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DIABETES MANAGEMENT

A TALE OF TWO CONDITIONS AND THE RESULTING OPPORTUNITIES FOR MEDTECH INNOVATORS

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1. Abstract

Diabetes Mellitus (or “Diabetes”) can be considered as two separate conditions; Diabetes Type 1(T1), a genetically caused chronic autoimmune condition, and Diabetes Type 2 (2), a reversible lifestyle condition.

These two conditions require two different management strategies to contain the escalating costs of the disease at a public health level. Diabetes of both forms cannot be managed by pharmaceutical measures alone; digital solutions and advanced medical technologies are needed to control the health and cost burden Diabetes imposes on society.

Diabetes T1 requires empowerment of patients to enable them to effectively self-manage their condition and minimise hypoglycaemic episodes and complications. Diabetes T2 requires preventative interventions and early-stage identification of “at risk” individuals to prevent the condition developing, as well as behavioural changes by diagnosed patients to reverse the condition.

This whitepaper explores the cost-effectiveness of interventions used in both types of the disease and uncovers the opportunities for medical technology innovators in this market.

2. Introduction

Diabetes Mellitus (or "Diabetes") is a metabolic disease characterised by an inability to regulate blood glucose concentrations. The resultant hyperglycaemia can lead to serious damage to the body's systems, especially the nerves and blood vessels. According to the World Health Organisation (WHO), an estimated 8.5% of adults had Diabetes in 2014 and Diabetes was the direct cause of 1.5 million deaths in 2019[1].

There are three main types of Diabetes, all of which are characterised by high levels of blood glucose;

- Type 1 Diabetes

An autoimmune condition where the immune system attacks and destroys insulin-producing cells in the pancreas. As a result, patients require the daily administration of insulin. Diabetes Type 1 (T1) is estimated to affect 400,000 people in the UK with incidence increasing by about four per cent each year[2].

- Type 2 Diabetes

Diabetes Type 2 (T2) is a condition where cells don't respond normally to insulin (also called insulin resistance). About 90% of people with Diabetes have type 2 Diabetes, totalling an estimated 3.5 million people in the UK[3]. This type of Diabetes is largely the result of excess body weight and physical inactivity[1].

- Gestational Diabetes

Develops in some pregnant women who have never had Diabetes. Gestational Diabetes usually disappears after childbirth but can increase the risk of the mother developing type 2 Diabetes later in life.

As well as the direct costs of treating the illness and associated complications, Diabetes has many indirect social and productivity costs, including those related to increased mortality and morbidity, as well as the need for informal care.

In 2010/2011, the total direct and indirect costs of Diabetes in the UK were estimated at GBP 23.7 billion, with most of the costs due to complications. The direct costs to the NHS account for about 10% of the NHS budget[4]. (Figure 1)

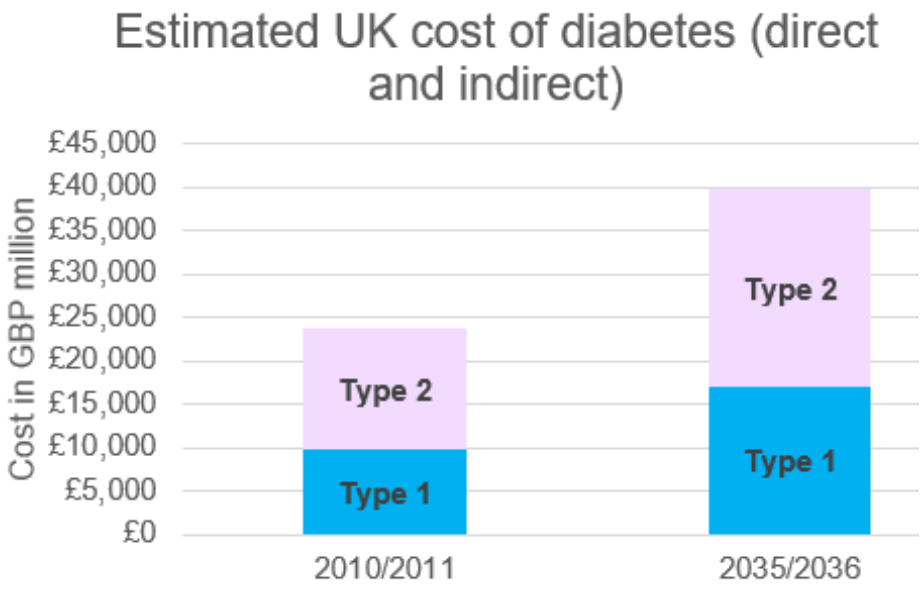

Figure 1 - Cost of Diabetes in the UK according to Hex et al [4]

Demographic changes and high obesity rates are expected to increase the prevalence of the disease, thus increasing the total burden to an estimated GBP 39.8 billion in 2035/36 in real terms, with direct costs accounting for around 17% of the NHS budget[4].

Complications from diabetes are forecast to account for GBP 16.9 billion in 2035/36 (Figure 2). Patients with diabetes admitted for routine surgery stay in hospital longer than those without, accounting for about 19% of the total UK diabetes costs. The actual management of Diabetes accounts for less than a quarter of NHS expenditure on Diabetes[4].

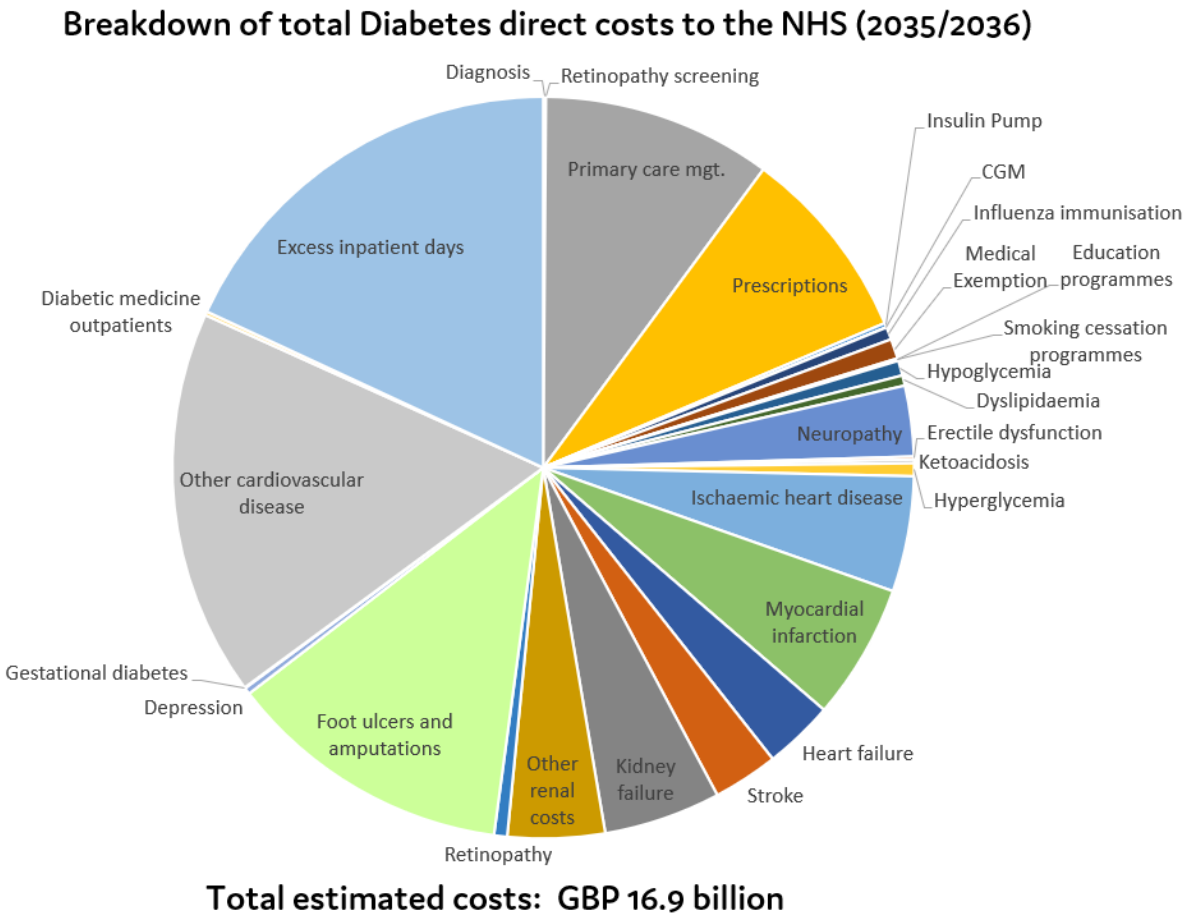

Figure 2 - Breakdown of total direct Diabetes costs according to Hex et al[4]

Opportunities for medical technology innovation in diabetes complications:

Opportunities for medical technologies are significant in complications such as diabetic foot ulcers, estimated to be worth GBP 2.1 billion in 2035/36[4]. Particular unmet needs present themselves in the early detection and monitoring of diabetic foot issues (for example using advanced thermal imaging solutions being developed by the likes of Celsius Health Ltd or smart insoles such as the products by Walk with Path Ltd.). Advanced wound care innovations which can translate faster wound healing into cost savings for the NHS such as the haemoglobin spray Granulox® by Mölnycke should see good uptake in years to come. The prosthetic foot market is forecast to experience healthy global growth rates of CAGR 6.7% (2022 – 2030) according to MDC Research, driven by an increase in the prevalence of diabetes[5].

Cardiovascular issues and diseases (including stroke, heart failure, ischaemic heart disease and myocardial infarction) are forecast to account for GBP 5.7 billion in 2035/36[4]; prevention of these potentially fatal conditions is crucial and fertile ground for digital health innovations such as novel approaches to electrocardiograms (ECGs) (e.g. a handheld ECG developed by Plessey Semiconductors, or the AI-based solution using 3D Vectorcardiography offered by Cardisio GmbH), as well as solutions predicting risks of exacerbations (e.g. liquid biopsy testing predicting the risk of stroke by Ischemia Care).

3. A tale of two conditions

Optimal disease management depends on the type of Diabetes, with very different approaches needed for type 1 versus type 2.

In Diabetes type 2 prevention is the key lever to reduce incidence rates, while changes in patient lifestyles, diet and, if needed, bariatric surgery can lead to the reversal of the condition in diagnosed patients.

Diabetes type 1 is a lifelong auto-immune condition, which cannot be reversed nor prevented. Optimal management of the condition requires empowering the patient to better self-manage and thus reduce the incidence of hypoglycaemic episodes and complications.

Diabetes of both forms is a disease which cannot be managed by pharmaceutical measures alone; digital solutions and advanced medical technologies are needed to control the health and cost burden Diabetes imposes on society.

4. Management of Diabetes Type 2

Prevention – the key weapon against T2

Diabetes type 2 is a condition which disproportionately affects patients of lower socioeconomic status. The condition displays higher prevalence rates amongst patients in disadvantaged socio-economic positions, as levels of obesity and smoking are higher, while amounts of physical activity and consumption of fresh fruit and vegetables are lower in the poorest households compared to those better-off[6].

Diabetes type 2 is a preventable condition and healthcare interventions aimed at preventing "at-risk" patients from developing Diabetes type 2 have a high likelihood of being considered cost-effective[7].

Although several organisations have recommended screening for Diabetes type 2 to reduce the burden of the disease[8,9], the evidence remains uncertain as to whether this would provide additional healthcare benefits[10]. Furthermore, the literature on the cost-effectiveness of Diabetes screening programmes shows conflicting results depending on the type of screening strategy adopted and suffers from high levels of uncertainty [11,12,13].

Screening for Diabetes type 2 remains a controversial topic, and the debate is exacerbated by the lack of definitive trial evidence that not only considers the screening, but also the subsequent treatment strategies. The UK currently does not recommend screening for Diabetes type 2 due to a lack of evidence. Instead, the National Institute for Health and Care Excellence (NICE) recommends a staged approach of using routine primary care data such as body-mass index (BMI) and blood pressure to identify "at-risk" patients for whom blood tests [14] (such as fasting plasma glucose (FPG) or HbA1C) should be ordered. Once individuals are confirmed as suffering from impaired glucose regulation (IGR), they can be deemed at "high risk of Diabetes" and lifestyle or pharmacological interventions should be applied to prevent or delay the onset of Diabetes type 2[15]. The effort applied in identifying "at-risk" patients should follow principles of vertical equity, with more investment to be targeted in geographical areas of where levels of obesity and smoking are more prevalent, and people may not have the means to buy fruit and vegetables regularly.

As well as lifestyle interventions delivered at the primary and secondary healthcare levels to "at-risk" patients, population-level preventative interventions deployed at the societal level, such as regulation of food marketing, restrictive taxes on high sugar content in foodstuffs, smoking bans, improved town planning and campaigns to promote physical activity, all contribute to lowering the prevalence of Diabetes type 2[16].

Self-Management & Reversal

Patients with Diabetes type 2 who can keep their HbA1C levels below 42mmol/mol without taking Diabetes medication are said to have reversed their Diabetes[17].

While medication such as metformin, sulfonylureas, gliptins and thiazolidinediones can help manage the condition by keeping blood sugar levels at a healthy range, it is a change in

lifestyle that can help a patient revert to the pre-Diabetes state and then again, the normal glucose tolerance.

Effective strategies to achieve remission include changes in diet[18, 19], physical exercise[20, 21,22] and bariatric surgery[23].

Opportunities for medical technology innovation in Diabetes type 2:

Digital technologies, which provide better identification of "at-risk" patients by analysing a variety of digital biomarkers collected via patients' mobile devices (e.g., smartphones and smartwatches or other wearables), combined with other data parameters such as genetic information and information on lifestyle and diet (e.g., data on the supermarket shopping list) to flag up potential "high risk" patients, are optimally positioned to add value to the preventative management of Diabetes T2. Combining data from consumer devices, credit or debit cards, supermarket loyalty cards, as well as other sources of digital biomarkers would create a dynamic picture of a person's Diabetes risk profile, enabling healthcare providers as well as patients themselves to intervene earlier and stand a better chance of preventing patients developing Diabetes in the first place.

Opportunities abound for digital lifestyle interventions which can lead to lasting behavioural change and help patients reverse their Diabetes. Innovators should be mindful though, that the market for user-facing lifestyle solutions such as mobile applications seeking to nudge users to eat healthier food and exercise more is very crowded, with low barriers to entry and fierce competition, making viable revenue generation challenging. Digital solutions which can demonstrate Diabetes reversal through the use of UK patient data in solid trials, such as Second Nature[24] and Oviva[25], are at an advantage when it comes to securing market share.

The market for bariatric surgery also presents attractive opportunities with substantial growth rates of a CAGR of 9.2% from 2022 to 2028 according to Orion Market Research[26].

5. Management of Diabetes Type 1

Patient empowerment & self-management

Patients diagnosed with Diabetes type 1 face a lifetime of monitoring their blood sugar levels, managing their diet and self-administering the required dose of insulin, imposing a significant burden on patients' lives. In particular, patients whose Diabetes is not so well-controlled can struggle to manage their condition smoothly. Hypoglycaemic episodes still do occur, and patients face an elevated risk of complications such as retinopathy, foot ulcers and amputations as well as ketoacidosis, neuropathy and kidney failure. Until recently, patients had to perform several finger-prick tests a day, drawing capillary blood just to keep track of their blood sugar levels; a painful and inconvenient process, leading to nonadherence and thus poorly controlled Diabetes.

Empowering these patients to better self-manage their condition is the key to reducing the rate of complications and hospitalisations they experience. The approval of real-time continuous glucose monitors (rtCGM) such as the Freestyle Libre, the Dexcom G6 and the Medtronic Guardian and their recommendation by the UK National Institute for Health and

Care Excellence (NICE) have revolutionised patients' lives. The CGM technology drastically reduces the need for finger-prick testing and enables patients and their loved ones to monitor their levels throughout the day and night[27]. Most of these CGMs connect to users' mobile phones where a digital health management platform provides continuous visibility of their blood sugar levels alongside trend analysis, digital diaries, medical and dietary advice and patient communities.

> *"After I had my CGM, when I saw the numbers in front of me and had to confront them, that changed everything for me. Even I can't argue when the data is staring me right in the face." Este Haim, Diabetes Type 1 patient[28]*

Such is the success of CGMs that patients with Diabetes type 2 have started using them[29]. Though their use in Diabetes type 2 can indeed be a powerful driver of behaviour change[30,31,32], the relative cost-effectiveness of their use in Diabetes type 2 may not be uniform across all patient sub-groups[33]. However, there appears to be a real patient and consumer drive to use CGMs to better understand how one's lifestyle and diet are affecting blood sugar levels; even patients without Diabetes have started using them to better understand their metabolic biodata and make better decisions on their health and lifestyle. We can already see CMG devices such as Level, SuperSapiens and Abbott's Lingo specifically targeting consumer markets to enable better dietary and lifestyle choices and help athletes optimise their performance[34].

Continuous Glucose Monitors make financial sense for a healthcare system as well, as shown by a recent retrospective analysis of US medical claims data which estimates the reduction in Diabetes-related medical care costs from the use of rtCGMs at USD 424 per patient per month[35]. Health-economic evaluations of rtCGMs, in general, tend to show high levels of cost-effectiveness[36,37,38].

However, knowing your blood sugar levels is only one piece of the puzzle; patients need to then inject the appropriate amount of insulin to keep themselves at an even keel. Most patients do this via injection pens; this requires the patient to self-administer the required dose of insulin based on their blood sugar level readings. New, connected injection pens (such as Novo Nordisk's NovoPen® and Medtronic's InPen™) wirelessly connect to the patient's smartphone and automatically log the time and dose of insulin administered. The digital health management platforms holding this information are accessible to patients, their loved ones and healthcare professionals and replace the traditional pen-and-paper logbooks. Digital multi-device platforms such as Glooko and Tidepool also draw data from patients' CGM. Bigfoot Biomedical has recently launched a smart, connected injection pen cap which connects wirelessly to a patient's CGM and automatically recommends the right insulin doses, tracks administered doses and alerts the patients in case of missing doses. The app in a smartphone is but an additional interface which users and healthcare professionals can use.

The next evolution from continuous glucose monitoring is the connection of the CGM to an insulin pump; these so-called hybrid closed-loop systems (HCL) continuously monitor blood

sugar levels and calculate the amount of insulin required via a controlling algorithm. Examples include the Medtronic 780g and 670g, the Tandem Tslim Control and the CamAPS FX system. These systems automatically adjust the insulin dose required based on the blood sugar readings. The state of the technology at the moment provides predictive high and low blood sugar minimisers which work along with an automated basal rate, but meal-time boluses must still be programmed manually.

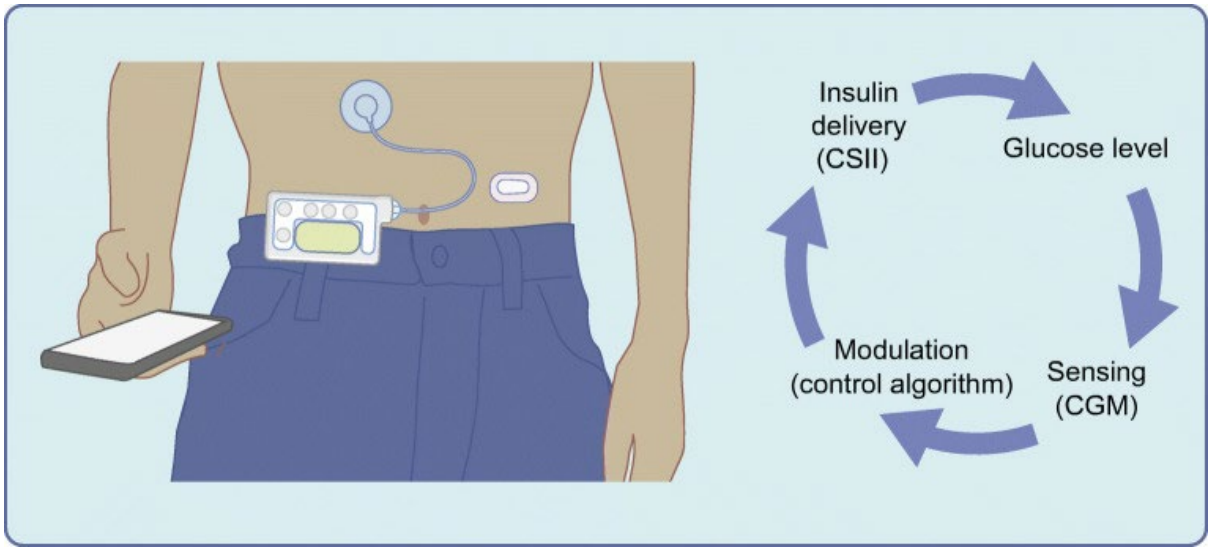

Figure 3 - Schematic of the configuration of closed-loop insulin delivery. Shared with permission by Dr Hovorka[39]

The NHS in England currently does not allow for funding of a hybrid closed-loop system and patients have to apply for their CGM and insulin pump separately. However NICE is currently reviewing a hybrid closed loop system application, and decisions are expected in the first half of 2023[40]. Once approved, these systems are expected to radically improve patient health outcomes for diabetes type 1.

Traditional insulin pumps use a thin cannula to deliver the insulin to the patient: this cannula needs changing regularly and can snag and get caught on things. Novel patch pumps are tubeless; products like the Omnipod 5 by Insulet , sit directly on the skin and deliver the right amount of insulin when in a closed loop.

The development of a fully closed-loop system, which would not require patients to manually enter meal-time boluses, has not been possible yet as the amount of bolus insulin required depends on how many carbohydrates a meal contains. Furthermore, the slow absorption of insulin following subcutaneous delivery limits its use in closed-loop systems.

The development of faster-acting insulin analogues such as Fiasp by Novo Nordisk has drastically lowered absorption times, and the inclusion of a secondary hormone such as glucagon or pramlintide or the use of adjunctive therapies alongside the faster-acting insulin seeks to further relieve the burden of Diabetes type 1 by minimising the need for manual intervention by the patient. At the moment, these so-called dual-hormone closed-loop systems are not yet commercially available although several are in development[41]. Nevertheless, the relative unpredictability of meal sizes and carbohydrate content as well as

the degree of physical activity undertaken by a patient and the amount of stress a patient is under will still require manual management by the patient as a fully closed system without patient activation can result in compromised glycaemic control[42,43].

Development of a new generation of ultra-fast acting insulins (UFIs) such as Lilly's Lyumjev™, may reduce the need for dual-hormone closed-loop systems altogether. Early studies on fully closed-loop insulin-only systems using UFIs have shown promising results[45] , though further studies will be needed to assess efficacy and safety in a real-world setting over a longer period of time. Interesting developments can also be seen in the use of fully closed-loop systems for in-patient use outside of diabetes; a recent study showed the effective us of these system in patients receiving enteral and parenteral nutrition in hospitals[44].

Technology development in smart data analysis and artificial intelligence combining CGM data with other biomarkers such as heart rate would be needed to further optimise closed-loop systems and alleviate the burden of the disease[45].

Opportunities for medical technology innovation in Diabetes type 1:

A proliferation of Diabetes management mobile apps and digital diaries for Diabetes type 1 in the 2010s was followed by consolidation of the market and acquisition of many of these small apps by larger players in the Diabetes market [such as, for example, the acquisition of mySugr by Roche in 2017]. The current state of the mobile app market for Diabetes type 1 is crowded and focused on consolidating data streams from a variety of sources to facilitate better self-management by the patient (e.g., Sugarmate). Many apps also provide visibility of a patient's blood sugar levels to carers, family members and loved ones, for example, the open-source Nightscout and Nightguard apps created by a community of parents who wanted to monitor their children's CGM data from anywhere in the world[46].

The trend for using CGMs as a consumer product in the healthy population presents a significant opportunity for technology companies who want to enter the market bypassing the regulatory burden of a medical device certification or established CGM companies who want to diversify into the consumer market. Applications of CGM technology beyond Diabetes include optimisation of athletic performance, enhancement of physical activity, improvement of nutritional behaviour, stress regulation and screening for Diabetes[47]. However, the readings alone do not suffice; careful analysis and interpretation of the data are necessary to present actionable insights to the user. Digital coaches powered by artificial intelligence (AI) providing personalised advice will play an important role in the future consumer use of this technology. As the consumer market relies on out-of-pocket payments by users, price sensitivity is likely to be higher. However, the sensor accuracy needed to inform wellness and lifestyle decisions does not need to be at the same level as for a certified medical device; lower-cost sensor technologies could be used to achieve a lower price point and gain a competitive advantage in the consumer market. One prime example is Nemaura Medical's sugarBEAT, whose UK licensee, MySugarWatch, is running a direct-to-consumer campaign in the Daily Mail[48].

"Embarking on the consumer phase of our UK licensee's campaign in support of the commercialization efforts around sugarBEAT is very exciting, and we are looking forward to continuing our support for our licensee," Nemaura CEO Faz Chowdhury[49]

Digital platforms and software to facilitate better self-management of Diabetes are expected to experience a tremendous growth rate of a CAGR of 9.9% in the next 10 years, according to Fact.MR[50]. Platform providers and Software companies who manage to interface with a multitude of blood glucose monitors, injection pens and pumps and other wearables (such as smart watches) are likely to be at an advantage over brand-specific platforms.

The development of ultra-fast acting insulins is expected to spur innovative developments in fully closed-loop systems, bypassing the need for a dual-hormone system. Early studies show that adequate control could potentially be achieved with insulin-only systems. Furthermore, we expect closed-loop systems to branch out into non-diabetes use; particularly for in-patients who struggle with glycaemic control, such as patients on enteral or parenteral nutrition or patients on dialysis.

The growing use of sensors, wireless transmitters, pumps and algorithms in the management of Diabetes type 1 creates a significant amount of energy to make it all work. Currently, the system uses batteries to provide the power needed. However, these need to be replaced or charged regularly to support the constant use of the system. Though the industry is developing longer-life batteries, the most significant leap forward is expected to come from energy-harvesting; the use of body-generated energy (through heat, sweat, movement or other), combined with low-power wireless technologies [51]. Reducing dependence on batteries will not only reduce the cost of device maintenance but also address the environmental issue of battery waste. This well-known issue presents attractive opportunities for wireless technology companies who seek to penetrate the healthcare market, such as system-on-chip (SoC) supplier Atmosic Technologies.

6. Conclusion

Diabetes type 1 and type 2 are two separate conditions which require two very different disease management strategies by national healthcare providers to control the cost of managing and treating patients.

Diabetes type 2, being the bigger market, requires prevention and reversal as the main disease management strategies. Since prevention requires a lifestyle change, digital solutions and apps which facilitate a healthier diet and higher physical activity levels can tap into this buoyant market; mobile health apps are forecast to grow at a 17.7% compound annual growth rate (CAGR) from 2021 to 2028[52]. However, this is a very crowded market with low barriers to entry. Digital platforms which draw on data from a variety of biomarkers to generate dynamic personal risk profiles for Diabetes can capitalise on the opportunity presented by NHS' National Service Framework for Diabetes which recommends screening for sub-groups of the population at increased risk of developing Diabetes[53]. A niche opportunity exists in components for bariatric surgery, which is being

increasingly used to facilitate patients' disease reversal in combination with a lifestyle change.

Diabetes type 1, although the smaller of the two markets, has seen the most remarkable technological innovation with real-time continuous glucose monitors (rtCGM) being almost universally used in the developed world to help patients better manage their blood sugar levels. Digital solutions which work across many different devices and aggregate CGM readings with exercise levels and medication dosage to provide patients with actionable insights such as recommended insulin dosage settings, alerts for missing doses and connection to an ecosystem linking patients, carers, loved ones and physicians, are set to experience significant growth rates in the coming 10 years. The use of CGMs by patients with Diabetes type 2 is increasingly seen as a good way of triggering and supporting behaviour change and ultimately a reversal of the condition, though it may not always be considered cost-effective by insurers or payment bodies. An interesting trend observed is the use of CGM technology by non-diabetics to better manage their health, diet and athletic performance; attractive opportunities exist for technology providers who can offer CGMs at a low enough price point to be palatable for a consumer audience that pays out-of-pocket.

Complications from both types of diabetes such as diabetic foot and cardiovascular issues are expected to present opportunities for innovative medical technologies in early detection, monitoring and treatment.

The most important underlying technological need for enabling a connected digital ecosystem in both types of disease is the provision of energy to power it all. We expect a significant leap to come from combining low-power wireless technologies with technologies which can harvest energy generated through body heat, sweat, movement or other latent forms of untapped energy.

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