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## Flash Glucose Monitoring System for Diabetes



*Image courtesy of Abbott Diabetes Care*

**Authors:** Eugenia Palylyk-Colwell, Caitlyn Ford

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This report, originally posted in June 2017, has been updated to reflect the following changes, finalized in March of 2018:

- Statements were added regarding the methodology used to produce the report to improve transparency, including information on search time frames and the evidence synthesis approach.
- Updates to the presentation of evidence were made to provide more clarity, including information about study comparisons and conditions under which the technology was investigated.
- Appropriate attribution of report content to the professional and consumer versions of the device (FreeStyle Libre), where provided in the source articles, has been added.
- The changes do not include an updated literature search or inclusion of any further evidence that may have emerged since the original search-end date of February 10th, 2017.
- The consumer version of the FreeStyle Libre system intended for personal use by patients with diabetes received regulatory approval in Canada (June 2017) and the US (September 2017).<sup>1</sup> As of August 2017, the FreeStyle Libre system has been commercially available in Canada.<sup>2</sup> The report has not been updated to reflect these developments.

## Summary

- FreeStyle Libre is a glucose monitoring system that uses a sensor implanted in the arm that a health care provider scans with a specialized reader for a record of glucose levels, trends, and patterns in people with diabetes.
- There are two versions of the technology – a professional version (FreeStyle Libre Pro) and a consumer version (FreeStyle Libre).
- Studies on the FreeStyle Libre device have investigated its diagnostic test performance and accuracy, its clinical effectiveness (e.g., hypoglycemia, glycated hemoglobin, patient satisfaction, and safety), and its cost-effectiveness.
- As of February 2017, the FreeStyle Libre Pro had regulatory approval but was not being sold in Canada and could be purchased through the manufacturer’s American website.

## Issue

In its clinical practice guidelines, the Canadian Diabetes Association — now known as Diabetes Canada — recommends that people living with diabetes regularly monitor their glucose (blood sugar) levels to confirm and treat low blood sugar, or hypoglycemia, to adjust their dosage of insulin, and to provide information to their health care providers about their diabetes management.<sup>3</sup> The recommendations also note that the frequency of self-monitoring blood glucose (SMBG), which typically involves finger sticks and testing using capillary blood-glucose monitors, should be individualized. It has been recommended, though, that in people using insulin more than once a day, self-monitoring should be undertaken at least three times daily and before and after meals, especially if using rapid-acting, mealtime insulin.<sup>3</sup> Some people with hard-to-control type 1 diabetes may opt for continuous glucose monitoring with devices that continuously measure glucose levels using a sensor implanted under the skin.<sup>3</sup> Other people may opt for continuous monitoring because they find the number of finger sticks required for self-monitoring to be painful and inconvenient.

A new approach to glucose monitoring, called flash glucose monitoring, is becoming available and may offer people with type 1 and type 2 diabetes a less painful and more convenient option when intensive glucose monitoring is needed. Flash glucose monitoring differs from traditional SMBG and continuous glucose monitoring in that it does not require calibration by the user. Also, it does not continuously measure blood glucose and provide alarms for glycemic events but, rather, provides a result when prompted by scanning the sensor.

## Methods

Horizon Scanning bulletins aim to summarize available information about new or emerging technologies based on a limited literature search and information provided by manufacturers. These bulletins are not systematic reviews and do not involve detailed critical appraisal. They are not intended to provide recommendations for or against a particular technology.

## Literature Search

A limited literature search was conducted using the following bibliographic databases: PubMed, MEDLINE, Embase, and the Cochrane Library. Grey literature searching included relevant sections of the *Grey Matters* checklist (<https://www.cadth.ca/grey-matters>). No methodological filters were applied. The search was limited to English-language documents published between January 1, 2012 and January 18, 2017. Conference abstracts published between January 1, 2015 and January 19, 2017 were included in the search results. Regular alerts were established to update the search, and citations retrieved before February 10, 2017 were incorporated into the report.

## The Technology

The FreeStyle Libre system (Abbott Diabetes Care Inc., Alameda, California) is a flash glucose monitoring system that provides a record of an individual's glucose levels, trends, and patterns for up to 14 days.<sup>4,5</sup> The FreeStyle Libre system generates an ambulatory glucose profile — a different way of assessing glucose levels on a continuous 24-hour basis that shows how day-to-day decisions and behaviours impact the control of blood sugar levels.<sup>6</sup>

Similar to continuous glucose monitoring, flash glucose monitoring relies on the measurement of glucose concentrations in the interstitial fluid — the fluid surrounding cells — rather than directly measuring glucose levels in the blood.<sup>5</sup> The FreeStyle Libre technology consists of a small, round, disposable, and water-resistant sensor approximately the size of two stacked quarters that is applied to the back of the individual's upper arm.<sup>4</sup> The sensor continuously measures glucose in the interstitial fluid through a small, 5 mm long-by-0.4 mm-wide filament inserted just under the skin. The sensor records glucose levels every 15 minutes, capturing up to 1,340 glucose results for up to 14 days, and displays current, eight-hour historic and trend glucose data when scanned.<sup>4</sup>

There are two versions of the technology, a professional version (FreeStyle Libre Pro) and a consumer version (FreeStyle Libre). For clarity, the consumer device will be referred to as such throughout the report where applicable. The FreeStyle Libre Pro system is intended for professional use only; i.e., the person with diabetes does not interact with the system. Rather, the sensor attachment is inserted by a health care provider in a clinic setting and scanned by a health care provider to receive the data retroactively.<sup>5,7</sup> Information about the individual's glucose levels is stored in the sensor which, in turn, is accessed by passing a specialized, hand-held reader over the sensor when the individual returns to the clinic or physician's office.<sup>4</sup>

The consumer version of the system, the FreeStyle Libre, is inserted and scanned by the person with diabetes rather than the health care provider. The patient may apply the sensor on their own and view information about their glucose levels. The consumer version is currently under review by the US FDA<sup>4,8</sup> and is already available in more than 35 countries worldwide (Jessica Sachariason, Abbott Diabetes Care, Alameda, CA: personal communication, 2017 Mar 10).

Flash glucose monitoring differs from continuous glucose monitoring in that information about the person's glucose levels and trends is available from the FreeStyle Libre system only when the sensor is scanned. In comparison, continuous glucose monitoring systems monitor and send information to a device or display monitor, without interruption, throughout the day, and can alert a user if glucose levels are outside a pre-set limit.<sup>3</sup>

An important distinction of the FreeStyle Libre system compared with continuous glucose monitoring is that it is factory-calibrated and does not need daily calibration (requiring finger sticks) by the user.<sup>9</sup> It also has a longer period of sensor use — 14 days versus seven days — and reads results in seconds, and it can be used by people with type 2 diabetes.<sup>10,11</sup> Two other key differences are that the FreeStyle Libre system is not equipped with alarms (or notifications) that will sound in the event of out-of-range glucose values and it lacks the ability to connect with insulin pump systems that continuously deliver short-acting insulin.<sup>10,12</sup>

## Availability

The FreeStyle Libre Pro system received a Class III medical device licence from Health Canada in November of 2016.<sup>13</sup> The approval extends to three components of the system: the reader kit, the sensor kit, and software.<sup>13</sup> As of March 2017, the company noted that "the system does not appear to be commercially available in Canada yet; however, it can be ordered online directly from the manufacturer's US website" (Jessica Sachariason: personal communication, 2017 Mar).<sup>5,10 a</sup>

In September 2016, the FDA approved the FreeStyle Libre Pro system for people with diabetes aged 18 years and older.<sup>14,15</sup> The consumer version of the FreeStyle Libre system intended for personal use was under review by the FDA.<sup>4,11,16,17</sup> In Europe, the consumer version of the FreeStyle Libre system received a CE mark in September of 2014 authorizing its use in adults, and a subsequent CE mark in February 2016 authorizing use in children and teens (aged four to 17 years).<sup>8,18,19</sup>

## Cost

The FreeStyle Libre reader (consumer version) is listed at C\$49 and each individual sensor at C\$89. The starter pack including one reader and two sensors is listed at C\$227.<sup>20</sup>

In the US, the FreeStyle Libre Pro reader costs US\$65 and each individual sensor costs US\$60.<sup>11</sup> In the UK, it is reported that the cost for a starter pack of the FreeStyle Libre consumer system including one reader and two sensors is approximately £170.<sup>21</sup>

## Who Might Benefit?

To date, continuous glucose monitoring has been used primarily by well-informed people with type 1 diabetes who have been trained on how to use it.<sup>10</sup> In contrast, flash glucose monitoring may be a more accessible technology for people with type 2 diabetes, as it may enable appropriately trained people to monitor their glucose levels regularly after a meal or physical exercise, pending the availability of the consumer version of the system.<sup>10</sup> It has been suggested that the FreeStyle Libre Pro system will be used primarily by people with type 2 diabetes;

<sup>a</sup> See page 3 for details regarding regulatory changes that have occurred since the initial publication of the report.

it could also benefit long-term users of continuous glucose monitors who find the alarms with most of these systems to be bothersome.<sup>10,22</sup>

## Current Practice

The measurement of glycated hemoglobin (A1C) is the preferred standard for assessing long-term blood-glucose control in people with both type 1 and type 2 diabetes.<sup>23,24</sup> A major drawback of A1C is that it does not provide information about fluctuations in glucose levels; i.e., it is possible for A1C to remain within the target range while glucose levels fluctuate between periods of low glucose (hypoglycemia) and high glucose (hyperglycemia) levels throughout the day.<sup>23</sup> Other glucose monitoring methods including SMBG, continuous glucose monitoring, and other methods like flash glucose monitoring may provide insight into these fluctuations.<sup>25</sup>

Self-monitoring of blood glucose using finger sticks and capillary blood-glucose testing provides discrete “snapshots” of glycemic control at the test times. It is currently recommended as an integral component of diabetes self-management by Diabetes Canada (formerly the Canadian Diabetes Association).<sup>3</sup> The recommended timing and frequency of SMBG depends on the type of diabetes and the treatment prescribed. It also depends on the individual's need for information about glucose levels and the ability to use the test information to modify behaviour or adjust treatment.<sup>3</sup> Self-monitoring may present challenges for some patients because of its time-intensive nature and the discipline required to maintain records of daily blood-glucose results over the long term.<sup>23</sup> Continuous glucose monitoring has been used in people with type 1 diabetes to provide comprehensive, continuous glycemic profiles, which can improve glycemic control and reduce hypoglycemia.<sup>3,23</sup> Notably though, continuous glucose monitoring systems still require self-monitoring for calibration of the system.<sup>3</sup> Self-monitoring must be done at least every 12 hours and also in “real time” to confirm interstitial fluid measurements before making changes to therapy or treating suspected hypoglycemia.<sup>3</sup>

## The Evidence

Nine published studies of the FreeStyle Libre system, used in adults, were identified.<sup>12,26-33</sup>

The identified studies evaluated the device under different conditions.<sup>8</sup> Specifically, there was variation in the device-reading mechanism (patient, health care provider, both, or none), and in the study conditions (duration of use, frequency of reading, adjunct glucose monitoring methods such as SMBG). Some studies failed to report this information, so the context of use was unclear.

No studies explicitly reported whether the professional or consumer version of the device was used, so it was not possible to present the summary of evidence by version of the device. One study allowed participants to scan the sensor and use readings to inform blood-glucose management (reflective of the intended use of the consumer version of the device).<sup>26</sup> One study allowed scanning of the sensor and use of readings to inform blood-glucose management but instructed participants to prioritize SMBG readings.<sup>27</sup> Other studies did not allow patient readings and only permitted health care professionals or study personnel to scan the sensor and interpret data (reflective of the intended use of the professional version of the device).<sup>28,29,31</sup> Two studies did not reflect intended use, as, in one case, measurements were only made during surgery and did not inform patient management,<sup>32</sup> and, in the other, the device was worn alongside two other continuous glucose monitors over a single day.<sup>33</sup> Two studies presented as letters to the editor did not contain sufficient information to determine how the device was used.<sup>12,30</sup>

Four of the studies were conducted on people with type 1 diabetes,<sup>12,26,27,33</sup> four on a mixed population of people with type 1 or type 2 diabetes,<sup>28-31</sup> and one study was on people undergoing cardiac surgery, where acute hyperglycemic events have been noted to occur (six out of 26 with a history of diabetes).<sup>32</sup> Six of the studies were funded by the manufacturer<sup>12,26,28-31</sup> and three were investigator-initiated.<sup>27,32,33</sup>

Five of the nine studies evaluated the performance and accuracy of the FreeStyle Libre system compared with other methods of measuring glucose.<sup>27,28,31-33</sup> The other four studies reported clinical outcomes (for example, hypoglycemia, A1C, patient satisfaction, and quality of life).<sup>12,26,29,30</sup> Of these, three were observational, single-arm studies<sup>12,29,30</sup> and one (the IMPACT Study) was a prospective, open-label, multi centre, randomized controlled trial.<sup>26</sup> The primary outcome in the IMPACT Study was the change in the amount of time spent in hypoglycemia from baseline to six months in 241 patients

with well-controlled type 1 diabetes who were randomized to either the FreeStyle Libre system and SMBG or to SMBG alone.<sup>26</sup> With the exception of four studies<sup>12,30,32,33</sup> including two studies (reported as letters to the editor) where the use of other methods of glucose monitoring was unclear,<sup>12,30</sup> the rest of the identified studies allowed patients to continue SMBG alongside the use of FreeStyle Libre.<sup>26-29,31</sup> One study explicitly emphasized prioritizing SMBG readings for diabetes management over other measures of blood glucose.<sup>27</sup>

We also identified two published studies of the FreeStyle Libre system used in children with type 1 diabetes.<sup>34,35</sup> One trial was funded by the manufacturer<sup>34</sup> and the other was independently funded.<sup>35</sup> The first study compared device performance and patient satisfaction between the FreeStyle Libre system and capillary blood-glucose testing in the same children (age range: one to 14 years).<sup>34</sup> The second was a pilot study to evaluate the feasibility and acceptability of the ambulatory glucose profile in children aged four to 17 years who were initiated on the FreeStyle Libre system.<sup>35</sup>

## Performance and Accuracy

The performance and accuracy of the FreeStyle Libre system in adults and children compared with SMBG or capillary blood-glucose testing, venous blood-glucose analysis, continuous glucose monitoring, or intravascular microdialysis continuous glucose monitoring, are summarized in Table 1. All the studies in Table 1 reported the overall mean absolute relative difference (MARD), expressed as a percentage. A lower MARD value indicates smaller differences, or per cent error, between methods. The overall MARD between the FreeStyle Libre system compared with capillary blood-glucose testing ranged from 10.0%<sup>31</sup> to 13.9%;<sup>34</sup> the MARD was 16.6% compared with self-monitored blood glucose,<sup>27</sup> and 18.1% compared with continuous glucose monitoring.<sup>27</sup> When directly compared with reference venous blood-glucose results, the FreeStyle Libre system had a MARD of 13.2%, while the continuous glucose monitoring systems evaluated had MARDs of 16.8% (Dexcom G4 PLATINUM) and 21.4% (Medtronic MiniMed 640G).<sup>33</sup> It should be noted that these MARD results were obtained under controlled conditions and that the accuracy and performance of these continuous glucose monitoring systems may vary considerably during periods of rapidly changing glucose levels, such as during exercise or after meals.<sup>33,36</sup>

The results of error grid analyses were also reported. This method describes the clinical accuracy of a test method compared with a reference method based on paired glucose samples and the clinical significance of the differences between them.<sup>37,38</sup> Various types of error grid analysis were used including Consensus, Clarke, and Parkes. The identified studies found that between 18.9% and 88.8% of the paired samples of the FreeStyle Libre system test method and the reference test method were within zone A — meaning that test values deviated by 20% or less from the reference value and these differences would not result in a different clinical decision.<sup>27,28,31-34</sup> In addition, the studies reported that between 91.6% and 100% of paired samples were within zones A or B — meaning that, although the difference may be more than 20%, the difference is unlikely to result in a different clinical decision.<sup>27,28,31-34</sup> There was also a high level of agreement between the FreeStyle Libre system and the other test methods, ranging from 76% agreement with continuous glucose monitoring to 95% agreement with venous blood glucose. Two studies reported the mean lag time in glucose levels associated with the FreeStyle Libre system compared with venous blood glucose, which ranged from 3.1 minutes to 4.5 minutes.<sup>28,31</sup> In the study of patients undergoing cardiac surgery, it was reported that, although both systems were reliable and no complications occurred, the intravascular microdialysis continuous glucose monitoring system was more accurate than the FreeStyle Libre system (which repeatedly measured a lower glucose value) based on comparison to reference measurements of arterial blood glucose.<sup>32</sup>

Two studies, one in adults<sup>28</sup> and the other in children,<sup>34</sup> reported that factors such as age,<sup>28,34</sup> body weight<sup>34</sup> or body mass index,<sup>28</sup> sex,<sup>34</sup> A1C level,<sup>28</sup> method of insulin administration,<sup>28,34</sup> and time of use (day versus night)<sup>34</sup> did not affect sensor accuracy.

## Hypoglycemia

The primary outcome in the IMPACT Study was the change in the amount of time in hypoglycemia — defined as hours per day with a glucose level of less than 3.9 mmol/L (70 mg/dL) from baseline to six months for patients using FreeStyle Libre alongside SMBG compared with those using SMBG alone.<sup>26</sup> The average amount of time participants experienced hypoglycemia was statistically significantly lower at six months for people who used the FreeStyle Libre system alongside SMBG (1.24 fewer

hours per day) compared with those who self-monitored their blood glucose.<sup>26</sup> Analyses of day and night results found that the amount of time spent below all hypoglycemic thresholds and the number of hypoglycemic episodes were also significantly reduced in patients who used the FreeStyle Libre system alongside SMBG compared with those who self-monitored their blood glucose.<sup>26</sup>

A single-arm study (reported in a letter to the editor) that prospectively assessed the impact of introducing the FreeStyle Libre system to people with type 1 diabetes over a 16-week period reported that hypoglycemic episodes, recorded and self-reported, reduced from 17 episodes in the first two weeks of the study to 12 episodes in the final two weeks of the study.<sup>12</sup> Another single-arm study of people with type 1 or type 2 diabetes that assessed aggregate data from ambulatory glucose profiles obtained using the FreeStyle Libre system (alongside continued SMBG) found that, despite having similar A1C values, patients with type 2 diabetes had different glycaemic characteristics and a different risk of hypoglycemia than those with type 1 diabetes.<sup>29</sup> It was noted that these data, which have important implications for therapeutic adjustments, were obtained within a short time and with minimal provider and patient input using the FreeStyle Libre system.<sup>29</sup>

In a single-arm study of the FreeStyle Libre system (alongside SMBG) in children with type 1 diabetes, sensor data were used to retrospectively determine glycaemic variability in the children during the course of the study.<sup>34</sup> Overall, the children were in the target glucose range of 3.9 mmol/L to 10.0 mmol/L (70 mg/dL to 180 mg/dL) approximately 50% of the time, or an average of 12.1 hours per day. This range was the same both during the day and at night, regardless of whether insulin was administered by insulin pump or by multiple daily injections.<sup>34</sup>

A subgroup analysis of the IMPACT Study noted that there was no significant interaction between participant age and time in hypoglycemia, in keeping with the results for the overall study population.<sup>39</sup>

## Glycated Hemoglobin

There are conflicting reports about the effects of the FreeStyle Libre system on A1C. In the IMPACT Study, although time spent in hypoglycemia was significantly reduced over the six-month period, A1C values remained essentially unchanged and were not statistically significantly different in participants who used

the FreeStyle Libre system alongside SMBG compared with those who used SMBG alone.<sup>26</sup> In contrast, two single-arm studies without control groups reported statistically significant reductions in A1C values following the introduction of the FreeStyle Libre system.<sup>12,30</sup>

## Patient Satisfaction and Compliance

In the studies that reported on measures of patient satisfaction in adults, all found a high level of patient satisfaction with the FreeStyle Libre system.<sup>12,26,28,30,31</sup> In the IMPACT Study, both patient satisfaction and overall treatment satisfaction were statistically significantly higher with the FreeStyle Libre system alongside SMBG compared with SMBG alone, although no difference was detected between groups when they were asked about diabetes distress, fear of hypoglycemia, or worry scores.<sup>26</sup>

In the study evaluating the FreeStyle Libre system in children, sensor application, wear, and use of the device compared with SMBG – based on their experience using both simultaneously – were rated favourably by most children and caregivers (84.3% to 100%).<sup>34</sup> In the second single-arm study in children, the FreeStyle Libre sensor was maintained in place for the full 14-day period in 65% of the children.<sup>35</sup> With the exception of minor discomfort, the system was well-accepted by the majority of children and parents, and would be used again by 60% of the study population.<sup>35</sup>

A subgroup analysis of the IMPACT Study reported in abstract form evaluated whether younger adults (less than 25 years of age) were less likely than older adults (25 years of age and older) to regularly use glucose monitoring devices.<sup>39</sup> After six months of use, there were no significant differences between these subgroups of participants in the number of scans, amount of sensor wear, or sensor-derived glucose results.<sup>39</sup>

## Impact on the Frequency of Self-Monitoring of Blood Glucose

The IMPACT Study also reported on the average number of daily finger-stick tests performed by all participants.<sup>26</sup> In users of the FreeStyle Libre system, testing was reduced from an average of 5.5 finger-stick tests per day during the baseline period to 0.5 tests per day (one test every two to five days) during the treatment phase, compared with 5.6 tests per day with SMBG alone.<sup>26</sup> The mean number of sensor scans per day in users of the FreeStyle Libre system was 15.1 during the



treatment phase.<sup>26</sup> A recent report based on real-world use of the FreeStyle Libre system found that people using the system checked their glucose levels an average of 16 times per day and that average glucose levels, A1C levels, the time spent in hypoglycemia, and instances of hyperglycemia, all decreased as scan rates increased.<sup>40</sup>

### Quality of Life

Various patient-reported outcomes (using instruments such as the Hypoglycemia Fear Survey, Diabetes Treatment Satisfaction Questionnaire, Diabetes Distress Scale [DDS], and the Diabetes Quality of Life Questionnaire [DQoL]) were reported in the IMPACT Study.<sup>26</sup> The results were inconclusive because, for some measures, differences between groups were statistically significant, whereas others were not.<sup>26</sup>

In one single-arm study, quality of life was measured using the DDS; reductions in the mean scale score, and emotional burden and regimen-related distress sub scores, were reported 16 weeks after introducing the FreeStyle Libre system.<sup>12</sup>

### Cost-Effectiveness

Three cost-effectiveness analyses, all reported in abstract form, were identified that compared the FreeStyle Libre system (although the conditions of use were unclear) with conventional SMBG, or continuous blood-glucose testing, in the UK and other European countries.<sup>41-43</sup> The abstracts reported that, compared with self-monitoring or continuous blood-glucose testing, the FreeStyle Libre system may be cost-effective in the context studied (the perspectives were unclear from the abstracts). Given the lack of access to full-text publications, many details of the study design and the reliability of the studies were unclear. No Canadian studies were identified and the aforementioned studies may not be generalizable to the Canadian setting.

### Safety

None of the studies reported serious device-related safety issues or malfunctions associated with the FreeStyle Libre system. In general, most of the adverse events reported for the FreeStyle Libre system were associated with the sensor and/or adhesive (e.g., local irritation, allergy events, itching, redness, rash, and insertion-site symptoms).<sup>26,28,29,34</sup>

Within the FreeStyle Libre Pro operator's manual it is noted that the clinical study forming the basis for the FDA approval of the FreeStyle Libre Pro system<sup>44</sup> found that, when the device

indicated glucose values at or below 60 mg/dL (3.3 mmol/L), indicating hypoglycemia, 40% of the time those values were actually in the range of 81 mg/dL to 160 mg/dL (4.5 mmol/L to 8.9 mmol/L).<sup>7</sup> The operator's manual states that interpretation of readings should therefore be based only on "trends and patterns analyzed over time, using the reports available (per the intended use)."<sup>7</sup>

Contraindications to the use of the FreeStyle Libre system are that the sensor must be removed before having a magnetic resonance imaging or computed tomography scan, or high-frequency electrical heat (diathermy) treatment, as the effects of these interventions on the performance of the FreeStyle Libre system have not been evaluated.<sup>7</sup> Furthermore, caution should be taken when the system is used with other implanted medical devices such as pacemakers, as the performance of the system when used concurrently has not been evaluated.<sup>7,45</sup>

## Concurrent Developments

Various non-invasive glucose monitors are currently in development or are awaiting regulatory approval. The GlucoTrack DF-F (Integrity Applications, Ashkelon, Israel) works in a manner similar to that of a pulse oximeter. It consists of a small sensor that is clipped to the earlobe and connected to a hand-held control and display unit.<sup>46</sup> The NovioSense (Novio Tech Campus, Nijmegen, Netherlands) is a small glucose sensor placed in the eye to continuously measure glucose levels in the tears.<sup>46</sup> It is anticipated that it may enter the market in 2018. The OrSense NBM-200G (OrSense, Petah Tikva, Israel) is a finger sensor that uses changes in the red and near-infrared spectrum of light passed through the finger to correlate with, and detect changes in, glucose concentrations.<sup>46</sup>

## Implementation Issues

The FreeStyle Libre system generates a large volume of data that may be overwhelming for the reader (whether health care professionals or consumers), although presenting the data as an ambulatory glucose profile may mitigate this issue for some users.<sup>10,47</sup>

Wearing the sensor could cause skin irritations or it could be perceived as unsightly.<sup>21</sup> Patient satisfaction and sensor wear-and-tear are important considerations, as one study reported that continuous glucose monitoring sensors were only worn

57% of the time by adults with type 1 diabetes enrolled in a randomized controlled trial to assess impaired awareness of hypoglycemia.<sup>48</sup> One of the single-arm studies of the FreeStyle Libre system reported that the sensor did not record any results in five patients (6.8%) because of primary sensor failure, despite being in place for 14 days.<sup>29</sup> In addition, 12 sensors (16.4%) had less than five days of data – either because they fell off or were removed early.<sup>29</sup>

Because the FreeStyle Libre Pro sensor must be replaced every 14 days by a health care provider, this may impact the number of clinician office visits for the person using the system.

For both continuous and flash glucose monitoring systems, because measurements are taken from interstitial fluid and not blood, there is a lag time in measurement of up to 15 minutes.<sup>22,49</sup> The lag time is longest if the glucose levels are changing rapidly (e.g., after eating, dosing of insulin, or exercising); therefore, it is still necessary to do a finger-stick and capillary blood-glucose test if a change in treatment is being contemplated.

There are no reusable components in the FreeStyle Libre system other than the reader. According to the operations manual, the sensor should not be reused and is not suitable for re-sterilization.<sup>7</sup> The sensor reader should be cleaned between patient use.<sup>7</sup>

As there is no patient interaction with the FreeStyle Libre Pro system, patients do not require training on the use of the system. This would change if the consumer version of the FreeStyle Libre system becomes available in Canada.

With the FreeStyle Libre Pro system, the clinic or physician's office is required to purchase only one FreeStyle Libre Pro reader, which can be used for multiple patients.

## Final Remarks

Flash glucose monitoring has been described as occupying a clinical space between continuous glucose monitoring and SMBG.<sup>23</sup> In principle, flash glucose monitoring using the FreeStyle Libre Pro system could enable a reduction in self-monitoring with finger sticks and capillary blood-glucose testing, depending on the circumstance. It is important to note that, although the need for routine finger sticks may be diminished, they are still required if a change in therapy (such as an adjustment of insulin dose) is being contemplated or if hypoglycemia is suspected.

For children, pain and discomfort of finger sticks and the need to wake up in the night to test blood-glucose levels when nighttime hypoglycemia is a concern, are challenges related to frequent self-monitoring.<sup>18</sup> The FreeStyle Libre system may reduce this inconvenience for children with type 1 diabetes who require intensive glucose monitoring; however, in North America, it is not currently approved for use in children.

Several studies are underway that may provide further information to inform the place of flash glucose monitoring within the current recommended diabetes management strategy.

Table 1: Performance and Test Characteristics of the FreeStyle Libre Flash Glucose Monitoring System

Study	Design	Comparator	MARD	Results of Error Grid Analysis <sup>a</sup>	Other Outcomes	Notes
Aberer et al. (2017) <sup>33</sup>	<ul style="list-style-type: none"> <li>N = 12 adult pts with T1DM</li> <li>Prospective</li> <li>FSL with 2 CGM systems (Dexcom and Medtronic) in same pts × 12 hours</li> </ul>	Plasma BG	Overall: <ul style="list-style-type: none"> <li>FSL vs. venous BG: 13.2%</li> <li>Dexcom vs. venous BG: 16.8%</li> <li>Medtronic vs. venous BG: 21.4%</li> </ul>	Parkes error grid percentage of overall paired results for FSL in: <ul style="list-style-type: none"> <li>zone A: 85.7%</li> <li>zones A or B: 100%</li> </ul> for Dexcom in: <ul style="list-style-type: none"> <li>zone A: 83.6%</li> <li>zones A or B: 99.3%</li> </ul> for Medtronic in: <ul style="list-style-type: none"> <li>zone A: 71.1%</li> <li>zones A or B: 98.6%</li> </ul>	Reported MARD after exercise, hypoglycemia, euglycemia, and hyperglycemia; and all sensors performed less accurately during hypoglycemia and best during hyperglycemia	<ul style="list-style-type: none"> <li>Venous BG levels were measured by laboratory analyzer every 5 minutes × 12 hours</li> <li>Funding by the European Commission</li> </ul>
Bailey et al. (2015) <sup>28</sup>	<ul style="list-style-type: none"> <li>N = 72 adult pts with T1DM or T2DM</li> <li>Retrospective</li> <li>FSL in same pts × 14 days</li> </ul>	Capillary BG	<ul style="list-style-type: none"> <li>FSL vs. CBG: 11.4%</li> <li>FSL vs. venous BG: 12%</li> </ul>	Consensus error grid percentage of paired results for FSL in: <ul style="list-style-type: none"> <li>zone A: 86.7%</li> <li>zones A or B: 99.7%</li> </ul> Clarke error grid percentage of paired results for FSL in: <ul style="list-style-type: none"> <li>zone A: 85.5%</li> <li>zones A or B: 99.0%</li> </ul>	Mean lag time between FSL and venous BG was 4.5 min. ± 4.8 min. (r <sup>2</sup> = 0.95)	<ul style="list-style-type: none"> <li>Venous BG levels were measured by laboratory analyzer during 3 in-clinic visits</li> <li>Funding by Abbott Diabetes Care</li> </ul>
Bonora et al. (2016) <sup>27</sup>	<ul style="list-style-type: none"> <li>N = 8 adult pts with T1DM</li> <li>Prospective</li> <li>FSL × 14 days</li> </ul>	CGM	<ul style="list-style-type: none"> <li>FSL vs. CGM: 18.1% ± 14.8%</li> <li>FSL vs. SMBG: 16.6% ± 11.6%</li> </ul>	Clarke error grid percentage of paired results for FSL in: <ul style="list-style-type: none"> <li>zone A: 62.4%</li> <li>zones A or B: 91.6%</li> </ul>	<ul style="list-style-type: none"> <li>FSL and CGM: r<sup>2</sup> = 0.76</li> <li>FSL and SMBG: r<sup>2</sup> = 0.86</li> </ul>	<ul style="list-style-type: none"> <li>Funding by the University of Padua</li> </ul>

Study	Design	Comparator	MARD	Results of Error Grid Analysis <sup>a</sup>	Other Outcomes	Notes
Ji et al.(2017) <sup>31</sup>	<ul style="list-style-type: none"> <li>• N = 45 adult pts with T1DM or T2DM</li> <li>• Prospective</li> <li>• FSL (2 sensors per patient) × 14 days</li> </ul>	Capillary BG or venous YSI (BG)	<ul style="list-style-type: none"> <li>• FSL vs. CBG: 10.0%</li> <li>• FSL vs. venous BG: 10.7%</li> </ul>	<p>Consensus error grid percentage of paired results for FSL in:</p> <ul style="list-style-type: none"> <li>• zone A – <ul style="list-style-type: none"> <li>◦ vs. CBG: 87.0%</li> <li>◦ vs. venous BG: 82.6%</li> </ul> </li> <li>• zones A or B – <ul style="list-style-type: none"> <li>◦ vs. CBG: 99.9%</li> <li>◦ vs. venous BG: 99.9%</li> </ul> </li> </ul> <p>Clarke error grid percentage of paired results for FSL in:</p> <ul style="list-style-type: none"> <li>• zone A – <ul style="list-style-type: none"> <li>◦ vs. CBG: 88.8%</li> <li>◦ vs. venous BG: 85.1%</li> </ul> </li> <li>• zones A or B – <ul style="list-style-type: none"> <li>◦ vs. CBG: 99.5%</li> <li>◦ vs. venous BG: 99.1%</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Mean lag time between FSL and venous BG was 3.1 minutes (95% CI: 2.5 to 4.3)</li> <li>• FSL and CBG: <math>r^2 = 0.94</math></li> <li>• FSL and venous BG: <math>r^2 = 0.95</math></li> </ul>	<ul style="list-style-type: none"> <li>• Venous BG levels were measured by laboratory analyzer during 3 in-clinic visits</li> <li>• Funding by Abbott Diabetes Care</li> </ul>
Schierenbeck et al. (2016) <sup>32</sup>	<ul style="list-style-type: none"> <li>• N = 26 adult pts undergoing cardiac surgery</li> <li>• Prospective</li> <li>• FSL and MD-CGM in same pts over mean of 23.7 hours</li> </ul>	Arterial blood analyzed using blood gas analyzer	<ul style="list-style-type: none"> <li>• MD-CGM range: 2.5% to 12.6%</li> <li>• FSL range: 12.0% to 52.1%:</li> </ul>	<p>Clarke error grid percentage of paired results for FSL in:</p> <ul style="list-style-type: none"> <li>• zone A: 18.9%</li> <li>• zone A or B: 99.1%</li> </ul> <p>and for MD-CGM in:</p> <ul style="list-style-type: none"> <li>• zone A: 94%</li> <li>• zone A or B: 100%</li> </ul>	Both systems followed the trend of true BG (as per arterial blood gas analysis) well, but FSL repeatedly underestimated the BG value	Funding by Mats Kleberg Foundation and the Signe and Olof Wallenius Foundation

Study	Design	Comparator	MARD	Results of Error Grid Analysis <sup>a</sup>	Other Outcomes	Notes
Edge et al. (2017) <sup>34</sup>	<ul style="list-style-type: none"> <li>N = 89 children (4 to 17 years) with T1DM</li> <li>Prospective</li> <li>FSL for 14 days</li> </ul>	Capillary BG	FSL vs. CBG: 13.9%	Consensus error grid percentage of paired results in: <ul style="list-style-type: none"> <li>zone A: 83.8%</li> <li>zones A and B: 99.4%</li> </ul>	Pts in the target BG range approximately 50% of the time (mean 12.1 hours/day)	Funding by Abbott Diabetes Care

BG = blood glucose; CBG = capillary blood glucose; CGM = continuous blood-glucose monitoring; CI = confidence interval; Dexcom = Dexcom G4 Platinum continuous glucose monitoring system; FSL = FreeStyle Libre system; MARD = mean absolute relative difference; MD-CGM = intravascular microdialysis continuous glucose monitoring; Medtronic = Medtronic MiniMed 640G insulin pump; pts = patients; SMBG = self-monitoring of blood glucose; T1DM/T2DM = type 1 and type 2 diabetes mellitus; vs. = versus; YSI = Yellow Springs Instrument Company.

<sup>a</sup>Error grid analysis pairs glucose samples in five zones (A, B, C, D, and E).<sup>32</sup> Values in zone A are within 20% of the reference value and differences would not result in a different clinical decision. Values in zone B exceed a 20% difference from the reference value, but the difference is unlikely to result in a different clinical decision. Therefore, the more values in zones A and B, the higher the clinical accuracy of the test method relative to the reference method.

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