MEETING REPORT

7th Annual Symposium on Self-Monitoring of Blood Glucose (SMBG), May 8–10, 2014, Helsinki, Finland

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Abstract

International experts in the fields of diabetes, diabetes technology, endocrinology, mobile health, sport science, and regulatory issues gathered for the 7th Annual Symposium on Self-Monitoring of Blood Glucose (SMBG). The aim of this meeting was to facilitate new collaborations and research projects to improve the lives of people with diabetes. The 2014 meeting comprised a comprehensive scientific program, parallel interactive workshops, and two keynote lectures.

News from Around the World

Challenges and Role of New Technologies in Management of Type 1 Diabetes

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Rising prevalence, cost, and obesity. Approximately 30 million (10%) people in the United States have diabetes. The United States currently spends over \$245 billion annually on the direct and indirect costs associated with diabetes, an increase of 41% from 2007. It is estimated that approximately one in three Americans will have diabetes by 2050 and that, globally, almost more than 600 million people will have diabetes by 2035. The prevalence of diabetes is greatest among older individuals. In the United States, 27% of those individuals with diabetes are >65 years of age.

Glycated hemoglobin and hypoglycemia issues. Although earlier studies showed that lower glycated A1c (HbA1c) is associated with increased hypoglycemia, a recent study by Lipska et al.¹ showed that the curve for hypoglycemia risk is “J”-shaped: the risk becomes greater when HbA1c levels rise about 8.5% and thus may not be related to intensification of insulin therapy. However, in a recent report² that compared type 1 diabetes cohorts from the T1D Exchange Registry (n = approximately 26,000) and Germany and Austria (n = approximately 85,500), it was found that European pediatric patients had significantly lower HbA1c levels than the T1D Exchange cohort (7.4% vs. 8.2%; P < 0.001), but with a lower percentage of patients having experienced one or more severe hypoglycemic events during the past year (2% vs. 3%; P = 0.19).

Role of new technologies: mobile technologies. Use of mobile technologies is becoming increasingly important. In a recent 6-month randomized study of people with type 1 diabetes, investigators looked at the use of a blood glucose meter (iBGStar[®]; Sanofi, Bridgewater, NJ) connected to an iPhone[®] (Apple, Cupertino, CA) (treatment group, n = 50) compared with use of a traditional blood glucose meter (Accu-Chek[®]; Roche Diagnostics, Indianapolis, IN) (control group, n = 50).³ It was hypothesized that the ability to communicate with physician offices without having to attend clinic visits would facilitate better glycemic outcomes. At 6 months, the treatment group showed a significantly greater reduction in HbA1c than the control group (−0.51% vs. −0.15%; P = 0.036).

Continuous glucose monitoring. Use of continuous glucose monitoring (CGM) has been associated with HbA1c reductions of approximately 0.5–1.0%. Although it is generally thought that CGM use is only effective in people with good glycemic control, an early study showed benefits in both groups: greater time spent in target range among people with >9% HbA1c and less time spent in the hypoglycemic range in people with ≤7.0% HbA1c.⁴ Additionally, a more recent prospective study showed that use of CGM in combination with CSII provided greater glycemic benefits as compared with CGM use combined with multiple daily insulin injections (MDI) therapy.⁵

Despite these benefits, uptake of CGM technology has been relatively slow. Recent data from the T1D Exchange Registry show that only 9% of registered patients use CGM.

Closed-loop systems. It is generally accepted that the pathway to achieving the ideal closed-loop system involves

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five key steps: (1) a sensor-augmented insulin pump (SAP); (2) an SAP with a threshold-suspend (TS) feature that automatically stops insulin infusion when glucose drops below a preset level (low glucose suspend [LGS]); (3) an overnight closed-loop system; (4) a predictive closed-loop system; and (5) a closed-loop “bionic” system that mimics biologic response.

In a recent study that evaluated SAP therapy with and without the TS feature in people with type 1 diabetes with nocturnal hypoglycemia, investigators found that the mean area under the curve for nocturnal hypoglycemic events was 38% lower in the TS group than in the control group ($P < 0.001$).⁶

Although many of the steps required for an effective closed-loop system have already been developed or their development is ongoing, one challenge that remains is developing rapid-acting insulins with a faster onset of action.

Summary. We have traditionally focused on improving HbA1c; however, recent data show that even modest reductions in HbA1c result in significant decreases in complications. It is important to pay more attention to hypoglycemia, particularly in older patients, because this is the largest and fastest growing part of the population. Mobile technologies will play an increasingly important role in diabetes management as diabetes prevalence increases. Cost and implementation hurdles must be considered.

The Evolving Role of Diabetes Management Solutions

Translating Glucose Data into Clinically Meaningful Action with Diabetes Management Solutions (DMS)

Matthias Axel Schweitzer, Roche Diabetes Care, Mannheim, Germany

Personalized diabetes management. Personalized diabetes management is based on a model of care recently proposed in a position article by Ceriello et al.⁷ The model incorporates collaborative use of structured self-monitoring of blood glucose (SMBG) data into a formal process that individualizes therapy via a recurring cycle of six defined steps: (1) structured patient education; (2) initiation of structured glucose monitoring; (3) electronic documentation and visualization of glucose data and other key information; (4) analysis of data; (5) selection/initiation of personalized therapy regimen; and (6) assessment of therapy efficacy.

Roche Diagnostics is developing “product solutions” that are designed to facilitate implementation of these steps through glucose monitoring technologies that support use of structured testing, assist patients in therapy decision-making (e.g., meters with integrated bolus advisors), and provide seamless downloading of data for more accurate and efficient data interpretation.

Use of SMBG: frequency and regimens. The T1D Exchange Registry provides evidence of a strong correlation between the frequency of SMBG and glycemic outcomes. Findings from a recent study of 148 people with type 1 diabetes in Japan provide additional support for this correlation.⁸ Earlier studies from Kaiser Permanente and more recent trials have shown similar relationships between SMBG frequency and glycemic outcomes in individuals with type 2 diabetes.

Data from these studies have been used to support current clinical guidelines (2013 from the American Diabetes As-

sociation [ADA]), which recommend a minimum of three or four tests per day and for many patients six to eight times per day. This level of frequency was supported by a recent study finding that a testing frequency of more than four times per day has the highest influence on glycemic control.⁹

Structured SMBG regimens. Numerous recent studies have shown that use of structured testing regimens improves glycemic control and other outcomes.^{10,11} Although these studies provide strong support for the International Diabetes Federation guidelines through controlled and observational study designs, a recent commentary by Selker et al.¹² proposed a more formal “efficacy-to-effectiveness” (E2E) clinical trial design for evaluating behavior-based interventions such as those used in structured SMBG studies. Efficacy trials would be used to evaluate interventions in relatively homogeneous samples of participants with adherence to rigorous clinical protocols, whereas effectiveness trials would generate heterogeneous samples with protocols that approximate real-world clinical care settings. This approach was used in the STeP trial,¹⁰ a cluster randomized controlled trial (RCT) that demonstrated the efficacy of structured SMBG when used as the primary component of a comprehensive intervention. A follow-up survey of clinicians enrolled in the STeP study (STeP PLUS) found that the structured testing intervention was still being used in practices 2 years after the STeP study had been completed.

Findings from the STeP PLUS survey not only provide additional support for the efficacy of the intervention, but they also suggest a relatively high level of effectiveness in real-world clinical practice. The effectiveness of the STeP intervention has since been demonstrated in several observational studies, the most recent being the STeP IT UP study, which followed 98 non-insulin-treated patients in Australia.¹³

Importance of “connectivity.” Roche Diagnostics is very close to achieving connectivity through the Accu-Chek® Connect system. The system automatically uploads blood glucose meter and insulin pump data to a smartphone application. The data are then automatically sent to a “cloud” storage platform, which can be accessed by diabetes patients/caregivers and their healthcare providers. Although further studies are needed to evaluate the medical value of the system, the concept of using technology that connects patients with their healthcare providers and thus enables them to interact in meaningful ways has already been tested.

New technology priorities. Looking ahead, Roche Diagnostics will continue to focus on advanced technologies to develop products that support personalized diabetes management. The company also has a robust research program in place to evaluate the efficacy and effectiveness of these product solutions as they become available. The goal is to help individuals with diabetes achieve their treatment targets.

Diabetes Management Solutions for Data Collection, Sharing, Patient Management, and Reimbursement

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Background. The Greater Buffalo United Accountable Healthcare Network (GBUAHN), Buffalo, NY, is part of a

New York State initiative to make healthcare services more efficient for Medicaid patients and improve the well-being of the community. The goals of this initiative are to reduce ambulatory-sensitive admissions, emergency room utilization rates, and 30-day re-admission rates.

Health Home model. The Health Home model is an integrated approach to care, authorizing a single organization to coordinate all care, including follow-up after medical visits and referrals to social services that Medicaid and other forms of insurance generally do not reimburse. A “care navigator” is assigned to work closely with each patient to ensure that he or she receives needed care and services. Fundamental to the Health Home model are six core competencies:

1. *Comprehensive care management* requires an environmental approach, encompassing both physical and behavioral care plans. A key component of this competency is setting goals for each patient and establishing processes to track mental and physical assessments, reassessments, and treatment plans, combining Internet technology with face-to-face interactions.
2. *Care coordination* is a process of providing a continuum of care to patients within and outside of the clinician office, which is monitored, accessed, and tracked through the use of various modes of technology.
3. *Health promotion* involves educating patients about their disease and management plans. The rationale for this is that educated patients are more amenable to adhering to the medical recommendations of their healthcare providers.
4. *Comprehensive transitional care* utilizes a team of “health navigators” within GBUAHN who oversee and coordinate patient care for approximately 100 patients each. The health navigators take a “concierge” service approach to patients, looking at both their diabetes care and any mental health issues that can make diabetes difficult to manage. This holistic compilation fosters concise documentation and proactive care.
5. *Individual and family support* taps into the strengths of individual accountability and family support to facilitate improved adherence to treatment and empower patients.
6. *Referral to community resources* involves partnering with community organizations that can provide additional support to patients.

Utilization of information technology. Health information technology (HIT) is critical to the integration of medical, behavioral, social, and addiction services into a single stream of delivery. GBUAHN has invested heavily in several specific HIT tools to facilitate integration of services. These tools include:

- Electronic health records to perform documentation tasks, populate patient registries, and create structured data
- Patient registries to act as the central database for patient monitoring and care management within the care coordination loop
- Health information exchange on a real-time basis to enable coordination of care
- Risk stratification to classify patients by their health status and health risk

- Automated outreach to generate messaging to patients who need preventive or chronic disease care and mental health management
- Referral tracking to ensure member compliance and adherence to plan of care and receipt of test result
- Patient portals to engage patients and/or family members in healthcare self-management and coping strategies, respectively
- Telemedicine to engage patients between face-to-face visits and to help reduce those in-person encounters
- Remote patient monitoring to allow for quick physician intervention and enable patient control of chronic conditions
- Advanced population analytics that allow evaluation of patient population segments and assessment of organizational performance.

Expanding the Health Home model into a Medical Neighborhood. The Medical Neighborhood builds upon the Health Home model and serves as a continuous and coordinative ecosystem that begins with patients’ primary care and links to broader communities (e.g., pharmacies, faith-based organization), while accounting for social and environmental factors that impact health. An example of this is GBUAHN’s alliance with Rite Aid, a national pharmacy chain. Rite Aid provides a designated care coach, who assists patients in achieving specific goals such as smoking cessation, blood pressure coaching, medication reconciliation, and diabetes management. Although the primary focus of the Medical Neighborhood is on meeting the needs of the individual patient, it also incorporates aspects of population health and overall community health needs in its objectives.

Results from the BABE Study, a Retrospective Study on the Use of Accu-Chek® Combo and its Bolus Advisor in a Pediatric Population

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(NOTE: The BABE study results have been submitted for publication. Because of the editorial restrictions of the journal, only a description of the study and a summary of the findings can be presented here.)

Background. Safe and efficacious use of basal-bolus insulin therapy is often challenging in children and adolescent patients. Use of insulin pumps with an integrated automated bolus advisor can address the inherent challenges of basal-bolus therapy by eliminating the need for manual meal and correction bolus insulin calculation. Use of automated bolus advisors improves preprandial and postprandial glycemic control, reduces hypoglycemic episodes, and facilitates more persistent intensification of insulin therapy when used in conjunction with data management software; however, the relationship between frequency of automated bolus advisor use and glycemic improvement has not been well studied in this population.

Bolus Advisor Benefit Evaluation study. The Bolus Advisor Benefit Evaluation (BABE) study was a single-center, retrospective cohort evaluation that assessed the impact of

frequent use of the Accu-Chek® Aviva Combo system bolus advisor feature on glycemic control among 104 pediatric type 1 diabetes patients on insulin pump therapy treated at a pediatric diabetology clinic in Germany. In the study, HbA1c values, hypoglycemia, insulin parameter changes, mean blood glucose, and glycemic variability (SD) were assessed at baseline and after 3 and 6 months of bolus advisor use. For the assessment, patients were categorized as follows: high-frequency users, which included patients who reported regularly using the bolus advisor feature $\geq 50\%$ of the time, and low-frequency users, which included patients who reported $<50\%$ bolus advisor use.

Summary of findings. At 6 months, over two-thirds of patients reported high-frequency use of the bolus advisor. Frequent bolus advisor use was associated with improved glycemic control with no increase in hypoglycemia but with persistent monitoring/adjustments of therapy. Subanalyses showed that this improvement persisted for 24 months; similar benefits were seen among adolescent frequent users.

Excellence in Sports Through New Digital Technologies—How Ample Data Are Condensed and Converted into Smart Athletic Action

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Background. Throughout the last decades there have been many innovations regarding the way we can control the different parameters that affect athletics. To leverage these innovations, we utilize a complete coaching process, which involves the following: pregame analyses of various player parameters (physiology and interaction with other players); game analyses of player performance (both competing teams); and postgame analyses to determine player and team effectiveness during the game and identify ways to improve performance.

The goal of the analyzing process is to transform raw data into identifiable performance indicators that are associated with success. These indicators are then validated and utilized to create sports performance profiles.

Current data management. Current data management technologies are used to measure athletes' physiologic status (heart rate, blood lactate) during practice and competition. A global positioning system (GPS) is used to associate these measurements with performance. For example, it is possible to track and measure the specific times and distances a specific soccer player ran during a match. Using innovative photocell technology, it is also possible to analyze and assess the players' reaction and velocity in an objective way.

Data and video analysis technologies are also used for scouting. Scouting means preparation for a given competition by studying the opposing team. Acquiring information about the strengths/weaknesses and prior performance of a competitive team and its players and the ability to process and analyze this information allows us to prepare more effectively for an upcoming competition.

Game analysis. Two lines of research are generally used to analyze team and player performance during competition:

biomechanics and notational analysis. Through video analysis, the performance indicators that are most closely associated with game success can be identified. This allows coaches to compare and evaluate players from their own teams and from others.

Notational analysis to assess performance in team sports is used in current sport science research and is used by coaches when preparing their teams and players. Notational analysis is based on team sports and game situation and focuses on analyzing tactical and technical situations. Again, the purpose of this is to identify indicators of quality and performance. In basketball, for example, coaches are looking for ways to optimize the resources of both players and team and to meet the demands of a specific competitive team within a specific game. The parameters are never the same because of different competitive teams, venues (e.g., home vs. away game), and other circumstances (e.g., regular season play vs. championship game).

The overall goal of these analyses is to create a performance index for each player. This allows coaches to compare the reactions and interactions of players throughout the game. The index is calculated by adding the positive aspects of a given player's performance and then subtracting the negative aspects. For example, in basketball, the index may use number of points scored by a player (positive) versus number of missed shots (negative). Players can then be compared with other players to identify those who are most important to the team.

Summary. The revolution of the information communication technology has enhanced the understanding of sports, providing a wide and objective knowledge of the game and its basic components. Members of technical staff need to become experts in the team and in the individual players before being able to help them to improve their performance.

Keynote Lecture

Early Programming of Health and Disease—with Focus upon Type 2 Diabetes and Related Metabolic Outcomes

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Role of early nutrition. In the late 1980s, David Barker hypothesized that metabolic diseases, such as coronary heart disease (CHD), type 2 diabetes, and hypertension, originate in response to undernutrition during fetal life and infancy due to developmental plasticity; low birth weight was considered to be a proxy for maternal undernutrition. This hypothesis was supported by a study of CHD in more than 15,000 individuals, which showed a significantly higher mortality rate among both men and women with a birth weight of ≤ 5 pounds.¹⁴ Similar relationships between birth weight and other metabolic diseases have been demonstrated in a study¹⁵ that linked low birth weight with increased risk for impaired glucose tolerance and type 2 diabetes. The Helsinki Birth Cohort Study¹⁶ showed that the risk for CHD was highest in those individuals with low weight at birth but high body mass index (BMI) at 11 years of age.

The role of genes. Type 2 diabetes is often described as a genetic disorder; however, the role of genes in diabetes risk

may not be as great as once thought. Around 60 risk genes for type 2 diabetes have been identified so far. The most important one appears to be *TCF7L2*, with the risk allele having an odds ratio of 1.3; however, the risk allele for the majority of these genes is only around 1.05–1.10.

Low birth weight is associated with elevated fasting insulin, a marker of insulin resistance and type 2 diabetes.¹⁷ Because there is also an association between the peroxisome proliferator-activated receptor (PPAR)- γ 2 gene and type 2 diabetes, whether the effects of the Pro12Ala polymorphism of the PPAR- γ 2 gene on insulin concentrations in adult life are modified by birth weight was also assessed.¹⁸ Results showed that the effects of the Pro12Pro and Pro12Ala polymorphism of the PPAR- γ 2 gene in elderly individuals were dependent upon birth weight, which suggests a gene–environment interaction.

Impact of lifestyle. In a 2004 study, results showed that subjects who were predisposed to type 2 diabetes because of a small birth size were strongly protected from glucose intolerance by regular exercise.¹⁹ However, exercise does provide the same protection in everyone.

Impact of meal composition. Recently, the impact of growth during infancy on postprandial responses to a fast-food meal and a meal that followed the macronutrient composition of the dietary guidelines was investigated.²⁰ Among the 24 subjects studied, results showed that small birth weight and slow early growth predicted postprandial triglyceride and insulin responses.

Environmental programming. The Dutch famine birth cohort study allowed researchers to look at the long-term impact of famine exposure in 2,414 individuals born during 1944–1945.²¹

It was found that people who had been exposed to famine in mid- or late gestation had reduced glucose tolerance. Although exposure during early gestation also affected glucose metabolism, it was also linked to other health issues such as a more atherogenic lipid profile, higher BMI, depression, and a higher risk for CHD.

Programming can take place through many mechanisms. Maternal stress during pregnancy can influence the health of the offspring during adulthood, by reprogramming hormonal systems like the hypothalamic–pituitary–adrenal axis. If the nutritional intake is not adequate, this could program the liver enzymes in a way that leads to changes in lipid and glucose metabolism and, potentially, to metabolic disease. Prenatal experiences can also affect body composition.

Extremely stressful experiences during early childhood can affect health later in life as well. An example of this is a study that looked at a cohort of adults who, as children, had been evacuated from their homes during World War II.²² In addition to higher prevalence of both cardiovascular disease and type 2 diabetes, the hypothalamic–pituitary–adrenal axis responses to psychosocial stress of these individuals also were significantly different from those of individuals who were not evacuated during the war.

Prenatal health. A study by Godfrey et al.²³ sought to confirm associations between umbilical cord CpG methylation and child's adiposity in a group of children from the

Southampton Women's Survey. Investigators measured the methylation status of CpGs in the promoters of candidate genes in DNA extracted from umbilical cord tissue obtained at birth in children who were later assessed for adiposity. It was shown that higher umbilical cord RXRA chr9:136355885 + methylation is associated with lower maternal carbohydrate intake during early pregnancy and increased fat mass in the children at 9 years of age. These results confirm that maternal dietary intake during pregnancy has a massive influence on obesity and body composition of the offspring through epigenetic mechanisms.

Epigenetics. Various factors within our environment can influence our genes, such as smoking, obesity, diet, medications, stress, and many others. It is also believed that these epigenetic changes are inherited from the mother to the child without any changes in the DNA sequence.

Impact of maternal obesity. With the growing trend toward unhealthy dietary habits and sedentary lifestyles, maternal obesity is an increasingly important concern. Even 20 years ago, a relationship between maternal obesity during pregnancy and prevalence of type 2 diabetes in offspring was detected among Pima Indians.²⁴ However, unlike the earlier studies discussed above, the relationship between birth weight and diabetes risk was “U-shaped,” with increased risk associated with both low (<2,500 g) and high (>4,500 g) birth weight.

More recently, it was reported that maternal obesity during pregnancy was associated with premature death from cardiovascular events in adult offspring. It is interesting that the consequences of maternal obesity in offspring tend to be gender specific: whereas diabetes and stroke are more prevalent in females, the prevalence of CHD is greater in males.

It is well known that obese women have more pregnancy complications, which are associated with cardiovascular risk in both women and their offspring. Within the next decade, >70% of fertile women will be overweight/obese. Because women are more receptive to advice about lifestyle before/during pregnancy, interventions that encourage healthy lifestyles in women prior to pregnancy would be valuable.

An example of this type of intervention is the RADIEL study (2008–2013), a randomized controlled multicenter intervention trial in women at high risk for diabetes (either a previous history of gestational diabetes or prepregnancy BMI of ≥ 30 kg/m²).²⁵ Participants planning pregnancy or in the first half of pregnancy were parallel-group randomized into an intervention arm, which received lifestyle counseling; the control arm received usual care given at their local antenatal clinics. Although results have not been published, very significant reductions in the development of gestational diabetes within the intervention group have been seen.

Summary. Several studies have demonstrated strong relationships between maternal health status (and early childhood experiences) and the development of several metabolic diseases in later life. It is, therefore, important to view disease prevention from a “life course” perspective. Interventions that target women before they get pregnant provide the greatest opportunities to prevent cardiovascular disease in two generations.

mHealth—How Is It Shaping Medicine?

Accu-Chek® Connect Reports Utility and Efficiency Study (ACCRUES): Methodology and Potential Implications

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Background. The clinical utility of SMBG is dependent upon the accuracy of the data reported and users' (clinicians' and patients') ability to accurately analyze and interpret the data in an efficient manner.

Although patients often have difficulty interpreting and acting upon the SMBG data recorded in their logbooks, a major obstacle for clinicians is obtaining complete and accurate data from patients.

Although use of diabetes management software and other diabetes-related measures has been shown to enhance glycemic control,^{26,27} the accuracy in interpreting data presented by these programs and the time required to use them effectively have not been well studied.

The Accu-Chek Connect Reports Utility and Efficiency Study. It was hypothesized that making data available in a format that facilitates identification of glucose patterns and other key information will likely improve accuracy and efficiency of data analysis and interpretation. To test this hypothesis, investigators conducted the Accu-Chek Connect Reports Utility and Efficiency Study (ACCRUES).

Study aim. The aim of the study was to assess the ability of clinicians, patients, and patient caregivers who are naive to diabetes management software to obtain and interpret data from SMBG, insulin administration, and carbohydrate intake, using the Accu-Chek Connect software compared with standard logbook use. For the study, screenshots of the various reports generated by the system were presented to the participants via a Web portal accessed from their computers.

Methods. This was a multicenter, prospective, self-controlled, randomized, virtual study. Investigators enrolled participants for five study groups: (1) 30 clinicians; (2) 20 patients treated with MDI; (3) 20 patients treated with continuous subcutaneous insulin infusion (CSII); (4) 20 caregivers of pediatric MDI-treated patients (≥ 18 years); and (5) 20 caregivers of pediatric CSII-treated patients (≥ 18 years).

An expert panel of diabetes specialists reviewed six clinical cases based on actual data from diabetes patient histories (three MDI, three CSII) and determined the correct multiple-choice responses regarding identification of meaningful diabetes information, recognition of glycemic patterns, and determination of appropriate diabetes management decisions. Cases were presented to the five study groups in software reports and standard logbook views in random order for analysis and interpretation via a secure Web portal.

Measurements included comparisons of performance relating to accuracy and time required to identify key diabetes information (e.g., SMBG statistics, insulin administration, carbohydrate intake), to identify clinically significant glycemic patterns, and to answer multiple-choice questions to determine appropriate treatment adjustments. Following the case assessments, participants were asked to complete a preference

questionnaire regarding their experiences with the software reports. Results from the study will be reported in mid-2014.

Potential implications. The study results may provide essential information regarding the accuracy and speed of the ability of patients, caregivers, and clinicians to obtain and act upon information relevant to diabetes management from the software reports compared with standard logbook presentations. Positive results would suggest that use of the software program could lead to improved glycemic control, enhanced safety, more appropriate selection of therapies, and, ultimately, better clinical outcomes. These benefits could potentially improve patient motivation and satisfaction, quality of patient-clinician interactions, and efficiency during clinic visits, office workflow, and cost efficiency.

Next steps. Roche Diagnostics is in the process of implementing a pilot study to evaluate user (patient, caregiver, and clinician) satisfaction and engagement when using the Accu-Chek Connect diabetes management system in real-life practice settings.

A Unique, Customizable Data Mining Module for Healthcare Professionals—A European Pilot Project

Maria-José Comellas, Roche Diagnostics, Barcelona, Spain

(NOTE: The talk was presented on behalf of Marta Ramón, Hospital Sant Joan de Déu, Barcelona, Spain.)

Background. Most patients use traditional logbooks to record their SMBG values; however, the format in which the data are presented can make it difficult to identify patterns. Although there are now many software programs that clinicians can use to download and analyze SMBG data, there are some associated barriers. Using these data management tools can be time intensive and cumbersome, and clinicians are required to learn to use and interpret the various charts and graphs. There is also the perception that they provide too much data for analysis within the short time available during clinic visits. Moreover, detecting patterns of glycemic control and other components of care can often be difficult. Automated pattern recognition tools are needed to support both clinicians and patients for more effective diabetes management.

Alertas pilot evaluation. The Alertas evaluation is a pilot project funded by Roche Diagnostics, Spain, that assessed the efficacy and efficiency of using an automated pattern detection module. The module is a component of the emminens eConnecta Web solution, a Web-based platform developed in Spain to assist healthcare professionals and patients in diabetes management. The module provides automatic pattern detection for hypoglycemia, hyperglycemia, and glucose variability to support treatment decision-making. The module allows clinicians to individualize the data output configurations for each patient. The objective of the project was to assess the time spent analyzing data and the number of patterns detected with the alerts module compared with the time and patterns detected without the module.

Design and methods. For the project, 16 clinicians (most of whom had experience with downloading glycemic data)

evaluated downloaded glycemic data presented in four patient data reports. The data reports were as follows: case 1, bolus calculator data over 4 weeks; case 2, bolus calculator data over 8 weeks; case 3, insulin pump data over 4 weeks; and case 4, insulin pump data over 12 weeks. Target ranges and hypoglycemia thresholds were specified for each data report.

Cases were presented to participants who were asked to visually analyze the data and identify all of the key patterns they detected. Participants' answers were recorded, and the time required to complete each case was measured and documented.

Results. The median time required by healthcare professionals to detect patterns of the four reports without the module was between 7 to 12 min, and the median number of patterns detected were between seven to 10. For example, results from case 1 showed that although 81% of participants were able to correctly identify patterns of hypoglycemia trends and hypoglycemia after lunch, only 63% identified a pattern of nocturnal hypoglycemia, and only 31% of participants identified hyperglycemia overcorrection. The summary of the percentage of nondetected patterns for the four cases without the module showed that they varied from 19% (hypoglycemia and hyperglycemia trend) in cases 1–3 to 87% (SD out of range) in case 2.

Conclusions. Overall, the results demonstrated that a significant amount of time is required to analyze patterns from patients downloads, approximately 10 min per case. There are many patterns to detect (glycemic and insulin data, device use, SMBG adherence) in most patient cases, and some patterns are more difficult to detect than others. These findings suggest that pattern analysis may be more efficient using an automated pattern detection system that allows clinicians to accurately detect more patterns in less time. Although these results should be confirmed in a new evaluation with a larger number of participants and cases, the clinical benefits of using an automated pattern detection system should be investigated in a larger clinical study.

Summary. SMBG is the most accessible way to assess diabetes status; however, patterns of glycemic control are not always easy to detect or interpret. The Web-based *emminens*® eConecta solution provides a unique, customizable automated pattern detection module that can support both clinicians and patients by making data analysis more efficient.

Can Apps Help to Improve Management of Chronic Diseases? Introduction of a Successful Example in Asthma

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Challenges to managing chronic diseases. In Europe, approximately 20–40% of the population ≥ 15 years of age report a long-standing health problem, and two-thirds of individuals who have reached pensionable age have at least two chronic conditions. Currently, individual chronic diseases account for 2–15% of national health expenditures in some European countries. In the United States, prevalence of obesity has increased significantly.

Effective management of chronic disease requires coordinated input from a wide range of health professionals. Additionally, patients must have full access to the medications and monitoring technologies needed to manage their diseases. Patients must also be actively engaged in their treatment regimens. Most countries have not been successful in addressing the needs and challenges of chronic disease because of inefficiencies in care delivery, specialists' lack of access to patient information, and difficulties in coordinating care.

Use of mobile technology may provide an answer. The recent increase in mobile phone penetration in developed and developing countries has already created an infrastructure that can be used by healthcare providers and patients for managing chronic diseases. Additionally, advances in technology have resulted in the development of sophisticated smartphones that can facilitate patient self-management of chronic illnesses. Specifically, mobile health (mHealth) technology applications (apps) can effectively monitor patients' status and clinical outcomes and improve treatment adherence. The generated data can easily be shared with the healthcare team, which can improve coordination of care regardless of patients' geographical location.

A key challenge to using mobile health technology is the large number of health-related apps currently available (over 40,000), many of which are ineffective, and many clinicians are reluctant to recommend apps to their patients. Moreover, most apps work in a silo; they do not communicate with patients' healthcare providers.

AsthmaMD app. AsthmaMD was created in 2010 to bring new solutions to managing asthma, a common disease that affects 9% of Americans at some point in their lives. Currently, AsthmaMD is the leading app in the United States, with 100,000 active users, and it is the most commonly prescribed asthma app. The app has undergone numerous iterations to achieve a "physician friendly" platform that allows user information to be easily shared with physicians. As users enter the date and severity of their asthma events, the app graphs these events within the color-coded risk zones (red, yellow, green) in real time. This allows clinicians to monitor patient status and recommend medication changes as needed.

In addition to improving acute asthma control, the app reminds users to take their medication, thereby enhancing chronic symptom management, which in turn has the potential to reduce hospitalizations and improve posthospitalization management. Although clinicians have some concerns about the app, using the app does not require a significant amount of time, and it prompts patients to schedule clinic visits when they see that their level of control is suboptimal.

The app developers recently collaborated with the statistical department at the University of California Los Angeles to analyze pollution levels as they compare with asthma data from AsthmaMD users in California. Through the integrated GPS function in the smartphone, which identifies the exact location of users, the developers were able to show a direct relationship between high ozone levels and asthma exacerbation. Given this relationship, the app developers can predict the locations where users are at high risk for asthma events and send out early warnings. In another study, the app developers conducted a 6-month comparison of >6,000 users

and found that active users had significantly greater improvements in outcomes than sporadic users.

Success factors for app development. Two key success factors are applicable when developing a mobile health app. First, it is important to define a clear goal for the app. For diabetes management, potential goals may include the following: increasing adherence to glucose monitoring; enhancing communications between patients and clinicians; delivering education in diabetes management; reducing hospitalizations; or identifying glucose trends. Second, developers should not try to simulate paper tools and forms; rather, they should use the power of the technology to its fullest.

Summary. There is a large, fast-growing market for mobile health apps for government organizations, insurance providers, and pharmaceutical/medical device companies. Given the existing mobile communications infrastructure and increasing penetration of smartphone use, consumers are more likely to use mobile technology for their health-care needs. There is a growing body of evidence that demonstrates the direct clinical benefits of utilizing mobile health technology.

The Impact of mHealth on the Advancement of Health Care

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Background. The number of mHealth apps continues to increase. In 2012, there were over 13,000 smartphone apps; today there are approximately 18,000 of them. Across all platforms, there are more than 40,000 available; however, less than 1% has been evaluated scientifically.

Designing user-centered, just-in-time adaptive interventions. The most recent data show that approximately 26% of downloaded mhealth apps are used only once and that 74% of these apps are abandoned by the 10th use.²⁸ To encourage greater adoption and sustained use, many developers are designing mHealth technologies within the context of user-centered, just-in-time adaptive interventions (JETAIs). To evaluate these JETAIs, researchers are conducting studies that look at both clinical outcomes and user perceptions of value, burden, and engagement, which are key factors in the adoption and abandonment of mHealth technologies.²⁹

An example of a JETAI is the txt2stop smoking cessation app, which was evaluated in a randomized trial that assessed the impact of using the app in 11,194 participants.³⁰ Users received five messages per day for the first 5 weeks, followed by three messages per week for 26 weeks. During the study, investigators saw that participants began to experience cravings when the number of messages decreased. In response, investigators added messages to help participants manage their cravings. Additional messages were sent to further encourage participants. At 6 months, investigators saw significant improvements in smoking cessation rates.

Use of mHealth in diabetes self-care. In a recent cluster-randomized study,³¹ investigators assessed the impact of

using a diabetes management mHealth communication system compared with standard care in community primary care practices. The intervention included mobile software, a patient Web portal, and a clinician Web portal. Utilizing mobile software, people with type 2 diabetes entered self-care information on a mobile phone and received automated, real-time educational, behavioral, and motivational messages specific to the entered data. The patient Web portal included a secure messaging center (for patient-provider communication), personal health record with additional diabetes information, learning library, and a logbook that patients could use to review historical data. The clinician portal provided analyzed patient data that were linked to standards of care and evidence-based guidelines. At 12 months, mHealth patients showed a significantly greater reduction in HbA1c, regardless of baseline values, than patients managed with standard care: -1.9% versus 0.7% ($P=0.001$).

A key learning from the study was the importance of providing patients with real-time, actionable messages at clinically relevant moments and that the interaction is contextually relevant. Use of the mHealth intervention also created educational opportunities; patients received quick educational messages that were tailored to their unique profile and actions, thus enhancing patient learning and retention. The investigators also saw that linking evidence-based guidelines to the analyzed patient data enhanced clinicians' decision-making.

Current mHealth research: defining interventions and targets. Most of the research involving mHealth utilization is in the pilot study phase; however, some research is moving into the efficacy phase, but few are investigating the effectiveness of these interventions. Although large trials will be required to demonstrate both efficacy and effectiveness, it is important to recognize the value of smaller trials when evaluating mHealth. Researchers must also rethink the end points that are used in trials. In diabetes research, change in HbA1c is the end point used in many studies; however, this may not be the most appropriate end point for assessing diabetes-related mHealth. It is also important to explore other applications of the technology, not only as an intervention per se but also as a means of collecting and sharing research data.

International mHealth innovation. A significant amount of mHealth innovation is taking place internationally, especially in areas where communication infrastructures are sparse or nonexistent. Recent data show that the largest growth in mobile phone and Internet penetration is occurring in the developing countries of Europe/Central Asia, East Asia/Pacific, and Sub-Saharan Africa. Many of these countries are using mobile phones for population health.

Summary. Consumers, healthcare providers and the healthcare industry have different needs, perceptions, and expectations regarding mHealth technologies and applications. Although more than 40,000 mHealth apps are currently available, most are abandoned after short periods of use. Designing mHealth technologies/products (not just apps) that are user-centered, provide real-time interactions, and are adaptive to user needs may encourage sustained use.

News from the World of Insulin Pumps and CGM

The Clinical Benefits of CGM—Do Randomized Controlled Trials Tell You Everything?

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Background. Conventional meta-analysis of RCTs comparing CGM and SMBG in type 1 diabetes have shown only modest improvement in HbA1c with little or no reduction in severe hypoglycemia or improvement in quality of life.^{32,33} Although meta-analyses are often viewed as the “gold standard” for evaluating medical efficacy, current approaches to these assessments may mask the true value of CGM in clinical use.

RCTs can be misleading and inappropriate. Recent RCTs of CGM versus SMBG have shown only modest benefit in improving glycemic control and little or no improvement in quality of life; however, this is likely due to the populations studied and/or the trial designs used. For example, many of these studies included patients with only slightly elevated HbA1c, low frequency of severe hypoglycemia, and high quality of life scores at baseline.

Additionally, most of the trials included in current meta-analyses were not designed or powered to test the effect of CGM on severe hypoglycemia. It is also possible that the quality of life instruments used were not sensitive enough to detect changes in this measure, masking any benefits of CGM use in these trials. Another factor to consider is the frequency of sensor usage during these trials, which was often very low in some of the groups studied.³² In order for meta-analysis to be meaningful, trial participants must use the technology regularly.

Individual patient data meta-analysis for modeling the effect of CGM versus SMBG. It was hypothesized that the likely determinants of outcomes associated with CGM use are frequency of sensor use, baseline glycemic control, and, perhaps, age. To test this hypothesis, an individual patient data (IPD) meta-analysis was conducted to model the effect of these variables on CGM versus SMBG use.³⁴ With the IPD design, it is possible to perform meta-regression using covariates and outcomes for each trial patient.

We selected RCTs of real-time CGM versus SMBG use by people with type 1 diabetes that had been published up to 2010. Analysis showed that every 1% HbA1c increase at baseline increases the CGM effect by 0.126%, whereas every 1 day per week of sensor usage increases the effect by 0.15%. The effect of sensor usage completely disappears, however, when sensor usage falls below 4 days per week. Patient age showed only a very small effect.

The value of observational studies for meta-analysis. Although observational studies carry some risk of bias, there are several advantages to using these trials in meta-analyses compared with RCTs. They are usually longer in duration, include larger numbers of participants, and usually include patients with unresolved clinical problems, which makes them more representative of the general patient population for whom CGM is intended. Observational studies of people with type 1 diabetes with a high rate of severe hypoglycemia

in spite of insulin pump therapy and structured patient education have shown a marked reduction in hypoglycemia with CGM. In one recent observational study of 35 people with type 1 diabetes with problematic hypoglycemia and hypoglycemia unawareness, CGM use was associated with HbA1c improvement (0.4%; $P < 0.005$) and a reduction in severe hypoglycemic events, from a median of 5.0 (0.75–7.25) to 0 (0–1.25) episodes per year ($P < 0.001$).³⁵

Insulin pumps with low-glucose insulin suspend. Both observational studies and RCTs involving people with type 1 diabetes with problematic glycemic control have shown that use of CGM-linked insulin pumps with LGS functionality helps to reduce the severity and duration of hypoglycemia.^{36,37}

Real-life benefits of CGM. Recently, an online survey of 100 patients (50 children, 50 adults) with real-time CGM experience was conducted.³⁸ Respondents were asked to express, in their own words, their personal experiences with real-time CGM, including any benefits, problems, or drawbacks to using the glucose sensor. Respondents were overwhelmingly positive with respect to improved metabolic control, food and exercise management, physical and psychological well-being, and quality of life during CGM use.

Summary. RCTs and conventional meta-analysis of CGM versus SMBG can sometimes be misleading because of inappropriate patient selection. IPD meta-analysis shows the main determinants of outcome on CGM are baseline HbA1c and sensor usage.

Observational studies provide useful additional information because they include patients who are more representative of those for whom CGM use is intended. Additionally, observational studies and RCTs in problem patients who use LGS pumps have shown marked reductions in severe hypoglycemia. Patient responses to CGM are overwhelmingly positive.

Expert Debate: CGM or an Insulin Pump—What Is the Most Appropriate Next Step for an Insufficiently Controlled MDI Patient?

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Background. MDI, supported by frequent SMBG, is the standard of care across Europe. In most European countries, intensification of MDI therapy is largely indicated and funded when current therapy is suboptimal. In this debate, Evans and DeVries discussed the current evidence and debated the ideal positioning of technology in the type 1 diabetes pathway.

Mark Evans

Pathway for intensifying therapy in suboptimally controlled MDI patients. The proposed pathway for intensifying insulin therapy presents three options: (1) transition to CSII and then to SAP if needed; (2) add CGM to the current MDI regimen and then to SAP if needed; and (3) direct transition to SAP. However, CGM is generally less available than insulin pump therapy.

Current meta-analyses show very modest effects of CGM on HbA1c and no effect on severe hypoglycemia; however, it

is important to note that many factors may impact the findings of these analyses, such as the HbA1c values, the generation of CGM technology evaluated, and the frequency of sensor use. As reported by Choudhary et al.,³⁵ the main determinants of CGM effect on lowering HbA1c appear to be baseline HbA1c of the study populations and sensor usage.

Other challenging factors are the outcome metrics used in various studies. Although rate of severe hypoglycemia is often used as an outcome metric, the challenge of using this measure is that severe hypoglycemia is infrequent and tends to cluster. Quality of life is another outcome metric commonly used. However, because the studies included in meta-analyses often use different methods for assessing quality of life, comparing these data is equally challenging.

Usefulness of CGM in hypoglycemia unawareness. Ly et al.³⁹ conducted a randomized clamp study to determine whether use of real-time CGM with preset alarms at specific glucose levels would improve the counterregulatory response to hypoglycemia in adolescents with type 1 diabetes with hypoglycemia unawareness. At 4 weeks, the adrenaline response during hypoglycemia was greater in the CGM group than in the standard therapy group, suggesting that real-time CGM is a useful clinical tool to improve hypoglycemia awareness.

Restoration of hypoglycemia awareness by CSII and/or CGM was also examined in the recently reported Hypo-COMPASS study.⁴⁰ In a subset of 18 subjects who underwent stepped hyperinsulinemic-hypoglycemic clamp studies before and at the end of the study period, after the intervention, investigators found that glucose concentrations at which subjects first felt hypoglycemic increased and that symptom and plasma metanephrine responses to experimentally induced hypoglycemia were significantly higher ($P=0.02$).⁴¹ This showed that poor hypoglycemia awareness and defective counterregulation can be improved, even in long-standing diabetes. Of note is that all intervention groups (whether using CSII and/or CGM or neither) benefited equally.

Summary. In summary, from a practical standpoint, it is easier to start with CSII in people who have suboptimal control using MDI therapy and then add CGM if needed.

Hans DeVries

The options for intensifying therapy in suboptimally controlled MDI-treated patients are as follows: transition to CSII, then addition of CGM if needed; add CGM, then transition to CSII if needed; and direct transition to the combination of CSII with CGM. The first option—transition to CSII and addition of CGM if needed—was explained by Mark Evans. The other two options, although perhaps less conventional, have their own merits.

Intensification of MDI with CGM before CSII. Comparison of MDI- and CSII-treated people in the JDRF CGM study³² showed little difference in HbA1c improvement due to CGM between both groups. These findings suggest that both MDI- and CSII-treated patients may benefit from CGM, although the number of MDI-treated patients studied in the JDRF CGM study was relatively small.

In addition, findings from patient case reports suggest that adding CGM to MDI therapy can be beneficial as well. A

patient case of a 37-year-old woman with a 20-year duration of type 1 diabetes and hypoglycemia unawareness was presented. The patient experienced recurrent severe hypoglycemia and had once been found unconscious by one of her children. After initiation of CGM, the patient reported that the CGM tracings alerted her to the need of reducing her insulin dosage, a recommendation she had previously resisted. During the first 2 months of CGM use, she reduced her insulin dose by almost 50% and experienced no severe hypoglycemia; some symptoms of hypoglycemia were restored. Although her HbA1c increased 1.2% (from 6.6% to 7.8%) during this time period, it later decreased and has remained consistent at <7.0%.

Evidence for transitioning to CSII and CGM simultaneously. The effects of transitioning from MDI therapy to CSII in combination with CGM have been reported in three recent studies. The RealTrend study,⁴² which compared transition to CSII versus CSII with CGM, showed that use of SAP for insulin improved glycemia more effectively than conventional insulin pump therapy during the first 6 months of pump use in patients who wear CGM sensors at least 70% of the time. In the STAR 3 trial,⁴³ patients (adults, adolescents, and children) who were transitioned to SAP insulin therapy demonstrated a reduction in mean HbA1c levels that was 0.6% higher than in the MDI group. Results from the Eurythmics study⁴⁴ also showed a significant reduction in HbA1c in the SAP insulin group from baseline (8.46% to 7.23%) compared with the MDI group (8.59% to 8.46%). Improvements in the SAP insulin group were achieved without an increase in the percentage of time spent in hypoglycemia. The SAP group also showed improvements in Problem Areas in Diabetes and Diabetes Treatment Satisfaction Questionnaire scores.

Summary. “One size fits all” solutions tend to be suboptimal in medicine. When failing MDI therapy, evidence suggests that outcomes can be improved with transition to CSII, addition of CGM, or transition to CSII and CGM simultaneously. The decision should be individualized to meet each patient’s unique requirements.

Inpatient Trial of Closed-Loop Control with Intraperitoneal Insulin Delivery via Accu-Chek® DiaPort Versus Subcutaneous Insulin Delivery—Results from Montpellier and Santa Barbara

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Closed-loop insulin delivery. The aim of closed-loop insulin delivery systems is to maintain blood glucose levels as close to normal as possible in individuals with type 1 diabetes. Closed-loop insulin delivery is based on CGM and prediction of glucose levels according to action of insulin infusion driven by a control algorithm. When the CGM device detects changes in glucose levels, the control algorithm adjusts the amount of insulin infused by an insulin pump.

The main limitation of the system is the inherent delay in action, peripherally (approximately 20 min) and in the liver (approximately 100 min), when insulin is delivered subcutaneously. This delay makes it difficult to control postprandial glucose levels without inducing later hypoglycemia.

Because of this, the effectiveness of closed-loop insulin delivery is limited to overnight and between-meal periods; patients must alert the system (announcement) before meals about expected carbohydrate intakes so that a bolus dose can be computed to limit the rise in postprandial glucose.

Intraperitoneal insulin infusion. Recent studies have shown that use of intraperitoneal insulin infusion from implantable pumps (IPs) more closely resembles physiologic events than does subcutaneous insulin infusion, resulting in tight glucose control with a low incidence of hypoglycemic events.⁴⁵ When insulin is directly infused into the peritoneal cavity and diffuses to the hepatic venous portal system, the pattern of insulin appearance in the plasma more closely resembles physiologic events than does subcutaneous insulin infusion. A more recent study⁴⁶ showed that long-term use of intraperitoneal infusion can restore the glucagon response to hypoglycemia.

Integration of an IP into a closed-loop insulin delivery system. In a recently completed study, investigators evaluated a closed-loop system that included IP insulin delivery via the Accu-Chek DiaPort system (Roche Diagnostics GmbH, Mannheim, Germany), which enables continuous intraperitoneal insulin infusion into the abdomen, near the liver. Subjects underwent two 24-h closed-loop insulin delivery evaluations: (1) with subcutaneous fast-acting insulin analog infusion and (2) with intraperitoneal regular insulin infusion (IP). For both trials, CGM was obtained from a Dexcom[®] SEVEN[®] PLUS CGM system (Dexcom, Inc., San Diego, CA). Results showed that percentages of time spent in 70–180 mg/dL and 80–140 mg/dL blood glucose ranges were both significantly increased with IP infusion compared with subcutaneously infused insulin: 65 ± 9 versus 42 ± 14 ($P = 0.01$) and 40 ± 7 versus 24 ± 13 ($P = 0.02$), respectively. Mean blood glucose levels (in mg/dL) were also significantly lower with the use of the IP infusion system and resulted in a significant reduction in time spent above and below target range. These findings support the effectiveness of faster insulin action using the Accu-Chek DiaPort system in the reduction of postmeal excursions following unannounced meals in closed-loop conditions.

Conclusions. Significant improvements have been achieved in the development of closed-loop insulin delivery systems. However, the inherent delay in insulin onset and activity associated with subcutaneous insulin infusion has limited the use of this technology to overnight and between meals; meal challenges remain difficult to control optimally with no meal announcements. Recent studies have shown that use of IP insulin infusion allows more effective closed-loop control without increasing hypoglycemia than subcutaneous fast-acting insulin analog infusion.

Clinical Use of a Novel Insulin Pump System— First Experience from a European Multicenter Study of the Accu-Chek[®] Insight System

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Background. Within the last decade, new insulin pump systems with additional functions have expanded the adop-

tion of insulin pump use. Use of automated bolus calculators has been shown to improve glycemic control in both young patients with type 1 diabetes and in experienced type 1 patients with long-term insulin pump experience.^{47–49}

Several studies have also shown that use of insulin pump therapy is also associated with increased user satisfaction among individuals with type 1 diabetes⁵⁰ and type 2 diabetes.⁵¹ A significant example of this is a study by Hofer et al.,⁵² who examined a database of 11,710 children, adolescents, and young adults treated with insulin pump therapy. They found that only 463 (4%) of these patients switched from insulin pump treatment to MDI therapy.

Accu-Chek Insight insulin pump European Union study. The aim of this 6-month open, prospective, multicenter study is to evaluate insulin pump therapy in routine clinical practice, using the Accu-Chek Insight insulin pump (Roche Diagnostics GmbH, Mannheim, Germany). Eligible participants include adults with type 1 or type 2 diabetes who are currently being treated with MDI or another insulin pump system. The study will enroll 80–95 patients from 11 clinical sites located in the United Kingdom, Austria, and France. Patients will be trained to use the new insulin pump device between the screening visit and visit 2. All participants will use real-time CGM for 1 week, and they will be instructed to eat both high- and low-fat meals.

The primary objective will be expressed as the rate of error messages per 100 patient-years, which will be confirmed by insulin pump uploads. Secondary objectives for the study include:

- Type and frequency of pump signals (e.g., reminders, errors, warnings, alarms, maintenance messages)
- Type and frequency of adverse events (serious/nonserious) possibly related or related to the study device and/or study procedures
- Participant satisfaction and important components of health-related quality of life
- Change in HbA1c from screening to month 3 and month 6
- Utilization of insulin pump functions (e.g., basal rate profiles, temporary basal rates, bolus types)
- Change in CGM-derived parameters from month 3 to month 6

Key issues to be elucidated. The relationship between meal composition and glycemic response remains controversial. In a recent crossover study,⁵³ 17 subjects with type 1 diabetes on insulin pump therapy wore blinded CGM devices for 3 days, during which time they ingested two test meals with the same carbohydrate content but different fat and protein contents. The results showed that the intake of a high-fat meal involved a different glycemic response compared with a low-fat meal; as fat was added to the meal, the postprandial glucose level remained higher for a longer period of time. Although the average difference was not statistically significant, there was extreme variability in individual reactions among participants.

A more complicated issue is determining which bolus types may be more effective for postprandial control and whether there is enough evidence to make recommendations. Several studies have been published regarding this issue; however, the recommendations are mostly mixed. Therefore,

providing individual advice regarding bolus types is the most preferable option; equipping patients with a CGM device would be helpful. Although evidence does not support one specific type of bolus over another, it is important to note that frequent use of different bolus types (dual-wave or square-wave) may be beneficial.⁵⁴

Investigators will further explore these issues in the study by evaluating the impact of refresher training relating to the capabilities of the Accu-Chek Insight insulin pump to match specific meal contents with different types of insulin boluses and the influence on CGM-derived parameters. From these assessments, investigators will prepare case studies, which may benefit clinicians.

Current status of the study. Currently, 41 patients have been recruited into the study: 18 in Austria and 23 in the United Kingdom. Patient enrollment is expected to start soon in France. The study is not expected to be completed before early 2015. The Vienna and Graz sites have the longest-standing experience with the pump.

Although the study is ongoing, some preliminary results are available. Among the 10 patients who were enrolled in the study at Hietzing Hospital, Vienna, there have been no severe adverse events caused by the study device. In only one case has the pump had to be replaced because of a recurring error. Additionally, the time required for pump training was short, involving one or two training sessions of 60–90 min each. The patients were very satisfied with the ease of handling of the device, and the use of CGM also led to positive feedback.

Why and How SMBG and CGM Accuracy Impact on Clinical Outcome

What Accuracy Is and Why It Matters

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Why does accuracy matter? Accurate glucose values are a prerequisite for the consecutive actions involved in diabetes management (e.g., calculation of an insulin bolus, titration of a basal insulin, changes in oral medications). However, unless the glucose test results are totally implausible, they are not questioned by users; it is often assumed that the glucose concentration value displayed on a blood glucose meter is correct.

Although some people would acknowledge that the “true” glucose concentration might not be exactly the number that is displayed, they may assume it is clinically acceptable. Even this view, however, is often too optimistic. If a blood glucose meter system has an analytical error of up to 20% and if this error is randomly distributed, this becomes clinically significant, for example, when the measured glucose is in the hypoglycemia range. In simulation studies⁵⁵ that modeled the clinical impact of inaccurate measurement, when the actual glucose level is 60 mg/dL, a 20% analytical error would result in missing 10% of hypoglycemic events. However, when the analytical error is 15%, only 4% of hypoglycemia is missed. Because inaccurate measurement can lead to failure in detecting hypoglycemic events, induced hypoglycemic events (due to wrong calculation of an insulin bolus based on an inaccurate glucose value), increased glycemic variability,

and even an increased HbA1c, it becomes clear that accuracy does matter.

International Organization for Standardization 15197 Standard for Accuracy: 2003 versus 2013. The International Organization for Standardization (ISO) 15197 accuracy standard specifies requirements for in vitro glucose monitoring systems that measure glucose concentrations in capillary blood samples and procedures for the verification and the validation of performance by the intended users. Under the previous ISO standard (2003), it was required that 95% of glucose values must fall within ± 15 mg/dL at blood glucose concentrations <75 mg/dL and within 20% of blood glucose values ≥ 75 mg/dL. Only one lot of test strips was required for accuracy evaluations. However, concerns about blood glucose meter accuracy prompted the development of the new ISO standard (2013), which now requires that $\geq 95\%$ of glucose values fall within ± 15 mg/dL of the results of the manufacturer's comparison or reference procedure at glucose concentrations <100 mg/dL and within $\pm 15\%$ for values ≥ 100 mg/dL. Manufacturers are required to test three test strip lots for their evaluations, and all three lots must meet the accuracy requirements.

An additional requirement of the new ISO standard is that 99% of all glucose values must fall within the risk zones A (no effect on clinical action) and B (little or no effect on clinical outcome) of the Parkes Consensus Error Grid for type 1 diabetes. Although the ISO standard provides needed guidance for evaluating the accuracy of blood glucose monitoring systems, it is important to note that this standard is not binding; manufacturers have the option of following or not following it. Unfortunately, many manufacturers have chosen the second option. Several studies have shown that many blood glucose meters meet neither the old nor the new ISO standards.^{56–58}

It is interesting that the U.S. Food and Drug Administration (FDA) recently cleared a blood glucose monitoring system that failed to meet even the previous ISO standard; however, the clearance document requires that the manufacturer clearly states in its packaging that this meter should not be used to calculate insulin dosages or to calibrate CGM systems. This is concerning because these are the typical scenarios in which blood glucose meters are used.

How can accuracy be described? Two primary factors impact the accuracy of a given system: (1) precision and (2) trueness. Precision (random error) refers to how closely the measured values are clustered regardless of how they relate to the true value; it is calculated and reported as SD or coefficient of variation. Trueness (systematic error; bias) refers to how far above or below the measured values are relative to the true value. The combined calculations of precision and trueness reflect the accuracy (total error) of the measurement system. The basic terminology within the context of SMBG is discussed in more detail in a recent publication.⁵⁹

A third factor that can impact accuracy is interference, which refers to any endogenous or environmental substance or condition that interacts with the measurement process and, subsequently, alters the result. The most common interferents affecting blood glucose monitoring systems are uric acid, vitamin C, hematocrit, and oxygen pressure; however, oxygen pressure is a problem mainly in monitoring systems that use glucose oxidase as the enzyme for measurement.

With its blood glucose monitoring systems, Roche Diagnostics is testing more than 200 compounds to determine their potential interference with blood glucose. When the compounds are drugs, Roche Diagnostics usually tests them at three times their maximum therapeutic level, in accordance with the Clinical Laboratory Standards Institute (CLSI) guidelines.

Although many substances can interfere with blood glucose monitoring accuracy, it is important to focus on the most common interferents when addressing this issue. For example, both low and high hematocrit values can interfere with blood glucose measurement. When determining the hematocrit range that would be permitted for their latest blood glucose monitoring systems, Roche Diagnostics queried hospitals and laboratories in various countries. Analysis of a sample of almost 500,000 outpatients from Germany showed that about one in 50 patients had a hematocrit <30%, one in 400 had a hematocrit <25%, and one in 3,000 had a hematocrit <20%. Although the reference intervals in the literature (which usually comprise 95% of the “apparently healthy” population) showed ranges of 35–47% (female) and 40–52% (male), the Roche analysis strongly suggests that a blood glucose meter that permits hematocrit values above 30% only is unacceptable.

What is the most accurate method to measure glucose? The most accurate method for measuring glucose is isotope dilution gas chromatography/mass spectrometry (ID-GC/MS) methodology. Although other methodologies (e.g., Yellow Springs Instruments [YSI], blood gas analyzer with a glucose electrode, clinical chemistry analyzer) are usually more accurate than current blood glucose meters, they are not as accurate as many people believe. Only recently, a proficiency testing scheme was conducted in 463 clinical chemistry laboratories in Germany. The true values of the samples tested were determined using ID-GC/MS methodology. The testing allowed a $\pm 15\%$ deviation from the reference value. Analysis of results showed that 435 (94%) laboratories achieved this accuracy target. However, even among those laboratories that passed the test, both high and low biases among the laboratories were detected, which suggests that normal laboratories are not always correct and are not always suitable to evaluate blood glucose meters.

These findings are important because the types of laboratories that participated in the proficiency testing are often used to assess blood glucose meter accuracy. As a result, any biases that are inherent to comparison methodologies used are attributed to the blood glucose meter being evaluated, not the comparison method. Additionally, the new ISO 15197 and CLSI EP-7 guidelines for blood glucose meter accuracy testing are extremely complicated and may not be feasible for most laboratories.

Summary. Most patients, clinicians, and payers assume that all blood glucose monitoring systems provide accurate measurements of glucose concentrations; however, it is known that some systems have an analytical error of up to 20% of the true glucose value. Although the clinically relevant consequences of this variance can be minimized by reducing the analytical error to 15%, which is a requirement of the new ISO 15197 (2013) accuracy standard, many current blood glucose monitoring systems do not fulfill these accu-

racy criteria. The three main factors impacting blood glucose monitoring system accuracy are precision, bias, and interference. Nonspecialized laboratories are likely unsuitable for assessing the accuracy of blood glucose monitoring systems.

Impact of Measurement Accuracy on Clinical Outcome—Consequences for SMBG and CGM

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Background. Despite advances in glucose monitoring technology, achieving acceptable levels of accuracy remains a challenge. It is well known that many of today’s blood glucose meters have large errors, even when tested under controlled conditions. Incorrect user technique (e.g., mis-coding meters to test strips) can exacerbate errors and increase the risk for hypoglycemia.^{55,56}

Because clinical outcome trials are inherently difficult to execute and likely unethical because of the potential danger to study participants, use of computer simulations to assess the influence of blood glucose meter and CGM errors on insulin dosing and glycemic response is a viable alternative to clinical trials.

University of Virginia/Padova type 1 diabetes mellitus computer simulator. The University of Virginia/Padova type 1 diabetes mellitus simulator uses data from approximately 350 individuals, pooled from several large studies, using triple-tracer protocols. With these tracers, developers were able to quantify key glucose “fluxes” (physiological processes) within each patient. Based on these fluxes, a mathematical model was created to represent the glucose–insulin interactions in humans. An individual is represented by 26 independent parameters within this model framework. The *in silico* population includes 300 simulated subjects, and different insulin treatment strategies (e.g., SMBG-based insulin dosing) can be simulated with varied scenarios (e.g., insulin timing, meals).

In 2008, the FDA accepted the University of Virginia/Padova simulation platform for replacement of preclinical trials in automated insulin dosing studies that had previously been performed in animals. This greatly accelerated research activities in artificial pancreas development.

Assessing the effects of errors in SMBG systems on glycemic control. In a 2010 study, we used the *in silico* simulator to assess the relationship among SMBG errors and risk for hypoglycemia, glycemic variability, and long-term glycemic control.⁵⁵ Using the ISO 15197 (2003) accuracy standard, four *in silico* experiments were performed to assess the probability of missing a hypoglycemic value (<60 mg/dL) when the SMBG error was 20%, 15%, 10%, and 5%. Results showed that no hypoglycemia would be missed at an error rate of 5%; however, the probability of missing hypoglycemia increased to 1%, 3.5%, and 10% for error rates of 10%, 15%, and 20%, respectively. It is important to note that only 79% of the 34 blood glucose meters evaluated in a recent study met the 2003 ISO standard for accuracy.

In the second part of the study, the effects of SMBG error rates (5%, 10%, 15%, and 20%) when using insulin to correct a blood glucose value of 200 mg/dL to a target of 100 mg/dL were assessed. Within the 100 adult *in silico* patients

evaluated, the incidence of overcorrection, resulting in hypoglycemia (≤ 70 mg/dL), was 0% at SMBG error rates of 5% and 10% but increased to 3.5% at 15% error and 5.5% at 20% error.

Assessing CGM performance in silico. We recently used the in silico simulator to evaluate the performance of an experimental CGM system (Atos-P; Roche Diagnostics GmbH, Mannheim, Germany) in 100 adult in silico patients. The Atos-P sensor performance was compared with those of two currently available CGM systems (CGM1, CGM2), using several simulation conditions: normoglycemia; hyperglycemia caused by underestimated carbohydrate intake; hypoglycemia caused by insulin stacking; exercise-induced hypoglycemia; hypoglycemia due to overestimation of carbohydrate intake at meals; and nocturnal hypoglycemia.

Results showed that the Atos-P sensor had greater overall accuracy, as measured by the mean absolute relative difference, compared with the other sensors: 8% versus 17% for CGM1 and 11% for CGM2. Performance differences were even more striking at hypoglycemic glucose levels. At a glucose level of <55 mg/dL, the Atos-P mean absolute relative difference was approximately 12% compared with that of CGM1 (approximately 45%) and of CGM2 (approximately 21%). Atos-P performance was also much better when accuracy was measured at various rates of glucose change.

Significant differences between the sensors were seen in the probability of hypoglycemia detection: 8% for Atos-P, 63% for CGM1, and 16% for CGM2. Delays (average) in hypoglycemia detection were also very different: 2 min for Atos-P, 24 min for CGM1, and 13 min for CGM2. Moreover, distribution of CGM values when hypoglycemia was detected was also significantly narrower with the Atos-P sensor. When values <55 mg/dL were detected, the means were 56 ± 6 mg/dL with Atos-P, 78 ± 12 mg/dL with CGM1, and 62 ± 10 mg/dL with CGM2.

Summary. Simulation platforms provide a unique tool to explore the details of sensor errors and their impact on treatment. Use of the in silico simulator with SMBG seems to indicate a clear advantage in meters with $<10\%$ error 95% of the time. Additionally, CGM modeling allows for exploration of hypoglycemia detection characteristics in early, preclinical settings, thus facilitating better designs of clinical studies.

Current FDA and EU Regulatory Requirements for Blood Glucose Meters for Self-Monitoring and Why They May Sometimes Be Insufficient

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Background. The FDA in the United States and the In Vitro Device (IVD) Directive in the European Union (EU) regulate SMBG systems through two entirely different pathways.

In the United States, IVDs are regulated by the FDA's Center for Devices and Radiological Health. Within that center, there is a specific Office for In Vitro Diagnostics and Radiological Health. There is also regulation of laboratory testing, administered by the Centers for Medicare & Medicaid Services through the Clinical Laboratory Improvements Act. Through this act, the Centers for Medicare & Medicaid

Service sets requirements for laboratory professional education and proficiency testing.

In the EU, the European Commission drafts the medical device and IVD regulations, assisted by the European Parliament and Council. The national competent authorities are then responsible for transposing the European requirements into their own national regulations. Because anomalies have been entered into various national regulations, the requirements are not always completely identical in all countries. Although national authorities have oversight responsibilities within their own markets, third-party certification bodies in the various countries have direct contact with manufacturers of SMBG systems and are responsible for reviewing products, their design, and all related technical documentation.

U.S. and EU IVD regulatory structures. In the United States, the legal tool for regulating IVDs is the Code of Federal Regulations Title 21 (21CFR). Part 862 of the code lists provisions for clinical chemistry and clinical toxicology devices. These provisions identify SMBG systems as Class II, medium risk. The regulatory instrument used in the EU is the European Directive on IVD-Medical Devices (98/79/EC). This directive covers IVDs that fall into four product categories: general; self-tests; Annex IIa (most critical); and Annex IIb (moderate risk). SMBG systems are the only self-tests listed under Annex IIb. In both the United States and EU, the level of risk dictates the level of assessment that is required and the rate of intervention by the FDA or third-party certification body.

How the regulations impact SMBG systems. In the United States, SMBG systems are classified as Class II (moderate risk) products. The requirements for Class II (moderate risk) devices allow manufacturers to use the 510(k) clearance process to obtain approval for marketing their SMBG systems. This process requires that manufacturers demonstrate the "substantial equivalence" their new products have to those already being marketed. This eliminates the requirement for premarket approval by the regulator, and the FDA is not directly involved in assessing the product. When following the 510(k) route, manufacturers must notify the FDA at least 90 days in advance of their intention to market their product, and they can only market the product after receiving FDA clearance. In these cases, new evidence regarding clinical performance is not required unless the product has some degree of novelty.

In the EU, SMBG systems are also defined as moderate risk (Annex II) devices with involvement of notified bodies. These bodies are responsible for auditing the design and production of the devices. The products must be registered, and manufacturers must notify competent authorities of any incidents associated with their products. This information is kept in a central database. Currently, there is no requirement for clinical performance evidence for SMBG systems in the EU; however, proposed revisions of the regulations will require this evidence in the future.

Key standards and guidelines. The FDA stipulates the standards to which products must comply. It is interesting that these can be U.S. standards or global standards (ASTM, IEC); however, the FDA must provide a rationale for using global alternatives. Although the FDA provides guidelines

for staff and manufacturers that outline its regulatory procedures and demands, these guidelines are not legally binding but should generally be followed to avoid potential liability issues.

The EU utilizes “harmonized standards,” which give a presumption of conformity with the relevant “Essential Requirements” of the IVD Directive detailed in Annex I. There are several guidelines in the EU, including the Commission’s MEDDEVs. Again, although these guidelines are not legally binding, it is advisable to follow them.

Impact of changes on SMBG systems. Changes in the regulations and regulatory processes are needed to ensure the quality of SMBG systems. In January 2014, the FDA issued new draft guidance for both over-the-counter and point-of-care SMBG systems. The new guidance focuses specifically on the needs of the patients and the factors that are critical to patients’ ability to accurately use the device and interpret test results. In the EU, recent major regulatory change involves unannounced audits of manufacturing sites by notified bodies to ensure the integrity of the product materials. Further changes are on the way with the revision of the IVD Directive, although unlikely to take effect until the end of this decade. Despite these changes, questions regarding product quality remain open.

Summary. Before committing to purchasing or recommending a specific SBMG system, clinicians are advised to investigate whether there have been any problems with the device. The national and trade press, social media, medical conferences, and official regulatory Web sites are valuable sources of information regarding any quality issues associated with a specific SMBG system. Moreover, clinicians who experience problems with a device are urged to submit user reports to alert others.

Hot Topics in Diabetes

The Program for the Prevention of Type 2 Diabetes in Finland (DEHKO)

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Background. In the Finnish Diabetes Prevention Study,⁶⁰ we reported a 58% reduction in risk for developing type 2 diabetes in patients who received individualized dietary counseling and free access to a fitness facility. Moreover, the effect of the intervention was sustained over 13 years of follow-up.⁶¹ The question is whether interventions to prevent diabetes can be developed and successfully implemented in real-life community settings.

FIN-D2D project. Finland was the first country to implement a national initiative for diabetes prevention and care, the Diabetes Program for the Prevention and Care of Diabetes (DEHKO) 2000–2010, which was designed to translate the scientific evidence from the prevention trials into daily healthcare practice and public health action. The implementation component of this initiative was the FIN-D2D project, conducted from 2003 to 2007 in five central hospital districts with a combined population of 1.5 million people.

FIN-D2D utilized three main approaches: (1) a population strategy aimed at improving dietary habits, body weight control, increasing physical activity in the entire nation, and increasing awareness of type 2 diabetes and its risk factors; (2) an individualized prevention strategy for those at high risk; and (3) a program for early detection and management for people with screen-detected type 2 diabetes.

Implementation of the population strategy included health promotion and obesity prevention through public awareness campaigns and coordination with national and local authorities, health providers, and other organizations. Mass media played an important role in raising awareness. From 1980 to 1993, diabetes was mentioned in the media 1,300–1,500 times; however, the number of diabetes mentions in the media tripled during 2000 to 2006. Awareness of FIN-D2D within the five target districts grew significantly.

The second strategy utilized the Finnish Diabetes Risk Score (FINDRISC) as the screening tool for high-risk patients, which included females with gestational diabetes and individuals with CHD. The FINDRISC tool was developed to provide a simple, inexpensive, and reliable way to identify people at high risk of type 2 diabetes in the general population without the need for blood draws or other measures that require medical equipment or trained personnel. The tool was administered in physician offices and made available on the Internet. During the project period, approximately 100,000 individuals were screened in primary care clinics, and more than 250,000 used the Internet screening site, resulting in a significant increase in the number of individuals with newly diagnosed diabetes. The FINDRISC is now used in many other countries across Europe.

Oral glucose tolerance tests were used to diagnose diabetes in high-risk individuals and also those with impaired fasting glucose or impaired glucose tolerance. The baseline results of the FIN-D2D showed that among the middle-aged population, only 58% of men and 67% of women had normal glucose tolerance; the disturbances of glucose metabolism were closely associated with obesity and central obesity. Nurses, primary care physicians, and occupational healthcare providers played a key role in the screening and diagnosis activities. In addition to the screening efforts, models of care and quality criteria for more intensive management of newly diagnosed people with type 2 diabetes were developed.

Impact of the FIN-D2D interventions. Within the first year of the project, investigators saw improvements in risk factors, such as body weight, blood pressure, and cholesterol levels, among high-risk individuals. High-risk people whose body weight decreased by >5% had a 69% lower 1-year incidence of type 2 diabetes compared with those whose weight did not change. On the population level, follow-up data have shown that obesity in Finland has started to decrease. Moreover, the predicted risk of cardiovascular disease decreased in both sexes during the 1-year follow-up and was associated with the improvement in glucose tolerance status.

Conclusions. This first national type 2 diabetes prevention program showed that prevention in real-life community settings is possible. Because of substantial media coverage during the program period, there is now high awareness of obesity and type 2 diabetes in Finland. However, there are many barriers and challenges that must be considered when

planning and implementing community-based type 2 diabetes prevention.

Diabetes Management in Thailand—Burden, Cost, Outcomes, and Future Perspectives

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Diabetes prevalence and treatment. Thailand has a total population of approximately 66.8 million. The average life expectancy is 73.3 years, which is higher than the average for Southeast Asia. Approximately 3.2 million Thai adults have diabetes, and an estimated 4.1 million have prediabetes. The number of adults with diabetes is expected to increase to 4.3 million by 2035.

Nearly all individuals who have been diagnosed with type 2 diabetes are treated with glucose-lowering medications. Most (70.6%) diabetes patients are treated with oral medications, and 15.8% are treated with both oral medications and insulin. However, the percentage of treated patients who are controlled (fasting plasma glucose <7.2 mmol/L) is low: 7.5% of men and 33.9% of women. Only approximately 8.5% of individuals with type 2 diabetes use SMBG with an average testing frequency of 6.3 tests per month.

Clinical impact of diabetes. In Thailand, diabetes is the second leading cause of death in women and the 10th leading cause of death in men. Among individuals with diabetes, the leading cause of death is infection (22%), followed by heart disease (20%) and stroke (17%). Data regarding diabetes complications in Thailand show that approximately 33% of individuals have diabetic retinopathy and approximately 23% have neuropathy. However, the percentage of individuals with diabetes having a history of stroke and CHD is relatively low (<6%).

Cost of diabetes. A recent study⁶² found that early treatment costs of diabetes are significantly lower before complications emerge, whereas the cost for patients who have been hospitalized is more than nine times greater than for patients without complications. Studies also suggest that in-hospital care for individuals with complications accounts for up to one-half of all direct medical costs associated with diabetes in Thailand. Moreover, national health data show the rate of hospitalization is rapidly increasing.

The average cost of illness per diabetes patient was U.S. \$880 in 2008, approximately 21% of the per capita gross domestic product of Thailand. More recently, the total annual cost of diabetes was estimated to be over \$1.5 billion. As of 2012, 98% of Thai citizens have had healthcare coverage.

Current challenge of type 2 diabetes care in Thailand. A key challenge is the prevalence of undiagnosed diabetes remaining high. But, because access to diabetes care is hampered by the low diagnosis rates, increased screening is needed. To address this issue, a risk score to identify individuals at high risk of developing diabetes was developed for the Thai population.

In Thailand, <30% of people with diagnosed diabetes have HbA1c values <7.0%. Although lowering HbA1c is a key factor in reducing diabetes complications, glycemic control is not sufficient to prevent or delay these outcomes. However,

most people with diabetes have not been sufficiently aggressive in controlling risk factors; <10% of patients in Thailand achieve their treatment goals for HbA1c, blood pressure, and lipids.

Summary and conclusions. The number of people with diabetes in Thailand is rising. This is driven by increasing obesity and an aging population. Approximately one-half of all people with diabetes know they have it; many more are at risk.

The burden of diabetes to the individuals, their families, and economy is substantial, and the cost of treating diabetes is rising quickly. Thailand's national health policy should continuously promote and emphasize the importance of exercise and health diabetes to support diabetes prevention.

Additionally, regular and widespread screening for diabetes in high-risk populations is essential; universal screening for diabetes complications is also important to assess the appropriateness of therapy. Finally, it is important that efforts be made to educate clinicians and people with diabetes to improve adherence to treatment regimens.

Success Factors for Diabetes Management: Healthcare Professional–Patient Interaction, Motivation, and Behavior Change

Transition of Diabetes Care from Pediatric to Adult Care Providers: Improving the Delivery of Care and Translating Advances in Technology and Therapies to Day-to-Day Practice

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Background. Approximately 480,000 of the 1.9 billion global population of children 0–15 years of age have type 1 diabetes. The prevalence of type 1 diabetes is growing at a rate of 3% per year.

Tens of thousands of children with type 1 diabetes are transitioning to adulthood annually. Current data indicated that average age of transfer is 19–20 years; however, approximately 37% of 18–25-year-olds are still seen in pediatric clinics.⁶³ Adolescents are more vulnerable to poor glycemic control compared with adults.⁶⁴

Transitioning from pediatric to adult care is concerning given the changing demographics among young adults. Most do not marry until their late twenties, and many are continuing their education and are experiencing changes in employment and residence.

With transition from adolescents to young adults, we often see a shift from family to peers for support. Moreover, young adults lose the support from the pediatric diabetes team as they shift to different models of care or move to a different geographical location. Even more concerning is that young adults often feel invincible and may participate in high-risk behaviors.

Loss of support systems and a greater tendency toward unhealthy behaviors can be exacerbated by mental health issues. Approximately one third of adolescents with type 1 diabetes suffer from psychiatric disorders. They often have lower self-esteem and greater rates of depression, which can lead to worsening of glycemic control. Additionally, youths (particularly females) with diabetes are at increased risk for eating disorders.

Current research on transition programs. Among the available evidence regarding transition from pediatric to adult care is a Canadian survey of 154 young adults with type 1 diabetes transferring from a pediatric diabetes program to adult care.⁶⁵ Results showed that 24% had left their pediatric program without a referral, 31% had a lapse of 6–12 months in their diabetes care, 11% were lost to follow-up, and 52% either experienced a problem, had lapse of care >12 months, or had no current diabetes care at all.

Although there are currently no published RCTs, the JDRF Canadian Clinical Trial Study Group recently initiated an 18-month, multicenter RCT.⁶⁶ The study will enroll a minimum of 188 patients who are transitioning from pediatric to adult care, assessing the proportion of subjects who fail to attend at least one outpatient adult diabetes visit during the second year after transition.

Roles and responsibilities. The role of the pediatric care team is to prepare adolescents and young adults for transition to adult care. This involves assisting in patient goal setting, helping to identify an appropriate support network, and working with the patient to select an adult care provider. The team should conduct a knowledge/skills assessment and provide remedial training to address any deficits. It is important that a summary of each patient's history be compiled and provided to the adult care provider. It may also be beneficial to schedule a final pediatric visit after the first adult visit.

The role of the adult care team is to provide care that is tailored to the needs of the young patient. Care providers should discuss practice logistics and access to team members with new patients. In providing care, team members should review the patient's history and, with the patient, review therapy goals, discuss options and identify potential obstacles to optimal care. Working with the patient, the team then formulates a management plan.

Achieving optimum transition. Both the pediatric and adult care teams should develop a formal plan to facilitate transition. Within the pediatric setting, the plan should include:

- A list of adult care providers who will accept transitioning patients
- A transition policy that is shared with other providers, staff, youths, and families
- A list of current and future transition candidates
- A transition curriculum that includes a checklist of skills to master, timeline, readiness assessment, and transition summary
- A transition coordinator.

Within the adult care setting, the team should develop a privacy and consent policy that is shared with all providers, staff, youths, and families and establish a process for accepting transition patients. This process should include an assessment of skills, a readiness assessment, and a transition summary package. It is critically important that the team establishes and maintains communication with the referring provider to continually assess and improve the process.

Resources. Several resources have been developed to assist patients, patient families, and healthcare providers with the transition process. The National Diabetes Education

Program provides information and recommendations regarding transition on its Web site (www.YourDiabetesInfo.org/transition).

In 2011, the ADA worked with several relevant medical organizations to develop recommendations for transitioning pediatric patients to adult care. Similarly, the Endocrine Society, in partnership with several stakeholder organizations, developed a set of transition care resources specific to type 1 diabetes. The Endocrine Society Web site provides tools for patients, families, and pediatric and adult care providers (<https://www.endocrine.org/education-and-practice-management/practice-management-resources/clinical-practice-resources/transition-of-care>).

How can we use technology to aid transition? Because adolescents and young adults utilize technology in virtually all areas of their lives, there are significant opportunities to leverage this technology. Engaging interactive formats, such as videos and games, can be used to provide education and facilitate daily self-care behaviors. For providers, technology offers ways to analyze and interpret patient data, communicate with patients, and share information with other healthcare providers. There are several online communities, such as Glu (<https://myglu.org>), College Diabetes Network (collegediabetesnetwork.org), and Students with Diabetes (hscweb3.hsc.usf.edu/studentswithdiabetes), which can provide additional support and learning to these younger adult patients.

Why Is It So Difficult to Change Behavior?

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Ways of thinking. The “Triune Brain” is a model that describes how the human brain is organized. The model hypothesizes that the human brain is made up of three interconnected brains: reptilian, limbic, and neocortex. The reptilian brain is located at the base of the brain stem and is the oldest and most primitive brain, controlling heartbeat, breathing, and basic sensory functions. The limbic system, located in the center of the brain, controls and records reactions to emotional situations. Surrounding the limbic system is the neocortex. The neocortex makes up two-thirds of the total brain mass and controls reasoning, learning, and problem-solving.

The “minimize threat–maximize reward” principle describes the fundamental organization and function of the brain in response to stimuli. According to this principle, the brain is constantly checking the environment for potential threats and rewards. If the brain perceives a situation that is associated with a potential negative outcome (via neocortex), emotion (via limbic system) takes over, prompting an avoidance response.

Although the avoidance response is generally associated with responses to physical survival (e.g., fight or flight), it is important to understand that the same neural network is used in response to social situations. Essentially, we respond to the threat of emotional pain the same way we respond to the threat of physical pain. This is referred to as our “social brain.”

Social brain. The social brain operates within five domains: status, certainty, autonomy, relatedness, and fairness.

Each of these domains can positively or negatively impact patient responses.

For example, if individuals feel their status is diminished, they will perceive and respond to this as a threat. Because most patients view their clinicians per se as having elevated status, they are already experiencing a threat response prior to their clinician interaction. Regarding certainty, the brain likes to know what will happen in the future. When patients are told that they have diabetes, they immediately become uncertain about their future welfare, which, again, triggers a threat response. Loss of autonomy induces a similar threat response when patients feel that they have lost control of their lives. Relatedness refers to patients' perception of being "in or out" of a social group. If patients feel they are all alone with their diabetes, they will feel threatened. Perception of fairness can also influence patients' responses; many patients with diabetes feel that life has treated them unfairly.

It is generally thought that decisions were made in a logical, factual way. We are now discovering that emotions play a major role in decisions. Work by Antonio Damasio⁶⁷ suggests that we are incapable of making decisions without an emotional component; an emotional component is required in order to make a decision.

Barriers to behavior change. The first barrier to changing behavior involves the "learning machine/pattern machine" paradox. As human beings, we are continually learning new things and are changing our behavior accordingly; however, we have also established patterns of behavior. The challenge for healthcare providers is to get patients to convert new behaviors into behavior patterns that they will follow automatically without thinking.

The second barrier is the "prospection and optimism bias." This refers to an individual's self-perception of immunity to known negative consequences of a given behavior. Examples of this are individuals who are aware of the complications of uncontrolled diabetes, yet they take little or no action to control their diabetes because they believe they will not be affected by these complications.

The third barrier relates to the perceived difficulties of adopting a particular behavior. If the behavior requires additional effort (mental or physical), which is registered in the neocortex, the brain reverts back to the limbic (emotional) system, which perceives this change as a threat.

The fourth barrier is "future magic me." This refers to an individual's belief that, although he or she is unable to adopt the desired behavior immediately, he or she will be able to start the behavior in the future.

Practical tips and techniques for helping patients overcome barriers to change. After providing the technical knowledge to patients regarding their diabetes self-management, it is important to make this information meaningful to them within the context of their own life situations. One way to do this is to help patients visualize how the self-care behaviors will fit into their lifestyles. Providing detailed examples of how people in similar circumstances have adopted these behaviors successfully can help patients create a meaningful vision of these behaviors in their own minds. If patients cannot visualize the behavior, they will not adopt it. It is also important to have patients write down the behavior changes they intend to make. Individuals who write detailed

descriptions of how they will initiate their new behaviors are more successful than those who simply visualize the behavior.

Another strategy is to start with behavior changes that are small and not perceived as difficult. When patients begin to adopt these behaviors as their new behavior patterns, healthcare providers can then gradually "upgrade" the patient to more significant health behaviors.

Finally, it is important to structure interactions in a way that allows patients to feel "clever" about their understanding of themselves and their perceptions of what they must do in managing their diabetes. These "feel good" moments trigger a dopamine response, which, in turn, supports adoption of the desired behaviors.

Where Does Behavior Change Start? An Overview of Empirically Validated Concepts

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Background. On average, people spend almost 9,000 hours per year managing their diabetes on their own. As a result of these burdens, people with diabetes are at greater risk of suffering from psychological problems, such as depression and anxiety.

Despite the availability of new diabetes management tools, use of these technologies is, to a great extent, dependent upon the patient. Therefore, it is important that healthcare providers recognize that patients are in control of their daily self-management decisions, are responsible for putting these decisions into practice, and have to live with the consequences. Our approach to helping patients address the burdens of diabetes and more effectively manage their disease utilizes three key concepts: timing, targets and tailoring.

Timing. One critical learning period in patients' lives is the onset of diabetes. This is the time when diabetes is high on the priority list in a patient's life. The exceptional engagement in diabetes management provides an opportunity for healthcare professionals to model effective self-care behaviors. For example, when children in Germany are first diagnosed with type 1 diabetes, they and their parents can stay in the hospital ward for 2 weeks to learn effective self-care behaviors and experience success or "mastery" in managing diabetes. These experiences contribute to their belief in self-efficacy, which, in turn, supports the patients in their self-management behaviors.⁶⁸

Another critical time is the transition period from adolescence into young adulthood, when young people learn to take responsibility for their self-management and parents to let go. During transition, it is important that healthcare providers assess both the maturity of the child and the willingness of the parents to gradually relinquish responsibility. It is known that greater difficulties with diabetes management occur when freedom is given prematurely to the child, but also when parents are overcontrolling, which can significantly inhibit effective self-management on the part of the child.

Targets. The unanimity of purpose among the diabetes team members is pivotal to deliver effective patient care. Team cohesion involves establishment of agreement upon metabolic goals and a common philosophy of care as well as a

unified way of communicating with the families. The overall goal is to support patients in their ability to make autonomous, informed decisions in their self-management efforts.⁶⁹

Tailoring. The third concept is personalizing care to each patient, taking into consideration the patient's age, experiences, individual problems, needs, priorities, strengths, and weaknesses.

The prevalence of depression is high among people with diabetes. Although psychological therapies have been used to help people with diabetes deal with their depressive symptoms, evidence from meta-analyses has shown that these approaches are often only minimally effective. Psychological interventions, for example, have shown slight improvements in HbA1c and psychological distress in children and adolescents, but not in adults.⁷⁰ Results of these approaches have been slightly better in people with type 2 diabetes.⁷¹

Another treatment used is mindfulness-based stress reduction, an 8-week program that focuses on the "detached self-observation." Although mindfulness-based stress reduction is used as a method for reducing stress, anxiety, and depression in adults with chronic conditions, the effects reported in meta-analyses are mixed.⁷² Mindfulness-based cognitive therapy, however, has been shown to help recovered, depressed patients to prevent depressive relapse.⁷³

When tailoring care to people with depressive symptoms, it is important to distinguish between clinical or subclinical depression and diabetes-related distress. Reduction of diabetes distress is associated with improvements in HbA1c, but not in depressive symptoms or major depressive disorder.⁷⁴ Use of diabetes education programs to treat depression has been effective in improving glycemic control but not in reducing depressive symptoms.⁷⁵ Thus, by applying the appropriate treatment (i.e., psychological therapy versus self-management education), we will be able to address the psychological problems and needs of the patient.

Summary. The role of the healthcare professional is to help patients to make autonomous, informed decisions regarding their medication, weight, nutrition, and physical activity and to assist them in the behavior change process. An effective team acts upon a shared philosophy, follows common goals, and utilizes structured principles to individualize therapy, initiating interventions at the time when they will be most effective.

Acknowledgments

We thank all the presenters for their contributions. Funding for the development of this manuscript was provided by Roche Diagnostics GmbH, Mannheim, Germany.

Author Disclosure Statement

R.H. and A.M. are employees of Roche Diagnostics GmbH. C.P. has received consulting fees from Roche Diagnostics GmbH.

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