



Flash Forward: A review of flash glucose monitoring

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Flash Forward:**A review of flash glucose monitoring**

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Novelty Statement:

- The Freestyle Libre is a novel interstitial flash glucose monitor designed to replace finger-stick glucose tests, available in the UK National Health Service, subject to local health authority approval, from November 2017.
- In this narrative review, we summarise the current evidence on HbA1c, hypoglycaemia and quality of life from randomised and observational studies.
- Device accuracy data are presented, both stand alone and in comparison to existing continuous glucose monitors and blood glucose meters
- We discuss advantages, disadvantages, adverse events and summarise key practice/safety areas aimed at helping clinicians and funders to make informed decisions about its future role in diabetes management.

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8 Medtronic, Animas, Roche, Sanofi, Insulet and Novo Nordisk, serving on advisory
9 panel for Abbott Diabetes Care, Roche, Sanofi, Minimed Medtronic, Animas and
10 Novo Nordisk, grants to attend educational meetings from Sanofi, Novo Nordisk and
11 Takeda. EGW has received speaker honoraria from Abbott Diabetes Care,
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13 has served on advisory panels for Abbott Diabetes Care, Eli Lilly, Sanofi Aventis,
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Abstract:

The FreeStyle Libre flash glucose monitor became available on prescription (subject to local health authority approval) in all four nations of the United Kingdom from November 2017, a watershed moment in the history of diabetes care. Calibration free, the FreeStyle Libre is a disc worn on the arm for 14 days which is designed to largely replace the recommended 4-10 painful finger-stick blood glucose tests required each day for the self-management of diabetes. This review discusses clinical data from randomised and observational studies, considers device accuracy metrics and deliberates its popularity and the potential challenges that this new device brings to diabetes care in the UK. In randomised trials, FreeStyle Libre use is associated with a reduction in hypoglycaemia and, in observational studies, improvements in HbA1c. User satisfaction is high and adverse events are low. Accuracy of the FreeStyle Libre is comparable to currently available real-time continuous glucose monitors in adults, children and during pregnancy; the cost of the FreeStyle Libre is lower. Glucose data can be visualised in multiple devices and platforms, summarised in an ambulatory glucose profile to aid pattern recognition and insulin dose adjustment. There is a need for appropriate education, of both users and health care professionals, to harness the full benefits. Further randomised studies to assess the long-term impact on HbA1c, particularly in those with high baseline HbA1c and specific age groups such as adolescence and young adults are warranted. The potential impact on complications, is yet to be realised.

Introduction:

Type 1 diabetes is a demanding lifelong condition. It requires individuals to measure blood glucose multiple times a day, facilitating insulin dose adjustment in the unrelenting endeavour to achieve normoglycaemia and minimise the future risk of micro and macrovascular complications [1]. Despite major progress in the care of people living with Type 1 diabetes, many fail to achieve modern glycaemic targets. A key barrier in achieving near normal glucose levels is this need for frequent finger-stick blood glucose monitoring, perhaps only second to the risk and fear of hypoglycaemia[2]. Pain and inconvenience are recognised reasons for non-adherence with self-monitoring of blood glucose [3, 4].

Remarkably, self-monitoring of blood glucose (SMBG) has only been an option since the 1970s [5]. Its introduction was met with controversy. Despite Sonksen reporting “insulin dosage and type were found to be much easier and more predictable than with urine-glucose analysis...hypoglycaemic episodes were less frequent, 70% of patients preferred blood-tests to urine tests and 92% would like to buy their own meter if the price was right” it was not until the 1980's that uptake became more widespread. Blood glucose monitoring is now accepted as the standard of care with NICE (NG17) recommending 4-10 measurements per day [6].

In 1999 MiniMed received FDA approval for the first retrospective continuous glucose monitor (CGM) device in the USA [7]. Since then, a number of retrospective and real-time CGM options have been introduced including MiniMed iPro, Enlite 2, Enlite Enhanced, Enlite 3 (Medtronic Inc, Northridge, CA, USA), DexCom STS (Short Term Sensor), Dexcom 3, 7, Gen 4 and 5 (Dexcom Inc, San Diego, CA, USA), and Navigator I and II (Abbott Diabetes Care, Alameda, CA, USA). These devices have been evaluated in a range of studies which have demonstrated consistent use of real-time CGM (rtCGM) is associated with improvements in HbA1c and reductions in hypoglycaemia [8, 9]. However, widespread adoption of these devices has been hampered by several factors including cost, accuracy of earlier devices and user acceptability.

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3 Three years ago, in 2014 a new category of device was born: the FreeStyle Libre
4 Flash Glucose Monitoring System (Abbott Diabetes Care, Alameda, CA). The
5 FreeStyle Libre device is a white disc, worn on the arm for 14 days. As implied by
6 the term “flash glucose monitoring” the user can obtain glucose results instantly by
7 scanning the glucose sensor with the reader, or their mobile phone, producing real-
8 time on-demand glucose data. A recent International Consensus on CGM has
9 coined the term ‘intermittently viewed CGM’ (iCGM) to describe flash glucose
10 monitoring [10]. While both rtCGM and the FreeStyle Libre will allow users to
11 monitor interstitial glucose levels, only rtCGM will alarm to alert users to the potential
12 risk of hypoglycaemia or hyperglycaemia. With the FreeStyle Libre, such trends can
13 only be viewed after physically scanning the sensor. A further contrast between
14 rtCGM and the FreeStyle Libre is the need for rtCGM systems to be calibrated at
15 regular intervals using finger-stick glucose levels. The FreeStyle Libre device, which
16 utilises wired enzyme technology, is factory calibrated and does not need finger-stick
17 glucose calibration during use, with stability of the sensor up to 14 days.
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29 Abbott provided users with the option of direct on-line purchase of the FreeStyle
30 Libre, without prior health care professional approval. This, combined with the
31 relatively low cost and advertising led to a demand which exceeded the
32 manufacturer’s expectations. Shortly after launch, orders were suspended while a
33 new factory was built. In this review, we aim to explore the reasons underlying the
34 popularity of this device, discuss the clinical data, accuracy and challenges that this
35 new device brings to diabetes care in the UK. To provide readers with most up to
36 date information we have included both published papers as well as conference
37 abstracts (Table 1). Data presented in some conference abstracts are preliminary in
38 nature.
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47 **Randomised controlled trials (Table 1):**

48 The largest study to evaluate FreeStyle Libre is the IMPACT randomised controlled
49 multicentre European trial [11]. This study included 239 participants with well
50 controlled (HbA1c \leq 59 mmol/mol, 7.5%) Type 1 diabetes and intact awareness of
51 hypoglycaemia, a third of which used CSII therapy. FreeStyle Libre use was
52 associated with a 38% reduction in time spent in hypoglycaemia (<3.9 mmol/l) with
53 no change in total daily insulin dose. The reduction in hypoglycaemia was achieved
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3 within 2 weeks, despite no training on glucose data interpretation and no health care
4 professional contact during this period, suggesting that users intuitively understood
5 how to react to the data (Figure 1). There was an increase in glucose time in range
6 combined with a reduction in glycaemic variability. HbA1c was unchanged. FreeStyle
7 Libre users were scanning 15/day on average, a behaviour sustained over the 6
8 month follow up. FreeStyle Libre utilisation was high at >90% with high treatment
9 satisfaction. It is important to highlight that those with impaired awareness of
10 hypoglycaemia (IAH) were not included in IMPACT.
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17 Reddy et al from London have assessed the FreeStyle Libre in a randomised, non-
18 masked parallel group study compared to rtCGM (Dexcom G5) in people with Type 1
19 diabetes who had experienced a severe hypoglycaemic event in the last 12 months
20 or had impaired awareness of hypoglycaemia (IAH) (Gold score \geq 4) [12]. After a 2-
21 week run in, 40 participants using intensified multiple daily injections were
22 randomised to either Dexcom G5 rtCGM or FreeStyle Libre for 8 weeks. The
23 reduction in percentage time spent in hypoglycaemia <3.3 mmol/l was significantly
24 greater in those using the Dexcom G5 rtCGM compared to FreeStyle Libre (-4.3%,
25 $p=0.0006$). However, there was no significant difference in the Gold score or HbA1c
26 from baseline to end point between the groups. They concluded that rtCGM has
27 significantly greater benefit in those with IAH than FreeStyle Libre. These findings
28 lend support to the NICE Type 1 diabetes in adults (NG17) recommendations for the
29 use of rtCGM use in those who have either recurrent severe hypoglycaemia or loss
30 of awareness of hypoglycaemia [6].
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41 The FreeStyle Libre has also been assessed in those with Type 2 diabetes on
42 intensive insulin therapy in a large multi-centre European study of 224 participants
43 [13]. Despite less frequent sensor scans than were seen in IMPACT (8 vs 15 per
44 day), time in hypoglycaemia (<3.9mmol/l) reduced by 0.47 ± 0.13 h/day compared
45 with controls, representing a 43% reduction in time spent in hypoglycaemia. HbA1c
46 was unchanged. Treatment satisfaction was higher in users and no device related
47 serious adverse events were reported, suggesting that flash glucose monitoring also
48 offers a suitable replacement to SMBG in those with Type 2 diabetes who are on
49 intensive insulin therapy.
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Observational studies (Table 1)

Adults:

A range of observational studies have evaluated the FreeStyle Libre. Dover et al prospectively assessed the FreeStyle Libre in 25 participants and described improved glucose control, reduced hypoglycaemia and improved quality of life [14]. The mean HbA1c of $8.0 \pm 0.14\%$ (64 mmol/mol) reduced to $7.5 \pm 0.14\%$ (59 mmol/mol) after 16 weeks. Those with a baseline HbA1c $>7.5\%$ (58 mmol/mol) experienced a greater $-0.59 \pm 0.15\%$ reduction. There was a significant reduction in hypoglycaemia and diabetes distress. A key behavioural change associated with FreeStyle Libre use was an increase in those delivering the insulin bolus 15-20 minutes pre-meal as per recommendations. McKnight and Gibb, subsequently reported FreeStyle Libre use in approximately 3% of their Type 1 diabetes clinic population in Edinburgh [15]. FreeStyle Libre use was associated with a significant change in HbA1c versus non users (-0.2% versus $+0.1\%$, respectively). Of those with a HbA1c $>7.5\%$ ($>58 \text{ mmol/mol}$), 32% of FreeStyle Libre reached target HbA1c compared to only 9.8% of non-users ($p < 0.001$).

A study in Israel of 31 people with poorly controlled Type 1 or Type 2 diabetes noted an HbA1c decrease of $1.33 \pm 0.29\%$ after 8 weeks of FreeStyle Libre [16]. For those who continued using the device ($n=27$), the change was maintained for 24 weeks ($1.21 \pm 0.42\%$; $p = 0.009$).

Holcombe et al (conference abstract) assessed the FreeStyle Libre in a small group of 13 people with Type 1 diabetes [17]. Mean HbA1c reduced from 75 (9.0%) to 65 (8.1%) mmol/mol, with increased time in target (29 vs 24%) and reduced hypoglycaemia (82 vs 95 minutes). All subjects demonstrated a reduction in their PAID (Problem Areas in Diabetes) scores. Glucose monitoring increased from 3 finger-stick tests per day to 11 scans per day. They also commented in their abstract that the device facilitated virtual contact and support.

Children and young adults:

Campbell et al. evaluated the use of FreeStyle Libre as a replacement for SMBG in young people (4-17 years) ($n=76$, 58% CSII users, 46% males age 10.3 ± 4.0 years,

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3 baseline HbA1c $7.9\pm 1.0\%$ (63 mmol/mol), T1D duration 5.4 ± 3.7 years with Type 1
4 diabetes in a single arm European multi-centre trial [18]. After 2 weeks' baseline
5 masked (blinded) wear, participants used FreeStyle Libre for 8 weeks. Time in range
6 (70-180 mg/dL) and HbA1c significantly improved vs. baseline, 1.0 ± 2.8 hours/day
7 (mean \pm SD), $p=0.0056$ and $-0.4\pm 0.6\%$, $p<0.0001$ respectively. Mean FreeStyle Libre
8 scan frequency was 12.9/day, whereas SMBG reduced from a median of 8.0
9 (baseline) to 1.0/day during open use. Diabetes Treatment Satisfaction
10 Questionnaire showed improved treatment satisfaction for parents ($n=70$), 21.7 ± 6.6
11 (mean change score \pm SD), $p<0.0001$ and teens (13+years) ($n=23$), 18.7 ± 5.6 ,
12 $p<0.0001$.

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21 These studies add to the growing clinical perception that FreeStyle Libre is desirable
22 and beneficial for people living with Type 1 diabetes. However, it is important to note
23 that improvements seen during observational studies cannot be solely ascribed to
24 the FreeStyle Libre device as other factors such as additional education or simply
25 being observed may contribute to improvements. Nonetheless, the authors have
26 observed striking reductions in HbA1c with FreeStyle Libre use in those with very
27 poorly controlled diabetes (HbA1c >86 mmol/mol, 10%) who are doing little or no
28 glucose monitoring. Unfortunately, such individuals are rarely included in clinical
29 studies.

30 31 32 33 34 35 36 37 **User satisfaction and insights:**

38 **Adults:**

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40 User feedback on FreeStyle Libre is generally very positive. Olafsdottir et al.
41 explored treatment experience in 58 adults with Type 1 diabetes [19]. FreeStyle
42 Libre scored favourably with scores of 9/10 for 'My experience of the FreeStyle Libre
43 was very positive' and 9.4/10 for 'I would like to use FreeStyle Libre in my daily life'.
44 They reported it was easy to use (9.8/10), easy and trouble free insertion (9.1/10)
45 and importantly they felt it was easy to interpret information on the FreeStyle Libre
46 screen (9.6/10). Authors also compared their findings for FreeStyle Libre user
47 satisfaction (overall score 8.22 to 9.8 out of 10) with their earlier studies of Dexcom
48 G4 and Enlite sensor which used the same questions (overall score 72.5 to 90 out of
49 100 for Dexcom G4 and 42.1 to 86.1 out of 100 for Enlite).

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3 Ish-Shalom reported their experience in Israel with the FreeStyle Libre [16]. All users
4 (n = 31) were highly satisfied and stated that they would like to use flash glucose
5 monitoring in the future. In addition, users unanimously stated that it was easy to use
6 and painless. Health care professionals reported that the data presentation,
7 particularly the ambulatory glucose profile (AGP), was an outstanding tool, enabling
8 better and easier control of glucose levels. [16].
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14 **Children / Young adults:**

15 Families of children who have used the device are generally satisfied. McPhater et al
16 contacted the families of 19 FreeStyle Libre users. They reported that the sensor
17 was easy to insert and was an easier method of checking glucose than SMBG
18 (Preliminary analysis, conference abstract) [20]. The majority found the sensor lasted
19 14 days. Most perceived that glucose control had improved during use due to
20 improved awareness of glucose levels, and changes in self-management behaviour,
21 particularly around hypoglycaemia. Although trend data was useful most users did
22 not alter self-management as a result. Confidence in nocturnal glucose control was
23 improved. One quarter did not continue to use the sensors due to limited sensor
24 duration and blood glucose discrepancies compared to SMBG.
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33 Another user evaluation in the paediatric population also described high user
34 satisfaction with the majority rating the device favourably for sensor application
35 (84.3–92.1%), sensor wear and use (87.2–100%), comparing use to SMBG (85.4–
36 97.5%) [21].
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42 **Real-world use of FreeStyle Libre:**

43 The manufacturer has evaluated the association of the real-world scanning with
44 FreeStyle Libre and glucose control measures. A large number of readers
45 (n=50,831) with 279,446 sensors (86.4 million monitoring hours by 63.8 million
46 scans) were analysed [22] (Figure 2). Users performed an average of 16.3 scans per
47 day (median:14, interquartile range: 10-20). Estimated HbA1c reduced ($p<0.001$) as
48 scan rate increased, from 8.0% (64 mmol/mol) to 6.7% (50 mmol/mol) from the
49 lowest (mean 4.4 scans/day) to highest (mean 48.1 scans/day) groups, while time
50 below 3.9, 3.0 and 2.5 mmol/l decreased by 15%, 40% and 49%, respectively (all
51 $p<0.001$).
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Adverse events:

As one would expect, most adverse events were related to the medical grade adhesives used to secure the sensor for 14 days. Sensor-wear-related symptoms were recorded as adverse events in the IMPACT trial if the effects were severe and lasted for >7 days, or if the user required prescription medication for the event to resolve [11]. IMPACT reported 13 device-related adverse events in 10/119 users in the intervention arm which were related to wearing the sensor, and were categorised as mild (three cases), moderate (four cases), and severe (six cases). Six of 120 intervention arm and one of 121 control arm participants withdrew from the study due to adverse events. For participants with adverse events involving skin symptoms, symptoms (including severe) were resolved by use of barrier products (eg, Cavilon spray) or drug therapy (eg, zinc ointment, Fenistil gel, or hydrocortisone cream), or by relocating the device to another area [23]. Investigations have since identified isobornyl acrylate as the likely agent causing contact dermatitis [24]

Since completion of the IMPACT trial, minor design changes have been made to FreeStyle Libre. These changes are expected to improve breathability of the skin that is in contact with the sensor and to facilitate the exclusion of moisture between the sensor–skin interface [23]. During the children’s study, five device related adverse events were reported in five (6%) participants: allergic reaction, blister, pink mark/scabbing and abrasion on sensor removal [21].

Assessing sensor accuracy

There are no consensus guidelines for the best metric to assess of accuracy of rtCGM and flash glucose monitoring devices. As a result, a variety have been used, the majority of which are affected by glucose excursions so comparing across studies may lead to misleading conclusions [25]. Ideally different sensors should be compared in the same individual exposed to same glucose fluctuations.

Accuracy of CGM devices is expressed using standards originally designed for assessing the accuracy of SMBG [26]. Numerical accuracy is based on mean or median absolute relative deviation (ARD) (sensor glucose-reference glucose/reference glucose*100) and/or International Standardization Organisation criteria

(ISO)[27]. Glucose data are non-normally distributed so median ARD is usually lower than mean ARD. In 2013 International Standardization Organisation criteria (ISO) (ISO: 15197:2013) were drawn up, requiring that 95% of blood glucose results should be within ± 0.83 mmol/L of laboratory results at concentrations of under 5.6 mmol/L or within $\pm 15\%$ of laboratory results at concentrations of 5.6 mmol/L or more [27]. In contrast, clinical accuracy is often expressed using the Clarke or consensus error grid analyses [28, 29]. Error grid analyses assign a specific level of clinical risk to any possible error. Each point on the grid (true glucose, measured glucose) is associated with 1 of 5 risk levels. In both, Clarke or consensus error grid error grids, zones A and B errors denote minimal risk to the user.

Accuracy of FreeStyle Libre:

Accuracy in adults:

FreeStyle Libre provides interstitial glucose results without the need for finger-stick glucose calibrations. This removes the risk of sensor inaccuracies due to user errors such as not washing hands before a glucose test or delay in glucose entry[30].

In a study funded by the manufacturer, Bailey et. al. assessed the accuracy of FreeStyle Libre in seventy-two study participants with type 1 or type 2 diabetes in four clinical sites in USA [31]. A sensor was inserted on the back of each upper arm for up to 14 days. Three sensor lots were used in the study. There were three scheduled in-clinic visits during the 14-day sensor wear period, where venous blood samples were collected every 15 min over an 8-h period for YSI analyzer (Yellow Springs Instrument, Yellow Springs, OH) reference tests. At least eight capillary glucose tests, using the glucose meter built into the reader, were required to be performed on each day of the sensor wear, both at home and in the clinic.

In total, 13,195 capillary glucose and 12,172 YSI reference (venous) results were paired with sensor glucose results. The percentages of results in Zone A of the Consensus and Clarke Error Grids were 86.7% and 85.5%, respectively. The percentages of sensor results in Zones A and B of the Consensus and Clarke Error Grids were 99.7% and 99.0%, respectively, whereas 86.2% and 82.8% of sensor results were within 0.8 mmol/l or 20% of capillary glucose reference and venous

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3 reference, respectively (percentage within 0.8 mmol/l or 15% of reference data not
4 reported).

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8 The overall mean ARD was 11.4% for sensor results with capillary glucose
9 reference. The overall mean ARD in the clinic alone for sensors' results with capillary
10 glucose reference and with YSI reference was 12.1% and 12%, respectively. Mean
11 ARD was comparable when the reference glucose was below 100mg/dl and above
12 100mg/dl. Looking at the performance of individual sensors approximately 55%
13 appear to have a mean ARD \leq 10% while about 10% of sensors had mean ARD
14 values \geq to 16%. Percentage of sensor glucose levels in Zone A of the Clarke error
15 grid was lower on day 1 (around 72%) compared to day 2 to 14 (85% to 89%).
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22 During an independent study, Olafsdottir et. al. assessed the accuracy of the
23 FreeStyle Libre device in fifty-eight adults with type 1 diabetes for 10–14 days and
24 measured capillary blood glucose levels with the HemoCue blood glucose
25 measurement system at least six times a day simultaneously [19]. For the entire
26 study period, the mean ARD was 13.2%. For glucose values <4 , 4–10, and >10
27 mmol/L, the mean ARD was 20.3%, 14.7%, and 9.6%, respectively. Of note, during a
28 post-hoc analysis authors found that 19.9% of glucose values measured by
29 FreeStyle Libre deviated more than 20%, and 7.9% of glucose values measured by
30 FreeStyle Libre deviated more than 30% from the HemoCue reference. Authors have
31 raised concerns about the clinical impact of such high deviations when used for
32 dosing insulin.
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42 ***Accuracy during OGTT:***

43 Another study by Fokkert et al. has compared the accuracy of FreeStyle Libre during
44 14 day home use and during an oral glucose tolerance test [32]. Interestingly they
45 also compared the accuracy of device when worn in the back of the arm and in the
46 abdomen. Percentage of data points in the zone A of the Clarke error grid was
47 significantly higher when the sensors were worn in the back of the arm (85.5%)
48 compared to abdomen (64%). Authors found the FreeStyle Libre tended to report
49 lower results in lower glucose ranges, and higher results than expected in the higher
50 ranges. Following a standardized glucose load, a slower rise in glucose level was
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3 observed for FreeStyle Libre as compared with reference methods during the first
4 45–60 min after glucose load ingestion.
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7 ***Accuracy in children:***

8 Accuracy of FreeStyle Libre in children has been assessed during a multi-centre UK
9 based study [21]. Those aged 4–17 years, with Type 1 or Type 2 diabetes treated
10 with multiple daily injections of insulin or CSII, and monitoring blood glucose >2/day
11 were eligible to participate. Participants wore the sensor for up to 14 days and were
12 asked to perform four blood glucose tests daily (FreeStyle Optium test strips, Abbott
13 Diabetes Care), each immediately followed by an interstitial fluid glucose sensor
14 measurement (data masked to participants) to allow comparison of results between
15 sensor and blood glucose. Clarke error grid analysis demonstrated 83.8% of results
16 in zone A and 99.4% of results in zones A and B. Overall mean ARD was 13.9%,
17 median ARD was 10.4%. For paired results at lower glucose concentrations, with
18 capillary glucose <5.5 mmol/L (n=1468), mean absolute difference (MAD) was 0.75
19 mmol/L; for paired results at higher glucose concentrations capillary glucose, 5.5 to
20 10.0 mmol/L (n=2090), mean ARD was 13.5%; and capillary glucose >10.0 mmol/L
21 (n=1935), mean ARD was 10.6%.
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33 ***Accuracy in pregnant women:***

34 Scott et. al. have evaluated the accuracy of FreeStyle Libre in 74 women during
35 pregnancy (Type 1 diabetes n=24, Type 2 diabetes n=11 and gestational diabetes
36 n=39, average gestation was 26 weeks, average age was 30 years, and 66.2% using
37 insulin) [33]. The study was conducted across 9 UK sites and 4 in Austria.
38 Compared to capillary glucose, consensus Error Grid analysis showed 88.1% of
39 FreeStyle Libre readings were within zone A and 99.8% were within zones A & B.
40 Overall Mean ARD was 11.8%. Results show good agreement between the
41 FreeStyle Libre and the capillary glucose for pregnant women with diabetes,
42 indicating the device is safe and accurate for use by this population.
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51 ***Head to head comparison with rtCGM and blood glucose meters***

52 Aberer et. al. recently compared the FreeStyle Libre with Dexcom G4 Platinum
53 (Dexcom) and Medtronic MiniMed 640G (Medtronic) systems[34]. A total of 12
54 individuals with Type 1 diabetes were included in a single-centre, open-label study
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3 over 12 hours. Hypo and hyperglycaemia were induced and venous plasma glucose
4 values measured every 5 minutes for 12 hours. The study also included a short bout
5 of exercise (30 minutes, 50% VO₂ max). Across all glycaemic ranges including
6 exercise, FreeStyle Libre exhibited the lowest and Medtronic the highest mean ARD.
7 The systems fulfilled ISO 15197:2013 criteria by 73.2% (FreeStyle Libre), 56.1%
8 (Dexcom) and 52.0% (Medtronic). The mean ARDs (SD) in the entire glycaemic
9 range were 13.2% (10.9) (FreeStyle Libre), 16.8% (12.3) (Dexcom) and 21.4 (17.6)
10 (Medtronic), respectively. All sensors performed less accurately during
11 hypoglycaemia and best during hyperglycaemia.
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19 In another study, Bonora et. al. compared FreeStyle Libre with Dexcom G4 rtCGM
20 sensor upto 14 days in 8 individuals with Type 1 diabetes under usual care
21 conditions [35]. Average glucose profiles and mean ARD versus capillary glucose
22 were broadly similar between the two systems, though the comparative performance
23 varied significantly among individuals. For example, compared with SMBG,
24 participant 5 had a mean ARD of 14.9% with FreeStyle Libre and mean ARD of
25 37.4% with Dexcom G4 sensor. Compared with capillary glucose, range of MARD for
26 FreeStyle Libre among the 8 participants were 10.7 to 20.4% and with Dexcom G4
27 ranged from 7% to 37% indicating marked heterogeneity. There are no head to head
28 studies comparing FreeStyle Libre device with the latest generation of Dexcom G5
29 rtCGM.
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38 The accuracy of the Freestyle Libre, with a MARD of 11.4% is comparable to many
39 commercially available blood glucose meters. Blood glucose meters should fulfil the
40 ISO criteria but when tested independently this was not found to be the case.
41 Ekhlaspour et al. assessed 17 different commercially available glucose meters
42 against the Yellow Springs reference method (YSI 2300) to determine the MARD.
43 The accuracy varied widely between MARD of 5.6% to 20.8%. Overall, 9 of 17
44 meters assessed had a MARD >12%, raising the possibility that some blood glucose
45 meters could potentially be less accurate than the FreeStyle Libre[36]
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54 ***Evaluation of FreeStyle Libre with Potentially Interfering Substances:***

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3 The manufacturer has undertaken tests to evaluate the FreeStyle Libre with 16
4 potentially interfering substances (supplemental table 1) [37]. Testing confirmed no
5 clinically significant interference for the substances tested, with the exception of
6 ascorbic acid and salicylic acid. Taking ascorbic acid may falsely raise and salicylic
7 acid may slightly lower sensor glucose readings. Level of inaccuracy depends on the
8 amount of interfering substance. Detailed information available in supplemental table
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14 15 16 **Summary of accuracy:**

17 In conclusion, FreeStyle Libre appears to have comparable accuracy to currently
18 available rtCGM systems such as Dexcom G4 and may even have superior accuracy
19 to Medtronic Enlite sensors, without the need for calibration. A small number of
20 sensors can have higher MARD levels in the range of 16-20%. None of the currently
21 available interstitial glucose sensors meet the ISO 15197:2013 criteria for capillary
22 glucose meters; although in independent testing, many blood glucose meters also
23 fail this criteria.
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30 31 **Adjunctive vs non adjunctive use:**

32 The term non-adjunctive refers to the use of interstitial glucose data for insulin
33 dosing without the need for additional finger-stick glucose checks. Presently two
34 glucose monitoring systems are licenced for non-adjunctive use in Europe and the
35 USA: Dexcom G5 system and FreeStyle Libre system.
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40 FreeStyle Libre is designed to replace blood glucose testing in the self-management
41 of diabetes including the dosing of insulin except in three main conditions. These
42 are: during rapidly changing glucose values, to confirm sensor-reported
43 hypoglycaemia or impending hypoglycaemia and if symptoms do not correspond
44 with the glucose value displayed. Under these circumstances, the manufacturer
45 advises confirmation with a finger-stick glucose level. Further, Kovatchev and
46 colleagues, using simulation techniques has calculated a minimal accuracy of a
47 mean ARD of $\leq 10\%$ for rtCGM to reach sufficient safety when sensor glucose data
48 are used for insulin dosing decisions [38]. As outlined in above accuracy studies, a
49 small number of FreeStyle Libre sensors will have a MARD $>15\%$ and unless the
50 user cross checks with finger-stick glucose it is not possible to know how an
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3 individual sensor is performing. Accuracy of day 1 of the sensor is lower than other
4 days. A recent statement from the German Diabetes Society, as well as others, have
5 highlighted pros and concerns of using Dexcom G5 / FreeStyle Libre in a non-
6 adjunctive manner[39-41]. FreeStyle Libre users can perform a finger-stick (ideally
7 fasting /when glucose not rapidly changing) to assess sensor accuracy. Also, the
8 Driver and Vehicle Licencing Agency (DVLA) in UK states that blood rather than
9 interstitial glucose should be checked prior to driving [42].
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15 **Challenges:**

16 ***Funding and reimbursement in UK:***

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19 In November 2017, the FreeStyle Libre became available on prescription in the
20 United Kingdom, bringing it into line with several other European countries (France,
21 Belgium, Sweden among others) where FreeStyle Libre is reimbursed. NICE have
22 published a medtech innovation briefing (MIB) on the FreeStyle Libre [43] and has
23 summarised the utility as well as gaps in the evidence base, including the
24 uncertainties around resource impact which depends upon the extent to which
25 improved glucose control translates into fewer complications, reduced emergency
26 admissions and less use of glucose test strips. However, in England funding is
27 subject to local approval. Given the financial pressures on the NHS, there is concern
28 that variation in local policies for funding will result in inequitable access, further
29 widening variation in diabetes care. In an attempt to overcome this, the Regional
30 Medicine Optimisation Committee (RMOC) have published recommendations for
31 funding in select groups. ([https://www.sps.nhs.uk/articles/regional-medicines-
32 optimisation-committee-freestyle-libre-position-statement/](https://www.sps.nhs.uk/articles/regional-medicines-optimisation-committee-freestyle-libre-position-statement/)).
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43 ***Education:***

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45 There is a recognised need for health care professionals to equip themselves with
46 the skills required to support users of both flash glucose monitoring and rtCGM [44].
47 Health care professionals can be reassured that fundamentally, the skills required to
48 make the most of the data are essentially the same principles as intensive insulin
49 therapy: aiming for a basal insulin which keeps the glucose relatively stable over-
50 night, aiming for insulin: carbohydrate ratios which bring the glucose into target by
51 the next meal and insulin sensitivity factors which correct a higher glucose, bringing
52 it into target 4-5 hours later without causing hypoglycaemia. In the authors
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3 experience, flash glucose monitoring is an educational tool. Many adjust basal
4 insulin to minimise nocturnal hypoglycaemia and bolus 15-20 minutes pre-meal to
5 reduce post-prandial hyperglycaemia. These behavioural changes reflect the unique
6 insights continuous glucose data provide vs isolated finger-stick glucose levels.
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10 11 ***Ambulatory Glucose Profile:***

12 Flash glucose data can be displayed as an ambulatory glucose profile (AGP) (Figure
13 3). The AGP displays the data over a 24 hour period with median glucose levels, the
14 25-75th and 10-90th percentiles as well as excursions and the tendency for hypo or
15 hyperglycaemia throughout the day. This display allows for ease of hypothesis
16 generation, while eliminating “noise” from outliers. An expert group in the USA
17 concluded that standardisation of continuous glucose data reporting using the AGP
18 would be of benefit [45] Matthaei et al have since developed a useful consensus
19 statement on the interpretation of the AGP [46].
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28 ***Summary and Personal perspectives:***

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30 From the authors' perspective, FreeStyle Libre is a significant advance in the
31 management of diabetes. Many users describe it as 'life changing'. Key advantages
32 and disadvantages are summarised in Table 2. The FreeStyle Libre allows on
33 demand access to glucose data with no need for calibration and no risk of alarm
34 fatigue. The sensor needs replaced infrequently and has a accuracy similar to
35 rtCGM. FreeStyle Libre data can be visualised in multiple devices and platforms as
36 an AGP to aid pattern recognition and insulin dose adjustment. We encourage
37 appropriate education of both users and health care professionals, to harness the full
38 benefits. As a more affordable option for continuous glucose data, we support
39 access to this technology for all people with diabetes who are treated with intensive
40 insulin therapy. Further randomised studies to assess the long-term impact on
41 HbA1c, particularly in those with high baseline HbA1c and specific age groups such
42 as adolescence and young adults are warranted.
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References

1. Daneman D. Type 1 diabetes. *Lancet* 2006; **367**:847-858.
2. Murata T, Tsuzaki K, Yoshioka F, Okada H, Kishi J, Yamada K, *et al.* The relationship between the frequency of self-monitoring of blood glucose and glycemic control in patients with type 1 diabetes mellitus on continuous subcutaneous insulin infusion or on multiple daily injections. *Journal of diabetes investigation* 2015; **6**:687-691.
3. Vincze G, Barner JC, Lopez D. Factors associated with adherence to self-monitoring of blood glucose among persons with diabetes. *Diabetes Educ* 2004; **30**:112-125.
4. Mostrom P, Ahlen E, Imberg H, Hansson PO, Lind M. Adherence of self-monitoring of blood glucose in persons with type 1 diabetes in Sweden. *BMJ open diabetes research & care* 2017; **5**:e000342.
5. Sonksen PH, Judd SL, Lowy C. Home monitoring of blood-glucose. Method for improving diabetic control. *Lancet* 1978; **1**:729-732.
6. National Institute for Health and Care Excellence. Type 1 diabetes in adults: diagnosis and management. <https://www.nice.org.uk/guidance/ng17> 2015.
7. Bode BW, Sabbah H, Davidson PC. What's ahead in glucose monitoring? New techniques hold promise for improved ease and accuracy. *Postgrad Med* 2001; **109**:41-44, 47-49.
8. Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, *et al.* Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial. *JAMA* 2017; **317**:371-378.
9. Lind M, Polonsky W, Hirsch IB, Heise T, Bolinder J, Dahlqvist S, *et al.* Continuous Glucose Monitoring vs Conventional Therapy for Glycemic Control in Adults With Type 1 Diabetes Treated With Multiple Daily Insulin Injections: The GOLD Randomized Clinical Trial. *JAMA* 2017; **317**:379-387.
10. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, *et al.* International Consensus on Use of Continuous Glucose Monitoring. *Diabetes Care* 2017; **40**:1631-1640.
11. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kroger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. *Lancet* 2016; **388**:2254-2263.
12. Reddy M, Jugnee N, El Laboudi A, Spanudakis E, Anantharaja S, Oliver N. A randomized controlled pilot study of continuous glucose monitoring and flash glucose

1
2
3 monitoring in people with Type 1 diabetes and impaired awareness of hypoglycaemia.
4 *Diabet Med* 2017.

5
6 13. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline JP, Rayman G. Use of Flash
7 Glucose-Sensing Technology for 12 months as a Replacement for Blood Glucose Monitoring
8 in Insulin-treated Type 2 Diabetes. *Diabetes therapy : research, treatment and education of*
9 *diabetes and related disorders* 2017; **8**:573-586.

10
11 14. Dover AR, Stimson RH, Zammitt NN, Gibb FW. Flash Glucose Monitoring Improves
12 Outcomes in a Type 1 Diabetes Clinic. *J Diabetes Sci Technol* 2017; **11**:442-443.

13
14 15. McKnight JA, Gibb FW. Flash Glucose Monitoring is associated with improved
15 glycaemic control but use is largely limited to more affluent people in a UK diabetes centre.
16 *Diabet Med* 2017; **34**:732.

17
18 16. Ish-Shalom M, Wainstein J, Raz I, Mosenzon O. Improvement in Glucose Control in
19 Difficult-to-Control Patients With Diabetes Using a Novel Flash Glucose Monitoring Device. *J*
20 *Diabetes Sci Technol* 2016; **10**:1412-1413.

21
22 17. Holcombe A, Karunakaran V, Streeting J, Addington H, Smyth S. Trial of FreeStyle
23 Libre in a local service: impact on diabetes outcomes. *Diabetic Med* 2017; **34**:160-160.

24
25 18. Campbell F, Kordonouri O, Murphy N, Stewart C. FreeStyle Libre Use for Self-
26 Management of Diabetes in Children and Adolescents. *Diabetes* 2017; **66 Suppl. 1A**:LB28-
27 LB28.

28
29 19. Olafsdottir AF, Attvall S, Sandgren U, Dahlqvist S, Pivodic A, Skrtic S, *et al.* A Clinical
30 Trial of the Accuracy and Treatment Experience of the Flash Glucose Monitor FreeStyle
31 Libre in Adults with Type 1 Diabetes. *Diabetes Technol Ther* 2017; **19**:164-172.

32
33 20. McPhater A, Gardiner M, Modgil G. The impact of the Libre device for families and
34 children with Type 1 diabetes. *Diabetic Med* 2017; **34**:104-104.

35
36 21. Edge J, Acerini C, Campbell F, Hamilton-Shield J, Moudiotis C, Rahman S, *et al.* An
37 alternative sensor-based method for glucose monitoring in children and young people with
38 diabetes. *Archives of disease in childhood* 2017; **102**:543-549.

39
40 22. Dunn T, Xu Y, Hayter G. Evidence of a strong association between frequency of flash
41 glucose monitoring and glucose control measures during real-world usage. *Diabetes*
42 *technology & therapeutics* 2017; **19, Suppl. 1**:A12-A12.

43
44 23. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kroger J, Weitgasser R. Cutaneous
45 adverse events related to FreeStyle Libre device - Authors' reply. *Lancet* 2017; **389**:1396-
46 1397.

47
48 24. Herman A, Aerts O, Baeck M, Bruze M, De Block C, Goossens A, *et al.* Allergic
49 contact dermatitis caused by isobornyl acrylate in Freestyle(R) Libre, a newly introduced
50 glucose sensor. *Contact dermatitis* 2017.

- 1
2
3 25. Bailey TS. Clinical Implications of Accuracy Measurements of Continuous Glucose
4 Sensors. *Diabetes Technol Ther* 2017; **19**:S51-S54.
5
- 6 26. Clarke W, Kovatchev B. Statistical tools to analyze continuous glucose monitor data.
7 *Diabetes Technol Ther* 2009; **11 Suppl 1**:S45-54.
8
- 9 27. International Organization for Standardization. ISO 15197:2013, In vitro diagnostic
10 test systems -- Requirements for blood-glucose monitoring systems for self-testing in
11 managing diabetes mellitus. <https://www.iso.org/standard/54976.html> 2013.
12
- 13 28. Clarke WL, Cox D, Gonder-Frederick LA, Carter W, Pohl SL. Evaluating clinical
14 accuracy of systems for self-monitoring of blood glucose. *Diabetes Care* 1987; **10**:622-628.
15
- 16 29. Parkes JL, Slatin SL, Pardo S, Ginsberg BH. A new consensus error grid to evaluate
17 the clinical significance of inaccuracies in the measurement of blood glucose. *Diabetes Care*
18 2000; **23**:1143-1148.
19
- 20 30. Hoss U, Budiman ES. Factory-Calibrated Continuous Glucose Sensors: The Science
21 Behind the Technology. *Diabetes Technology & Therapeutics* 2017; **19**:S44-S50.
22
- 23 31. Bailey T, Bode BW, Christiansen MP, Klaff LJ, Alva S. The Performance and
24 Usability of a Factory-Calibrated Flash Glucose Monitoring System. *Diabetes Technology
25 & Therapeutics* 2015; **17**:787-794.
26
- 27 32. Fokkert MJ, van Dijk PR, Edens MA, Abbes S, de Jong D, Slingerland RJ, *et al.*
28 Performance of the FreeStyle Libre Flash glucose monitoring system in patients with type 1
29 and 2 diabetes mellitus. *Bmj Open Diabetes Research & Care* 2017; **5**.
30
- 31 33. Scott E, Kautzky-Willer A. Accuracy evaluation of Freestyle Libre Flash Glucose
32 Monitoring System when used by pregnant women with diabetes. *Diabetes technology &
33 therapeutics* 2017; **Volume 19, Supplement 1**:A84-A84.
34
- 35 34. Aberer F, Hajnsek M, Rumpler M, Zenz S, Baumann PM, Elsayed H, *et al.* Evaluation
36 of subcutaneous glucose monitoring systems under routine environmental conditions in
37 patients with type 1 diabetes. *Diabetes Obesity & Metabolism* 2017; **19**:1051-1055.
38
- 39 35. Bonora B, Maran A, Ciciliot S, Avogaro A, Fadini GP. Head-to-head comparison
40 between flash and continuous glucose monitoring systems in outpatients with type 1
41 diabetes. *Journal of endocrinological investigation* 2016; **39**:1391-1399.
42
- 43 36. Ekhlaspour L, Mondesir D, Lautsch N, Balliro C, Hillard M, Magyar K, *et al.*
44 Comparative Accuracy of 17 Point-of-Care Glucose Meters. *J Diabetes Sci Technol* 2017;
45 **11**:558-566.
46
- 47 37. Abbott Diabetes Care. Evaluation of Abbott Diabetes Care FreeStyle Libre Flash
48 Glucose Monitoring System with Potentially Interfering Substances: Document number
49 EDMS025771. *Data on file* 2017.
50
51
52
53
54
55
56
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58
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3 38. Kovatchev BP, Patek SD, Ortiz EA, Breton MD. Assessing sensor accuracy for non-
4 adjunct use of continuous glucose monitoring. *Diabetes Technol Ther* 2015; **17**:177-186.
5
6 39. Freckmann G, Schluter S, Heinemann L, Diabetes Technology Working Group of the
7 German Diabetes S. Replacement of Blood Glucose Measurements by Measurements With
8 Systems for Real-Time Continuous Glucose Monitoring (rtCGM) or CGM With Intermittent
9 Scanning (iscCGM): A German View. *J Diabetes Sci Technol* 2017; **11**:653-656.
10
11 40. Shapiro AR. Nonadjunctive Use of Continuous Glucose Monitors for Insulin Dosing:
12 Is It Safe? *J Diabetes Sci Technol* 2017; **11**:833-838.
13
14 41. Price D. Commentary Regarding Shapiro, "Nonadjunctive Use of Continuous
15 Glucose Monitors for Insulin Dosing: Is It Safe?". *J Diabetes Sci Technol* 2017; **11**:839-841.
16
17 42. Driver and Vehicle Licensing Agency (DVLA). Assessing fitness to drive – a guide for
18 medical professionals.
19 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/596959/assessing-fitness-to-drive-a-guide-for-medical-professionalspdf 2017.
20
21
22
23
24 43. National Institute for Health and Care Excellence. FreeStyle Libre for glucose
25 monitoring. <https://www.nice.org.uk/advice/mib110> 2017.
26
27
28 44. Diabetes UK. Diabetes UK Consensus Guideline for Flash Glucose Monitoring.
29 https://www.diabetes.org.uk/resources-s3/2017-09/1190_Flash%20glucose%20monitoring%20guideline_SB_V9%5B4%5Dpdf?_ga=213708337613396328401505301182-20569738801505301182 2017.
30
31
32
33 45. Bergenstal RM, Ahmann AJ, Bailey T, Beck RW, Bissen J, Buckingham B, *et al.*
34 Recommendations for standardizing glucose reporting and analysis to optimize clinical
35 decision making in diabetes: the Ambulatory Glucose Profile (AGP). *Diabetes Technol Ther*
36 2013; **15**:198-211.
37
38
39 46. Matthaai S, Antuñña DeAlaiz R, Bosi E, Evans M, Geelhoed-Duijvestijn N, Joubert M.
40 Consensus recommendations for the use of Ambulatory Glucose Profile in clinical practice.
41 *The British Journal of Diabetes* 2014; **14**:153-157.
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Table 1: Summary of randomised and observation studies of Freestyle Libre evaluating changes in the HbA1c and/or hypoglycaemia

Reference	Study population	Intervention and duration	Outcomes
Randomised Controlled Trials			
Bolinder et. al (11)	Adults with T1D, HbA1c \leq 7.5% and intact awareness of hypoglycaemia.	Parallel groups. FSL (n=120) vs. self-monitoring (n=121) for 6 months.	38% reduction in time in hypoglycaemia (<3.9 mmol/l). No change in HbA1c. FSL reduced glucose variability; mean number of scan 15/day and mean number of SMBG 0.5/day.
Reddy et. al. (12)**	Adults with T1D with impaired awareness of hypoglycemia or severe hypoglycaemia.	Parallel groups (n=40) FSL vs. real-time CGM (Dexcom G5) for 8 weeks.	Higher reduction in % time in hypoglycaemia (<3.3mmol/l) from baseline to endpoint with G5 – median difference between groups -4.3%, p=0.006.
Haak et. al. (13)	Adults with T2D with HbA1c level 7.5–12.0%, on intensive insulin therapy.	Parallel groups FSL (n=149) vs. self-monitoring (n=75) for 6 months.	43% reduction in time in hypoglycaemia (<3.9 mM, p<0.01). No change in HbA1c. FSL reduced glucose variability; mean number of scan 8/day and mean number of SMBG 0.3/day.
Observational Studies			
Dover et. al. (14)	Adults with T1D	16 weeks, Use of FSL under routine care (n=25)	Mean HbA1c reduced from of 8.0% to 7.5% (-0.48%, p<0.01). Episodes of hypoglycaemia <4.0 mM reduced from 17 in the first 2 weeks to 12 in the final 2 weeks of use (p=0.19). Significant reduction in the Diabetes Distress Scale (p<0.01).
McKnight et. al (15)	Adults with T1D	Routine clinic use of FSL(n=100 current users). Duration of follow-up not available.	HbA1c reduced by -0.2% compared with a 0.1% rise in non-users. HbA1c >7.5% sub-group, 32.2% of FSL users and 9.8% of non-users (p< 0.01) had reached target at their last clinic visit.
Ish-Shalom et. al (16)	Adults; T2D and T1D HbA1C \geq 7.5%	12 to 24weeks use of FSL (n=31).	HbA1c reduced by -1.3% at 8 weeks (p< 0.01). For those patients who continued using FSL (n = 27), the change was maintained for 24 weeks, -1.2% (p<0.01).
Holcombe et	Patients with T1D	FSL use - Duration of	HbA1c improved from 9.0% to 8.1%. Time spent in target

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al (17)**		follow up not specified (n=13).	increased (24% vs 29%), time spent below target reduced (95min vs 82min).
Campbell et al (18)**	Children (4 to 17 years) with T1D	2 weeks masked use (baseline) followed by 8 weeks open label use (n=76).	Time in range (3.9 to 10 mM) improved vs. baseline by 1.0±2.8 hours/day, p<0.01. HbA1c improved vs. baseline, -0.4±0.6%, p<0.01. Scan frequency of FSL was 13/day, SMBG reduced from 8.0 to 1.0/day during open use.

**Conference Abstract.

FSL= Freestyle Libre; T1D= Type 1 Diabetes; T2D=Type 2 Diabetes; SMBG=Self monitored blood glucose

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Table 2: Advantages and disadvantages of flash glucose monitoring.

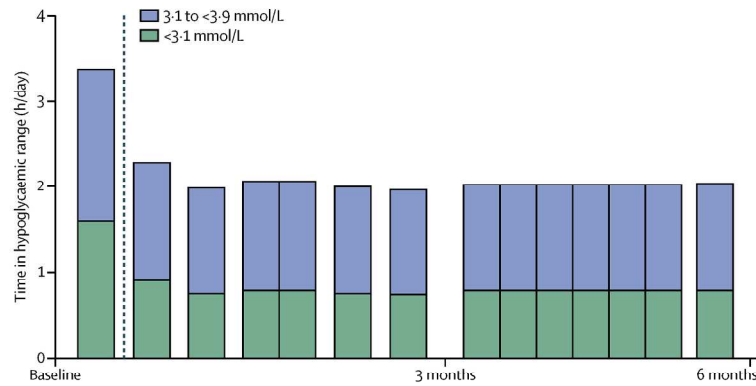
	Advantages	Disadvantages
Set up and ease of use	User friendly, easy to set up and insert and generally well tolerated [31]. The 'on demand' glucose data may be preferable for some to real-time continuous glucose monitoring (rtCGM) which features alarms to alert to rising/falling glucose.	Some experience skin reactions related to the adhesive or sensor may fall off within the intended 14 day use.
Hypo-glycaemia	FreeStyle Libre leads to a reduction in biochemical hypoglycaemia in patients with both Type 1 and Type 2 diabetes [11,13]. In the IMPACT trial this occurred within the first 2 weeks of use, despite no training on glucose data interpretation.	There is a ~5 minute lag between FreeStyle Libre and blood glucose. Therefore, falling blood glucose may read higher on the reader than blood glucose. In this instance blood glucose should be relied on. Dexcom G5 rtCGM is likely to be superior to FreeStyle Libre for reducing hypoglycaemia in those with impaired awareness (12).
Glucose control	FreeStyle Libre facilitates frequent glucose monitoring which has been associated with lower HbA1c [2,4]. IMPACT randomised controlled trial demonstrated increased time in range and reduced glycaemic variability while observational studies have reported reduction in HbA1c [14,15,16, 17, 18]. Provides insight into glycaemic variability, easily viewed as an ambulatory glucose profile in clinic. Due to low cost can also be used intermittently, for instance for 2 weeks pre-clinic to provide detailed insight into glucose levels.	FreeStyle Libre use is associated with lower HbA1c in observational studies. However, to date no randomised controlled trials have demonstrated a reduction in HbA1c. Bolus calculators are useful tools which assist with accurate insulin dose calculation. The bolus calculator in the Freestyle Libre reader requires the user to perform a finger-stick blood glucose measurement to use the calculator; interstitial glucose values cannot be entered.
Finger-stick blood glucose monitoring	FreeStyle Libre reduces the need for the NICE recommended 4-10 blood glucose finger sticks per day; in IMPACT SMBG reduced from 5.5 to 0.5 tests per day.	Blood glucose must be relied on when: <ul style="list-style-type: none"> • Glucose levels are rapidly changing • If hypoglycaemia or impending hypoglycaemia is displayed • When scanned glucose results do not correspond with user symptoms • To use the FreeStyle Libre reader bolus calculator • For driving as per UK Driver and Vehicle Licencing Agency (DVLA) regulations
Post-prandial glucose	FreeStyle Libre use provides information on post prandial glucose excursions, leading to a significant increase in user delivery of insulin bolus 15-20 minutes pre-meal (14).	Users need to consider the ~4 hour action profile of rapid acting insulin analogues when contemplating the need for a post-meal insulin correction dose which carries the risk of insulin stacking and

		hypoglycaemia.
Driving	FreeStyle Libre trend arrows allow corrective action to be taken, facilitating informed decision making and hypoglycaemia avoidance as an adjunct to blood glucose monitoring in relation to driving.	The Driver and Vehicle Licencing Agency (DVLA) in the UK currently requires that blood glucose, not interstitial glucose, must be checked and relied on prior to driving (38).
Accuracy	Accuracy is similar to other available real CGM systems, (no data comparing dexcom G5) although there are few head to head studies published (33, 34). The FreeStyle Libre mean absolute relative deviation (MARD) is lower than many commercially available blood glucose meters (36).	To ensure the accuracy of the FreeStyle sensor, a blood glucose in the fasting state can be useful for cross-reference as a small number of sensors may have MARD > 15%.
Calibration	The FreeStyle Libre does not require calibration which is a benefit; calibration of real time CGM requires 2 or more blood glucose measurement per day. Calibration alarms can be an unwelcome intrusion.	In the event of an inaccurate FreeStyle Libre sensor, it cannot be calibrated and should be returned to the manufacturer for a replacement.
Alarms	No alarms, therefore no risk of 'alarm fatigue'.	The lack of alarms is a concern for those with impaired awareness of hypoglycaemia who are likely to be dependent on alarms to alert them to impending hypoglycaemia (12).
14 day wear	Replacing the sensor every 14 days, compared to every 6 or 7 days can reduce the 'diabetes burden' associated with the number of tasks needed for diabetes management. Most report sensor insertion as quick and painless [31].	Once placed on the skin, FreeStyle Libre cannot be moved for 14 days which may limit clothing options for some who prefer to have the device hidden from view. A minority will experience skin reactions to the FreeStyle Libre or sensor may fall off before 14 days
Data display	The LibreLink app allows integrated use of FreeStyle Libre with android smart phones. The mobile phone is used to scan the sensor which reads glucose data using near field communication (NFC), removing the need to carry an additional reader. LibreLink can be used to review glucose data, the ambulatory glucose profile (AGP) and estimated HbA1c, facilitating user review of results without the need to download data to a computer. The LibreLinkUp up also allows parents and carers to 'follow' the user and their glucose results remotely using the app on their mobile phone.	Users should carry blood glucose monitoring equipment with them as back up.
Cost	Flash glucose monitoring in the UK NHS will cost £35 per sensor, less than half the price of alternative CGM systems, potentially making it more accessible to a greater proportion of people living with diabetes. At this price it is cost equivalent to ~8 blood glucose tests per day.	None of the currently available randomised controlled trials have demonstrated cost savings in terms of reduced acute admissions, HbA1c or long term complications.

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For Peer Review

Figure 1. IMPACT study, Bolinder et. al. (11): Time in hypoglycaemic range during baseline and treatment phase in the intervention group using flash glucose monitoring. Grouped bars indicate analysis performed over 2 week periods and then averaged. Dashed line marks the start of the intervention.



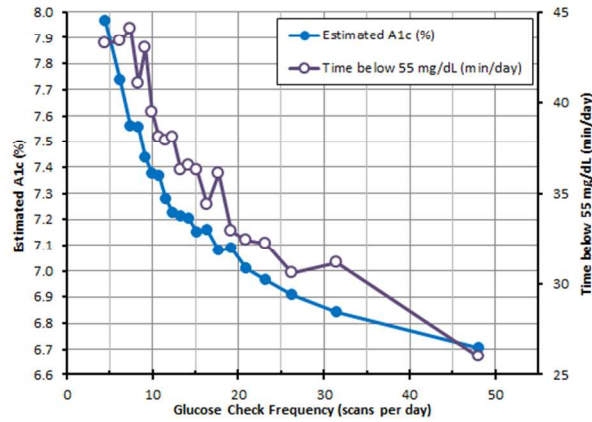
Reprinted from the Lancet, Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kroger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet 2016; 388:2254 with permission from Elsevier.

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338x190mm (230 x 230 DPI)

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Figure 2. Dunn et al. Real world data from >51,000 FSL readers demonstrating an association between glucose monitoring frequency and estimated HbA1c [22]



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Figure 2. Dunn et al. Real world data from >51,000 FSL readers demonstrating an association between glucose monitoring frequency and estimated HbA1c [22].

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Figure 3. Example of an Ambulatory Glucose Profile.

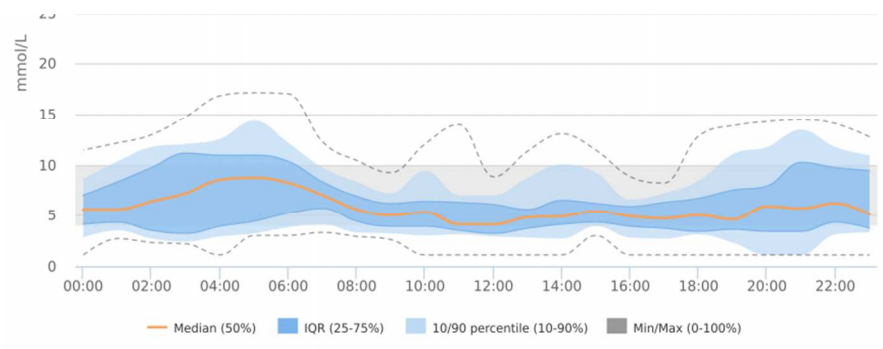


Figure 3. Example of an Ambulatory Glucose Profile.

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Supplemental Table 1: Reproduced with permission from Abbott Diabetes Care

Evaluation of Abbott Diabetes Care FreeStyle Libre Flash Glucose Monitoring System with Potentially Interfering Substances:

Prepared by Abbott Diabetes Care R&D Technical & Scientific Support Team, UK

The FreeStyle Libre system has been evaluated with 16 potentially interfering substances. The table below lists the substances evaluated, the therapeutic or normal concentration, and the test concentration of the substance

Substance	Upper Limit of Therapeutic Concentration or Normal Concentration		Interferent Test Concentration	
	mmol/L	mg/dL	mmol/L	mg/dL
Paracetamol	0.20	3	1.32	20
Ascorbic Acid	0.114	2.01	0.34	6.02
Bilirubin (unconjugated)	0.02	1.23	0.34	20.01
Cholesterol	5.18	201.24	13.0	503.1
Creatinine	0.115	1.3	2.65	30
Dopamine Hydrochloride	1.96 µmol/L	0.03	0.85	13
Ephedrine	0.6 µmol/L	0.01	0.61	10
Ibuprofen	0.340	7	2.42	49.96
L-Dopa	0.010	0.2	0.25	5
Methyldopa	0.036	0.75	0.12	2.5
Salicylic Acid	2.17	29.95	4.34	59.89
Tetracycline	0.011	0.5	0.09	4
Tolazamide	0.16	5	3.21	100
Tolbutamide	0.40	10.8	3.70	100
Triglycerides	5.6	500	34.0	3000
Uric Acid	0.476	8	1.40	23.52

Interference testing confirmed there was no clinically significant interference for all the substances tested except for ascorbic acid and salicylic acid. Therefore, a limitation has been included in the product labelling for these substances:

Taking ascorbic acid while wearing the sensor may falsely raise your sensor glucose readings. Taking salicylic acid may slightly lower your sensor glucose readings. The level of inaccuracy depends on the amount of the interfering substance active in your body. Ascorbic acid is an endogenous substance, baseline circulating levels of plasma ascorbic acid have been reported as 1.00 mg/dL (0.057 mmol/L) for subjects not taking ascorbic acid supplements¹. Common recommended daily amounts (RDA) of ascorbic acid range from 60 to 120 mg. Additional analysis of the effects of supplements resulting in ascorbic acid levels above normal circulating levels was performed². The data suggests that ascorbic acid intake at the maximum of the RDA range may elevate sensor glucose by up to 4.3 mg/dL (0.24 mmol/L) at low glucose concentrations and by up to 1.3% at high glucose concentrations (when compared to glucose results in the presence of baseline circulating ascorbic acid levels).

The use of salicylic acid for analgesic purposes (1g dose) results in plasma salicylic acid concentrations of 1.7 – 8.0 mg/dL (0.12 – 0.58 mmol/L)³ such doses may decrease sensor results by up to 5.5%²

¹Perrone G, Hideshima T, Ikeda H, Okawa Y, Calabrese E, Gorgun G, Santo L, Cirstea D, Rajee N, Chauhan D, Baccarani M, Cavo M, Anderson KC. Ascorbic acid inhibits antitumor activity of bortezomib in vivo. *Leukemia* 2009;23:1679-1686.

²Data on file Abbott Diabetes Care.

³Brantmark B, Wahlin-Boll E, Melander A. Bioavailability of Acetylsalicylic Acid and Salicylic Acid from Rapid- and Slow-Release Formulations, and in Combination with Dipyridamol. *European Journal of Clinical Pharmacology* 1982;22:309-314.