BJ, Seydel ER: Factors influencing the use of a Web-based application for supporting the self-care of patients with type 2 diabetes: a longitudinal study. *J Med Internet Res* 2011; 13:e71.
 21. Brown RF, Butow PN, Dunn SM, Tattersall MH: Promoting patient participation and shortening cancer consultations: a randomised trial. *Br J Cancer* 2001;85:1273–1279.
 22. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L, Nanni G, Pomp A, Castagneto M, Ghirlanda G, Rubino F: Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med* 2012;366:1577–1585.
 23. Buse JB, Caprio S, Cefalu WT, Ceriello A, Del Prato S, Inzucchi SE, McLaughlin S, Phillips GL 2nd, Robertson RP, Rubino F, Kahn R, Kirkman MS: How do we define cure of diabetes? *Diabetes Care* 2009;32:2133–2135.
 24. Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, Bantle JP, Sledge I: Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med* 2009;122:248–256.e5.
 25. Pournaras DJ, Aasheim ET, Søvik TT, Andrews R, Mahon D, Welbourn R, Olbers T, le Roux CW: Effect of the definition of type II diabetes remission in the evaluation of bariatric surgery for metabolic disorders. *Br J Surg* 2012;99:100–103.
 26. Bolen SD, Chang HY, Weiner JP, Richards TM, Shore AD, Goodwin SM, Johns RA, Magnuson TH, Clark JM: Clinical outcomes after bariatric surgery: a five-year matched cohort analysis in seven US states. *Obes Surg* 2012;22:749–763.
 27. Marsk R, Jonas E, Rasmussen F, Näslund E: Nationwide cohort study of post-gastric bypass hypoglycaemia including 5,040 patients undergoing surgery for obesity in 1986–2006 in Sweden. *Diabetologia* 2010;53:2307–2311.
 28. de Beaufort CE, Swift PG, Skinner CT, Aanstoot HJ, Aman J, Cameron F, Martul P, Chiarelli F, Daneman D, Danne T, Dorchy H, Hoey H, Kaprio EA, Kaufman F, Kocova M, Mortensen HB, Njølstad PR, Phillip M, Robertson KJ, Schoenle EJ, Urakami T, Vanelli M; Hvidoere Study Group on Childhood Diabetes 2005; Continuing stability of center differences in pediatric diabetes care: do advances in diabetes treatment improve outcome? The Hvidoere Study Group on Childhood Diabetes. *Diabetes Care* 2007;30:2245–2250.
 29. Govan L, Wu O, Briggs A, Colhoun HM, Fischbacher CM, Leese GP, McKnight JA, Philip S, Sattar N, Wild SH, Lindsay RS; Scottish Diabetes Research Network Epidemiology Group: Achieved levels of HbA1c and likelihood of hospital admission in people with type 1 diabetes in the Scottish population: a study from the Scottish Diabetes Research Network Epidemiology Group. *Diabetes Care* 2011;34:1992–1997.
 30. Bryant W, Greenfield JR, Chisholm DJ, Campbell LV: Diabetes guidelines: easier to preach than to practise? *Med J Aust* 2006;185:305–309.
 31. Nimri R, Weintrob N, Benzaquen H, Ofan R, Fayman G, Phillip M: Insulin pump therapy in youth with type 1 diabetes: a retrospective paired study. *Pediatrics* 2006;117:2126–2131.
 32. Pickup JC: Insulin-pump therapy for type 1 diabetes mellitus. *N Engl J Med* 2012;366:1616–1624.
 33. de Vries L, Grushka Y, Lebenthal Y, Shalitin S, Phillip M: Factors associated with increased risk of insulin pump discontinuation in pediatric patients with type 1 diabetes. *Pediatr Diabetes* 2011;12:506–512.
 34. Berthe E, Lireux B, Coffin C, Goulet-Salmon B, Houlbert D, Boutreux S, Fradin S, Reznik Y: Effectiveness of intensive insulin therapy by multiple daily injections and continuous subcutaneous infusion: a comparison study in type 2 diabetes with conventional insulin regimen failure. *Horm Metab Res* 2007;39:224–229.
 35. Wainstein J, Metzger M, Boaz M, Minuchin O, Cohen Y, Yaffe A, Yerushalmy Y, Raz I, Harman-Boehm I: Insulin pump therapy vs. multiple daily injections in obese Type 2 diabetic patients. *Diabet Med* 2005;22:1037–1046.
 36. Raskin P, Bode BW, Marks JB, Hirsch IB, Weinstein RL, McGill JB, Peterson GE, Mudaliar SR, Reinhardt RR: Continuous subcutaneous insulin infusion and multiple daily injection therapy are equally effective in type 2 diabetes: a randomized, parallel-group, 24-week study. *Diabetes Care* 2003;26:2598–2603.
 37. Herman WH, Ilag LL, Johnson SL, Martin CL, Sinding J, Al Harthi A, Plunkett CD, LaPorte FB, Burke R, Brown MB, Halter JB, Raskin P: A clinical trial of continuous subcutaneous insulin infusion versus multiple daily injections in older adults with type 2 diabetes. *Diabetes Care* 2005;28: 1568–1573.
 38. Monami M, Lamanna C, Marchionni N, Mannucci E: Continuous subcutaneous insulin infusion versus multiple daily insulin injections in type 2 diabetes: a meta-analysis. *Exp Clin Endocrinol Diabetes* 2009;117:220–222.
 39. Selam JL, Raymond M, Jacquemin JL, Orsetti A, Richard JL, Mirouze J: Pharmacokinetics of insulin infused intraperitoneally via portable pumps. *Diabetes Metab* 1985;11: 170–173.
 40. Giacca A, Caumo A, Galimberti G, Petrella G, Librenti MC, Scavini M, Pozza G, Micossi P: Peritoneal and subcutaneous absorption of insulin in type I diabetic subjects. *J Clin Endocrinol Metab* 1993;77:738–742.
 41. Schaepelynck-Bélicar P, Vague P, Simonin G, Lassmann-Vague V: Improved metabolic control in diabetic adolescents using the Continuous Glucose Monitoring System (CGMS). *Diabetes Metab* 2003;29:608–612.
 42. Oskarsson PR, Lins PE, Backman L, Adamson UC: Continuous intraperitoneal insulin infusion partly restores the glucagon response to hypoglycaemia in type 1 diabetic patients. *Diabetes Metab* 2000;26:118–124.
 43. Saudek CD, Duckworth WC, Giobbie-Hurder A, Henderson WG, Henry RR, Kelley DE, Edelman SV, Zieve FJ, Adler RA, Anderson JW, Anderson RJ, Hamilton BP, Donner TW, Kirkman MS, Morgan NA: Implantable insulin pump vs multiple-dose insulin for non-insulin-dependent diabetes mellitus: a randomized clinical trial. Department of Veterans Affairs Implantable Insulin Pump Study Group. *JAMA* 1996;276:1322–1327.
 44. Liebl A, Hoogma R, Renard E, Geelhoed-Duijvestijn PH, Klein E, Diglas J, Kessler L, Melki V, Diem P, Brun JM, Schaepelynck-Bélicar P, Frei T; European DiaPort Study Group: A reduction in severe hypoglycaemia in type 1 diabetes in a randomized crossover study of continuous intraperitoneal compared with subcutaneous insulin infusion. *Diabetes Obes Metab* 2009;11:1001–1008.
 45. Heinemann L, Nosek L, Kapitza C, Schweitzer MA, Krinelke L: Changes in basal insulin infusion rates with subcutaneous insulin infusion: time until a change in metabolic effect is induced in patients with type 1 diabetes. *Diabetes Care* 2009;32:1437–1439.

46. King AB, Armstrong DU: A prospective evaluation of insulin dosing recommendations in patients with type 1 diabetes at near normal glucose control: basal dosing. *J Diabetes Sci Technol* 2007;1:36–41.
47. Atlas E, Nimri R, Miller S, Grunberg EA, Phillip M: MD-Logic artificial pancreas system: a pilot study in adults with type 1 diabetes. *Diabetes Care* 2010;33:1072–1076.
48. Murphy HR, Rayman G, Lewis K, Kelly S, Johal B, Duffield K, Fowler D, Campbell PJ, Temple RC: Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial. *BMJ* 2008;337:a1680.
49. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Tamborlane WV, Beck RW, Bode BW, Buckingham B, Chase HP, Clemons R, Fiallo-Scharer R, Fox LA, Gilliam LK, Hirsch IB, Huang ES, Kollman C, Kowalski AJ, Laffel L, Lawrence JM, Lee J, Mauras N, O'Grady M, Ruedy KJ, Tansey M, Tsalikian E, Weinzimer S, Wilson DM, Wolpert H, Wysocki T, Xing D: Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 2008;359:1464–1476.
50. Scaramuzza AE, Iafusco D, Rabbone I, Bonfanti R, Lombardo F, Schiaffini R, Buono P, Toni S, Cherubini V, Zuccotti GV; Diabetes Study Group of the Italian Society of Paediatric Endocrinology and Diabetology: Use of integrated real-time continuous glucose monitoring/insulin pump system in children and adolescents with type 1 diabetes: a 3-year follow-up study. *Diabetes Technol Ther* 2011;13:99–103.
51. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Bode B, Beck RW, Xing D, Gilliam L, Hirsch I, Kollman C, Laffel L, Ruedy KJ, Tamborlane WV, Weinzimer S, Wolpert H: Sustained benefit of continuous glucose monitoring on A1C, glucose profiles, and hypoglycemia in adults with type 1 diabetes. *Diabetes Care* 2009;32:2047–2049.
52. Hammond PJ, Amiel SA, Dayan CM, Kerr D, Pickup JC, Shaw JAM, Campbell FM, Greene SA, Hindmarsh PC: ABCD position statement on continuous glucose monitoring: use of glucose sensing in outpatient clinical diabetes care. *Pract Diab Int* March 2010;27:66–68.
53. de Vries JH, Avogaro A, Benesch C, Bruttomesso D, Caldwell K, Cobelli, Doll W, Del Favero S, Heinemann L, Hovorka R, Leelarathna L, Luijck YM, Mader J, Magni L, Nodale M, Place J, Renard E, Toffanin C; AP@HOME CONSORTIUM: Comparison of two closed loop algorithms with open loop control in type 1 diabetes. Presented at the American Diabetes Association, 72nd Scientific Sessions, Philadelphia, 2012.

Address correspondence to:

Hilary Hoey, M.A., M.D., FRCPI, FRCPC UK

Ivy House

Main Street

Leixlip, Co. Kildare, Ireland

E-mail: hilaryhoey@eircom.net