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EXECUTIVE SUMMARY

Diabetes isone of the greatest worldwide health challenges of the twenty-first century. Worldwide, it is estimated that 285 million people live with diabetes, 26 million of whom live in the United States. Despite advances in disease treatment in the last two decades, the prevalence and incidence of diabetes is increasing at alarming rates. In addition, there are great challenges and improvements to be made in the management of the disease both from a healthcare provider and individual perspective. Elements for improvements in the care of people with diabetes include better self-management through disease prevention and control. Glucose monitoring is an essential factor of disease managementto achieve blood glycemic control. Nevertheless, effective and consistent monitoring remains a challenge for many diabetic patients primarily because of the invasive nature of currently available glucose monitoring devices. These devices require patients to extract a drop of blood by pricking their finger. For many patients, this process is painful, inconvenient and contributes to suboptimal frequency of glycemic level monitoring. Invasive and painful monitoring is one of the causes of poor patient compliance both with treatments and overall disease self-management. Moreover, in the past two decades there have been few, if any, advances in non-invasive blood glucose monitoring devices. A new breath-based glucose detection device called Easy Check™, currently under development, is designed to test the glucose levels of a person with diabetes by simply analyzing their exhaled breath through a hand-held device. This non-invasive testing device mayimprove patient monitoring of glycemic levels, leading to better self-management of this chronic condition. When commercialized, Easy Check will represent a paradigm shift in diabetes self-management, as it will likely minimize one of the most obstinate barriers in diabetes self-management.

I. Diabetes: The Problem and the Cost

Diabetes remains one of the greatest worldwide health challenges of the twenty-first century. According to the major health organizations and diabetes foundations worldwide, the prevalence and incidence of diabetes has reached epidemic proportions [1,2]. In 2005, the World Health Organization estimated that 220 million people worldwide had diabetes [5]. By 2010, this figure had risen to 285 million people, or 6.4% of the world's adult population. In some countries, such as the United States, the prevalence is even higher (8.3% of the population) [3]. By 2030, however, the worldwide figure is expected to double from 2005 figures to 438 million, corresponding to 7.8% of the adult population [2].

Diabetes is one of the major contributors of premature illness and death in non-communicable diseases. According to the Centers for Disease Control and Prevention (CDC), diabetes is a major cause of heart disease and stroke and the leading cause of kidney failure, non-traumatic lower-limb amputations, and new cases of blindness among adults in the United States. Moreover, it is the seventh leading cause of death in the United States [6]. Worldwide, the number of deaths attributable to diabetesincreased 5.5% in the three-year period from 2007 to 2010. This increase is largely due to a 29% increase in the number of deaths attributed to diabetes in the North America & Caribbean region, followed by significant, yet lower, increases in other regions (12% in South East Asia Region, including China and India, and 11% in Western Pacific Region) [2].

Currently, the largest age group affected by diabetes is people between 40-59 years. Due to the aging population in most developed countries, the largest age group that will be affected by 2030 will be the 60-79 age group, with some 196 million cases [2]. Type 2 diabetes, formerly called non-insulin-dependent or adult-onset diabetes, accounts for 90% of diabetes around the world. This type of diabetes usually occurs in adults and is typically diagnosed several years after onset, once complications have already arisen. Years back, type 2 diabeteswas rarely seen in children but now is becoming more common. Type 1 diabetes, formerly called insulin-dependent, juvenile or childhood-onset diabetes, requires daily administration of insulin because of the deficient insulin production in the body. Type 1 and gestational diabetes (when the onset or first recognition is during pregnancy), comprise the other 10% of diabetes cases. Lastly, pre-diabetes is a condition in which individuals have blood glucose or A1C levels higher than normal but not high enough to be classified as diabetes. These individuals have an increased risk of developing type 2 diabetes, heart disease and stroke [6].

When taken all together,diabetes presents demographic, economic and human challenges. Due to its chronic nature, the severity of its complications and the means required to control them, diabetes is a costly disease, not only for the affected individual and his/her family, but also for the health authorities [2]. In the United States alone, the total healthcare costs of a diabetic patient is approximately 2.3 times higher than what expenditures would be in the absence of diabetes [3]. Not only is diabetes costly, but due to the rising incidence, these costs are skyrocketing. In 1997, for example, the cost of treating diabetes in the United States was

US$44 billion. However, by 2007, it is estimated that this cost soared to $116 billion. This latter figure only takes into account direct medical costs. Once indirect costs (disability, work loss, premature mortality) are factored in, the total cost of the disease was estimated to be $174 billion in 2007. Factoring in the additional costs of undiagnosed diabetes, pre-diabetes and gestational diabetes brings the total cost of diabetes in the United States in 2007 to $218 billion [6].

These statistics, which were jointly produced by the CDC, National Institute of Health (NIH), American Diabetes Association (ADA), and other organizations, offer the most recent and comprehensive assessment of the impact of diabetes in the United States. [7]. As aforementioned, a person with diabetes usually incurs medical costs which are significantly higher than those of a person without diabetes. The largest components of medical expenditures attributed to diabetes are hospital inpatient care (50% of total cost), physician office visits (9%), diabetes medication and supplies (12%), and retail prescriptions to treat complications of diabetes (11%) [10]. The latter two (23% of direct costs) include diabetes management supplies (syringes, glucose testing meters, test strips and insulin pumps), insulin and/or other diabetes drugs and therapeutics, other medications related to diabetes (cholesterol-lowering drugs, high blood pressure medication, etc.), as well as frequent diagnostic tests [9].

Those living with diabetes face ongoing medication and supply costs. In the United States in 2002, the costs for insulin and delivery supplies, oral agents to lower blood glucose and other outpatient medications attributable to diabetes were estimated at $7.0 billion, $5.0 billion, and $5.5 billion, respectively. With the prevalence of diabetes in the United States expected to more than double by 2050, the cost for diabetic supplies alone will exceed $40 billion [12].

There is no doubt that diabetes is a costly disease, both from a tangible perspective (direct costs) as well as an intangible one (pain, anxiety, inconvenience and generally lower quality of life). It has been postulated that, through disease prevention programs and better self-management, these costs can be reduced, both for the benefit of patients, as well as their families and all stakeholders (physicians, payors, government, society).

It has been postulated that, through better self-management, the costs associated with diabetes can be reduced.

II. Tackling Diabetes through Management

"The pandemic of diabetes threatens to overwhelm clinicians' collective ability to treat the associated metabolic abnormalities and long-term complications" [15]. Yet, even though there has been remarkable progress in the past decade related to the treatment of diabetes and its complications, there has been relatively little progress in the prevention of diabetes. There is a lack of clinical data or research demonstrating thattype 1diabetes can be prevented. Type 1 diabetes is characterized by the body's inability to produce insulin due to the immune system attacking the insulin-producing cells. In 2009, the landmark Diabetes Control and Complications Trial (DCCT), demonstrated that intensive therapy to achieve targeted glycated hemoglobin (HbA 1c) levels, reduced the development and progression of retinopathy, nephropathy and neuropathy by 30% to 76% in type 1 patients. While the DCCT and other trials demonstrated significant improvements in the long-term prognosis of diabetes, they nonetheless offered little insight into preventing type 1 diabetes [15,16].

Other studies, such as the Diabetes Prevention Programs (DPP), a CDC funded study of3,234 people at high risk for diabetes, showed that pre-diabetics at risk for developing type 2 diabetes can prevent or delay its onset through lifestyle changes [13]. Participants in the DPP lifestyle intervention group reduced their risk of developing diabetes by 58 percent during the study [15]. The DPP and other studies have added to understanding of the prevention of type 2 diabetes and have shown that, to some extent, the long-term complications of diabetes and onset of diabetes can be delayed [17].

This, however, is not enough to make a significant impact on the diabetes pandemic. Other strategies besides prevention, such as disease self-management have proven more beneficial in the outcome of the disease. As with most diseases, effective control of diabetes requires that patients actively engage in the self-management of their health [18]. Diabetes self-management education (DSME) is defined as the ongoing process of facilitating the knowledge, skill and ability necessary for self-care, and is often referred to as the cornerstoneof diabetes care[26]. Unlike other illnesses or conditions which are largely managed by healthcareproviders, diabetes is largely managed by the person who is affected. In fact, it has been estimated that more than 99% of diabetes care and 98% of diabetes outcomes can be attributed to the person with the condition [19].

Of the seven self care behaviors cited by the American Association of Diabetes Educators (AADE) -- healthy eating, taking medications, healthy coping, being active, self-monitoring,reducing risk and problem solving -- self-monitoring of blood glucose (SMBG) is a key component of the treatment regimen [21]. SMBG provides immediate feedback on the person's glycemic level thereby enabling the person to adjust, as needed, to achieve desired glycemic control [20]. The AADE asserts that a diabetic who regularly carries out a program of SMBGand who is informed about how to interpret the results of glucose monitoring, can very well see improvement in overall glycemic control and reduce the incidence ofcomplications [22,23].

Many studies support the importance of SMBG in diabetes management. The Retrospective Study Self-Monitoring of Blood Glucose and Outcome in People with type 2 Diabetes (ROSSO), studied 3,268 people – 1,479 of whom practiced SMBG for at least one year, while 1,789 did not – and found that morbidity as well as mortality were significantly lower in the SMBG group [27]. Other analyses from ROSSO suggest a positive correlation between SMBG and better clinical outcomes, including reductions in all-cause mortality combined with severe non-fatal events, mostly myocardial infarction or stroke [29, 30]. Another analysis suggests that severe diabetic complications, such as myocardial infarction and stroke, can be delayed in those patients practicing SMBG compared to those who do not [30]. Further, the data suggested that SMBG can also be cost-effective from a health economics standpoint [31].

According to ADA, type 1 and type 2 diabetics takingmultiple insulin injectionsshould check their blood glucose levels at least four times per day. There are no guidelines for daily testing for those with type 2 diabetes who are on less frequent injections or oral medication or who control their diabetes through diet and exercise[25]. For other type 2 patients, optimal SMBG frequency varies depending on the pharmaceutical regimen and whether patients are in an adjustment phase or at their target for glycemic control[28]. Most healthcare professionals agree that SMBG provides valuable information. However, many studies have found that patients do not follow recommended treatment guidelines. A cross-sectional survey conducted at the largest health maintenance organization in the United States amongst 44,181 adults with type 1 and 2 diabetes,revealed alarmingly low rates of SMBG and poor compliance with recommended frequency of checking. Only 40% of patients with type 1 diabetes and 33% of patients with type 2 diabetes reported compliance with recommended SMBG frequency (three to four times daily for type 1 diabetes and once daily for type 2 diabetes) [25].

In light of this, any strategies that improve the compliance and frequency of SMBG should be embraced – not only because SMBG is an integral part of self management education, but because it tackles an important facet of the diabetes pandemic – management.

III. Glucose Monitoring: Essential, Complicated and Painful

Poor blood glucose management leads to complications such as kidney failure, heart disease, impotence, blindness, and amputation because it fails to identify the important peaks, valleys, and trends that lead to the eventual micro-vascular complications of diabetes. There is a considerable amount of knowledge about the positive effects of adherence to therapy and compliance with recommended testing guidelines.

Many studies have been undertaken to identify basic social and psychological factors that may be related to diabetics, and to comprehend why some diabetics have difficulty adhering to SMBG as recommended by their healthcare providers.

A study presented at the last Scientific Session of the American Diabetes Association of 416 adults with type 1 or 2 diabetes, showed that motivational obstacles play a significant role in SMBG utilization. Study participants with type 1 and 2 diabetes reported that testing constantly reminded them that they have diabetes (45% and 53%, respectively), and that the testing itself is painful (34% and 35%),frustrating (26% and 25%) and time consuming (25% and 25%) [31].

Glucose monitoring devices have improved substantially in the last decade, and although some studies have shown that the pain associated with finger pricking has been reduced, they also show that the pain has not been eliminated [34]. According to a review performed by Heinemann, it appears that "the depth of the needle tip while penetrating the skin and the depth of needle penetration are key for pain induction" [34].

Performing SMBG repeatedly several times per day for many years/decades is not only annoying to the patient but also has physical consequences such as massive scarring/callous formation and loss of sensibility/perception hindrance [34]. Heinemann goes on to argue that the pain associated with finger pricking is most probably the main reason why patients refrain from SMBG. Heinemann further argues that SMBG monitoring is even more difficult in children and that the monitoring itself, for both adults and children, is probably more painful than a subcutaneous injection of insulin for those insulin-dependent patients[34.]

Diabetics would perform SMBG more frequently and have improved quality of life with non-invasive SMBG.

Other studies, in both diabetes patients and healthcare providers, have cited that compliance is low because SMBG is still based on the painful and laborious process of the invasive procedure of drawing blood and feeding it into a testing device. Wagner reported that 63% (nearly two-thirds) of respondents skipped SMBG because of the invasiveness of the procedure. They concluded that invasiveness is a common and serious barrier to SMBG and that “diabetics would perform SMBG more frequently and have improved quality of life with non-invasive SMBG” [33]. Other studies mirror this finding, citing that pain is a major barrier for performing SMBG [24,25].

Setting aside the physical and psychological factors of SMBG, there are also financial factors to consider. Worldwide, the market for self-monitoring of blood glucose (SMBG) approached $8.8 billion in 2008, representing an approximate 12.5% compound annual growth rate since 1994 [35]. Moreover, the SMBG testing market accounted for 22% of the entire in vitro diagnostics industry. In the United States alone, this amounted to $3.4 billion [35]. Given that the prevalence of diabetes in the United States is expected to more than double by 2050, the cost of testing alone could double as well. These figures almost solely account for testing strips as the majority of the cost is in the strips, not the device.

Given the cost and pain implications, it is no surprise that scientists and researchers have searched for non-invasive techniques to monitor blood glucose since the advent of the first commercial glucose testing devices in the 1970s [39]. These problems have promoted a new area of routine glucose analysisresearch - noninvasive indirect glucose determination. Noninvasive methods are based on the analysis of sweat composition, electro-conductivity of skin, laser radiation absorption in muscles, and occlusion spectroscopy, also known as near-infrared spectroscopy.

The single most active area of non-invasive glucose research involves near-infrared spectroscopy whereby glucose is measured by focusing a beam of light into the eye andobtainingan optical signature or fingerprint of the tissue content produced by the diffuse light that escapes the tissue it has penetrated[38,39]. The absorbance of light by the skin is due to its chemical components (i.e., water, hemoglobin, melanin, fat and glucose) and the glucose concentration can be determined by analyzing the optical signal changes in wavelength, polarization or intensity of light [38]. Although widely touted for years as offering the most promise, after nearly two decades of research, experts in this field agree that the near-infrared approach has not achieved clinical or commercial success to date [39]. Other technologies cited above likewise yielded similarly disappointing results.

In 2006, FDA authorized the use of two types of non-invasive glucometers. Beyond any doubt, their appearance inthe market was a considerable breakthrough in the field of non-invasive determination of glucose concentration for patients. However, everyday use of these devices entails technical and personal challenges, and therefore, these devices have not been accepted in the market and presently have limited or no health or commercial value to diabetes stakeholders.

More recent technology includes the emergence of continuous blood glucose monitoring (CBGM), where a sensor implanted under the skin provides continuous glucose measurements. This technology records blood sugar levels throughout the day and night and is used to measure an average blood sugar for up to three days. All of this is accomplished while the diabetic participates in daily activities at home [35, 37].Depending on the manufacturer, sensors can be worn for up to seven days, whereby the sensor is then removed at the doctor's office and the information stored in the monitoring system is downloaded electronically for review by the healthcare professional. While clinical evidence suggests that this technology offers diabetes patients a better means of continuous glucose control (through minute by minute measurements), the technology is intended for discovering trends in glucose levels, not for day-to-day monitoring or long-term self-care. Thus, it is not a replacement for SMBG [35].

Further, CBGM has been labeled by some as non-invasive; however, as it involves inserting a sensor underneath the skin, the technology cannot be classified as non-invasive and is better labeled minimally invasive [38].

In summary, none of the aforementioned methods have yielded commercially-viable devices due to low precision of the analysis and the difficulty in developing a portable device for self-checking. Thus, the search is still active to seek a technology that is convenient, portable and painless to replace finger pricking. If a device were to be developed, the barrier to more frequent measurement of glucose levels would be reduced, positively impacting the management of the disease [34].

IV. Easy Check: Overview of Breath-Based Glucometer Technology

Given the setbacks of previous technologies, a team of researchers has focused on breath-based technologies as a means of detecting levels of blood glucose. It is known from clinical practice and medical research that the presence of increased levels of acetone in the exhaled breathindicates excessive glucose in the blood. Based on this premise and on recent scientific success in developing methods for highly-sensitive chemical analysis, especially the possibility to determine nano-impurities of many substances in gases, the possibility of developing a portable, accurate and painless device has becomea reality [39-41].

Acetone concentration in healthy people's exhaled breath does not exceed 1-3 mg/m3. Glucose concentration in the blood of healthy people measured simultaneously amounts to 4-8 mmol/liter. In diabetics, acetone concentration in the exhaled breathreaches 8-10 mg/m3 at the same normal glucose content in blood equal to 4-8 mmol/liter. The increase in acetone concentration in comparison to the norm (1-3 mg/m3) points to the appearance of excessive glucose in blood. As a result, research was undertaken to produce a device that determines acetone concentration rapidly in exhaledCO-2, without blood sampling and correlates the acetone concentration to glucose concentration in blood[40].

To this end, PositiveID Corporation (PSID) is developing a device called Easy Check™ with proprietary technology for determining acetone concentration in exhaled air. The Easy Check technology is based on a patent-pending reagent cell that mixes the patient's exhaled air with a proprietary chemical compound,triggeringa chemical reaction. The reaction is measured and software in the device then interprets the measurement and correlates the patient's acetone level to the level of glucose in the body. The device functions as follows:

- The patient breathes into the single-use capsulecontaining the chemical sensor and into the air-flow sensor of the compact EasyCheck device
- The device then forces the air from its air chamber into the reagent chamber
- The patient's expired air molecules create a "very large" molecule to achieve a chemical reaction measured by the device's optical sensor.

Previous data on acetone/glucose correlation was insufficient for reliable statistics. Now, the discovery of the use of a proprietary chemical compound containing the Na-Np heavy molecule complex to generate a chemical reaction able to be reliably measuredhas brought the knowledge of acetone-glucose correlation to a new level. The portability of the reagent cell containing the heavy molecule may make it a viable method for patients to use to measure acetone levelsoutside a laboratory setting andconsequently enable the collection of plentiful data. Thus, not only is the technology novel in that it uses spectrometry (see Figure 1)to measure changes in the acetone level; it is also novel in its ability to use tiny emitters and software in a hand-held device for interpretation and reading of glucose levels.

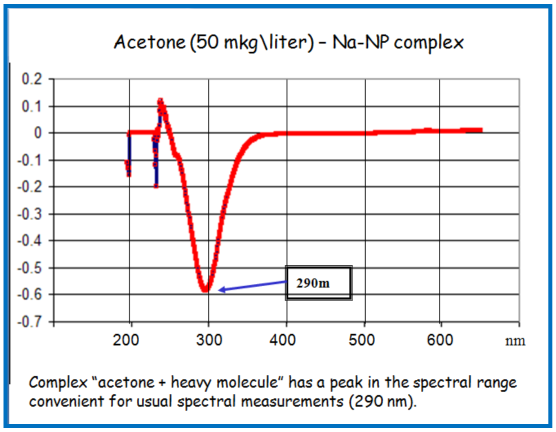

Figure 1

The Easy Check reagent capsule will be a single-use capsule that is discarded once the patient obtains a reading. In contrast to test strips, there should be little to no waste as the patient will not be manipulating the capsule prior to inserting it in the device. The device is expected to provide a reading in five to seven seconds, with the same accuracy tolerances as present day glucometers, in a safe and pain-free testing alternative [42,43].

Based on successful preliminary laboratory tests that validated its proprietary technology, PSID continues its development of Easy Check, the portable non-invasive breath-based glucometer. The laboratory results included breath tests conducted at PSID's research facility outside Tel Aviv, Israel under the guidance of Dr. Vadim Goldstein, D.Sci., Chemistry. The results depict a consistent correlation of blood glucose levels (see Figure 2) as compared with a standard blood glucose meter that are within acceptable industry standards [44]. With further testing, calibration,and development of the device's software and algorithms, the results may yield a non-invasive device applicable to a significant portion of the diabetic patient population.

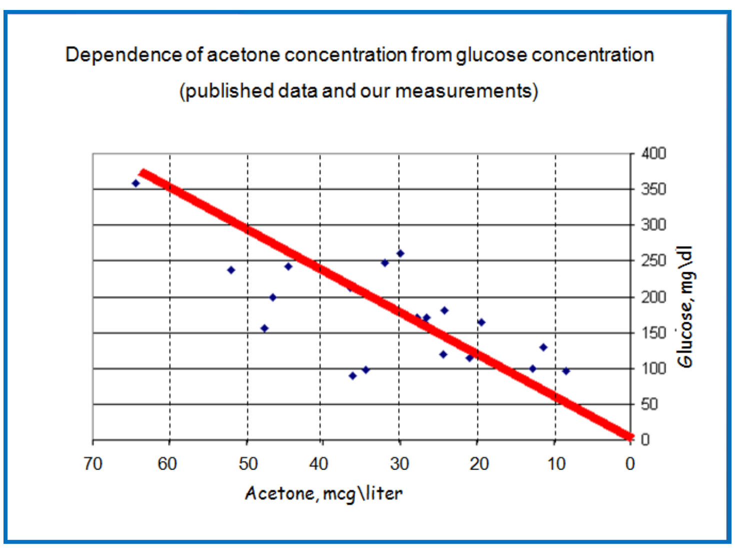

Figure 2

The latest prototype is 5 in. x 3 in. x 1 in. and weighs approximately eight ounces. The device, using advanced microprocessor and laser technology, has self-calibrating capabilities to help ensure accuracy of each test. In summary, the device, assuming successful continued development, fulfills the requirements for ideal devices – easy to handle, low weight, high-quality design and a relatively high precision (20%). Easy Check has the added advantage of not causing infection during the sampling process and, more importantly, not causing pain or embarrassment if the patient cannot perform the sampling in private.

The company expects to complete the second generation of its prototype during 2011. Pre-clinical trial protocols are now being formulated under the guidance of the foremost endocrinologists in Israel, leading to a possible FDA submission in 2012.

V. Conclusion

Given the diabetes epidemic worldwide, new strategies are needed to achieve better control of the disease. SMBG has been, and continues to be, a cornerstone of diabetes self-management. The positive correlation between frequent SMBG and better clinical outcomes is well documented and demonstrates that reductions in mortality, severe non-fatal events and diabetic complications can be achieved. These reductions would correlate to heath and economic benefits due to the costly nature of the disease.

It has been shown that the invasive nature of current devices in the market is a serious barrier to SMBG, primarily due to the pain. Eliminating this barrier with a lightweight, easy–to-use, accurate device by which to perform SMGB could result in an improved quality of life for a person with diabetes.

When commercialized, Easy Check may represent this long-awaited breakthrough by offering patients the first and only glucose testing device that is precise, portable and entirely non-invasive.

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