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Continuous Glucose Monitoring for Hypoglycaemia in Children: Perspectives in 2020

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Key words

Continuous Glucose Monitoring, Hypoglycaemia, Children, Hyperinsulinism, Machine Learning

Abstract

Hypoglycaemia in children is a major risk factor for adverse neurodevelopment with rates as high as 50% in hyperinsulinaemic hypoglycaemia (HH). A key part of management relies upon timely identification and treatment of hypoglycaemia. The current standard of care for glucose monitoring is by infrequent fingerprick plasma glucose testing but this carries a high risk of missed hypoglycaemia identification. High-frequency Continuous Glucose Monitoring (CGM) offers an attractive alternative for glucose trend monitoring and glycaemic phenotyping but its utility remains largely unestablished in disorders of hypoglycaemia. Attempts to determine accuracy through correlation with plasma glucose measurements using conventional methods such as Mean Absolute Relative Difference (MARD) overestimate accuracy at hypoglycaemia. The inaccuracy of CGM in true hypoglycaemia is amplified by calibration algorithms that prioritise hyperglycaemia over hypoglycaemia with minimal objective evidence of efficacy in HH. Conversely, alternative algorithm design has significant potential for predicting hypoglycaemia to prevent neuroglycopenia and consequent brain dysfunction in childhood disorders. Delays in the detection of hypoglycaemia, alarm fatigue, device calibration and current high cost are all barriers to the wider adoption of CGM in disorders of hypoglycaemia. However, machine learning, artificial intelligence and other computer-generated algorithms now offer significant potential for further improvement in CGM device technology and widespread application in childhood hypoglycaemia.

Background

Home testing of glucose was first made available to patients in 1925 by boiling a sample of urine with chemical reagents on the stove. Fortunately, steady progress was made throughout the 20th century with the development of Clinistix and Dextrostix to dipstick test urine and blood respectively¹. In 1979 Karam et al described their use of an early form of Continuous Glucose Monitoring (CGM) linked to a Dextrose infusion during insulinoma resection². However, progress with CGM stalled until 1999 when the Medtronic MiniMed Continuous Glucose Monitoring system was released. This allowed patients with Type 1 Diabetes Mellitus (T1DM) to monitor glucose profiles at home, retrospectively view them with their doctor and adjust treatment accordingly³. Rapid progress has been made over the last two decades with several devices now available for use in patients with diabetes (Table 1) including non-adjunctive devices wearable for 10 days with no requirement for calibration⁴.

Modern CGM devices consist of a wearable sensor that automatically measures glucose in interstitial fluid (ISF) several times a minute and reports an average every few minutes to a wireless receiver nearby. ISF glucose reacts with an enzymatic technology to liberate electrons and generate an electric current. Via a continuously shifting algorithm, this electrical current is converted to a blood glucose value⁵. This algorithm is finetuned via patient or factory calibration to ensure accuracy over the recording periods⁶ (Figure 1).

CGM devices are currently only licensed for patients with diabetes and most studies have targeted a reduction in HbA1C rather than hypoglycaemia episodes as a clinical end point. In this paper, we review the evidence available for the use of CGM in hypoglycaemia disorders and discuss future developments in this field.

The problem of hypoglycaemia

Recurrent episodes of hypoglycaemia lead to inadequate cerebral glucose supply. In the developing brain of neonates and infants, this can lead to serious long-term neurological impairments ranging from mild neurocognitive dysfunction to epilepsy, hemiparesis and severe mental retardation⁷.

Several studies have demonstrated the significant impact of neonatal hypoglycaemia on long-term neurodevelopmental outcomes^{8,9} with evidence of persistent MRI changes in these patients¹⁰.

Hypoglycaemia secondary to hyperinsulinism is even more devastating, with almost 50% of children demonstrating neurological impairments¹¹ regardless of the persistence of disease¹². Hypoglycaemia is difficult to predict in HH as insulin secretion is dysregulated, and recurrent hypoglycaemia blunts the clinical signs and counter-regulatory responses, resulting in unpredictable and often silent hypoglycaemia episodes¹³. While this paper concentrates mainly on non-diabetic disorders of hypoglycaemia it is worth noting the potentially devastating impact of hypoglycaemia on those with diabetes sometimes leading to “dead in bed” syndrome¹⁴. The cornerstone of management is the timely identification and treatment of such episodes. The current standard of care is patient observation and intermittent fingerpick testing, but this provides no details of trends and risks missing hypoglycaemia between infrequent tests. CGM provides a highly attractive alternative to monitor glucose trends and reduce the risk of hypoglycaemia events, but current evidence is scant in relation to both accuracy and efficacy in hypoglycaemia disorders in children.

Accuracy of CGM at hypoglycaemia

Accuracy of CGM devices is described as either analytical or clinical. Clinical accuracy is based on the mean accuracy of performance or the number of outliers⁵. Analytical accuracy can be reported as either trend or point accuracy, of which Mean Absolute Relative Difference (MARD) is the most commonly reported measure⁵. MARD is the average of the absolute error between all CGM values and is routinely calculated and reported as a key metric by manufacturers.

Despite significant improvements in CGM since first-generation devices¹⁵, accuracy is still not clinically acceptable at hypoglycaemia values^{16,17} and more so in non-diabetic patients: The best published MARD value in neonates at hypoglycaemia is 16%¹⁸ with only 86% of values in Zone A (allowing clinically correct decisions) on a Modified Clarke Error Grid (MCEG)¹⁹ (Figure 2). In the clinical setting these values are suboptimal when compared to manufacturers figures for patients with diabetes^{20,21}. Importantly, under controlled conditions elevated insulin has been reported to increase the discrepancy between recorded ISF glucose and plasma glucose in healthy volunteers and therefore further worsens the accuracy of hypoglycaemia-detection²². The mechanism underlying this has been suggested to be related to enhanced uptake of interstitial glucose by adipocytes that is not fully compensated for by increased delivery of glucose from the microcirculation²². In patients with HH, these observations are highly relevant to the accuracy of CGM in reporting hypoglycaemia as default profiles will over-report incidences of low glucose levels.

While MARD is the most commonly reported measure of accuracy, it is a cross-sectional value and does not account for the benefits of trend direction and rate of change that CGM can provide⁵. MARD is reported from clinical trial data but this represents the accuracy of the system within that context and should not be understood as a precise value to be used outside of the trial²³. In practice, this means that from a single MARD value it is not possible to ensure meter accuracy will meet ISO criteria, but it is highly likely if MARD falls between 3.25 and 5.25%²⁴. MARD is calculated by the sensitivity and specificity of values but without reference to the timing of hypoglycaemia alarms. If predictive alarms occur too early or late this will result in false positive or negative errors, thereby impairing the detection of clinical hypoglycaemia²⁵. In contrast to MARD, a more useful report of accuracy for a hypoglycaemia device is the false positive and negative rate as this will provide an indication of how effectively the device can alert the user to impending hypoglycaemia. A useful device should have false negative and positive rates of <5% and <10% respectively and will typically require a MARD of <7.5% to achieve this²⁵. Using such criteria, accuracy in reported studies are well short of expected standards with a false positive rate of 60% in neonates²⁶ and a false negative rate of 35% in HH²⁷ detracting from the confidence of use in clinical practice.

The accuracy of a CGM device is intrinsically linked to the calibration algorithm used to convert the raw electrical signal to a meaningful plasma glucose value. The accuracy of CGM at hypoglycaemia values is particularly affected by the calibration algorithm²⁸. If calibration is performed at a time of rapid glucose change (as is common in patients with dysregulated insulin secretion and wide glucose variability in HH and Glycogen Storage Disease) algorithm performance is seriously compromised⁵. Conversely, MARD is significantly improved if calibration glucose values are as widely spaced as possible²⁹.

Accuracy of CGM can also be improved through the alteration of associated algorithms. Guerra et al and Zavitsanou et al both showed an improvement in CGM accuracy using an online, automatically updating algorithm^{30,31}. Acciaroli et al demonstrated that a reduction in the frequency of calibrations from once a day to no calibration caused only a small deterioration in accuracy when using an automatically updating algorithm³². Personalisation of calibration algorithms further improves accuracy; King et al reported a Mean Absolute Difference of 24.5mg/dL during hypoglycaemia with raw sensor data but demonstrated an improvement to 11.5mg/dL with modelling of group interstitial glucose dynamics and to 10.4mg/dL when individual interstitial glucose dynamics were used. Finally, accuracy is improved when calibration is performed within the setting it is trying to detect. Monsod et al demonstrated no significant difference between sensor and plasma glucose levels when calibration was performed during hyperinsulinaemic, hypoglycaemic conditions²². These successes demonstrate the potential of algorithm personalisation for improvement of hypoglycaemia prediction and application potential for childhood hypoglycaemia.

Efficacy of CGM for detection and prevention of hypoglycaemia

Diabetes

Early trials of CGM in patients with diabetes showed a good reduction in HbA1C^{33,34} but did not demonstrate the expected³⁵ reductions in hypoglycaemia incidence³⁶. This may have been because trials were designed to reduce HbA1C rather than time in hypoglycaemia. More recently, trials

specifically investigating hypoglycaemia in patients with diabetes have shown good improvements³⁷, particularly overnight³⁸ and when using predictive alarms³⁹.

However, CGM devices have been designed for use in patients with diabetes where there is an established relationship between plasma glucose, insulin administration and carbohydrate intake. Despite sound theoretical reasons to anticipate benefit from CGM devices, their utility and efficacy in other conditions of hypoglycaemia cannot be assumed.

Neonates

Several studies have investigated the use of CGM in neonatal intensive care and found it well tolerated⁴⁰. Reducing painful procedures results in improved cognitive and motor function outcomes⁴¹ and is facilitated by CGM. Between 25%-80% of neonates demonstrated hypoglycaemia on CGM that had gone undetected by heelprick glucose monitoring^{42,43}. However, despite CGM also reducing the duration of hypoglycaemia episodes⁴⁴, the long-term clinical benefit is uncertain as undetected hypoglycaemia was not associated with worse neurological outcomes at follow up at two years of age⁴⁵.

GSD

Patients with Glycogen Storage Diseases (GSDs) are at risk of significant hypoglycaemia when exposed to prolonged fasting. Euglycaemia is maintained through regular meals, the provision of uncooked cornstarch, and often continuous overnight feeding, usually via gastrostomy⁴⁶. Several studies have demonstrated the utility of CGM in detecting unsuspected hypoglycaemia, particularly overnight^{47,48}. This allows for the manipulation of diet and treatment and, in GSD I, has been shown to be associated with reduced time in hypoglycaemia, reduction in liver size and improvement in biochemical markers of disease control⁴⁹. Further studies have since demonstrated improved detection of both hypoglycaemia and hyperglycaemia in patients with GSD I, III and IX⁵⁰. Intermittent use of CGM for glucose profiling in GSD patients is now standard practice in many centres as it provides a more accurate picture of a patient's daily profile than is obtainable from an inpatient stay. This has proven to be popular with families and has shown not only an improvement in markers

of disease severity but also increased adherence with medication and improved patient quality of life⁵¹.

Adrenal Insufficiency

Hypoglycaemia is considered a rare problem for adults with adrenal insufficiency (AI)⁵². However, in those with morning headache or discomfort, overnight CGM revealed hypoglycaemia in 5 out of 6 patients who had all demonstrated normal morning fingerprick glucose testing⁵³. Increasing hydrocortisone dosing not only prevented overnight hypoglycaemia but also resulted in resolution of symptoms⁵³.

Hypoglycaemia is a more frequent problem in children with AI but is still difficult to detect on routine monitoring. Cambiaso et al studied 11 children with AI and Growth Hormone Deficiency (GHD) who were normoglycaemic on routine testing. CGM revealed severe hypoglycaemia (<2.7mmol/L) overnight in three children, with time in hypoglycaemia ranging from 30 to 150 minutes⁵⁴. Those with hypoglycaemia had a lower daily dose of hydrocortisone (5.9 vs 8.5mg/m²/day, p=0.04) and repeat testing after dose increase revealed resolution of hypoglycaemia⁵⁴. This study demonstrates the added utility of CGM in detecting hypoglycaemia that would have otherwise been overlooked.

Hyperinsulinism

Hypoglycaemia in children with hyperinsulinism is not only unpredictable and often profound but is accompanied by the suppression of alternative fuels and a counterregulatory response. Therefore, children with HH are at an unacceptably high risk of brain injury⁵⁵ irrespective of the permanence of their disease¹². It is well established that the severity of hypoglycaemia in HH determines the extent of brain injury; by contrast, reducing the depth and frequency of hypoglycaemia may protect the vulnerable brain in neonates and infants from the irreversible effects of neuroglycopenia.

There have been no long-term studies on the use of CGM in children with hyperinsulinism to demonstrate unequivocal benefit. Anecdotal reports and case studies have commented on the usefulness of CGM in categorising the extent and degree of hypoglycaemia in children with HH⁵⁶. The

very poor accuracy in this patient group²⁷, may be due to increased discrepancies between plasma and sensor glucose at hyperinsulinaemia²². Despite this, CGM allows for a dynamic view of hypoglycaemia and enables clinicians to measure responses to treatment^{27,57}. Alsaffar et al used a factory-calibrated flash CGM device in a small group of children with HH and reported disappointing hypoglycaemia performance⁵⁸. As in previous studies⁵⁶, parents found glucose trends helpful but were not confident in relying upon CGM glucose levels alone in the regular monitoring of blood glucose⁵⁸.

In adult patients with HH, 28% of those studied had asymptomatic hypoglycaemia detected by CGM and required subsequent treatment alterations⁵⁹. In adult patients with hypoglycaemia secondary to insulinoma, CGM also identified significant hypoglycaemia in patients who were thought to be normoglycaemic. One patient was found to be severely hypoglycaemic ($<2.2\text{mmol/L}$) for 48% of the monitoring period with complete resolution following therapy with Diazoxide⁶⁰. The authors of this study acknowledged the significant impact that CGM had upon the treatment and monitoring of their patients and its superiority over fingerprick glucose monitoring. Similar results have been reproduced elsewhere; Sawyer et al demonstrated a reduction in the number of hypoglycaemic events and visits to the hospital for one patient with insulinoma after use of CGM⁶¹. Multiple centres have demonstrated the utility of CGM for diagnosis and surgical monitoring of patients with insulinomas^{62,63} and to detect hypoglycaemia in adult patients following bariatric surgery^{64,65}.

Acute illness in low-income settings

In low-income countries, paediatric hypoglycaemia is a life-threatening complication of many common diseases such as malaria and malnutrition⁶⁶. In sub-Saharan Africa, up to 7% of all hospital admissions are complicated by hypoglycaemia with an associated increase in the mortality rate from 4% to 20%⁶⁷. Malaria is accompanied by hypoglycaemia in up to 25% of cases⁶⁸ with an increase in the case fatality rate to up to 64% in those with hypoglycaemia⁶⁹. This hypoglycaemia prevalence is likely to be an underestimate as most hospitals in this setting use a single glucose test on admission as their screening and therefore risk missing inpatient hypoglycaemia⁶⁶. In a study of children with

malaria in Mozambique CGM demonstrated significantly more hypoglycaemia than previously thought and allowed better monitoring of severely ill patients at risk of life-threatening hypoglycaemia⁶⁶. However, CGM is expensive and is not routinely available in countries threatened by malaria. It is unlikely that CGM will be the first-line investigation in such countries unless the value of CGM is established beyond doubt and the price of CGM application and consumables reduces through economies of scale.

Problems and barriers to use of CGM

We have outlined the situations in which CGM is used for children with hypoglycaemia and discussed the positive impact it can have upon disease monitoring and even therapeutics. We have previously discussed the issue of accuracy of CGM at hypoglycaemia and here we will outline the other barriers to use of CGM in disorders of hypoglycaemia.

Lag time

The lack of reliability of CGM at hypoglycaemia is not only due to poor point accuracy but also relates to the issue of lag⁷⁰. Lag relates to the time delay between a change in plasma glucose and the reporting of this change by the device. Lag time is comprised of 1) Physiological lag due to the time required for glucose to diffuse from capillaries to the interstitium and is affected by skin blood flow, 2) Sensor reaction time related to the time required for glucose to diffuse from the interstitium into the sensor itself and 3) Sensor signal processing including the moving average filter and an artefact filter to allow data smoothing⁵.

The issue of lag time can result in significant under or overestimation of plasma glucose. When glucose is falling rapidly, lag is large and glucose can be overestimated by as much as 2.2mmol/L⁷¹ resulting in non-treatment of hypoglycaemia. However, this mismatch is highly variable and therefore cannot be reliably corrected by current device algorithms. Lag time can vary from 8-40 minutes depending on the device used, level of glucose, rate of change and skin blood flow⁷¹. Fortuitously, lag time problems may actually be beneficial in the identification of hypoglycaemia in

HH patient population where a spike in insulin and subsequent rapid drop in interstitial glucose is earlier than a slower subsequent decrease in plasma glucose. The lag on the device may, therefore, result in a more accurate reporting of tissue glucose than if there was no lag⁷¹. This may account for the lack of perceived lag reported in some in vivo studies⁷².

Alarms

As previously discussed, one of the primary benefits of CGM is its ability to predict an upcoming hypoglycaemia event using trend information. However, this prediction is only possible if device algorithms are accurate enough to alarm at appropriate times. False-positive and negative rates of 0-100% can be achieved by altering the alarm threshold on a device²⁵. Alarms on CGM devices do help to reduce hypoglycaemia episodes in those with diabetes⁷³ particularly when these alarms are predictive rather than reactive³⁹. However, alarm fatigue is a significant problem in those who use CGM⁷⁴: Patients with hypoglycaemia overnight only wake to 29% of alarms and parents of children with hypoglycaemia only wake to 37%⁷⁵. Furthermore, predictive alarms are based upon the linear correlations of glucose, carbohydrate and insulin in patients with diabetes over short periods and have not been designed for patients with HH who have more unpredictable hypoglycaemia events. Most devices do not contain predictive alarms and rely upon the user to identify impending hypoglycaemia using their judgement to make manual adjustments⁷⁶. Herein lies the potential to automate a glucose correction response to continuous glucose sensing to develop a closed-loop system for childhood hypoglycaemia.

Fingerprick testing

Historically CGM devices have required user calibration via the measurement of fingerpick glucose using a point of care glucometer. While many devices can now self-calibrate, some still require fingerprick calibration and this is a major patient complaint¹ and further source of potential inaccuracy as glucometers used for calibration vary widely and MARD can be as high as 17% in certain devices⁷⁷. The number of fingerprick tests can be reduced to once a day or less when calibration tools are implemented³². The most recent devices such as the Dexcom G6 and Freestyle

Libre are calibrated at production, obviating the need for post-insertion fingerprick plasma glucose calibrations.

Clinician inertia and usability

Physicians are considered one of the major barriers to wider adoption of CGM⁷⁶. Adoption of new technology by clinicians requires a significant investment in time and training for something that is likely to benefit only a small number of their patients. There is very little in the way of formal training available for clinicians using CGM particularly amongst those working with children with non-diabetic hypoglycaemia. There is also a need for continued improvement in the usability of CGM. This is related not only to the speed of connectivity between the sensor and the receiver/cloud storage device, but also the sites at which CGM is worn on the skin – which in neonates is limited, and the length of time that they can be worn. The Advanced Technologies and Treatments for Diabetes (ATTD) Congress devised a consensus recommendation for CGM data utilisation to try to aim interpretation and standardise use⁷⁸. The development of an automated interpretation of CGM data specific to those with hypoglycaemia disorders would go a long way to reducing this particular barrier to wider adoption of CGM.

Cost

In the United Kingdom, CGM is available under certain conditions for those with diabetes. In countries where individuals rely on health insurance to provide cover this situation is even more complicated and access more limited. No CGM manufacturer has a licence for use in hypoglycaemia disorders and correspondingly these are either paid for by patients or individual healthcare departments, usually only for investigative or research purposes. In low-income countries, the cost of CGM is completely prohibitive for all but the most well-off patients⁶⁶.

The future for hypoglycaemia prediction

CGM developments

Current CGM device manufacturers are focused on the use of CGM in patients with Type I and Type II Diabetes Mellitus with current development focusing on expansion to include pregnant women and ease of use for these patient groups. Sensors are likely to be further miniaturised with advancing technology and therefore become less invasive. For example, there are future plans to integrate CGM into contact lenses⁷⁹ and mouth guards⁷⁰ to measure tear and salivary glucose respectively as surrogates of interstitial glucose.

Predictive blood glucose algorithms

Patients have very different physiologies regarding glucose metabolism⁸⁰ and factors affecting blood glucose include but are not limited to: long and short term blood glucose history, insulin secretion/administration, physical activity, dietary intake, body mass index (BMI), stress level, amount of sleep, presence of illness, medications, smoking, menstruation, allergies and altitude⁸¹. CGM devices cannot currently process any of these factors to account for variability related to lifestyle choices.

There are three main types of blood glucose prediction algorithms: Physiological, Data-Driven and Hybrid (Table 2)⁸⁰. These algorithms often use a frequentist approach (regression analysis) to predict a single value but more recently a Bayesian approach (via Machine Learning, Artificial Neural Networks and Deep Learning) has been taken, resulting in a probability distribution for outcomes rather than a single value. Outcomes of all of these algorithms can either be a continuous glucose value or a classification such as the risk of hypoglycaemia⁸⁰ or the certainty/uncertainty of hypoglycaemia. Algorithms with a classification outcome are not suitable for projects such as the artificial pancreas where a continuous variable is required to calculate insulin delivery rate. However, they can provide significant benefit in the prediction of hypoglycaemia in children.

Early attempts at using CGM values to predict future continuous blood glucose values proved very inaccurate: Pappada et al demonstrated an MARD of 22% and a hypoglycaemia detection rate of only 2% using neural network algorithms⁸². Significant improvements have been made with Contreras et al achieving an MARD of 12% and employing a glucose specific cost function which takes in to account the clinical harmfulness of deviations from euglycaemia⁸³. Most recently Li et al used deep neural networks to achieve an MARD of 5% and 10% when their algorithm was tested on simulated and real patient data respectively⁸⁴. Due to large inter-patient variability, those algorithms which incorporated an element of personalisation improved their performance significantly⁸⁵.

Predictive algorithms work better in one specific circumstance than another⁸¹ and therefore algorithms predicting continuous variables often have a poor accuracy at detecting hypoglycaemia. Jensen et al developed a model to predict the incidence of nocturnal hypoglycaemia and, despite a long prediction horizon (PH) of 3-6 hours achieved a Receiver Operating Characteristic (ROC) Area Under the Curve (AUC) of 0.79 (equivalent to an algorithm correctly categorising independent variables 79% of the time) and a negative predictive value of 97%⁸⁶. Seo et al used a simple model with a PH of 30 minutes to predict postprandial hypoglycaemia with an AUC of 0.97 and high sensitivity and specificity of 89% and 91% respectively⁸⁷.

Recent studies have combined continuous value prediction with classification algorithms. Mosquera-Lopez et al devised a generalised classification model and applied individualised smoothing to improve hypoglycaemia prediction from 80% to 90%⁸⁸. Their continuous value prediction resulted in 99% of values in Zone A on an MCEG. While this was calculated with CGM values instead of fingerprick or laboratory plasma glucose values, the authors demonstrated the superiority of their predictions over that of Dexcom G6, highlighting the potential benefit of individualised algorithms⁸⁸. Vehi et al have recently developed an integrated system involving a classification approach for hypoglycaemia detection as well as a continuous variable prediction to allow the user to respond appropriately to a hypoglycaemia event. This not only allows a more personalised response to hypoglycaemia but reduces the chance of an undetected event⁸⁹.

The potential for computer-generated algorithms to improve the detection of hypoglycaemia is significant but requires considerable and robust real-life applications. Few algorithms to date have incorporated stress, medication or illness scenarios into their predictions; most studies compare predictions with CGM values rather than a gold standard and the majority only calculate MARD rather than the ability to predict hypoglycaemia. Furthermore, most algorithms are tested on simulated or historical patient data and not in patients, in real-time, and in real-life situations. Clearly, rigorous testing must be performed if predictive algorithms are to form a part of hypoglycaemia prediction and prevention clinical strategies in children with hypoglycaemia.

Conclusions

Detection of glucose levels at home has undergone significant changes over the last 100 years. Use of CGM is revolutionising the care of patients with diabetes and demonstrating significant improvements in clinical outcomes. However, the accuracy of CGM at hypoglycaemia remains poor and the efficacy of its use in disorders of hypoglycaemia in children is at best suboptimal. Small case series highlight the potential benefit of CGM in the management of these children but there are multiple barriers to regular clinical use. The use of computer-generated predictive algorithms which make use of CGM values is likely to form a significant part of hypoglycaemia prediction in the near future but will require investment and incentivisation by industry.

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Figure 1. Mechanism of action of a Continuous Glucose Monitoring device. *Diagrams show from left to right an increasing level of detail from the patient to the chemical reaction. Patients attach a sensor to their skin which automatically inserts a subcutaneous needle. This resides in the interstitial space and measures glucose concentrations. Via Glucose oxidase the sensor generates an electrical current proportional to the glucose concentration in the interstitium. This electrical current is passed through a continuously shifting algorithm to generate a glucose value which is transmitted wirelessly to the receiving unit or compatible smartphone for display to the patient.*

Figure 2. A Modified Clarke Error Grid (MCEG). *An MCEG can be used to compare clinical accuracy of values between a reference method and a new device. Values in Zone A will lead to clinically correct decisions being made. Values in Zone E represent a significant and dangerous over or underestimate of the true value and have the potential to trigger the opposite treatment to that required. Values in Zone D are unlikely to trigger the opposite treatment to that required but more likely a lack of treatment (e.g. a glucose bolus may not be given to a child in which it is required). Values in Zone C are at risk of triggering an appropriate response but likely at a lesser magnitude than required. Values in Zone B will trigger clinical decisions that are not correct but are uncritical. Devices with more values in Zone A will offer a higher clinical accuracy than those with values in other areas.*

	Dexcom G6	Freestyle Libre	Medtronic Guardian	Medtrum A6
Calibrations	None	None	2/day (min)	2/day (min)
Warmup	2 hours	1 hour	2 hours	2 hours
Wear length	10 days	14 days	7 days	14 days
MARD	9%	11%	9%	9%
Low alarms?	Yes	No	Yes	Yes
Age limit	2 years +	4 years +	14 years +	2 years +

Table 1. Comparisons of four common CGM devices licenced for use in children. *Calibrations relate to the minimum fingerprick calibrations per day recommended by the manufacturers. Warmup time relates to the time from insertion of the device to when it begins to provide glucose readings. MARD = Mean Absolute Relative Difference and is a commonly reported accuracy measure. MARD values quoted here are those reported by the individual manufacturers. Low alarms? relates to whether the device provides an auditory alarm if blood sugar drops below a certain value. Information all obtained from manufacturer websites.*

Type of Algorithm	Description
Physiological	Model blood glucose dynamics based on a comprehensive knowledge of the patient's physiology. These models require extensive expert input to create but can then be used without any prior patient data.
Data Driven	These algorithms use data mining from large CGM datasets and regression analysis to provide a mathematical prediction of future glucose trends (known as a black-box approach). This requires less expert input initially but is dependent upon the availability of existing datasets and assumes similarities between those patients using the algorithm for prediction and those from whom the initial data was taken.
Hybrid	These models combine physiological knowledge with data-driven regression to produce a complex predictive algorithm.

Table 2. Description of the three main types of blood glucose predictive algorithm. *Different approaches are taken towards the prediction of blood glucose values, with each approach benefiting from a different strength. Multiple examples of each type of algorithm are available and vary widely in their predictive accuracy. Outcomes of all three types of algorithm can either be as a continuous glucose value or as a binary classification e.g.s hypoglycaemia or not.*