



# Glucose Monitoring in Congenital Hyperinsulinism

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The background of the slide is a collage of numerous colorful sticky notes in shades of pink, yellow, light blue, and light green. Each sticky note has a large, bold black question mark printed on it. The notes are scattered and overlapping, creating a dense, textured effect.

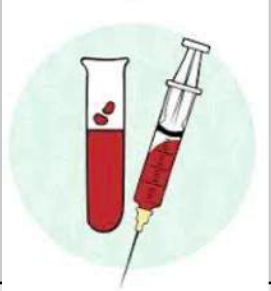
## **Why Glucose Monitoring is important in Congenital Hyperinsulinism (CHI)?**

- **CHI requires intensive blood glucose management by means of external enteral administration and regular medications**
- **Children with CHI at at risk of episodes of hypoglycaemia which can cause irreversible damage in the developing brain**
- **Sophisticated and patient-friendly accurate methods of measuring glucose levels are crucial to CHI successful management**

# Available methods for blood glucose monitoring

## Blood draw measurement

- **Gold standard for accuracy**



## Self-monitoring of blood glucose (SMBG)

- Fingertick
- Single “point-in-time” measurement → Often fails to detect nocturnal & asymptomatic hypos
- No indication of the direction or rate of change of glucose levels.
- **MARD (Mean absolute relative difference ) to the standard → 5-10%**
- Obtaining glucose data upon the patient’s decision to self-monitor



## Continuous Glucose Monitoring Devices

- Sensor under the skin measures the glucose in the interstitial space
- Recording glucose measurements every 5 minutes
- Lag of 5-25 minutes with the capillary glucose value
- **MARD (Mean absolute relative difference ) to the standard → Variable but higher to SMBG**
- Readings downloaded into a computer, reviewed Real-time (rtCGM) & intermittently (iCGM)

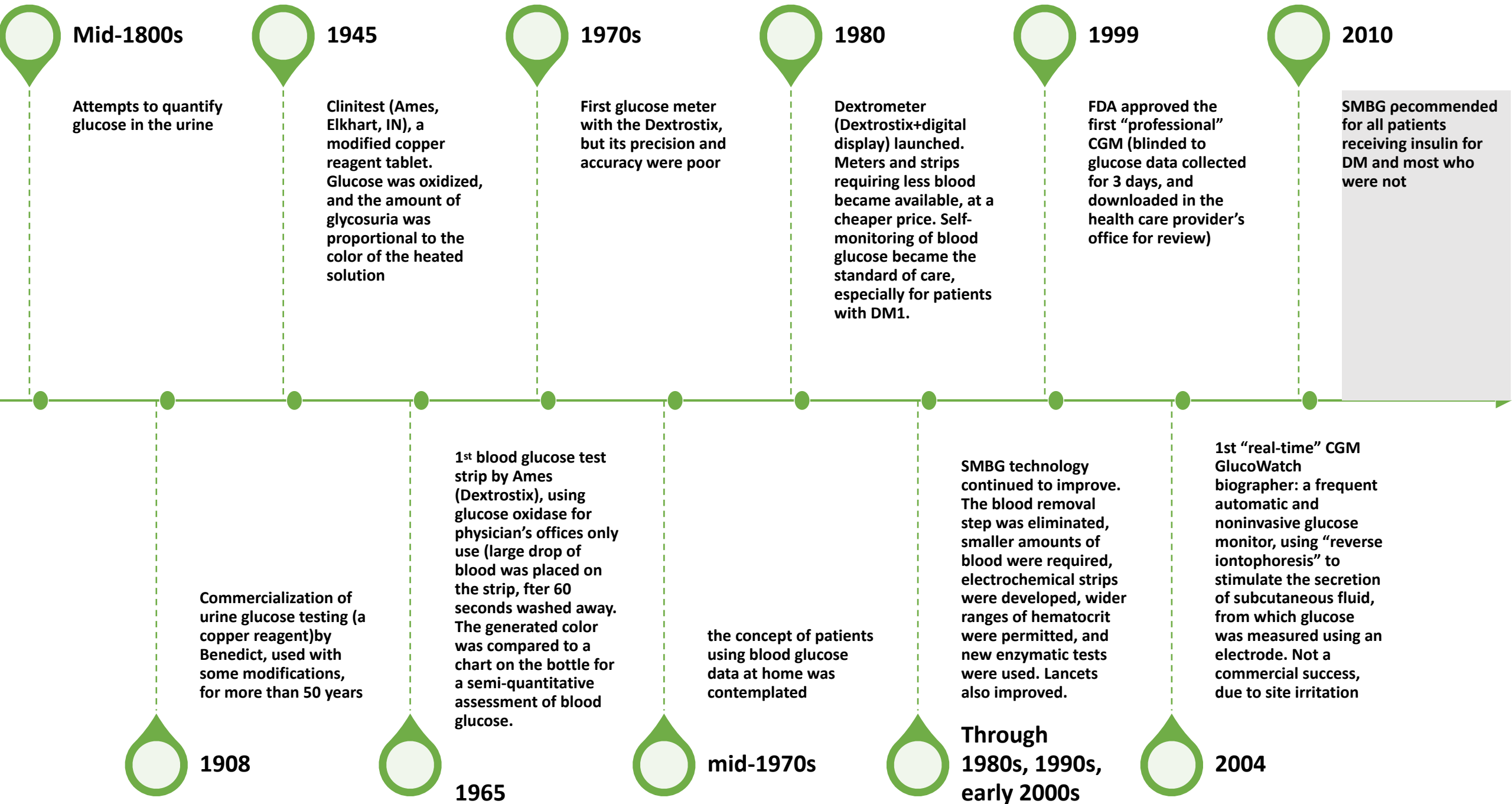


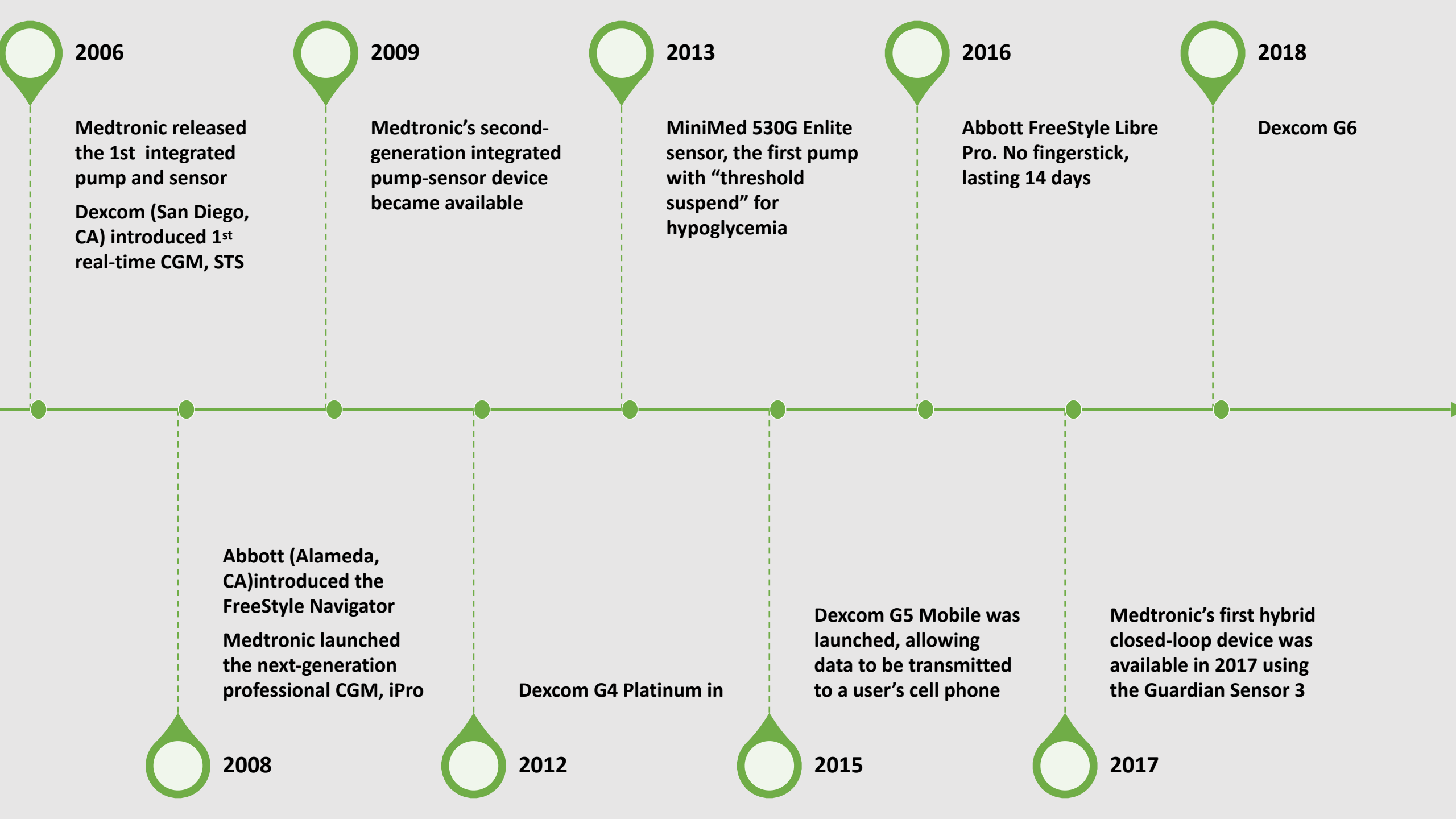


# Evolution of Glucose Monitoring Technology

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# Evolution of Guidelines for the use of CGM

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1999

FDA approved the first "professional" CGM (blinded to glucose data collected for 3 days, and downloaded in the health care provider's office for review)

2017

Advanced Technologies & Treatments for Diabetes (ATTD) Congress International  
in clinical practice CGM should be considered for use to help patients with diabetes improve glycaemic control provided that appropriate educational and technical support is available

2021

AACE Clinical Practice Guidelines

- DM1 with intensive insulin treatment & DM2 with less intensive treatment
- RT-CGM over IS-CGM to persons with diabetes with problematic hypoglycemia (frequent/severe hypoglycemia, nocturnal hypoglycemia, hypoglycemia unawareness) requiring predictive alarms/alerts; patients' lifestyle and other factors should also be considered

Endocrine Society recommended the use of CGM devices for adult patients with T1D in order to manage their blood glucose levels

2016

American Diabetes Association Guidelines for the use of Continuous Glucose Monitors (CGM) and Sensors in the School Setting

2018

National Institute of Health and Care Excellence (NICE)

- Adults & Children with DM1 access to Flash or CGM
- Some people with DM2 using insulin intensive therapy (2 or more inj/day) should have access to Flash, if they experience recurrent or severe hypos, if they cannot finger-prick test or if they would be advised to test >8 /day

2022



# Timeline of the Glucose Monitoring Evolution for DM

## 50 years

- Available tests for glycosuria for home use

## 30 years

- Available glucometers for home use

## Less than 20 years

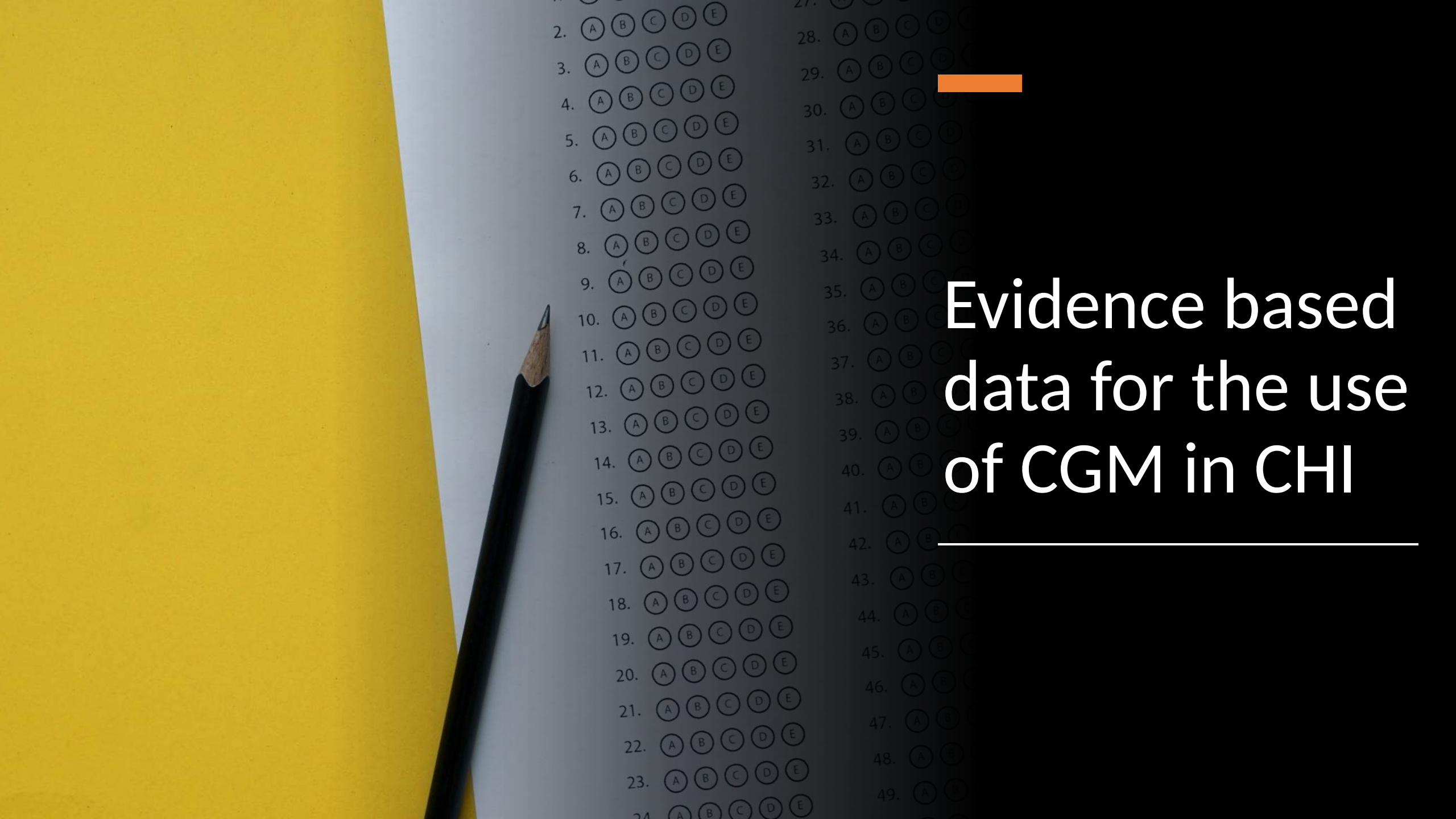
- Available CGM devices for home use
- Approved for DM
  - Frequent/severe hypoglycemia
  - Nocturnal hypoglycemia
  - Hypoglycemia unawareness

## CGM currently

- User friendly: Factory-calibrated; real-time readings/trend data, alarms, sharing data
- Revolutionized the way diabetes is managed
- Evidence supporting the use in DM is now vast and unequivocal

**Can we dare to dream the same evolution for children with CHI since they have:**

- ✓ Frequent/severe hypoglycemia
- ✓ Nocturnal hypoglycemia
- ✓ Hypoglycemia unawareness

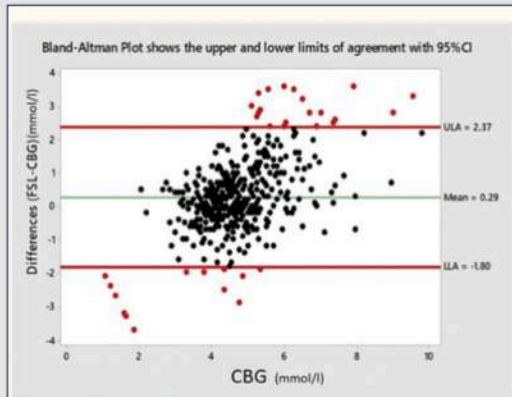


Evidence based  
data for the use  
of CGM in CHI

> Int J Pediatr Endocrinol. 2018;2018:3. doi: 10.1186/s13633-018-0057-2. Epub 2018 Mar 27.

## Continuous Flash Glucose Monitoring in children with Congenital Hyperinsulinism; first report on accuracy and patient experience

Hussain Alsaffar<sup>1</sup>, Lucy Turner<sup>2</sup>, Zoe Yung<sup>2</sup>, Mohammed Didi<sup>2</sup>, Senthil Senniappan<sup>2</sup>



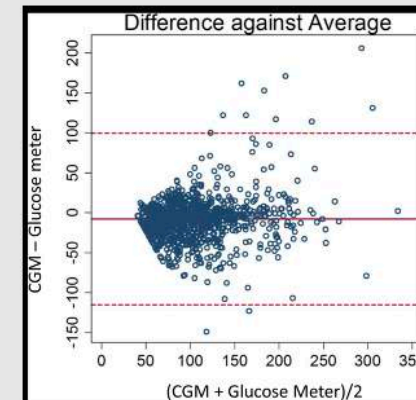
- ✓ MARD was 17.9%
- ✓ Despite the ease of using the FSL system, **concerns related to accuracy**, especially at low glucose values do remain although parents find the glucose trend to be very useful.
- ✓ Majority of the parents found the glucose trend on FSL to be useful to detect and prevent hypoglycaemic episodes. All parents felt that FSL is a very easy and convenient method to measure the glucose especially during sleep. A significant proportion of parents felt that FSL readings were not accurate and 56% of parents expressed interest to continue using FSL after the trial period

Clinical Trial > Horm Res Paediatr. 2019;92(5):319-327. doi: 10.1159/000506230.

Epub 2020 Mar 24.

## Continuous Glucose Monitoring Systems: Are They Useful for Evaluating Glycemic Control in Children with Hyperinsulinism?

Arpana Rayannavar<sup>1</sup>, Okan U Elci<sup>2,3</sup>, Lauren Mitteer<sup>1</sup>, Diva D De León<sup>4,5</sup>



- ✓ MARD was 17.47%
- ✓ **CGM is not a reliable method** to monitor for hypoglycemia, given the high number of false positive hypoglycemia readings.
- ✓ CGM can be useful in preventing unnecessary checks by glucose meter during times of normoglycemia. Therefore, the benefits of using CGM in patients with HI would be in guiding the need to check plasma glucose by glucose meter rather than point accuracy

> J Clin Endocrinol Metab. 2022 Jan 1;107(1):e246–e253. doi: 10.1210/clinem/dgab601.

## Continuous Glucose Monitoring in the Management of Neonates With Persistent Hypoglycemia and Congenital Hyperinsulinism

Myat Win <sup>1</sup>, Rowan Beckett <sup>2</sup>, Lynn Thomson <sup>3</sup>, Ajay Thankamony <sup>1 3</sup>, Kathryn Beardsall <sup>1 3</sup>

- ✓ Mean absolute relative difference of 11%.
- ✓ CGM highlighted the challenges of preventing hypoglycemia in these babies when using intermittent blood glucose levels alone, and the potential application of CGM as an adjunct to clinical care.

Case Reports > J Med Internet Res. 2020 Dec 4;22(12):e21770. doi: 10.2196/21770.

## Open-Source Technology for Real-Time Continuous Glucose Monitoring in the Neonatal Intensive Care Unit: Case Study in a Neonate With Transient Congenital Hyperinsulinism

Katarina Braune <sup>1 2</sup>, Mandy Wäldchen <sup>3</sup>, Klemens Raile <sup>1</sup>, Sigrid Hahn <sup>4</sup>, Tebbe Ubben <sup>5</sup>, Susanne Römer <sup>4</sup>, Daniela Hoerber <sup>6</sup>, Nora Johanna Reibel <sup>4</sup>, Michael Launspach <sup>2 4</sup>, Oliver Blankenstein <sup>7 8</sup>, Christoph Bührer <sup>4</sup>

- ✓ TIR for CGM remained consistently >90%, whereas time in hypoglycemia (<45 mg/dL) decreased.
- ✓ Mean glucose >70 mg/dL at 72 hours of life and thereafter
- ✓ Real-time information allowed us to better understand glycemic patterns and to improve the quality of glycemic control accordingly.
- ✓ Severe hypoglycemia was prevented, and measurement of serum levels of insulin and further lab diagnostics were performed much faster, while the patient's individual burden caused by invasive procedures was reduced.



## Efficacy of use of Continuous Glucose Monitoring System in patients with Congenital Hyperinsulinism

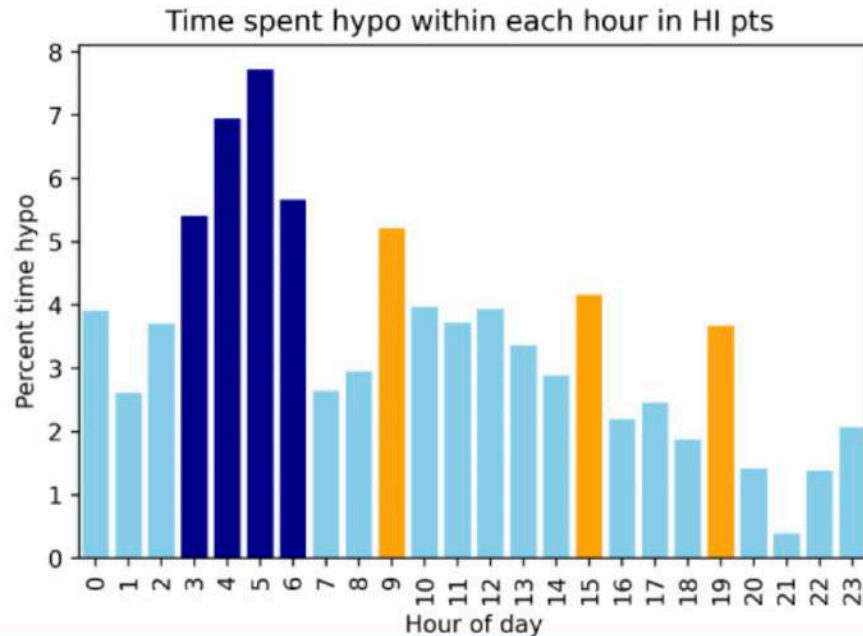
Y. Tropeano<sup>1</sup>, P. Purushothaman<sup>1</sup>, C. Gilbert<sup>1</sup>, K. Morgan<sup>1</sup>, L. Doodson<sup>1</sup>, A. Dastamani<sup>1</sup>  
1. Endocrinology Department, Great Ormond Street Hospital for Children, London, UK



- ✓ 12 weeks of use of Dexcom G6 rtCGMS →improvement of TIRN and a decrease in number of weekly hypoglycaemic episodes
- ✓ CGMS can assist CHI patients and families with more effective glycaemic control
- ✓ Studies are needed to assess the potential of CGMS as a decision-making tool in hypoglycaemia management of CHI patients

## Clustering of Hypoglycemia Events in Patients With Hyperinsulinism: Extension of the Digital Phenotype Through Retrospective Data Analysis

Chris Worth<sup>1 2</sup>, Simon Harper<sup>2</sup>, Maria Salomon-Estebanez<sup>1</sup>, Elaine O'Shea<sup>1</sup>, Paul W Nutter<sup>2</sup>, Mark J Dunne<sup>3</sup>, Indraneel Banerjee<sup>1 3</sup>



## Conclusions

- ✓ Digital phenotype of HI by describing the glycemic trends and identifying the timing of hypoglycemia measured by CGM.
- ✓ We have identified the early hours as a time of high hypoglycemia risk for patients with HI and demonstrated that simple provision of CGM data to patients is not sufficient to eliminate hypoglycemia.
- ✓ Focus must move to the human-computer interaction as an aspect of the digital phenotype that is susceptible to change rather than simple mathematical modeling to produce small improvements in hypoglycemia prediction accuracy.

# Insight into hypoglycemia frequency in congenital hyperinsulinism: evaluation of a large UK CGM dataset

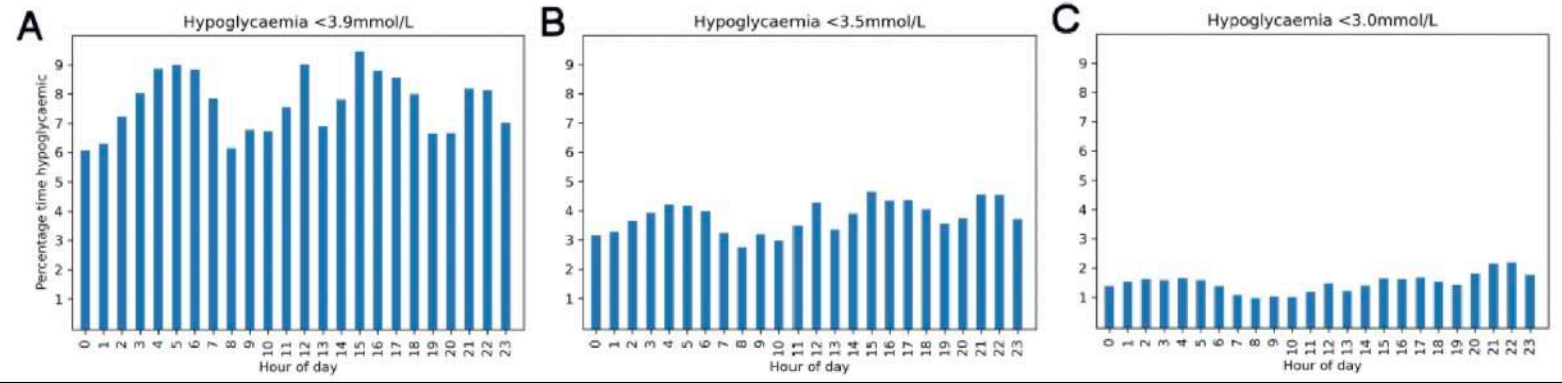
Chris Worth <sup>1,2</sup>, Yesica Tropeano, <sup>3</sup> Pon Ramya Gokul, <sup>1</sup> Karen E Cosgrove, <sup>4</sup> Maria Salomon-Estebanez, <sup>1</sup> Senthil Senniappan, <sup>5</sup> Antonia Dastamani, <sup>3</sup> Indraneel Banerjee <sup>1,6</sup>

## Methods

- ✓ Frequency/patterns of hypoglycemia by varying thresholds through a large CGM dataset, from CHI patients over a 5-year period
- ✓ Thresholds of 3.0/3.5/3.9mmol/L used to test change on hypoglycemia frequencies

## Results

- ✓ 63 patients, 3.4 million data points, representing 32 years of monitoring
- ✓ By UK consensus threshold 3.5, patients experienced a mean 1.3 hypoglycemic episodes per day
- ✓ % time hypoglycemic increased from 1.2% to 3.3% to 6.9% when threshold changed from 3.0 to 3.5 and 3.9
- ✓ **Merged data showed periodicity of hypoglycemia risk in 24-hour periods in all patients.**



Distribution of hypoglycemia over 24-hour periods showing periodically 3 peaks (03:00-06:00, 15:00-18:00, 21:00–22:00) with relatively low risk at 08:00. As hypoglycemia thresholds are reduced, the % time in hypoglycemia is reduced although periodicity is retained.

## Conclusions

- ✓ Large variations in hypoglycemia frequency when thresholds are altered from 3.5 to 3.0 or 3.9 mmol/L
- ✓ Periodicity of risk of hypoglycemia through the day.
- ✓ Such factors should be considered in routine clinical management and influence the design of interventional trials in CHI



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## CGM in CHI scientific studies

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**CGM data are used as primary or secondary endpoints to assess efficacy of the new drug in most of the protocols of clinical trials for children with CHI**

- ✓ **CGM percent time in range (specific glucose target)**
- ✓ **Extent of hypoglycemia (area over the glucose curve [AOC glucose] below specific glucose thresholds as measured by CGM)**
- ✓ **Rate of hypoglycemic episodes as measured by CGM**

**All protocols include self-monitoring of blood glucose for events of hypoglycemia and as a decision-making tool for rescue hypoglycaemia treatment**





User feedback

## Results

- Favorable use as offering parental reassurance, reduced fingerprick tests and predictive warnings
- Unfavourable aspects of alarms and questionable accuracy at low glucose levels
- Adolescents frustrated by the short proximity range for data transmission resulting in the need to always carry a separate receiver
- Overall, families were positive about the use of CGM but expected application to be tailored to their child's medical condition

## Conclusions

- **Patients and families with CHI using CGM noticed trends in glucose levels which motivated behavioural changes to reduce hypoglycaemia with advantages outweighing disadvantages**
- They expected CHI-specific modifications to enhance utility

> [Front Endocrinol \(Lausanne\)](#). 2022 Jul 19;13:894559. doi: 10.3389/fendo.2022.894559. eCollection 2022.

## **Families' Experiences of Continuous Glucose Monitoring in the Management of Congenital Hyperinsulinism: A Thematic Analysis**

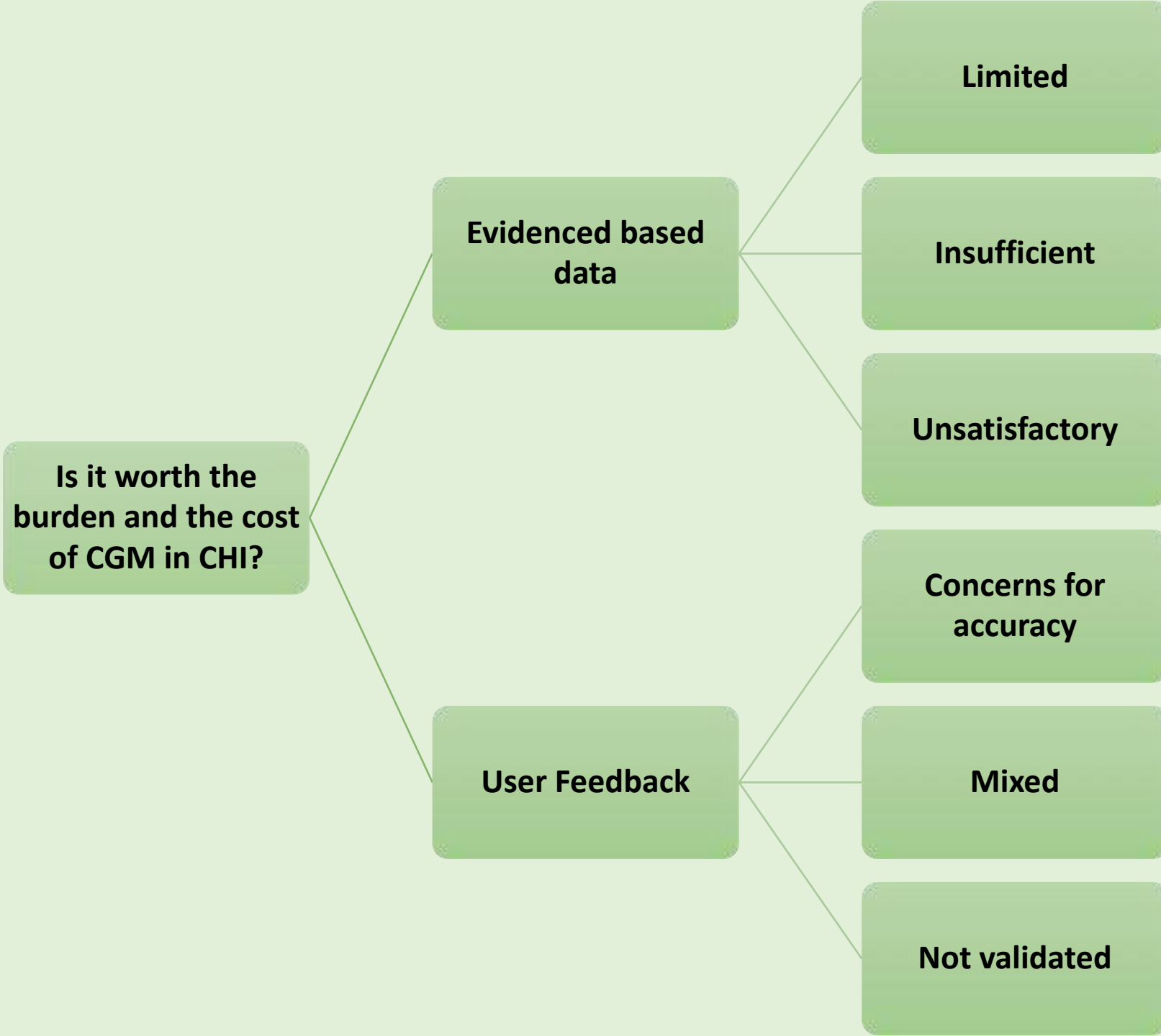
Sameera Hannah Auckburally <sup>1 2</sup>, Chris Worth <sup>1 3</sup>, Maria Salomon-Estebanez <sup>1</sup>, Jacqueline Nicholson <sup>4</sup>, Simon Harper <sup>3</sup>, Paul W Nutter <sup>3</sup>, Indraneel Banerjee <sup>1 5</sup>

## *Parental response*

- *6-year-old with CHI, negative genetics*
  - *Thank goodness for the CGM because the lows happened at times we would not have usually checked*
- *8-year-old boy with diffuse CHI, recessive ABCC8 subtype*
  - *He became more confident, more independent and can participate in all activities like all his peers. He really likes the CGM*
- *15-year-old boy with diffuse CHI, recessive ABCC8 subtype*
  - *CGM gave me a peace of mind*
- *18-year-old boy with CHI, GLUD1 subtype*
  - *GCM improved my and my wife's mental health*

## *Children with CHI response*

- *8-year-old with CHI, dominant ABCC8 subtype*
  - *Please can I keep the CGM that helps me to manage my blood glucose at school?*
- *18-year-old boy with CHI, GLUD1 subtype*
  - *GCM improved my anxiety*



**Should we dare to dream?**

**Machine learning, artificial intelligence computer-generated algorithms offer significant potential for further improvement in CGM device technology and widespread application in childhood hypoglycaemia**

**“I was so pleased to hear you now have continuous glucose monitoring - I shudder to remember the huge number of heel pricks we inflicted on babies so this is a huge step forward & very well done for introducing it ”**

***Sir Albert Aynsley-Green, Paediatric Endocrinologist, Founder of GOSHCHI,  
Children's Commissioner for England (2005–09)***

