Artificial Pancreas Systems for People With Type 2 Diabetes: Conception and Design of the European CLOSE Project

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Abstract

In the last 10 years tremendous progress has been made in the development of artificial pancreas (AP) systems for people with type 1 diabetes (T1D). The pan-European consortium CLOSE (Automated Glucose Control at Home for People with Chronic Disease) is aiming to develop integrated AP solutions (APplus) tailored to the needs of people with type 2 diabetes (T2D). APplus comprises a product and service package complementing the AP system by obligatory training as well as home visits and telemedical consultations on demand. Outcome predictors and performance indicators shall help to identify people who could benefit most from AP usage and facilitate the measurement of AP impact in diabetes care. In a first step CLOSE will establish a scalable APplus model case working at the interface between patients, homecare service providers, and payers in France. CLOSE will then scale up APplus by pursuing geographic distribution, targeting additional audiences, and enhancing AP functionalities and interconnectedness. By being part of the European Institute of Innovation and Technology (EIT) Health public-private partnership, CLOSE is committed to the EIT "knowledge triangle" pursuing the integrated advancement of technology, education, and business creation. Putting stakeholders, education, and impact into the center of APplus advancement is considered key for achieving wide AP use in T2D care.

Keywords

closed-loop, digital health, education, homecare, public-private partnership, France

Background

Design Options for Artificial Pancreas Systems

Massive progress has been seen in the advancement of artificial pancreas (AP) systems for the treatment of people with type 1 diabetes (T1D).[1] Recently the first (hybrid) AP system (MiniMed 670G) was granted marketing authorization for the treatment of people with T1D in the United States and the European Union.[2,3]

An AP system is a medical product that uses an algorithm informed by continuous glucose monitoring (CGM) data of a given patient, thereby regulating the infusion rates of a continuous subcutaneous insulin infusion through an insulin pump. In this way the AP is taking over control of the patient's blood glucose levels.[1] In a most advanced design the AP would mean a fully automated dosing of insulin to cover both basal and meal-related insulin requirements. Although this would not lead to a "technical cure" of diabetes, it should mimic glycemic control in healthy people most widely.[4] Some developers believe that a bihormonal AP with a coordinated infusion of both insulin and glucagon is necessary to fulfill this goal.[4] In an idealistic projection a fully automated AP system would represent a "connect-and-forget" solution reducing the burden for patients and caregivers of managing insulin therapy while most of the time approaching euglycemic blood glucose levels. Less automated solutions comprise hybrid AP systems requiring the user to adjust insulin boluses at mealtime as well as treat-to-range systems and systems minimizing hypoglycemia only.[4]

Clinical Evidence for the Safety and Effectiveness of AP Systems

Outpatient clinical trials provided substantial evidence for a safe and effective operation of (hybrid) APs in people with T1D.[5] Until now the longest real-life AP experience was provided by a study implemented by the EU-funded AP@home consortium,[1] which investigated 12 weeks of unsupervised AP use. As compared to sensor-augmented insulin pump therapy (SAP) the percentage of time in the predefined target ranges of sensor glucose concentrations (adults: 70-180 mg/dl, 3.9-10.0 mg/l; children/ adoles-cents: 70-145 mmol/l, 3.9-8.0 mmol/l) was significantly higher in both adults and children/adolescents, accompanied by reduced time in hypoglycemia and no change in total daily insulin doses when using the experimental AP system developed by the consortium.[6] The AP@home initiative also demonstrated a significant reduction of HbA1c (–0.2%, –1.6 mmol/mol) in adults with T1D combining AP and SAP as compared to SAP only over two months with a second experimental AP system.[7]

Only a few clinical trials investigated the AP usage in people with type 2 diabetes (T2D). Feasibility and safety of using a fully automated AP system was shown for people with T2D in a hospital environment.[8,9] A larger closed-loop inpatient study recently demonstrated that usage of a fully automated AP system increased the percentage of time in the predefined target range of sensor glucose concentrations (100-180 mg/dl, 5.6-10.0 mmol/l) as compared to a conven-tional subcutaneous insulin therapy, without increasing the risk of hypoglycemia and the amount of administrated insulin.[10]

Barriers to a Wide AP Usage in People With T1D

The tangible progress in AP development during the last decade caused a strong public and scientific enthusiasm, for example, the AP was selected as one of the 25 best inventions by *Time* magazine in 2013.[11] A high end-user interest in AP systems (APS) is documented by the commitment of open source APS innovation communities where people with diabetes develop "do-it-yourself APS."[12] Barriers to a wide commercialization of AP systems may include limitations of different technologies used to build such a system, but there are even more unanswered questions about liability, reimbursement[13] and psychosocial stress.[14] In fact, wearing an AP will affect multiple spheres of life related to health and disease, autonomy and control, social isolation, and acceptance, to name a few. Most favorable risk- and cost-benefit balances of AP operation in people with T1D may be demonstrable for children, pregnant women, hospitalized people, and people with comorbid conditions.

The CLOSE Initiative for AP Implementation in T2D Care

CLOSE is the acronym for Automated Glu*c*ose Contro*l* at H*o*me for People with Chronic Disea*se*. CLOSE stands for a project designed to overcome AP implementation barriers. The primary objective of the project is to develop superior risk-benefit and cost-benefit scenarios for AP operation, thereby achieving positive acceptance by users and caregivers and a high eligibility for reimbursement. To meet this objective, the project will put the AP into the center of comprehensive product and service packages (APplus) specifically tailored to defined T2D patient groups and care environments. In the design of APplus the project is going to realize an interactive collaboration with users, health care providers, and other stakeholders in diabetes care.

The consortium behind the project includes organizations with key capabilities in health care service provision as well as in the clinical development of AP systems and the market implementation and postmarket surveillance of diabetes technologies. These are complemented by competencies in the fields of health care research, economic modeling, quality assurance, and performance measurement as well as in the conceptualization and implementation of training and education. The collaborating consortium partners include two global health care corporations, a clinical contract research organization, a business school, two academic diabetology centers at maximum care hospitals, and two small-to medium-sized enterprises.[15]

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CLOSE receives funding from the European Institute for Innovation and Technology (EIT) and is part of an open knowledge and innovation ecosystem curated by the EIT Health public-private partnership.[15] EIT Health provides access to cocreation communities, living labs, and test beds. Moreover the knowledge and innovation community (KIC) exposes CLOSE to global start–up scenes, competitions for product & service ideas and innovative business models. The connection with EIT Health also facilitates the consistent integration of market-oriented research, education, and business creation, that is, the EIT "knowledge triangle."[15] This triangle matches well with the CLOSE strategy to achieving a high market acceptance for AP systems.

Going beyond technical development CLOSE considers itself as the successor of the "AP@home" project.[1] The development of an European Union–approved (CE-marked) medical device that uses a glucose clamp technology (ClampArt®) in a closed-loop setting[16] is another experience that informs CLOSE.

T2D Care Scenarios for AP Usage

Heterogeneity of People With T2D

Globally more than 400 million people suffer from diabetes (90-95% with T2D) with a rising trend projected toward >640 million by 2040.[17] From a life course perspective people with T2D exhibit an increased susceptibility to further health degeneration because of an increased risk of frailty and disability, premature aging, and the development of comorbid conditions. Accordingly T2D is part of the most prevalent chronic disease clusters[18] and is associated with premature mortality from multiple causes.[19] People with T2D allocatable to the top 10% of the overall cost distribution are likely to bear a high comorbidity burden, to be on insulin therapy, and to suffer from obesity and hypertension.[20] Direct treatment costs of people with T2D and significant comorbid conditions are up to five-fold higher than in people with T2D without comorbid conditions. This has been attributed to a high rate and length of hospital admissions.[21]

Recent recommendations recognize the diversity of people with T2D and go for a more people-centered care following personalized treatment goals.[22] Initiating an intensive insulin therapy for a tight glycemic control early in T2D may decelerate the loss of beta cell function[23] and in the longer run protect people from both micro- and macrovascular complications.[24] However, in elderly people with T2D and in people with advanced T2D both highly ambitious glycemic control goals and undertreatment of hyperglycemia could conflict with the management of geriatric syndromes and comorbid conditions.[25,26] Here the administration of insulin may follow a treat-to-range approach aiming at preventing catastrophic events from a massive deterioration of glycemic control. A treat-to-range approach might be suitable also for people with T2D who show a high volatility in glycemic control, for example, due to the use of complex treatments such as polypharmacy or renal replacement therapy.

Scopes of AP Application in T2D Care

Diabetes technologies including AP systems may represent valuable tools for advancing a more personalized and cost-effective management of people with T2D. Large clinical trials suggest that the use of both insulin pump therapy (OpT2mise)[27] and real-time glucose monitoring (DiaMonD)[28] may improve glycemic control in people with T2D, provided that guidance in selecting the people bene-fitting most from such technology will be available.

The diversity of people with T2D is mirrored by a range of potential scopes of AP usage in T2D management. For instance, introduction of the AP early after diagnosis of T2D might facilitate the transition to insulin therapy thereby helping to delay the onset of clinically overt diabetes complications. People with T2D already on insulin pump therapy might have a particularly positive attitude toward AP usage. For them the AP could be perceived as a logical and consistent enhancement of insulin pump functionalities. Probably some people on insulin pump therapy will show additional benefit from the transition to an AP system in terms of glycemic control. In the management of people with advanced T2D and elderly people with T2D AP usage could be expected to relieve users and caregivers from the burden associated with insulin administration. Here the AP usage might protect people from frailty, disability, and disease aggravation related to unrecognized episodes of massive dysglycemia. This could translate into lower rates of avoidable hospitalizations for actually ambulatory care-sensitive conditions, a well-recognized cost driver with a high impact on life quality for people with diabetes and their loved ones.[29]

A wide acceptance of the AP usage in T2D care will strongly depend on the identification of subpopulations and care settings where the AP could significantly improve the risk- and cost-benefit balances of T2D management as compared to established practice. Ultimately the develop-ment of cases for a cost-effective usage of AP systems in T2D care is a matter of interdisciplinary collaboration. AP case scenarios need to be validated in field studies that reflect real-life conditions of chronic care and the corresponding cost incurrence.

The CLOSE Approach to AP Implementation in T2D Care

Top Down Approach Toward Technical Requirements

CLOSE applies a top-down approach that consistently considers the impact of design options on AP manufacturing and maintenance costs, time-to-market, and user acceptance.

A design-to-cost analysis will critically investigate the influence of different insulin delivery and sensor designs, control units, insulin products and features for alarming and alerting and telemedical services on costs of care. Outcomes of design-to-cost analyses will be tested against costs-of-care revenue scenarios, feasibility, and the compliance with the new 2017/745 European Medical Device Regulation (MDR 2017/745).

Based on the published clinical data[8,9,10] CLOSE expects that only minor technical adjustments, if any, are needed to adapt existing T1D AP algorithms to people with T2D. Robustness of glycemic control might even be enhanced in T2D. Many people with T2D have a residual endogenous insulin secretion which may prevent them from a profound acute metabolic deterioration. This is expected to stabilize AP functioning against external and endogenous challenges and helps to improve the overall risk-benefit balance of AP operation. A focus will be laid on the ease of AP operation which will be assured by AP usability testing with different subgroups of patients with T2D.

Cocreation

The sheer numbers of people with T2D patients[17] along with expressed preferences[12,30] suggest that targeting T2D might be attractive when intending a fast and wide AP market acceptance. On the other hand the heterogeneity of users and their health care environments makes it unlikely that there will be a "one-fits-all" APplus solution.[4] Therefore investigating the different dimensions of T2D diversity and taking learnings from cocreation formats involving different stakeholders in T2D are key features of CLOSE.

CLOSE follows a cocreation approach by developing APplus in the framework of French homecare service provision. French homecare service providers (HSP) operate fully integrated chronic care platforms at the crossroads between patients, health professionals, payers, and prescribers while using proven methods and processes being based on established policies.[31] For instance, people with diabetes (both T1D and T2D) who are on insulin pump therapy are offered an integrated service portfolio coordinated by a multiprofessional HSP team (Figure 1). Following a medical prescription according to guiding policies,[32] the HSP team takes care of therapy initiation, pump maintenance, technical and dietary education, the provision of consumables, and the availability of telemedical consultations and home visits on demand. In France the services around insulin pump therapy are registered in the list of products and services qualifying for reimbursement (LPPR).[33]

French homecare service provision seems to be a real-world environment particularly suitable as a learning lab for cocreating an APplus product and service package meeting the needs and requirements of insulin-dependent people with T2D and their caregiver teams. Here learnings about the different stakeholders' perceptions of diabetes, their attitudes
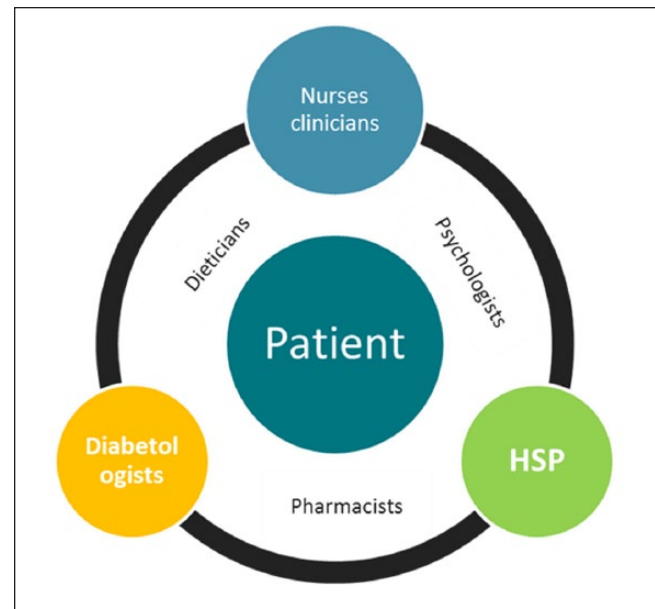

Figure 1. AP operation as part of a homecare service provision (HSP) platform requires interprofessional collaboration and patient education.

toward diabetes management, and their understanding of treatment success can immediately inform a customization of APplus solutions.

We anticipate that specifically tailored APplus packages could increase the adherence of both users and caregivers to a qualified AP use, thereby improving effectiveness in T2D care and achieving a high acceptance for AP systems from the side of patients, caregivers, and payers.

Training and Education

The heterogeneity of T2D implies that AP solutions will need explanation to different groups of users and health care professionals. CLOSE will enrich the AP by adding obligatory training and education modules. Training and education shall empower users for taking responsibility about their diabetes management, authorize caregivers for a knowledgeable installation and operation of the AP and help managing the diversity of expectations. In particular opportunities and pitfalls of wearing an AP will be addressed. By developing a train-the-trainer program, CLOSE will achieve a high compliance with agreed quality standards for AP usage.

Outcome Predictors and Performance Indicators

To achieve a high eligibility of the AP for reimbursement CLOSE is going to implement outcome predictors and performance indicators as part of APplus packages. Outcome predictors will help to identify T2D patients who might benefit most from AP usage. They will cover aspects along the lines of disease progression status, behavioral attributes and

the accessibility of care services. A panel of health- and process-related performance indicators will be used for measuring the impact of AP implementation on the quality and effectiveness of diabetes care.

When introducing AP-related outcome predictors and performance indicators CLOSE will follow a practice-oriented iterative learning approach. Different stakeholder and expert groups will be involved in making a meaningful choice from existing resources such as the T2D-related quality indicator system for ambulatory care (QiSA)[34] and established predictors of health deterioration potentially influenceable by AP usage.[35] The impact of glycemic control typologies on the individual outcome of AP usage will be assessed by means of a deviation analysis being based on the exploitation of real-life CGM profiles from T2D patients on insulin therapy.[36] The adequacy of predictors and indicators will be monitored within the framework of AP usage in real-life care environments. The outcome will feed into further refinement of the measurement tools. New predictors and indicators will be established if deemed useful.

The introduction of AP-related predictors/indicators will be backed by investigations in the more general conditions for APplus cost-effectiveness and its uptake by multiple stakeholders. Following the triple aim approach to optimizing the sustainability of health care.[37] AP implementation in T2D care should improve the interactions of the individual patient with the health care system (ie, his/her care experience), the health of the respective T2D subpopulation, and the per capita health care costs, thereby making the AP attractive for usage within the scope of pay-for-performance models.

In Perspective: Adaptability, Scalability, and Enhancement of APplus

For a wider distribution of AP usage it seems reasonable to assume that APplus should be highly adaptable to the requirements of different T2D patient subgroups and their specific care situations. This calls for an APplus portfolio containing an array of AP systems with and without carbohydrate counting and realizing different intensities of insulin therapy and degrees of automation. CLOSE will investigate algorithms with an automated meal detection module (eg, imaging-based food recognition) or with preprogrammed fixed boluses corresponding to the ingestion of low, intermediate, and high carb meals. Both treat-to-target and treat-to-range systems will be under consideration.

Using homecare as a learning lab and starting point, APplus shall be expanded to operation in assisted living facilities, nursing homes, and hospitals. Also APplus solutions for people having T2D without overt comorbid conditions or T1D are under consideration. Geographical upscaling will seek benefit from collaboration with regions and municipalities in a careful consideration of existing local/national competencies, health care structures, and payment models. Through the obligatory delivery of train-the-trainer programs

CLOSE will grow a network of certified caregivers that will guarantee a safe and cost-effective implementation of AP solutions around Europe and globally. Beyond technical adaptations the design of highly targeted training modules is predicted to be a main differentiator of APplus solutions tailored to the needs and requirements of different patient groups and care environments.

Adding capabilities for the exploitation of patient-generated health and behavioral data will functionally enhance the AP in the medium term. The utilization of self-learning algorithms and an increased interconnectedness with health and social service provision will close the loop between the users' state of health and customized care provision in a more comprehensive meaning. Converging with other strands of health innovations in chronic care enhanced AP systems will contribute to a fully integrated personalized diabetes management (iPDM).[38,39]

In view of the increasingly shorter lifecycles for digital technology-based health products and services an open and integrated approach to APplus postmarketing surveillance and enhancement might be essential for leveraging maximum impact on the sustainability of diabetes care in Europe and globally. By providing well curated innovation ecosystems, public-private partnerships such as EIT Health or the JDRF can considerably help overcome barriers to cost-effective and fully integrated personalized diabetes management.

Abbreviations

AP, artificial pancreas; APS, artificial pancreas system; CGM, continuous glucose monitoring; CLOSE, Automated Glucose Control at Home for People with Chronic Disease; EIT, European Institute of Innovation and Technology; EU, European Union; HbA1c, a glycated hemoglobin [N-(1-deoxy)-fructosyl-hemoglobin]; HSP, homecare service provider; iPDM, integrated personalized diabetes management; KIC, knowledge and innovation community; LPPR, list of products and services qualifying for reimbursement; MDR, medical device regulation; SAP, sensor-augmented pump therapy; T1D, type 1 diabetes; T2D, type 2 diabetes.

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References

1. Heinemann L, Benesch C, DeVries JH. AP@home: the artificial pancreas is now at home. *J Diabetes Sci Technol*. 2016;10(4):950-958.
2. US Food and Drug Administration. MiniMed 670G system approval letter. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160017S017a.pdf. Accessed August 17, 2018.
3. Medtronic. Medtronic receives CE mark for MiniMed 670G hybrid closed loop system. Available at: https://www.medtronic-community.de/wp-content/uploads/MiniMed_670G_Pressemitteilung.pdf. Accessed August 17, 2018.
4. Kowalski A. Pathway to artificial pancreas systems revisited: moving downstream. *Diabetes Care*. 2015;38(6):1036-1043.
5. Bekiari E, Kitsios K, Thabit H, et al. Artificial pancreas treatment for outpatients with type 1 diabetes: systematic review and meta-analysis. *BMJ*. 2018;361:k1310.
6. Thabit H, Tauschmann M, Allen JM, et al. Home use of an artificial beta cell in type 1 diabetes. *N Engl J Med*. 2015; 373(22):2129-2140.
7. Kropff J, Del Favero S, Place J, et al. 2 month evening and night closed-loop glucose control in patients with type 1 diabetes under free-living conditions: a randomised crossover trial. *Lancet Diabetes Endocrinol*. 2015;3(12):939-947.
8. Kumareswaran K, Thabit H, Leelarathna L, et al. Feasibility of closed-loop insulin delivery in type 2 diabetes: a randomized controlled study. *Diabetes Care*. 2014;37(5):1198-1203.
9. Thabit H, Hartnell S, Allen JM, et al. Closed-loop insulin delivery in inpatients with type 2 diabetes: a randomised, parallel-group trial. *Lancet Diabetes Endocrinol*. 2017;5(2):117-124.
10. Bally L, Thabit H, Hartnell S, et al. Closed-loop insulin delivery for glycemic control in noncritical Care. *N Engl J Med*. 2018;379(6):547-556.
11. Juvenile Diabetes Research Foundation. Artificial pancreas named top 25 best inventions of 2013. *Time*; November 14, 2013. Available at: http://www.jdrf.org/rockymountain/2013/11/14/artificial-pancreas-named-top-25-best-inventions-of-2013-by-time-magazine/. Accessed August 17, 2018.
12. Barnard KD, Ziegler R, Klonoff DC, et al. Open source closed-loop insulin delivery systems: a clash of cultures or merging of diverse approaches? [published online ahead of print August 6, 2018]. *J Diabetes Sci Technol*. doi:10.1177/1932296818792577.
13. Peyser T, Dassau E, Breton M, Skyler JS. The artificial pancreas: current status and future prospects in the management of diabetes. *Ann N Y Acad Sci*. 2014;1311:102-123.
14. Farrington C. Psychosocial impacts of hybrid closed-loop systems in the management of diabetes: a review. *Diabet Med*. 2018;35(4):436-449.
15. CLOSE project and consortium. . Available at: http://eit-health.de/activities/innovation-projects/close-diabetes/. Accessed August 20, 2018.
16. Benesch C, Heise T, Klein O, Heinemann L, Arnolds S. How to assess the quality of glucose clamps? Evaluation of clamps performed with ClampArt, a novel automated clamp device. *J Diabetes Sci Technol*. 2015;9(4):792-800.
17. International Diabetes Federation. *Diabetes Atlas*. 7th ed. Brussels, Belgium: International Diabetes Federation; 2015.
18. Laiteerapong N, Iveniuk J, John PM, Laumann EO, Huang ES. Classification of older adults who have diabetes by comorbid conditions, United States, 2005-2006. *Prev Chronic Dis*. 2012;9:E100.
19. Seshasai SR, Kaptoge S, Thompson A, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med*. 2011;364(9):829-841.
20. Meyers JL, Parasuraman S, Bell KF, Graham JP, Candrilli SD. The high-cost, type 2 diabetes mellitus patient: an analysis of managed care administrative data. *Arch Public Health*. 2014;72(1):6.
21. Schmitt-Koopmann I, Schwenkglenks M, Spinas GA, Szucs TD. Direct medical costs of type 2 diabetes and its complications in Switzerland. *Eur J Public Health*. 2004;14(1):3-9.
22. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38(1):140-149.
23. Kramer CK, Zinman B, Retnakaran R. Short-term intensive insulin therapy in type 2 diabetes mellitus: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2013;1(1):28-34.
24. Testa R, Bonfigli AR, Prattichizzo F, La Sala L, De Nigris V, Ceriello A. The "metabolic memory" theory and the early treatment of hyperglycemia in prevention of diabetic complications. *Nutrients*. 2017;9(5):E437.
25. Abdelhafiz AH, McNicholas E, Sinclair AJ. Hypoglycemia, frailty and dementia in older people with diabetes: reciprocal relations and clinical implications. *J Diabetes Complications*. 2016;30(8):1548-1554.
26. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. *Diabetes Care*. 2012;35(12):2650-2664.
27. Reznik Y, Cohen O, Aronson R, et al. Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial. *Lancet*. 2014;384(9950):1265-1272.
28. Beck RW, Riddlesworth TD, Ruedy K, et al. Continuous glucose monitoring versus usual care in patients with type 2 diabetes receiving multiple daily insulin injections: a randomized trial. *Ann Intern Med*. 2017;167(6):365-374.
29. Freund T, Campbell SM, Geissler S, et al. Strategies for reducing potentially avoidable hospitalizations for ambulatory care-sensitive conditions. *Ann Fam Med*. 2013;11(4):363-370.
30. Arnolds S, Heckermann S, Heise T, Sawicki PT. Spectrum of diabetes research does not reflect patients' scientific preferences: a longitudinal evaluation of diabetes research areas 2010-2013 vs. a cross-sectional survey in patients with diabetes. *Exp Clin Endocrinol Diabetes*. 2015;123(5):299-302.

31. Beuscart R, Bricon-Souf N, Brunetaud JM, Watbled L, Alao O, Bennani N. Homecare: the need for cooperative information systems. *Stud Health Technol Inform*. 2004;107(pt 2):1343-1347.

32. Lassmann-Vague V, Clavel S, Guerci B, et al. When to treat a diabetic patient using an external insulin pump. Expert consensus. Societe francophone du diabete (ex ALFEDIAM) 2009. *Diabetes Metab*. 2010;36(1):79-85.

33. Loge P, Delalande F, Reymond MC, Germain S. Factors Influencing reimbursement of medical devices in France. *Int J Technol Assess Health Care*. 2015;31(6):399-406.

34. QiSA. Available at: http://www.aok-gesundheitspartner.de/bund/qisa/themen/index_04875.html. Accessed August 17, 2018.

35. Chow LS, Smora R, Ma S, Seaquist ER, Schreiner PJ. Development of a model to predict 5-year risk of severe hypoglycaemia in patients with type 2 diabetes. *BMJ Open Diabetes Res Care*. 2018;6:e000527.

36. Reiterer F, Reiter M, Del Re L, Bechmann Christensen M, Nørgaard K. Analyzing the potential of advanced insulin dosing strategies in patients with type 2 diabetes: results from a hybrid in silico study [published online ahead of print April 21, 2018]. *J Diabetes Sci Technol*. 2018; doi:10.1177/1932296818770694.

37. Whittington JW, Nolan K, Lewis N, Torres T. Pursuing the triple aim: the first 7 years. *Milbank Q*. 2015;93(2):263-300.

38. Ceriello A, Barkai L, Christiansen JS, et al. Diabetes as a case study of chronic disease management with a personalized approach: the role of a structured feedback loop. *Diabetes Res Clin Pract*. 2012;98(1):5-10.

39. Kulzer B, Daenschel W, Daenschel I, et al. Integrated personalized diabetes management (PDM): design of the ProValue studies: prospective, cluster-randomized, controlled, intervention trials for evaluation of the effectiveness and benefit of PDM in patients with insulin-treated type 2 diabetes. *J Diabetes Sci Technol*. 2015;10(3):772-781.