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SYMPOSIUM

AP@home: A Novel European Approach to Bring the Artificial Pancreas Home

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Abstract

The development of an artificial pancreas (AP) made huge strides from 2006 to 2008 and a large number of activities are going on in this area of research. Until now, most AP systems under development were tested only under highly controlled conditions. The aim of our project, funded by the European Union, is to develop an AP system to such a level that it can be studied under daily life conditions at the home of patients with diabetes (hence AP@home). Based on a subcutaneous-subcutaneous closed-loop strategy (i.e., glucose sensing and insulin infusion in the subcutaneous tissue), two different approaches will be taken to achieve this aim: a two-port AP system and a single-port AP system. The two-port AP system will use off-the-shelf-components for the glucose sensor and insulin pump in combination with closed-loop algorithms generated in Europe. As to the single-port AP system, two different innovative single-port systems will be developed; in this case, continuous glucose monitoring and insulin infusion will take place via a single catheter. The first clinical trials with the two-port AP system under controlled clinical conditions have started and good progress has been made in the development of the single-port AP systems. We believe that our consortium of 12 European partners, which builds on existing achievements and close cooperation between academic centers and industry, can contribute substantially to the development of an AP system that can be used by patients in daily life.

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Introduction

The aim of this article is to describe the basic strategy that the European consortium AP@home plans to follow in its attempt to develop an artificial pancreas (AP) system that can be used in daily practice (at home) by patients with diabetes (*www.apathome.eu*). Two main development tracks toward a practically usable AP system will be followed (**Figure 1**):

- A two-port AP system by using already available continuous glucose monitoring (CGM) systems and insulin pumps (off the shelf);
- A single-port AP system by using only one catheter for glucose measurement and insulin delivery.

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Abbreviations: (ADICOL) Advanced Insulin Infusion using a Control Loop, (AP) artificial pancreas, (AP@home) Artificial Pancreas at home, (CGM) continuous glucose monitoring, (CLINICIP) Closed Loop Insulin Infusion for Critically Ill Patients, (CRC) clinical research center, (CRI) clinical research institute, (DIADVISOR) Personal Glucose Predictive Diabetes Advisor, (EU) European Union, (FDA) Food and Drug Administration, (ICT) information and communication technologies, (INCA) Intelligent Control Assistant for Diabetes, (JDRF) Juvenile Diabetes Research Foundation, (MPC) model predictive control, (PBA) phenylboronic acid, (PID) proportional integrative derivative, (RCT) randomized clinical trial, (SC) subcutaneous

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To meet these objectives, a consortium consisting of 12 partners from 7 different countries across Europe was established, which includes experts in the fields of information and communication technologies (ICT), nanotechnology, algorithms, numerical simulation and validation, system integration, telemedicine, clinical trials in diabetes technology and patient acceptance, and single-port AP system development. We believe that bringing together clinical experts with technical experts within one project is key for successful development of an AP system. The project is funded by the European Union (EU) within the Seventh Framework Programme. The overall project is divided into four objectives and eight work packages to structure the work that is required to fulfill our strategy. During the course of the project, we will perform clinical studies that support optimization of the closed-loop algorithms developed by members of our consortium. For example, we will run studies comparing the insulin action when insulin is applied by a patch pump vs a conventional insulin pump.

The ultimate goal of this project is to run a large, multinational, multicenter clinical study at the end of the 4-year project, allowing us to evaluate the feasibility and benefits of bringing an AP system into the home environment of patients with diabetes. For safety reasons, the data generated during such a study will be transferred online to a system that allows not only continuous remote monitoring of the performance of the AP system studied but also remote control by health care providers. Connecting the AP system wirelessly to a cell phone that alerts significant others or health care providers in case of hyper- and hypoglycemic alarms should result in better integrated care and management of diabetes. Therefore, implementation of ICT is an integral part of this project.

Background

To combine a continuous glucose monitoring (CGM) system with an insulin pump via a computer—which calculates appropriate insulin infusion rates depending on current glucose readings—is not a new idea; data have confirmed that this indeed is possible.[1–4] Attempts have been made in Europe to develop an AP system.[5,6] Three EU funded projects [ADICOL (Advanced Insulin Infusion using a Control Loop) in the Fifth Framework Programme, INCA (intelligent control assistant for diabetes) and CLINICIP (Closed Loop Insulin Infusion for Critically Ill Patients) in the Sixth Framework Programme] were aimed at developing AP systems for use in daily life or under the conditions of an intensive care unit.

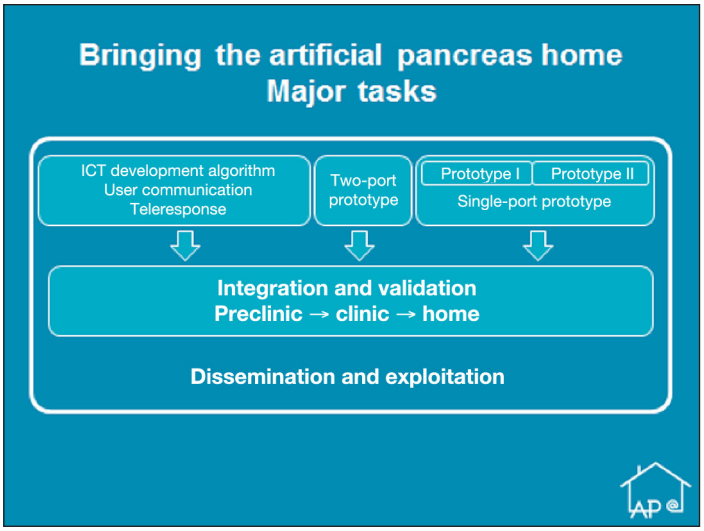

Figure 1. Basic concept of the AP@home project.

Clearly, one of the major bottlenecks for successful implementation of an AP system in daily practice is that available algorithms relating glucose information to insulin infusion rates have issues in handling vastly different requirements presented by each patient with diabetes during daily life: from the more benign situation during the night rest to a situation requiring a massive increase in insulin application after carbohydrate-rich meals to a situation in which a reduction in insulin supply is required, i.e., after physical exercise. In Europe, a number of internationally renowned academic research groups have worked intensively and successfully on optimization of such algorithms.[7–15]

A typical aspect of all investigations with different AP approaches that are under development internationally (>80 groups in academia and companies are working on this) is that these studies are performed under highly controlled conditions in clinical research centers (CRC). The main reasons for this are safety concerns and regulatory requirements. During a workshop by the Food and Drug Administration (FDA), representatives highlighted that from their perspective,

- Signals provided by the available CGM systems are not reliable enough to allow usage under daily life conditions;
- Algorithms developed to calculate appropriate insulin infusion do not allow optimal coverage of insulin requirements after meals, during the night, or after physical exercise;
- Insulin pumps used in different AP systems are not been fail-safe enough.

From our point of view, considerable variability of insulin absorption from the subcutaneous (SC) tissue further adds to the difficulties in achieving adequate glycemic control in all circumstances of daily life using the available AP systems and control algorithms. We believe that it is only when we have a better understanding of these factors, which will allow optimization of closed-loop algorithms, that an AP system will become available that is truly suited for daily diabetes management of patients at home.

Since the 1970s, the most constant statement made in numerous publications and presentations about AP systems was that "…in five years' time such a system will be practically available." Repeatedly raising the hopes of patients and physicians that a technical cure of diabetes will become available within a relatively short period of time—without being capable of delivering the proposed usable AP system in reality—has caused much frustration and skepticism. However, we believe that developments in diabetes technology have come to a point that will bring successful development of a practically usable AP system within reach.

Regulatory Aspects

Conducting clinical studies with a medical device such as an AP system requires approval by a local ethical committee and a governmental agency in most European countries. Until March 2010, regulatory-wise, it was easier to perform AP studies in the EU than in the United States. The FDA has been rather reluctant to approve such studies because of safety concerns (see explanations earlier). However, since a new medical device directive was implemented in Europe, the barriers for approval of AP studies have been raised considerably. Our experience with getting approval for the first clinical trials in our project taught us that there is quite some heterogeneity in the interpretation and handling of this directive by the regulatory agencies of different European countries. In consequence, getting approval for AP studies is more difficult than it was previously and now requires different levels of intensity in different countries. However, in contrast to countries outside of Europe, not every change in an insulin infusion rate must be confirmed by a health care professional or physician as long as appropriate safety measures are in place. Thus, unsupervised experiments at the home of patients with diabetes might then be possible, at least in some European countries. As a result, good or bad, the true performance of a given AP system can be evaluated under such circumstances.

AP@home Partners

The different partners in our consortium bring very different skills and knowledge to this project (**Figure 2**, **Appendix 1**). It is our belief that such a wide coverage of very different areas of research and development along with profound management and logistic capabilities are required to make such an undertaking successful in the end.

CGM Systems and Their Performance

Patients with diabetes have to "close the loop" themselves by monitoring their blood glucose with capillary measurements and adjusting their prandial mealtime insulin dose and basal insulin dose. Switching from this approach to an automated closed loop requires that the signals of a CGM system adequately drive the insulin infusion. Different CGM systems that are on the market for patient use rely on electrochemical technology that measures changes in glucose levels in the interstitial fluid. None of these CGM systems are clearly superior (which might of course change with new sensor generations and systems that are under development). All suffer from a certain delay between changes in blood glucose and interstitial fluid and signal drift over time. This delay is one of the motivations for developing algorithms that are able to estimate future glucose concentrations ahead of time using a prediction horizon of, 30 minutes. In addition, CGM signals are noisy and their signal-to-noise ratio shows a certain intersensor variability (as well as interbatch variability). Variability can also be observed between (interindividual) and within (intraindividual) patients; see Facchinetti and colleagues[16] for examples

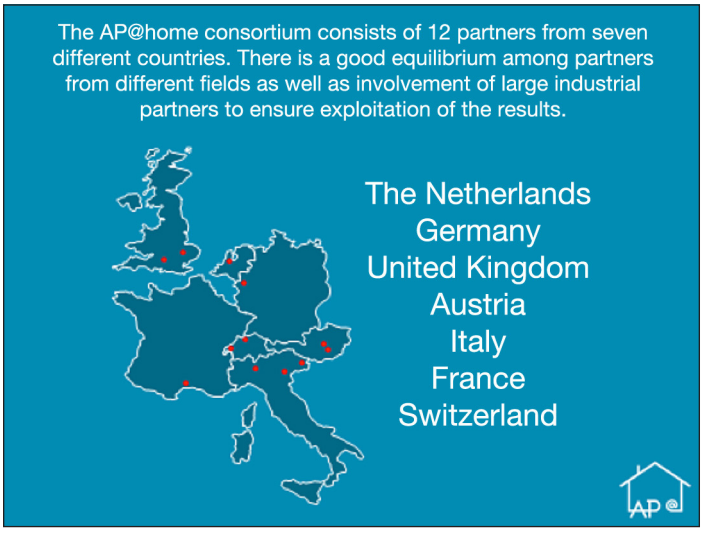

Figure 2. Location of the 12 partners of AP@home across Europe.

and comprehensive discussion. Another critical topic with all CGM systems is calibration, i.e., relying on the glucose signal measured in interstitial fluid to blood glucose by means of capillary blood glucose measurements. For instance, if this is performed while blood glucose changes rapidly or if this is not performed with sufficient frequency to compensate for drift, there might be an unnecessary difference between measured and real glucose levels. In light of these shortcomings, as discussed, e.g., in review papers,[17,18] there is a clear need for algorithms that are able to make the CGM sensor smarter in order to have more robust glucose data input to allow reliable AP performance. Therefore, within the AP@home project, a separate work package is devoted to calibration, denoising, and prediction of CGM signals with the aim of developing so-called smart sensors.

Insulin Absorption

The belief used to be that the major bottlenecks for developing an AP system were in producing a reliable CGM system, a small enough insulin pump, and a wearable computer with sufficient calculation power and battery life. Such technology and hardware has become available, however, it has become clear that another bottleneck for successful implementation of an AP system is insulin absorption. Without a fast and consistent change in insulin action once a change in insulin infusion rate is made as determined by the algorithm, blood glucose will respond too slowly and in an unpredictable manner. Beside a rapid onset of action (and decline of action), it is also important that a given amount of insulin infused into the SC tissue induces the same glycemic effect each and every time. In reality, the glycemic effect induced varies considerably intra- and interindividually. Thus, insulin is not simply a commodity that has to be infused but rather the distribution of the insulin application during the course of the day in reaction to the patient's current needs is key for a successful AP system. Also, from a safety perspective, appropriate dosing of insulin is critical, i.e., especially under at-home conditions. Overdosing should be avoided as much as possible. By employing ICT as an integral part of our approach, we believe that online access to the current glycemic situation of the patient and the possibility to interact with the patient and the AP system will mitigate the risk to an acceptable level.

With most available AP approaches, the algorithms used do not vary basal insulin infusion, which are more or less constant, or the relatively large insulin boli for a given meal with conventional continuous SC insulin infusion therapy, but rather the timing and dose of numerous small insulin boli applied subcutaneously over time. This allows the correction of certain deviations of blood glucose from the target level while also avoiding overinsulinization. The latter is associated with an increased risk of hypoglycemic events by relatively too large amounts of insulin circulating in blood. Clearly, if there is too long a delay in the glycemic response to a certain amount of insulin infused or the glycemic effect induced varies considerably, the level of glycemic control will differ from the target.

Within the AP@home consortium, we have a number of partners with a strong interest and background in insulin pharmacology. Therefore, one focus of our project is on insulin absorption. We have already started studies to investigate what is the intraindividual variability of insulin absorption and insulin action with insulin pumps, both with conventional and patch pumps. As to the attempts to increase the rate of insulin absorption from the SC insulin depot by applying ultrarapidly absorbed insulin formulations,[19,20] applying insulin into another compartment,[21] or inducing warmth at the injection/infusion site,[22] it remains to be studied whether these approaches allow better glycemic control with AP systems.

By answering these and related questions, we hope to provide information necessary to implement a successful AP system. We believe that it will not be possible to develop an ideal algorithm for closing the loop without an in-depth understanding of the impact of all factors driving insulin absorption from the SC insulin depot.

Algorithms

Algorithms ensuring better nocturnal metabolic control than standard care have been reported by members of our consortium.[23,24] Margins for improvement are still wide. Exercise and meals are additional obstacles to perfect glucose control. Algorithms for glucose control are classified as proportional integrative derivative (PID) or model predictive control (MPC).

Neither of these two approaches has clearly shown superior performance, although the MPC type is preferred by most, including our consortium. One of our aims is to optimize available algorithms by numerical computer simulations, to increase their robustness for field use. In computer simulations as well as subsequent verifications of the two-port AP system, we pay special attention whether it is possible to improve the algorithms by taking activity levels obtained by a motion detector into account

obtained from an integrated activity/motion detector. Clearly, optimized algorithms will use as input multi-parametric monitoring of health parameters that include glucose levels obtained via a smart glucose sensor and activity levels and, as output, control SC insulin administration via an insulin pump.

Another major focus of our algorithm development is determination of reliable hyper- and hypoglycemic alarms. These alarms serve as an input for the remote control feature of the AP systems that we are developing by establishing a wireless connection to a cell phone in case of an alarm to alert health care professionals and/or significant others. As a prerequisite of these activities, we will improve on the quality of the signals provided by the CGM systems by developing smart sensors, as described earlier.

One of the strengths of our consortium is that we have, as our partners, developers of *in silico* models of AP systems. Usage of *in silico* patients allows for evaluation of the performance of AP systems without having to perform a full clinical trial.[11,25]

Two-Port AP System

As a first step, we are developing an AP system by assembling a new two-port AP prototype by using existing components (i.e., a CGM system and an insulin pump) and connecting them through a notebook that has software to address the interfaces of these devices adequately and to run the control algorithm. This AP prototype is being built for research purposes. With this AP system, the skin will need to be punctured twice—once for the glucose sensor and once for the insulin infusion—which is why it is called a two-port AP system. The European input in this system is mainly the improved closed-loop algorithms developed by consortium members (see earlier) and their validation in clinical-experimental studies under controlled conditions and subsequently under daily life conditions (i.e., at home).

One of the aims with this system is to implement an improved remote hypoglycemia alarm. The hypoglycemia alarms will, via a wireless connection of the AP system to a cell phone, place an alarm call to health care providers or significant others. This validated eHealth part of the two-port AP system will then be implemented in our single-port AP approach (see description later). We compare the two EU-based algorithms available within the consortium in terms of glycemic control maintained under different conditions (night, meals, and exercise). Such studies (in combination with other small clinical studies, see descriptions earlier) allow us not only to test if this AP prototype can be used under at-home conditions but also allow optimization, verification, and validation of the available versions of the algorithms.

Single-Port AP System

A considerable hurdle for achieving patient acceptance for daily usage of any AP system is that it requires carrying around a number of devices at all times. The reluctance of many patients is illustrated by the large number who are not willing to use a CGM system regularly in addition to their pump in daily life.[26] If it became possible to reduce the number of skin perforations to one (i.e., single-port), this would reduce the barrier to practical usage of an AP system; however, this requires glucose sensing at the site of insulin delivery. Such an approach would therefore improve patient comfort and simplify diabetes care. Such single port systems are under development, mainly in Europe.

One of the key questions with this approach is whether infused insulin has an impact on measured glucose levels, e.g., does infused insulin induce a local drop in glucose levels that results in a difficult-to-predict deviation of the glucose levels measured in interstitial fluid? Data show that it is possible to use two needles inserted close to each other without interference.[27] Clinical experiments conducted by the University of Graz showed that a single-port approach is also feasible and that there is no need for more than one needle for both functions, i.e., glucose monitoring and insulin delivery.[28,29] By inserting a special indwelling catheter (i.e., a microperfusion or microdialysis probe) into SC adipose tissue of patients with diabetes and using the catheter for simultaneous insulin delivery and glucose sampling, glucose concentration observed at the tissue site of insulin delivery correlates well with that seen in plasma.

In the AP@home project, two different innovative approaches are being developed in parallel with the aim to have at least one functional single-port AP system at the end of the project:

- The first approach relies on a nanoporous, glucose stimuli-responsive material that changes its permeability for insulin with the patient's glucose levels;

- The second approach uses an insulin infusion catheter with an integrated glucose sensor that is inserted through a single skin perforation.

One of the aims of developing two single-port AP systems in parallel is to maximize the chances of success of this approach in general. It is not easy to predict which of the two approaches will become available first and which one will work better. It is not clear if both approaches will progress during the course of the project to clinical validation.

The first approach proposed by the Swiss company Sensile Medical (**Figure 3**) in close cooperation with an institute of the University of Lausanne is based on a glucose-responsive membrane. The system consists of three modules (from the outlet to the inlet):

(1) A glucose-responsive, composite, nanoporous needle inserted subcutaneously and capable of dynamically changing its porosity as a function of glucose concentration in the SC environment. The needle will be closed with a pressure valve that allows bolus insulin injection;

(2) A flow meter capable of dynamically measuring changes in permeability of the outlet using tiny amounts of insulin (50–500 nl);

(3) An off-the-shelf microliter pump developed by Sensile Medical that is capable of delivering precise amounts of insulin solution.

The insulin-solution flow dynamics will be measured by the flow meter and controlled by the glucose-responsive needle, whereas the overall amount of insulin infused in the body will be controlled precisely by the microliter pump. The glucose-responsive, composite nanoporous needle (developed by the University of Lausanne) consists of hollow fibers with nanopores that will be modified with a glucose-sensitive phenylboronic acid (PBA)-based hydrogel that can to change its volume in the presence of glucose.[30–33] Promising formulations of PBA hydrogel with a specific affinity for glucose at physiological conditions have been published.[34,35]

The second approach, developed by the University of Graz, modifies an insulin infusion catheter to accommodate a continuous, off-the-shelf glucose sensor. Two sensor placement concepts are being pursued (**Figure 4**): one placement concept involves modification of the holding pad of an insulin infusion cannula to accommodate a continuous glucose sensor (*ex vivo* sensor placement). The second placement concept involves integration of a continuous glucose sensor directly onto the shaft wall of an insulin infusion cannula (*in vivo* sensor placement). Whether the sensor is best placed outside the body within the insulin pump or within the body on the insulin delivery catheter is unknown and needs further investigation and development. With the latter approach (within the body), it was shown in a proof-of-principle study that simultaneous insulin delivery and glucose sampling at a single-port AP is possible.[28,29]

Within the first year of development of the two single-port approaches, both approaches have made good progress and the first clinical evaluations have been scheduled to begin.

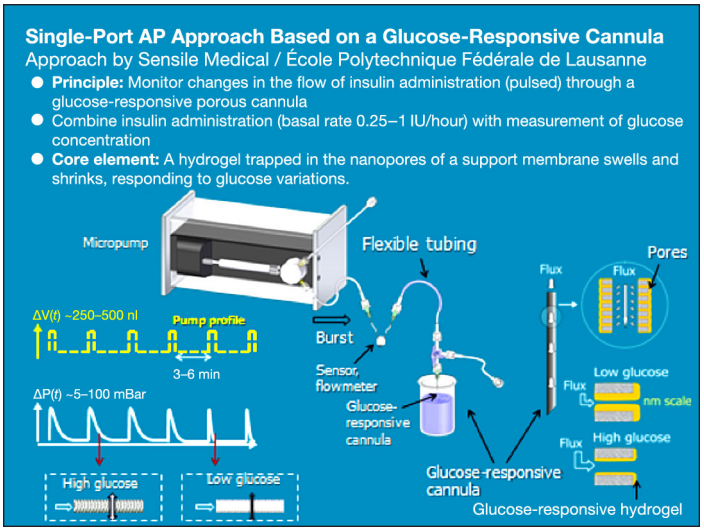

Figure 3. Single-port AP approach based on a glucose-responsive cannula.

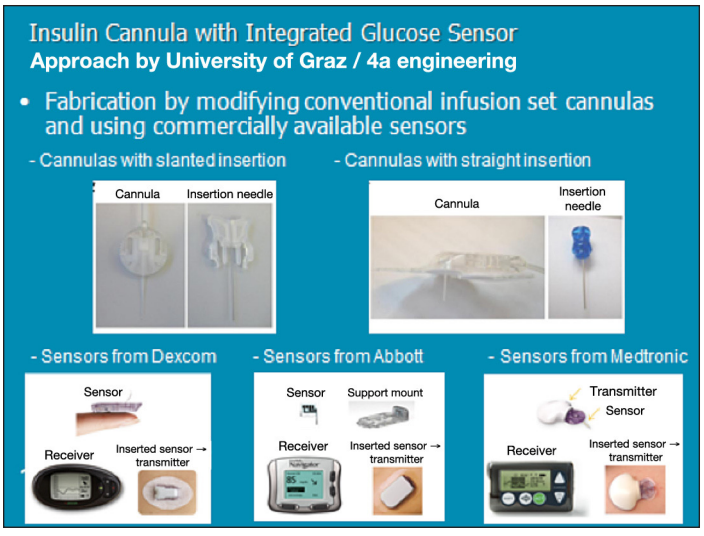

Figure 4. Single-port AP approach based on an insulin cannula with integrated glucose sensor.

Clinical Studies

Within the framework of this project, a number of different clinical-experimental and clinical studies will be performed. Clearly, these studies will be performed according to good clinical practice standards. All data generated during the clinical trials will be stored in a central data base hosted by Profil Institut für Stoffwechselforschung, Neuss, Germany, for subsequent analysis of the results of the trials.

Validation

Before the AP systems developed in our project can be studied under outpatient conditions, they must pass a clinical validation procedure that addresses safety, alarms, crisis management, and efficacy under different real-life situations such as nighttime, exercise, and meal intake as well as the concept of remote control by providing these alarms to the patient's significant other or health care professionals. The performance quality of the algorithms will be validated in comparison to standard therapy in a medium-sized, multicenter, randomized clinical trial (RCT). Additionally, if proven successful in computer simulations, one or both single-port AP systems will be evaluated in RCTs. This shall lead to an AP system that allows successful treatment and management of patients with diabetes at home, which has to be demonstrated in an appropriately designed RCT toward the end of our project.

Conclusions

By pooling and integrating European knowledge, technologies, expertise, and capacities, AP@home has the ambition to develop a two-port and/or single-port AP system that can be clinically tested. It is our belief, however, that the development of AP systems is an evolutionary one, i.e., even if a practically usable system becomes available, we foresee room for continuous improvement over time. Also, it may very well be that by employing other approaches, i.e., use of a bihormonal pump (infusion of insulin and glucagon), different AP systems will become available for different groups of patients with diabetes and their varying needs. Also, from a cost point of view, AP systems of different complexity might be required for different patient groups. This has been taken into account for clinical trials that aim to support the use of AP systems in comparison to standard care.

In line with the statement about the evolutionary development of AP systems, it is also of importance to clarify and define the expectations. The first generations of AP systems will probably not be a cure for diabetes in the sense that glycemic control of patients with diabetes will be brought to within the same range as that of healthy subjects. A first aim is to be better than standard practice; this would mean that, e.g., the risk of developing hypoglycemia is substantially reduced and that blood glucose levels remain in the euglycemic range 75% of the time. Setting expectations at a realistic level will also be important to get regulatory approval for using AP systems in daily practice. Regulatory people might be more focused on safety aspects, whereas diabetologists and patients are more focused on efficacy.

Our project will be performed in close communication with other international groups that are active in AP development, e.g., the Juvenile Diabetes Research Foundation (JDRF), which drives the development of a practically usable AP system in the United States and also in other countries. Some members of our consortium are active in an international project initiated by the JDRF (the Artificial Pancreas Project) and other ongoing EU projects related to diabetes and diabetes technology, e.g., the DIADVISOR (Personal Glucose Predictive Diabetes Advisor) project (*www.diadvisor.eu*).

By bringing together partners with a wide range of knowledge and expertise who are willing and able to work at a high scientific level, our hope is that the AP@home project will bring closed-loop technology a major step closer to becoming a reality. The key aspect will be that we not only raise expectations but also prove the feasibility of the AP system(s) we are developing under daily life conditions. Cleary, such a system has to be efficient, simple, and safe; otherwise it will not become a viable product that can be disseminated to patients with diabetes.

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Appendix 1.

The coordinators from the participating institutions in **Table A1** are coauthors of this paper.

Table A1.

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AP@home Partners

Academic Centers

- The Academic Medical Center at the University of Amsterdam, The Netherlands, has a track record in diabetes technology ranging from insulin therapy to continuous glucose monitoring to closed-loop investigations. J. Hans DeVries, scientific coordinator of AP@home, is based here.

- The University of Montpellier, France, has a long-standing interest in closed-loop trials in CRCs, combined with intravenous glucose sensing, intraperitoneal insulin delivery, and different closed-loop algorithms.

- The team from the Institute of Medical Science and Department of Paediatrics, University of Cambridge, United Kingdom, has performed a number of AP studies with algorithms developed in-house.

- The Department of Information Engineering, University of Padova, Italy, is focused on the data analysis of clinical trials, development of online methods for sensor optimization, and development of a type 1 diabetes simulator to perform *in silico* trials.

- In close cooperation with the University of Padova, the Department of Computer Engineering and Systems Science, University of Pavia, Italy, is working on the development and optimization of model predictive closed-loop algorithms. The University of Pavia also harbors a strong telemedicine group. The two groups have already performed a number of AP studies both in collaboration with the Department of Clinical Medicine, University of Padova, as well as with the University of Montpellier and the University of Virginia.

- The University of Graz, Austria, not only has a profound background in structurized diabetes education but also performs clinical studies and basic research. In cooperation with the University of Technology Graz and the Institute of Medical Technology and Health Management at Joanneum Research GmbH and 4a engineering, they bring a strong background in glucose sensor research and development to the consortium, with a special focus on one type of single-port AP system (see earlier).

Clinical Research Centers

- Profil Institut für Stoffwechselforschung, Neuss, Germany is an internationally renowned independent clinical research institute (CRI) with its main competence in diabetes and obesity. The coordinator (Lutz Heinemann) and project manager of AP@home (Carsten Benesch) work for this CRI.

Industrial Partners, Small- to Medium-Sized Enterprises, and Large Companies

- Sensile Medical, Switzerland, was founded in 2004. Sensile Medical serves as an incubator for innovative and technology-driven medical devices. Its core activity is the development of nanoliter-based systems for microdrug delivery. In cooperation with the École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland, they are developing a porous needle coated with glucose-responsive hydrogel for the other type of single-port AP system (see earlier).

- STMicroelectronics, Italy, is a large global semiconductor company with more than 45,000 employees. Their Advanced System Technology group brings knowledge on technical solutions for AP systems into our consortium as well as ICT knowledge.

- Triteq, United Kingdom, is specialized in electronic design and production. Their focus is on full design and preproduction facilities, covering a range of topics that are relevant for AP systems (safety critical control systems, remote diagnostics, and telemedicine).