Current and Emerging Technologies for Diabetes Care

Emmanuel André4*, Nathalie Jeandidier1, Noel Lorenzo Villalba1, Laurent Meyer1, Abrar-Ahmad Zulfiqar1,2, Samy Talha2,4, Mohamed Hajjam3 and Amir Hajjam El Hassani5

1Service de Médecine Interne, Diabète et Maladies Métaboliques de la Clinique Médicale B, Hôpitaux Universitaires de Strasbourg, 1, porte de l'Hôpital, 67091 Strasbourg cedex France
2Equipe de recherche EA 3072 “Mitochondrie, Stress oxydant et Protection musculaire”, Faculté de Médecine de Strasbourg, Université de Strasbourg (Unistra), Strasbourg, France
3Service d’Endocrinologie et de Diabétologie de la Clinique Médicale B, Hôpitaux Universitaires de Strasbourg, Strasbourg, France
4Service de Physiologie et d’Explorations Fonctionnelles, Hôpitaux Universitaires de Strasbourg, Strasbourg, France
5Predimed Technology, Strasbourg, France

*Corresponding Author: Emmanuel André, Service de Médecine Interne, Diabète et Maladies Métaboliques de la Clinique Médicale B, Hôpitaux Universitaires de Strasbourg, 1, porte de l’Hôpital, 67091 Strasbourg cedex France; E-Mail: emmanuel.andres@chru-strasbourg.fr

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Abstract

In recent years, several technological innovations have or should in the near future become part of the daily lives of diabetic patients as non-invasive glucose sensors, connected insulin pens, intelligent insulin pumps, artificial pancreas, telemedicine, and artificial intelligence. A review of the literature dedicated to these technologies supports the efficacy of these latter in diabetic patients. Mainly, these technologies have shown a beneficial effect on diabetes management with an improvement of: blood glucose control, with a significant reduction in HbA1c; patient ownership of the disease; patient adherence to therapeutic and hygiene–dietary measures; the management of co-morbidities (hypertension, weight, dyslipidemia); and at least, good patient receptivity and accountability. Especially, the emergence of these technologies in the daily lives of diabetic patients has led to an improvement of the quality of life for patients. To date, the magnitude of its effects remains debatable, especially with the variation in patients’ characteristics, samples selection and approach for treatment of control groups.

Keywords: diabetes mellitus, glucose sensors, connected insulin pens, intelligent insulin pumps, artificial pancreas, telemedicine, artificial intelligence, big data

Introduction

Worldwide the number of patients with diabetes mellitus is increasing. In industrialized countries, there are estimations that diabetes is one of the leading causes of death. Today, patient with diabetes spend time each day carefully tracking blood glucose levels, food intake and physical exercise to calculate when and how much insulin should be injected into their bodies. Living with diabetes requires constant vigilance and a strong sense of self-determination and efficacy.

In this context, diabetes, as many chronic diseases, benefits from both the contributions of molecular biology and innovative therapies (e.g., new insulins, immunotherapy, stem cell therapy, intestinal microbiote transplantation), and from major advances in technologies (e.g., sensors, infusion systems, connected objects) and in artificial intelligence (e.g., Big Data analysis) [1]. Combined with the Information and Communication Technologies (ICT) and the social and educational sciences, these technological advances will revolutionize the care of diabetic patients in the future [2].

This short narrative review focuses on new and current technologies, used in the field of diabetes mellitus.

Current Management of the Diabetic Patient

To date, the management of the diabetic patient is based on a balance of his diabetes (documented by the level of hemoglobin A1c [HbA1c]) with regard to his clinical phenotype, with personalized blood glucose targets [1, 3]. Intensive glucose control has been shown to delay or prevent the development of micro- and macrovascular complications related to diabetes [1]. In this context, optimal management of the diabetic patient is based on: patient ownership of the disease, therapeutic education, compliance with hygiene–dietary measures, therapeutic compliance and physical activity [3, 4].

The last two decades have seen major advances in technology, which has manifested in more accurate glucose monitoring systems and insulin delivery devices (‘insulin pump’). Increased understanding of the pathophysiological deficits underlying type 2 diabetes has led to the development of targeted therapeutic approaches such as on the small intestine (glucagon-like peptide-1 receptor analogues and dipeptidyl-peptidase IV inhibitors) and kidneys (sodium-glucose cotransporter-2 inhibitors).
For type 1 diabetic patient, intensive insulin therapy is the reference treatment (“gold standard”) [1, 3]. In this setting, large multicentre randomized trials have confirmed the effectiveness of intensive glycemic control on microvascular outcomes, but macrovascular outcomes and cardiovascular safety remain controversial with several glucose-lowering agents. Improvements in insulin formulations over the decades, including rapid-acting and long-acting insulin analogues that more closely mimic physiological insulin secretion, have increased the flexibility and efficacy of type 1 diabetes management.

Based on studies that have demonstrated the benefits on HbA1c, the frequency of acute hypoglycemic and hyperglycemic episodes, the external rapid analogue infusion pump associated with the Flash Glucose Monitoring™ system (Abbott Laboratory) (Figure 1) is currently the reference management for patients undergoing intensive insulin therapy [4].

For the type 2 diabetic patient, it is imperative, in addition to the balance of diabetes (e.g., using metformin, GLP1-agonist drugs or DPP-IV inhibitors recently launched on the market) and the prevention of its complications, to properly manage comorbidities as, overweight, dyslipidemia, arterial hypertension, smoking and sedentary lifestyle [3].

Non-Invasive Sensors for Glucose Self-Monitoring

For the diabetic patient, self-monitoring with a capillary blood glucose meter has long been the only way to understand his or her blood glucose control [5]. This self-monitoring gives a more or less truncated reflection of glycemic control (subject to interpretation) and above all allows the patient to adapt his insulin administration. In this setting, Holter glycaemia, followed by real-time continuous and long-acting insulin analogues that more closely mimic physiological insulin secretion, have increased the flexibility and efficacy of type 1 diabetes management.

The improvement in their accuracy (measured Mean Absolute Relative Difference [MARD], from 16–20% to 10–14%) allows direct adaptation of insulin without concomitant control of capillary blood glucose levels [6]. Clinical studies have validated this method, which replaces the classic capillary self-monitoring of blood glucose in the management of patients treated with intensive insulin therapy.

Connected Insulin Pens

Novo Nordisk recently announced its plans for a connected (“smart”) insulin pen, which will automatically record how much insulin was injected. For those on multiple daily injections, this means no logs, no forgetting doses or accidental insulin stacking, and access to the same computer-generated reports that help recognize patterns and optimize therapy as pump users. The new connected pens (NovoPen 6™ and the NovoPen Echo Plus™) are reusable, already approved in Europe (CE marked), and include a tiny screen that displays the last dose. They have piloted with great success in approximately 700 Swedish users with diabetes. A 2019 US launch may be possible, depend on how things go with the
FDA. Novo Nordisk’s connected insulin pens will integrate with the Abbott Freestyle Libre™ system, allowing Freestyle Libre™ users to see data about their insulin alongside their glucose readings (http://www.diabetesincontrol.com/new-smart-pens-hoped-to-change-the-way-we-treat-diabetes/).

Lilly has also joined the race to offer tech-enabled, smarter methods of insulin delivery to people with diabetes. Lilly plans to launch two systems: an Automated Insulin Delivery (AID) with Lilly’s own custom disk-shaped pump, CGM, and a hybrid closed loop control algorithm; and a smart insulin pen with a dosing decision (“titration”) support app (https://diatribe.org/lilly-developing-smart-pens-and-automated-insulin-delivery-pump). Lilly has been developing both products for two years, and the first trials are expected to begin next month. Dexcom’s CGM will be used in both, per an agreement announced in tandem with this news.

During a time of fast-paced innovation and competition in the world of diabetes, all three major insulin companies - Lilly, Novo Nordisk, and Sanoﬁ - are investing in digital health and connected delivery devices, though this represents the lowest commitment yet. Lilly will bring all the components together for smarter insulin delivery (both pump and injection), submit them to the FDA, and commercialize both systems. Bigfoot Biomedical is currently the only other company pursuing both injection- and pump-based automated delivery of insulin.

Intelligente Insulin Pumps

For type 1 and numerous type 2 diabetic patients (e.g., type 2 diabetic patients with cardiovascular complications), insulin therapy is the necessary treatment. In this setting, fast or slow insulin analogues are usually administered subcutaneously, with one or more injections per day (e.g., multiple injections in intensive therapy) [3, 4].

Recent years, progress has been made with the development of ultra-fast analogues (aspart Fiasp™, Novo Nordisk Laboratory, recently launched on the French market), which allow the maximum peak action to be advanced and reduce the duration of action, and therefore the quantity of insulin “on board”, by about 10 minutes [4]. They will limit the latency between flow rate changes and insulin levels in the blood, improving system performance. Nevertheless, the limitations of subcutaneous administration remain related to the still too long insulin kinetics, the reproducibility of imperfect absorption, and the absence of a first hepatic passage that is physiological.

In this context, studies have been carried out with the intraperitoneal route of administration. Compared to the subcutaneous route, this latter improves the HbA1c and is associated with a decrease in the frequency of severe hypoglycemia [8]. The outer surface of the peritoneum appears to be a promising site, and some bio-artificial pancreases already use this route (e.g., BAir® by Beta-O2 Technologies and MaillPan™ [for Macroencapsulation of PANcreatic ILÔts], Defymed Company), with kinetic and metabolic results comparable to those of the intraperitoneal route (https://www.defymed.com/mailpan/). An access port device at this site allows for optimized insulin delivery either by an external pump or by injections. On this model, the device ExOlin™ (Defymed Company) is under development (https://www.defymed.com/exolin/).

The connection of the Enlite™ sensor to the MiniMed Veo™ and 640G™ pumps (Medtronic Company) allows the automatic stopping of insulin infusion when a low interstitial glucose concentration is detected or predicted, dramatically reducing the occurrence of severe hypoglycemia (Figure 2) [4]. The recent reimbursement by the health insurance of this system in certain poorly balanced type 1 diabetic patients, subject to severe hypoglycemia under insulin therapy by pump and adapted self-monitoring, allows for management within the framework of the care of this precursor of the "artificial pancreas".

In this context, several “bolus calculators” have been developed, especially for the insulin pumps, offering a bolus dose by coupling the current blood glucose level and a predetermined insulin/glucose ratio [2].

Nowadays, these systems have been replaced by new intelligent systems based on algorithms (Artificial Intelligence [AI]) [2, 7]. These latter make it possible to propose a real adaptation of prandial and basal doses by integrating several parameters (glycaemia, insulin sensitivity, etc.) specific to the patient phenotype (personalized medicine). Self-learning, they are specifically adapted to the patient’s history of glycemic variations. They have shown their effectiveness on HbA1c, without increasing hypoglycemia, especially when coupled with nursing “coaching” (Diabeo™, Sanoﬁ Laboratory) [9]. This system is currently approved within the framework of telemedicine [9]. Coupled with an external 670G™ pump (Medtronic Company), other algorithms already allow automatic adaptation of basal rates, with the patient managing only bolus doses [7].
Artificial Pancreas for Glycemic Management

The rise of all these technologies that we have just seen has led to the recent appearance of the “artificial pancreas”, the “diabetic patient’s dream” [10]. Since the demonstration, in 2015, of its efficacy in ambulatory care, the results of 24 studies on 585 patients, compiled in a recent meta-analysis, have confirmed a significant improvement in the time spent in the target, the reduction of HbA1c and mean blood glucose, without an increase in hypoglycemia [10, 11].

To date, the artificial pancreas is based on a closed-loop insulin delivery system, integrating AI. Most of these devices are mono-hormonal (insulin) and semi-automatic, with the patient manually reporting food intake and physical activity. Many of these devices are expected to be quickly brought to market (e.g., Diabeloop™ from Medtech Company) [12]. The limitations of single-hormonal subcutaneous devices are related to sensor latency, kinetics of interstitial glucose changes, and reproducibility of peripheral administration of subcutaneous insulin.

In this setting, the bi-hormonal approach (insulin-glucagon), poses technical problems, as the stability of glucagon and the necessity of double reserves, but seems interesting to avoid hypoglycemia, especially during physical exercise [10, 11]. The addition of amylin or glucagon-like peptide-1 (GLP1) receptor analogue improves post-meal blood glucose levels by decreasing glucagon secretion; future years should make it possible to clarify the place of these molecules in the artificial pancreas.

Another approach would be to operate other sites that combine sensors and insulin delivery. A study combining a subcutaneous sensor and intraperitoneal insulin infusion showed better regulation of post-meal periods [13]. Intraperitoneal insulin, which is more physiological, could improve problems related to meals and physical activity. Projects to miniaturize the implantable system and reduce its cost are all assets for make it an attractive alternative.

Improving the skills and the capacities of algorithms, by using the databases set up (big data analysis), optimizing their self-learning capacity, their patient-specific adaptation capacity, and supplementing their information with multiple sensors collecting parameters other than blood glucose levels, could allow early detection of food intake, physical activity, stress, and adaptation of the system to specific situations (children, pregnancies, highly unstable diabetes) [14]. The connection of the system to a telemedicine and coaching platform is an evolution that is already underway in the system Diabeloop™.

Telemedicine for Diabetic Patients

A 2009 study conducted by Julie Polisena and her team at the Canadian Agency for Drugs and Technologies in Health found storing or sharing self-monitored blood glucose using home telehealth tools such as PDAs or fax machines, supported with physician feedback, showed improved glycemic levels and reduced hospitalizations (https://www.diabetesselfmanagement.com/diabetes-resources/tools-tech/smart-technology-diabetes-self-care/).

In this setting, In contrast, a systematic review of the use of cell phones in health promotion strategies found that of the ten studies that looked at cell phones and HbA1c, nine reported significant improvements in the blood glucose control (https://pdfs.semanticscholar.org/09b7/e93e051978a4385503d77108cf46a8306802.pdf?_ga=2.92810655.306525227.1579695813-556288028.1579695813).

In addition to improved diabetes-related health outcomes, knowledge, self-efficacy and better adherence to protocol scores were increased in subjects who practiced self-management behaviors.

Technology now has evolved beyond telehealth. Smart technology exists as wearables, implants, and mobile applications to track glucose levels, share data, access relevant information, communicate with both health-care providers and others with diabetes, and, ultimately, guide you in making better decisions.

There is an abundance of Smart Apps available today (https://www.ceceliahealth.com/blog/2018/1/22/the-use-of-smart-technology-for-diabetes-management/), with a variety of features such as monitoring food intake, carbohydrate intake, tracking physical activity, scanning the barcode of a food product and retrieving its nutritional information as well as offering suggestions for healthier options, healthy recipes, getting signed to create a community database where patients can share their stories etc. Some examples include apps such as Diabetik™, Fooducate™, Figwee™ and MyFitnessPal™, etc. To our knowledge, more than 350,000 applications are currently available for the general public, without medical CE marking.

In addition, several blood glucose monitors can be connected to an app that can be downloaded on a device and track blood glucose numbers as well as any adjustments that need to be made with medications. Some companies such as Glooko have developed Apps that can sync data collected from patient’s glucometers and fitness watches to downloadable software that can enable physicians with real-time tracking of patient data.
use of technology to implement medical and cost-effective health care management on a large scale for diabetes management. Compared to the first projects, most of these new generation projects incorporate: self-administered medical questionnaires or forms on: symptoms, signs of diabetes decompensation; tools for medical education, particularly disease self-appropriation, food hygiene, and physical activity; tools for patient motivation; tools for therapeutic and hygiene observance; tool to remote comorbidities (e.g., arterial hypertension, obesity, dyslipidemia); tools for interaction between the patient and healthcare professionals like telephone support centers, tablets, and Web-sites [2].

<table>
<thead>
<tr>
<th>Name of the Study</th>
<th>Results</th>
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<tr>
<td>The Utah Remote Monitoring Project (n=109)</td>
<td>Principal criteria: &lt;br&gt;• Mean HbA1c had decreased from 9.73% at baseline to 7.81% at the end of the program (p &lt;0.001). &lt;br&gt;• Systolic blood pressure (BP) had decreased from 130.7 mmHg at baseline to 122.9 mmHg at the end (p=0.0001). &lt;br&gt;Secondary criteria: &lt;br&gt;• Low-density lipoprotein content had decreased from 103.9 mg/dL at baseline to 93.7 mg/dL at the end (p=0.0263) &lt;br&gt;• Knowledge of diabetes and arterial hypertension have increased significantly (p &lt;0.001 for both). &lt;br&gt;• Patient engagement and medication adherence also have improved, but not significantly &lt;br&gt;• Per questionnaires at study end, patients felt the telemonitoring program had been useful.</td>
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<td>Randomized Trial on Home Telemonitoring for the Management of Metabolic and Cardiovascular Risk in Patients with type 2 Diabetes (n=302)</td>
<td>Principal criteria: &lt;br&gt;• Mean HbA1c difference of 0.33±0.1 (p=0.001) have been observed between the telemonitoring compared and the control group. The proportion of patients reaching the target of HbA1c (HbA1c &lt;7.0%) had been higher in the telemonitoring group than in the control group after 6 months: 33.0% vs. 18.7% (p=0.009) and 12 months: 28.1% vs. 18.5% (p=0.07). &lt;br&gt;• No difference had been registered for body weight, BP, and lipid profile &lt;br&gt;Secondary criteria: &lt;br&gt;• For quality of life (evaluated with the 36-item Short Form health survey), significant differences in favor of the telemonitoring group, as for physical functioning (p=0.01) and mental health (p=0.005). &lt;br&gt;• On an economic level, a lower number of specialist visits was reported in the telemedicine group: incidence rate ratio of 0.72 (95% confidence interval, 0.51–1.01; p=0.06).</td>
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<td>Study assessed the utility and cost-effectiveness of an automated Diabetes Remote Monitoring and Management System (DMRS) (n=98)</td>
<td>Principal criteria: &lt;br&gt;• No significant difference for mean HbA1c between the DRMS and control groups at 3 months: 7.60% vs. 8.10% and at 6 months: 8.10% vs. 7.90% (p=ns) &lt;br&gt;Secondary criteria: &lt;br&gt;• Changes from baseline to 6 months have been not statistically significant for self-reported medication adherence &lt;br&gt;• Changes of diabetes-specific quality of life have been not significant registered, except for the Daily Quality of Life-Social/Vocational Concerns subscale score (p=0.04)</td>
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<td>Telescot Diabetes Pragmatic Multicenter Randomized Controlled Trial (n=321)</td>
<td>Principal criteria: &lt;br&gt;• The Mean (SD) HbA1c at follow-up was 7.92% in the intervention group vs. 8.36% in the usual care group. For primary analysis, adjusted mean HbA1c was 0.51% lower (95% CI 0.22% to 0.81%, (principal criterion) (p=0.0007) &lt;br&gt;Secondary criteria: &lt;br&gt;• Adjusted mean ambulatory systolic BP has been 3.06 mmHg lower (95% CI 0.56–5.56 mmHg, p=0.017) and mean ambulatory diastolic BP has been 2.17 mmHg lower (95% CI 0.62–3.72, p=0.006) among people in the intervention group when compared with usual care after adjustment &lt;br&gt;• No significant differences were identified between groups in terms of: weight, treatment pattern, adherence to medication or quality of life &lt;br&gt;• The number of telephone calls was greater between nurses and patients in the intervention compared with control group: rate ratio of 7.50 (95% CI 4.45–12.65, p &lt;0.0001) but no other significant differences between groups in use of health services were identified between groups</td>
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The analysis of these different projects and studies shows that remote monitoring (telemonitoring) showed: improvements in control of blood glucose level, significant reduction in HbA1c; better appropriation of the disease by patients; greater adherence to therapeutic and hygiene-dietary measures; positive impact on comorbidities (arterial hypertension, weight, dyslipidemia); better patient’s quality of life; and at least, good receptiveness by patients and patient empowerment [2]. Moreover, a cost-effectiveness analysis found a potential of medical economy.

However to date, the magnitude of its effects remains debatable, especially with the variation in patients’ characteristics (e.g., background, ability for self-management, medical condition), samples selection and approach for treatment of control groups.

Over the last 5 years, new-generation telemedicine projects and studies have emerged in the setting of type 1 and type 2 diabetes [2, 9, 16, 17]. They support transmission and remote interpretation of patients’ data for follow-up and preventive interventions. These new generation telemedicine projects are often known as “telemedicine 2.0” projects, given that they all utilize new Information and Communication Technologies (ICT) and the Web (tools for the “e-Health 2.0”) [18]. These projects rely on the standard connected tools for monitoring diabetes, such as glucose meters, BP, heart rate monitors, weighing scales, and pulse oximeters, which relay the collected information via Bluetooth, 3G or 4G [2, 19]. They include continuous glycemetic monitoring solution and often a video-call.

Artificial Intelligence for Diabetes Management

In recent years, several informatics solutions or tools have been developed and used to optimize the management of chronic disease, such as: Artificial Neural Networks (ANN) algorithms, data mining software, ontology [2, 20]. These solutions or tools are called artificial intelligence (AI) and the support of “telemedicine 3.0”.

For this later, three clinical datasets are of particular interest: 1) patients’ phenotype; 2) patients’ electronic medical records containing physicians’ notes, laboratory test results, as well as other information on diseases, treatments, and epidemiology that may be of interest for association studies and predictive modeling on prognosis and drug responses; and 3) literature knowledge including rules on diabetes management [20].

In the setting of diabetes, two of the aforementioned telemedicine projects use AI in order to be able: firstly, to adjust the blood glucose level to the patient's activity (software Diabeo™, Sanofi Laboratory) [9]; and secondly, to predict patient risks of diabetes decompensation (https://www.predimed-technology.fr/solutions/plateforme-intelligente-my-predi/). In this later situation, the cloud-based software aggregates, cleans, and analyzes patient data to allow for identifying patterns that may indicate potential risks and provide predictive insights on healthcare outcomes, as the software MyPredi™ (Predimed Technology Company).

In the TELESAGE study, type 1 diabetic patients were randomized to usual quarterly follow-up (G1), home use of a smartphone recommending insulin doses (Diabeo™ software) with quarterly visits (G2), or use of the smartphone with short teleconsultations every 2 weeks but no visit until point end (G3) [9, 17]. At six-month, the mean HbA1c level: 8.41±1.04% in G3 vs. 8.63±1.07% in G2 vs. 9.10±1.16% in G1 (p=0.0019 for G1-G3 comparison). The Diabeo™ system gave a 0.91% (0.60–1.21) improvement in HbA1c over controls and a 0.67% (0.35–0.99) reduction when used without teleconsultation. There was no difference in the frequency of hypoglycemic episodes or in medical time spent for hospital or telephone consultations. However, patients in G1 and G2 spent nearly 5 h more than G3 patients attending hospital visits.

The DIABETe telemonitoring project, has been developed and designed to optimize home monitoring of diabetic patients by detecting, via a telemonitoring 2.0 platform, situations with a risk of decompensation of diabetes and its complications (e.g., myocardial infarction or chronic heart failure), the latter ultimately leading to hospitalization (https://www.predimed-technology.fr/solutions/plateforme-intelligente-my-predi/). The AI of the DIABETe platform (MyPredi™, tool of telemedicine 3.0) automatically generates indicators of “health status” deterioration, i.e., “warning alerts” for any chronic disease worsening, particularly diabetes, its macrovascular complications and cardiovascular comorbidities (e.g., arterial hypertension, chronic heart failure). For the patient, these situations may lead to hospitalization if not treated appropriately.

To our knowledge, this is one of the first projects that use AI in addition to ICT (telemedicine 3.0). The platform comprises connected nonintrusive medical sensors, a touchscreen tablet connected by Wi-Fi, and a router or 3G/4G, rendering it possible to interact with the patient and provide education on treatment, diet, and lifestyle (Figure 3) (https://www.predimed-technology.fr/solutions/plateforme-intelligente-my-predi/).

Figure 3: Telemedicine project: DIABETe.
Innovative technologies based on AI (machine learning, Big Data) are going to build the future of diabetology (“diabetology 3.0”); fully automated artificial pancreatic, telemedicine interventions preventing severe glucose degradations and helping with diabetes burden in a day-to-day basis. Moreover, these technologies will also be a major source to understand mechanisms of disease degradation and psychology and behavior of patients who have to cope with this. This will lead to a new optimized way of patient and disease management. Diabetologists will have to adapt to this new world.

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