Software Packages and Tools for the Analysis of Continuous Glucose Monitoring Data

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AUTHORS - Piersanti, Agnese; Giurato, Francesco; Göbl, Christian; Burattini, Laura; Tura, Andrea; Morettini, Micaela.
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ABSTRACT - The advancement of technology in the field of glycemic control has led to the widespread use of continuous glucose monitoring (CGM), which can be nowadays obtained from wearable devices equipped with a minimally invasive sensor, that is, transcutaneous needle type or implantable, and a transmitter that sends information to a receiver or smart device for data storage and display. This work aims to review the currently available software packages and tools for the analysis of CGM data. Based on the purposes of this work, 12 software packages have been identified from the literature, published until December 2021, namely: GlyCulator, EasyGV (Easy Glycemic Variability), CGM-GUIDE© (Continuous Glucose Monitoring Graphical User Interface for Diabetes Evaluation), GVAP (Glycemic Variability Analyzer Program), Tidepool, CGManalyzer, cgmanalysis, GLU, CGMStatsAnalyser, iglu, rGV, and cgmquantify. Comparison of available software packages and tools has been done in terms of main characteristics (i.e., publication year, presence of a graphical user interface, availability, open-source code, number of citations, programming language, supported devices, supported data format and organization of the data structure, documentation, presence of a toy example, video tutorial, data upload and download, measurement-units conversion), preprocessing procedures, data display options, and computed metrics; also, each of the computed metrics has been analyzed in terms of its adherence to the American Diabetes Association (ADA) 2017 international consensus on CGM data analysis and the ADA 2019 international consensus on time in range. Eventually, the agreement between metrics computed by different software and tools has been investigated. Based on such comparison, usability and complexity of data management, as well as the possibility to perform customized or patients-group analyses, have been discussed by highlighting limitations and strengths, also in relation to possible different user categories (i.e., patients, clinicians, researchers). The information provided could be useful to researchers interested in working in the diabetic research field as to clinicians and endocrinologists who need tools capable of handling CGM data effectively.

Software Packages and Tools for the Analysis of Continuous Glucose Monitoring Data

Agnese Piersanti[1], Francesco Giurato[1], Christian Göbl[2], Laura Burattini[1], Andrea Tura[3], Micaela Morettini[1,*]

[1] Department of Information Engineering, Università Politecnica delle Marche, Ancona, Italy.

[2] Department of Obstetrics and Gynaecology, Medical University of Vienna, Vienna, Austria.

[3] CNR Institute of Neuroscience, Padova, Italy

Running title: Software packages for CGM data analysis

* Correspondence: Micaela Morettini; m.morettini@univpm.it

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Abstract

The advancement of technology in the field of glycemic control has led to the widespread use of continuous glucose monitoring (CGM), which can be nowadays obtained from wearable devices equipped with a minimally invasive sensor, i.e., transcutaneous needle-type or implantable, and a transmitter that sends information to a receiver or smart device for data storage and display. This work aims to review the currently available software packages and tools for the analysis of CGM data. Based on the purposes of this work, 12 software packages have been identified from the literature, published until December 2021, namely: Glyculator, EasyGV, CGM-GUIDE©, GVAP, Tidepool, CGManalyzer, cgmanalysis, GLU, CGMStatsAnalyzer, iglu, rGV, cgmquantify. Comparison of available software packages and tools has been done in terms of main characteristics (i.e. publication year, presence of a Graphical User Interface, availability, open-source code, number of citations, programming language, supported devices, supported data format and organization of the data structure, documentation, presence of a toy example, video tutorial, data upload and download, measurement-units conversion), preprocessing procedures, data display options and computed metrics; also, each of the computed metrics has been analyzed in terms of its adherence to the American Diabetes Association (ADA) 2017 international consensus on CGM data analysis and the ADA 2019 international consensus on time in range. Eventually, the agreement between metrics computed by different software and tools has been investigated. On the basis of such comparison, usability and complexity of data management, as well as the possibility to perform customized or patients-group analyses, have been discussed by highlighting limitations and strengths also in relation to possible different user categories (i.e., patients, clinicians, researchers). The information provided could be useful to researchers interested in working in the diabetic research field as to clinicians and endocrinologists who need tools capable of handling CGM data effectively.

Introduction

Over the past twenty years, the advancement of technology for glycemic control has led to the widespread use of continuous glucose monitoring (CGM), which can be nowadays obtained from wearable devices equipped with a minimally invasive sensor - i.e., transcutaneous needle type or implantable - and a transmitter that sends information to a receiver or smart device for data storage and display[1]. Thanks to the progressive refinement in terms of accuracy, comfort, wearing time and ease of use, these wearable devices are gradually being used not only in addition but also in replacement to the standard self-monitoring of blood glucose (SMBG) through finger pricks[2–4]. Unlike SMBG that describes a single-point capillary blood glucose value, CGM technology allows close glucose tracking over time; it provides the possibility to precisely quantify glycemic control including average glucose, variability and target range[5], with clinical benefits in the management of therapy for people with diabetes, spanning from adults with type 1 and type 2 diabetes to children and adolescents with type 1 diabetes and diabetes in pregnancy[6–11]. Use of CGM technology has been also associated to a significant reduction of pain and discomfort in a cohort of young patients with type 1 diabetes[12].

In parallel with the advancement in CGM technology, the need of interpreting the large amount of produced data has led to the definition of lots of metrics useful to assess glycemic control[13,14], accompanied by data display modalities to assist clinicians and patients in the management of therapy adjustments and tracking of the related progresses. As a consequence, CGM data interpretation has been suffering from a lack of standardization, even though in the last ten years much work has been done to overcome this limitation[15]. In particular, a first important achievement was represented by the recommendation by the American Diabetes Association (ADA) for the adoption of a template report named Ambulatory Glucose Profile (AGP)[16]. Such template is currently adopted by the majority of

CGM devices manufacturers; however, international consensus on CGM data analysis and standard metrics that should be computed for clinical care has been reached only recently[17,18].

CGM data interpretation is facilitated by software packages and tools, which have different characteristics in relation to the intended users (i.e., researchers, clinicians and also patients) and provide partially different CGM reports and metrics. However, ascertaining which functionality fits for each user requirement is sometimes not so straightforward. To the best of our knowledge, a literature review that outlines the existing options is not yet present. Thus, this work aims to fill this gap by reviewing the currently available software packages and tools for the analysis of CGM data. A total of 12 software packages or tools have been identified from the literature (latest search: December 2021), being the main focus on non-commercially available solutions. The timeline of their first publication is shown in Figure 1.

Comparison of Available Software Packages and Tools in terms of Main Characteristics and Preprocessing Procedures

Main characteristics and preprocessing procedures of the available software packages and tools are summarized in Table 1. Details for each of them are provided in the related subsections in the following.

GlyCulator

GlyCulator[19–21], is an application available as a web-based Graphical User Interface (GUI) and its latest version available is Glyculator 3 (https://glyculator.btm.umed.pl/). Supported file format can be either *.csv, *.txt, *.xls or *.xlsx. Dataset loading can be performed specifying the CGM manufacturer among those supported or choosing to import a generic data format. After importing a generic data format, the user must select the sheet and columns corresponding to the glucose values and time and specify number of readings per day, number of header rows and column separator. An option to analyze specific periods is provided. In

addition, the user can choose measurement units of the CGM data (mmol·l^{-1} or mg·dl^{-1}) and an imputation method to fill missing values. The source code is, at the moment, available for Glyculator 2 (https://github.com/kpagacz/glyculator), but not for Glyculator 3. The computed metrics are easily accessible and downloadable in *.csv format from the online platform, together with the raw data file and the metadata file, and providing as display options the patients' daily CGM graphs and multi-patient time in range visualization in a downloadable analysis report (in .pdf).

EasyGV

EasyGV (easy Glycaemic Variability)[22,23] is a software application developed in Visual Basic and enabled in an Excel (Microsoft) workbook. The latest version EasyGV software v10 is freely available at the website: https://www.phc.ox.ac.uk/research/resources/easygv. The supported data frame is a single column containing glucose values in mmol·l^{-1}, which can be converted into mg·dl^{-1}. Other options are Sampling Interval (the time between each sample) and Interpolate (straight line estimation with settable maximum gap allowed, default value being 50 min). If time stamps are not included in the spreadsheet, the software does not allow the user to select specific periods of the day during the analysis. EasyGV does not provide display options.

CGM-GUIDE©

CGM-GUIDE©[24] (Continuous Glucose Monitoring Graphical User Interface for Diabetes Evaluation) was designed using MATLAB environment (The MathWorks, Natick, MA) version 2008b and has not been made publicly available. It provides a GUI with descriptions of user inputs and CGM-GUIDE© outputs. The supported file format is a basic *.xls data file, containing glucose readings only, thus requiring prior conversion to this data format from any CGM device. The only mentioned preprocessing steps are i) the deletion of gaps or null data points that will be not included in metrics computation and ii) the data collection time interval

checked against published statistical limits within which variability metrics can be accurately assessed; when an interval exceeds limits, an error message is displayed. Display options are: i) glucose trace with colored areas under hyper- and hypo-glycemic ranges; ii) "transition density profile", which allows visualizing and evaluating the dynamics associated with frequency of glucose fluctuations across critical glycemic regions; iii) rate of change and histogram of the rate of change computed for every recorded time interval.

GVAP

GVAP (Glycemic Variability Analyzer Program)[25] software package was designed in MATLAB environment version 2010b. It is freely available at https://sourceforge.net/projects/glyvariab/files/?source=navbar, providing open access source code and the possibility to build a standalone Windows-based application following a few steps in MATLAB environment. CGM data must be provided in an Excel table (*.xls) containing four columns and at least 101 rows, with the first row providing the labels: Date, Time, Glu (glucose, expressed in $mg \cdot dl^{-1}$), Index (a number used as a counter associated with each glucose value starting from 1). Date and Time should be in text format; the time interval within two consecutive rows, i.e., the sampling time, must be 5 minutes. In case of errors in data format and settings, GVAP provides an error message. The missing glucose data is calculated by linear interpolation. Available display options are i) glucose curve and ii) mean amplitude of glycemic excursion (MAGE) curve.

Tidepool

Tidepool Platform[26] is an open-source cloud-based comprehensive platform for diabetes data management; it can integrate information coming from different applications and devices, including insulin pumps, CGM devices, and blood glucose meters, together with providers' apps, to allow users to fully control their therapy in a single platform. The dashboard that combines all the data for visualization and interpretation is an application built on the platform

and named Tidepool Web, and its code, mainly based on JavaScript language, is fully available on GitHub (https://github.com/tidepool-org/blip) for usage by third-party developers. Tidepool is free for clinicians and diabetic patients. By paying a fee, it is also possible to access anonymized datasets donated by patients under the "Tidepool Big Data Donation Project", which has been created to help students, academics, and industry innovate faster and expand knowledge about diabetes.

Data can be uploaded by selecting a device from those supported (currently 50). A mobile app allows data visualization and event tracking adding notes about meals, carbohydrate intake, insulin boluses, exercise and all other events one wants to track. Different data visualization modalities are possible, showing hourly, daily, and weekly patterns, trends, and added notes about events. In Tidepool Web the user can also share access with his/her endocrinologist, diabetes educator, family doctor, researchers or family care team and control how they interact with it. A new app (the Tidepool Loop app) is under development and will be submitted to Food and Drug Administration (FDA) approval; it is designed to connect to commercially available insulin pumps and CGM devices using Bluetooth wireless communication to act as a controller. For what concerns CGM data, reports from 14 to 90 days can be downloaded into a *.txt file. Visualization options include: i) daily blood glucose readings (with colored lines depending on the target ranges set); ii) CGM trends related to 1 up to 4 weeks (also with the possibility to select only weekend-related data); iii) percentage spent in the selected ranges (represented through a bar graph) and iv) other information related to specific metrics and sensor usage (displayed through widgets). Further information about data visualization and interpretation, not only concerning CGM data, can be found at https://support.tidepool.org/.

CGManalyzer

CGManalyzer[27] is a free software package developed in R (a free software environment for statistical computing and graphics) and available on CRAN: https://cran.r-project.org/web/packages/CGManalyzer/index.html. Although there is a list of supported devices, it is possible to analyze data from any device, but it is necessary to modify some parameter settings in the R script used for data reading. Preprocessing functions include timeSeqConversion.fn(), to convert different time stamps into a general format represented by a sequence of time values; equalInterval.fn(), to adjust the data so that the time interval between two glucose values is equal (needed to calculate non-linear statistical parameters); fixMissing.fn(), to fix the missing values, when necessary, with different optionable methods. Moreover, this software allows comparing data of different populations, such as type 1 diabetes, type 2 diabetes, pre-diabetes and healthy people, giving the possibility to perform a complete study. Display options are i) glucose levels in several subjects at the same time (through the function boxplotCGM.fn()); ii) glucose levels in time (through the function plotTseries.fn()); iii) multiscale sample entropy (MSE[28]) both for each subject and for each group (through the function MSEplot.fn()); iv) "antenna plot" (through the function antennaPlot.fn()) to display, both for glucose levels and MSE at each scale, differences among pair of groups, reporting for each pair of groups the mean of difference and its confidence interval on the x-axis and the strictly standard mean difference (SSMD[29]) on the y-axis.

cgmanalysis

cgmanalysis[30] is a free software package developed in R and available on the CRAN repository at https://cran.r-project.org/web/packages/cgmanalysis/index.html; in addition, its source code is available on GitHub. There is a list of supported CGM devices; in case of data from different devices, it is necessary to provide a manually adjusted three-column *.csv file containing an identifier, ID, with sensor placement and removal time, time stamp and glucose

reading. Preprocessing is done through the function cleandata(), which makes data uniform converting them into a format ready to be analyzed by other functions and, if you option it, fills gaps using linear interpolation, with the possibility to set the maximum interval to allow interpolation and to enable sample removal in case of this interval is exceeded. Default daytime is defined as 6 a.m. to 10 p.m. and could be manually modified. The function cgmvariables() computes the metrics. Display options can be obtained through the function cgmreport() and are: i) the Aggregate Daily Overlay (ADO), with Tukey smoothing version showing median, interquartile range and 5th and 95th percentiles of CGM values over the 24-hour period (similarly to the AGP report); ii) the ADO Loess smoothing version, showing all CGM data points and an overlapped curve representing the mean; iii) color-coded representation of mean glucose for each subject.

GLU

GLU[31] is a software package developed in R environment and is freely available on GitHub at https://github.com/MRCIEU/GLU. There is a list of supported devices but in the case of devices other than those in the list a data analysis can be performed through the conversion to a general format. Preprocessing mainly involves data quality control which allows assessing the integrity of the data and consists of three steps: the resampling to 1-minute interval, the identification of outlier values and the processing of missing data through data imputation selecting among different possible approaches. GLU generates a *.csv file of derived metrics, producing three different summaries for different periods of the day, the daytime, the night-time and the whole day. The software also allows the user to specify optional arguments and these include nightstart and daystart, which specify the start time of day and night periods to adapt to different user habits; firstvalid and dayPeriodStartTime, which are mutual options to specify if the analysis start time should coincide with the time associated to the first glucose value reading obtained by the sensor or with a specifiable time of the day, default being the

nightstart; pregnancy and diabetes, that indicate if the data refer to pregnant women or diabetic patients respectively, to take into account specific characteristics of these populations and derive specific metrics. If none of these options is selected, summarizing variables are produced that assume that the participants come from a "general population". GLU display options are i) glucose trace versus time, also including indicators of events (if provided) including meal times, exercise, use of relevant drugs, and capillary blood sugar measurement levels; ii) Poincare graphs, to visualize the blood glucose variation, in which each point on the graph is the glucose level of the sensor in the time point t (on the x-axis) compared to the glucose value of the sensor at time t + 1 (on the y-axis) and iii) histograms of glucose measurements distribution.

CGMStatsAnalyser

CGMStatsAnalyser[32] is a freely available web-based application accessible at https://baker-biostats.shinyapps.io/CGMStatsAnalyser/.The supported data format is a two-column *.csv file, having in the first column the date and time stamp and in the second the glucose measurements in $mmol \cdot l^{-1}$. In addition to the generic format, there is only one directly supported device. Multiple CGM data files can be uploaded into the software using the dedicated button to statistically compare the summary metrics between groups of subjects. To perform statistical analysis between groups of subjects, a subject characteristic file in *.csv format must be uploaded, and its first column should contain the file names of the raw data files, while a second column should contain values related to the variable representing the characteristic under analysis. CGMStatsAnalyser enables the statistical comparison of metrics between groups of patients with different characteristics, possible selecting the metric to test and the variable chosen among those of the subject characteristic file. Furthermore, a summary of the test results is displayed and can be downloaded as a *.csv file. The CGM data from a specific file can be visualized using the Glucose profile section which provides the

trace of glucose with respect to time represented by the median value and the 5th and 95th percentiles. Interactive visualization of metrics can be displayed using violin plots, with the possibility to observe the different distributions according to a specified grouping variable. Moreover, a heatmap of the correlation between the computed metrics can be displayed and by clicking on the colored dot representing a specific pair of metrics, the value of the correlation coefficient and –log10(p-value) will be visualized.

iglu

iglu[33] is a free open-source software package, fully developed in the R environment and available on the CRAN repository, at https://github.com/irinagain/iglu. This platform provides the user with the ability to use a point-and-click GUI called Shiny App. The data accepted by the software can come from any device provided that the format of the data is characterized by the presence of three columns: the first containing the identification of the subject ('id'), the second containing date and time ('time') and finally, a third containing the measurement of blood sugar ('gl') expressed in mg·dl^{-1}. Display options are: i) glucose trace plot over time for each subject; ii) Lasagna plots, which allow visualizing data trends across different subjects or different days for the same subject by using color grids (using a settable gradient among the default blue to red or the color scheme from red to orange, which can be selected by the user by corresponding modification of the color_scheme); iii) change in the variability of glucose as the rate of change shown through a time-series graph (in which each glucose measurement point is colored reflecting the corresponding rate of change value), or through a histogram plot; iv) an AGP report organized in three panels: glucose statistics and time in ranges in the first, CGM glucose profile (with the respective quantiles) in the central and daily glucose profile with colored hyperglycemic and hypoglycemic areas in the third.

rGV

rGV[34] is a free open-source software package developed in R environment. It provides a GUI available at https://shiny.biostat.umn.edu/GV/. It supports any CGM device, after specifying some details about data to the function read.CGM, which enables data upload and cleaning, formatting to a general two-column frame containing only time stamps and glucose readings. Then, the GV() function allows metrics computation. Results can be given in $mg \cdot dl^{-1}$ or $mmol \cdot l^{-1}$. Display options are: i) plots of glucose trace over time; ii) rate of change of glucose over specified time intervals, and iii) a plot representing symmetrized blood glucose values over time, based on a function that transforms glucose readings to balance the amplitudes of hyper and hypoglycemic ranges and makes them symmetric around zero[35].

cgmquantify

cgmquantify[36] is a free open-source software package, developed both in Python programming language and R environment and available at https://github.com/DigitalBiomarkerDiscoveryPipeline/cgmquantify. Import functions are included to format data for use with the cgmquantify package: some CGM devices are supported, but the provided user guide also outlines how new data can be easily formatted in a three-column frame with one column for glucose, another column for datetime, and another column for the day. Display options are i) longitudinal CGM data, including mean, standard deviation and hyper- and hypoglycemia according to personalized or standard clinical thresholds; Locally weighted scatter plot smoothing (LOWESS) curves can also be displayed over the original CGM data to facilitate interpretation.

Comparison of Available Software Packages and Tools in Terms of Computed Metrics

A summary of the CGM metrics computed by the 12 software packages along with their description is given in Table 2. Details about the modality of metric computation are provided in the related subsections in the following. In order to perform a comparison of the available software packages and tools (with reference to their latest version) in terms of computable metrics, a standard CGM recording from the open D1NAMO dataset[37] was considered. The selected CGM recording pertains to a patient with type 1 diabetes (Subject 1) and was obtained through an iPro2 Professional CGM device. Results of the analysis are reported in Table 3. Results of the analysis for the whole D1NAMO dataset are provided as Supplementary material (SupplementaryAnalysis.xlsx).

GlyCulator

Computable metrics for GlyCulator are: mean, median, standard deviation (SD) and coefficient of variation (CV) of glucose trace, M100 (being the M-value[38] computed as the weighted average of transformed glucose with respect to the reference value 100 $mg \cdot dl^{-1}$), J-index[39] (being equal to $0.001 \times (mean + SD)^2$ for $mmol \cdot l^{-1}$), the mean amplitude of glucose excursion (MAGE[40]). In addition to the CV the other recommended metrics[17] are: percentage of time in hypoglycemic ranges (%TBR level 1 and 2), percentage of time in target range (%TIR), percentage of time in hyperglycemic ranges (%TAR level 1 and 2), the Glucose Management Indicator (GMI[41]), reports on data sufficiency (percentage of expected CGM readings), area under the glycemic curve (AUC) divided by the time in h, risk of hypoglycemia and hyperglycemia described by low/high blood glucose index (LBGI/HBGI[42]), and, on top of that, Glyculator additionally computes the glycemic risk assessment in diabetes equation (GRADE[43]). According to the same recommendations, all metrics are calculated in three different day intervals: 12:00 a.m.–6:00 a.m., 6:00 a.m.–12:00

a.m., and the whole day. Nighttime and daytime can be customized together with thresholds for time in ranges. The number of days the CGM was worn can be found in the downloadable metadata file.

EasyGV

Computable metrics in EasyGV are: mean, SD, CV, the continuous overall net glycemic action (CONGA[44]) with the possibility to define the time window length (default value is 60 min), Lability Index (LI[45]) with the possibility to define the interval (default value is 60 min), J-index, LBGI, HBGI, GRADE (also with the computation of the relative contribution of hypo-, eu- and hyperglycaemia to the GRADE risk score, expressed in percentage), MAGE (with the possibility to compute a modified version, MAGE-CGM, for peak-to-trough or trough-to-peak identification[46], more suitable for CGM readings; default is 0=off but turning it on it additionally eliminates short term fluctuations due to sensor inaccuracy using a fuzzy-logic algorithm), the mean of daily differences in glucose (MODD[47]), average daily risk range (ADRR[42]), mean absolute glucose (MAG[48,49]), M-value with the possibility to set the reference ideal glucose value (IGV, default is 120 leading to M-120 index), index of glycemic control (IGC[50]), personal glycemic state (PGS[51]), glycemic variability percentage (GVP[52]), %TIR, percentage of time spent in ranges at risk (%TBR and %TAR), and also ranges defined by customizable thresholds.

CGM-GUIDE©

Computable metrics in CGM-GUIDE© are: mean, SD, MODD, CONGA(n) for the indicated n hours, MAGE (computed according to the Fritzsche algorithm[53]), time spent within customizable thresholds (in h) and percentage of time spent in hyperglycemic/hypoglycemic conditions (also given in h) that can be easily interpreted as TIR, TAR and TBR, respectively, and AUC above and below the hyper-/hypoglycemic limit (AUC-high/low). The user inputs to provide are the threshold ranges and the hyper- and hypoglycemic limits.

GVAP

Computable metrics in GVAP are average area below/above under curve (being AUC-high/low divided by time in min), customizable %TBR and %TAR, CONGA (with a fixed time window of 60 min), MODD, and a slightly modified version of an existing MAGE algorithm, that also separately considers the mean of the upward excursions (MAGE+), or downward excursion (MAGE-)[54] and from which the metric Excursion frequency (EF) is also obtained. Possible settings include the meaningful excursions value, which can be set within 30-500 $mg \cdot dl^{-1}$ and the target range, which can be set within 50-240 $mg \cdot dl^{-1}$. For the calculation of Avg. AUC-high/low, %TBR/%TAR and MAGE, the program uses all the available data, but for CONGA and MODD only result from days with measurements available for the whole day can be included.

Tidepool

Metrics computed in Tidepool are time in ranges (%TBR, %TAR, % TIR), mean, sensor usage (percentage of expected CGM readings), GMI, minimum (min), maximum (max), SD, and CV; default thresholds are the recommended 54, 70, 180 and 250 $mg \cdot dl^{-1}$, and for the central range, representing the target range (i.e., between 70 and 180 $mg \cdot dl^{-1}$), thresholds can be customized.

CGManalyzer

In CGManalyzer, the function summaryCGM.fn() allows computation of the following metrics: number of subjects, min, 1st quartile (Q1), median, mean, 3rd quartile(Q3), max, number of missing values, SD, mean absolute deviation (MAD); MODD.fn(), CONGA.fn() and MSEbyC.fn() functions allow to calculate MODD, CONGA (with specifiable time window) and MSE, respectively. Comparison of any pair of groups can be performed both in terms of glucose values and MSE by using the pairwiseComparison.fn() function that computes in each pair of groups the following metrics: mean difference, confidence interval,

SSMD, P-value of two-sided t-test, along with providing mean, SD, and sample size for each group. Running the main code will also provide results of a feature based on SSMD, named class of effect size[55], representing the strength of the difference between groups.

cgmanalysis

In cgmanalysis, the computed metrics are percentage of sensor usage (percentage of expected CGM readings), mean, estimated glycated hemoglobin concentration (eA1c[56]), GMI, Q1, median, Q3, SD, CV, min, max, recommended and additionally customizable time in ranges both in minutes and percentages (%TAR, %TBR, %TIR), AUC, MAGE[54], number of local glucose peaks over/under a specified amplitude (excursions_over/under) also computed per single day, J-index, CONGA (with specifiable time window), MODD, LBGI, HBGI. It is also possible to compute some of the metrics separately for single day, daytime and nighttime. The cgmvariables() function allows specifying the time threshold values for excursions (defaults are 35 and 10 minutes for upper and lower, respectively) and the value that defines how large an excursion must be to be considered in the MAGE computation.

GLU

In GLU the derived metrics are AUC, Fasting Proxy, being the mean of the six lowest consecutive glucose values occurring during night, MAD (being equal to median(|glucose−median(glucose)|), Post-event AUC and Post-event time to peak[57], being the mean applied to the 15 minutes occurring 1-hour or 2-hour after an event and the number of minutes between the event and the subsequent glucose peak value, respectively, standardized Glycemic Variability Percentage (sGVP[58]), %TAR, %TBR, %TIR. An event could be a registered meal, medication or physical exercise. The time in ranges are computed with specific threshold values depending on particular conditions of glucose tolerance (using the arguments diabetes and pregnancy, whose values follow those recommended by the consensus[18]) or customizable.

CGMStatsAnalyser

In CGMStatsAnalyser, computable metrics are subdivided into main, secondary, and other CGM indices and can be selected from those available in the respective sections. The "Main CGM indices" section calculates six metrics; these are the mean blood glucose (MBG, corresponding to mean), MAGE[40], J-index, SD, CONGA for the indicated n hours; the AUC-high is elaborated as "Secondary CGM indices" and computed with the option of selecting 10 $mmol \cdot l^{-1}$ or 15 $mmol \cdot l^{-1}$ as threshold. Moreover, through the section "Other CGM indices" the user could choose to compute also the following metrics: primary glycemic variability (CV), percentage of time in level 2 hypoglycemic range, percentage of time in level 1 hypoglycemic range, percentage of time in target range, percentage of time in level 1 hyperglycemic range, percentage of time in level 2 hyperglycemic range, corresponding to the %TIR, %TAR, %TBR computed using the thresholds recommended in the consensus[17], eA1C[59], HBGI and LBGI.

iglu

In iglu, CGM data are processed to derive metrics that can be diversified into time-independent and time-dependent metrics. Time-dependent metrics requires evenly spaced data between glucose values. Therefore, to create a grid of equidistant glucose measurements, the CGMS2daybyday() function is used. The Active Percent (percentage of expected CGM readings) is automatically provided as part of the standardized output of the Ambulatory Glucose Profile (AGP) and can also be obtained directly by calling the active_percent() function. The computed metrics are AUC, ADRR, CV, CONGA (with specifiable time window), continuous glucose monitoring index (COGI[60]), eA1c[56], GMI, GVP, GRADE, HBGI, LBGI, hyperglycemia index (Hyper Index)[50], hypoglycemia index (Hypo Index)[50], index of glycemic control (IGC[50]), interquartile range (IQR), J-index, mean absolute glucose change per unit time (MAG), MAD (computed as $1.4826 * \text{median}(|gl - \text{median}(gl)|)$), MAGE[40]

(with the possibility to choose an alternative version implemented in iglu which emulates the manual MAGE computation), mean, MODD, median, M-value, Q1, Q3, Range, Rate of Change (ROC, being $(\text{glucose}(t_i) - \text{glucose}(t_{i-1}))/t_i - t_{i-1}$), Standard Deviation of the Rate of Change, SD, TAR, TBR, TIR. Time in ranges default thresholds are the recommended ones[17], but can also be customized.

rGV

The metrics that can be computed by rGV are: mean, SD, CV, GMI, J-index, CONGA (with specifiable time window), LI, MODD, MAG, Distance travelled[61], GVP, LBGI and HBGI (with the option of using their corrected version[62]), M-value, GRADE (with the relative contribution of hypo-, eu- and hyperglycaemia), AUC, MAGE[40], ADRR, time in ranges (%TIR, %TBR, %TAR) with customizable thresholds, number of episodes (below 54 $mg \cdot dl^{-1}$ and above 70 $mg \cdot dl^{-1}$) per day. It gives the possibility to compute metrics also based on EasyGV implemented metrics, to make comparisons.

Cgmquantify

The metrics that can be computed by cgmquantify are SD, CV, CONGA24 (with n fixed to 24 hours), GMI, HBGI, LBGI, ADRR, J-index, MAGE[40], mean of glucose outside range (MGE[46], default range is 1SD of mean), mean of glucose inside range (MGN, default range is 1SD of mean), MODD, eA1c, mean, median, min, max, Q1, Q3, Percentage of time spent outside range (POR, also given in minutes), Percentage of time spent inside range (PIR, also given in minutes). The computation of the POR and PIR is done considering the sum of time spent inside or outside a specifiable multiple of SD[63]. In addition to the computation of SD and CV considering the entire CGM trace, cgmquantify provides values of the aforementioned metrics separately for each day and computes the mean, median and standard deviation of all the SD and CV obtained for each separate day.

Discussion

This review outlined the 12 available software packages and tools for the analysis of CGM data, by highlighting the characteristics of each of them. Among the older ones, there is CGM-GUIDE, not fully available anymore, while others have been updated recently, such as the pioneers EasyGV and Glyculator; as for the more recent ones, such as cgmanalysis, GLU, and iglu, updated versions are continuously made available on GitHub and CRAN (non-necessarily with an accompanying paper). The MAGE software package[53], which takes its name from the homonymous metric, has been excluded from this review since, differently from the included ones, it relates to the calculation of a single metric. Packages that are branching out from existing ones were also excluded; this is the case of Continuous Glucose Data Analysis (CGDA[64]), an R package (also available at https://github.com/EvdVossen/CGDA) that has been developed starting from the existing cgmanalysis source code and customizing its own features. Analysis has been focused on the software solutions available in the public domain; however, for the sake of completeness, the main characteristics of commercial/proprietary software solutions are summarized in Table 4.

Some considerations about usability and data management complexity can be derived from the comparison of the available solutions in terms of main characteristics and pre-processing procedures. For users with no technical programming skill, software packages that do not provide a GUI (such as cgmanalysis, CGManalyzer, GLU and cgmquantify) will be, in general, more difficult to use; moreover, the availability of a video tutorial (as in the case of Glyculator and Tidepool), in addition to a detailed documentation, may represent an important advantage. Those who can engage in simple instructions in programming language, however, will evaluate the single software based on their programming-language skills and the availability of the platform; in the case of MATLAB and Excel-based packages, for instance, the respective license is required. Moreover, in the case of web-based solutions that

does not provide a downloadable version such as CGMStatsAnalyser, an internet connection is required and analysis is not allowed when the website changes domain or when is under maintenance. From the point of view of developers, which are often in strict contact with the community of users represented by researchers and clinicians, packages providing open-source scripts are very important since they allow for interoperability and standardization of the analyses, necessary to obtain comparable and reliable results. As for the complexity of data management, packages that directly support the data format downloadable from popular CGM devices will be more desirable since they reduce time for dataset preparation. However, this aspect is not the only one that determines level of complexity for data management. Indeed, CGManalyzer seems to be characterized by a higher level of complexity in data management with respect the other solutions, although it supports data format from popular CGM devices; conversely, EasyGV showed very low level of complexity albeit it does not. From the citation overview, Glyculator and EasyGV appeared as the most used in scientific literature and this could be ascribed to the simplicity in data management and use.

The possibility to customize the analyses, offering a large variety of metrics and display options, is a key issue for the comparison of the available solutions. Indeed, the number of metrics proposed in the literature and the variety of available data display options are growing with the spread of CGM use, but this results in a lack of standardization. When choosing among the available solutions for CGM analysis, clinicians that are willing to monitor their patients, in order to adjust and personalize therapies as well as track the related improvements, will prefer those software packages that provide metrics and data visualization options recommended by the international consensus[17,18]; from the present analysis the highest number of standard metrics is provided by cgmanalysis and iglu. By easily displaying multiple information at the same time, the AGP report represents a powerful visualization modality, which could even be enhanced taking its basic version as starting point[65,66]. The

iglu package provides a rather faithful reproduction of this display mode, similarly to all the proprietary software solutions. In particular, the stacked bar charts for the representation of the time in range, also part of the AGP report, have shown to be an advantageous representation as they are compact and simple in performing comparisons[67]. The software solutions Glyculator, Tidepool and iglu provide time in range visualization as option; however, in none of them the display option of time in range is automatically adjusted to account for different thresholds in different categories of patients (i.e., older patients, pregnant women and different diabetes type). While clinicians may be more interested in solutions that offer standardized metrics, on the other hand, researchers may be interested in all the metrics and display options that best meet the needs of the analyses, depending on the research question they want to address. In the case of advanced statistical analysis, i.e., applying machine learning methods, having a high number of computable metrics could be desirable; in this regard, iglu provides a total of 39 metrics, a very high number compared to the proprietary solutions, and the highest among the non-commercial ones. Thus, incorporating in the software packages metrics that are continuously coming out would allow the evaluation of their properties and limitations, evaluating possible correlations with existent ones and their usefulness in characterizing glycemic control. For instance, software authors should consider including metrics such as COGI (that uses TIR, TBR and CV) - now available in iglu - and the more recent Glycemia Risk Index (GRI)[68], a composite metric that uses both level 1 and 2 of TBR and TAR in its computation. It can be observed that, currently, not all the software solutions are able to provide at the same time breakout by level 1 and level 2, which would be required for computation of GRI. If the software provides the possibility to set customizable thresholds, the information related to breakout by the two levels can be still obtained “off-line”, by using a two-step running and then computing difference between the

values obtained by the two runs. However, this option cannot be acknowledged as a real solution and may be not immediate in all the cases and for all the users.

The quality of the assessment of glycaemic control requires an adequate sampling duration to achieve an appropriate level of accuracy in the derived metrics. Indeed, there are some metrics (i.e., MAGE) that become unreliable in the presence of a significant data loss or low sampling frequency[69]. Consensus recommendations expect a CGM data length higher than 70% over 14 days, which has been shown sufficient to report TIR in presence of small data loss[70]; metrics that evaluate hypoglycemia, especially in populations characterized by higher glycemic variability, are more unstable and require longer window lengths[71]. This set the importance to include data quality control metrics (as already provided by EasyGV, Glyculator, CGManalyzer, cgmanalysis and iglu), helping the user give the right importance to the presence of missing data and to the number of days available for the analysis. Moreover, from the point of view of discriminating differences between subjects, MAG and M-value were shown able in attenuating the influence of within subject variability[72]. On the other hand, packages that provide the possibility to compute metrics both interday and intraday (single day, daytime and nighttime) allow to account for differences not only inter- but also intra-person.

Assessing equivalence among metrics computed by different software solutions is not straightforward. For metrics having adjustable parameters (IGC and M-value, just to mention some), same settings among the various software solutions is required for comparison purposes. Apart from this aspect, possible source of discrepancies in computation of a specific metric can be found in raw data manipulation and transformation, which are performed in different ways by different software during the preprocessing steps; however, software packages that include some preprocessing for data quality control are preferable since they take into account that the use of raw CGM data could lead to unmeaningful results. A second

source of discrepancies may derive from the existence of plural ways to compute quantities having the same meaning, sometimes maintaining the same names and acronyms. An example is the case of the MAGE metric, which, requiring an algorithm for peak definition and detection, has been implemented in plural ways and showed poor agreement among different software solutions[73], as confirmed by results of this study. Even in the case of simpler metrics such as the AUC, the user can face problems in comparing results obtained with different tools (as also shown in the results of this study) since often units differ and sometimes normalization is performed across different time intervals. The best way to avoid misinterpretation of the computations is to rely on those tools that provide open-source code or at least a detailed package documentation. Moreover, some packages, such as cgmanalysis, are trying to gain validation against metrics obtained by proprietary tools of CGM devices[74]; however comparison is possible only in terms of final results, without having access to the procedure used for the computation.

Depending on the use, each of the reviewed solutions has some peculiarities that can be exploited while performing CGM data analysis. It has to be noted that the Tidepool platform presents also some additional services since it enables the patient to integrate data from all his/her devices (such as not only CGM but also insulin pumps, blood meters and ketone meters) in a single app, sharing them directly with the doctor and for this reason representing a powerful solution for telemedicine practice; however, this will rise the need of standardization of metrics related to insulin, as proposed in a very recent study[75]. Moreover, the consistent data collection could be of interest for researchers who apply for the Tidepool Clinical Study Platform, where one will have access to de-identified patient data. Research studies analysis could also benefit from those packages, such as CGManalyzer and CGMStatsAnalyzer, that allow performing group analyses, considering different populations at the same time.

However, choosing among all the available solutions, one could quickly realize that he/she may need more than one at the same time. There is a great need to collaborate on software coding, including consensus on best practices and standards, software quality control, documentation, training, and maintainability to work as a community that acts to integrate all the existing options and to continuously adapt to new arising issues.

Conclusions

In this review, an overview of the available software packages for the analysis of CGM data has been provided. Reported information could be useful to researchers interested in working in CGM data analysis, as to clinicians and endocrinologists needing tools capable of handling CGM data effectively.

Author contributions

Agnese Piersanti: Conceptualization (equal); data curation (lead); investigation (lead); visualization (lead); writing – original draft (lead). Francesco Giurato: data curation (equal); investigation (equal); writing – review and editing (equal). Christian Göbl: Investigation (equal); writing – review and editing (equal). Laura Burattini: Investigation (equal); writing – review and editing (equal). Andrea Tura: Conceptualization (equal); investigation (equal); writing – review and editing (equal); Micaela Morettini: Conceptualization (lead); investigation (equal); Supervision (lead); writing – original draft (equal).

Conflicts of Interest

Nothing to disclose.

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824

825 **Figure legends**

826 Figure 1. Timeline of software-package first publication.

827

Tables

Table 1: Overview information of software packages for CGM data analysis.

Name	Glyculator	EasyGV	CGM-GUIDE	GVAP	Tidepool	CGManalyzer	cgmanalysis	GLU	CGMStatsAnalyser	iglu	rGV	cgmquantify
Year of analysed version	oct-21	oct-20	dec-11	apr-15	sep-15	gen-18	oct-19	feb-20	gen-21	apr-21	jul-21	aug-21
GUI	yes	yes	yes	yes	yes	no	no	no	yes	yes	yes	no
Available	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	yes
Open source	no‡	no	no	yes	yes	yes	yes	yes	no	yes	no	yes
Citations	68	221	24	19	29	17	23	4	0	5	0	1
Programming Language#	R	Mi	Mat 2008b	Mat 2010b	JS	R	R	R	app	R	R	R, Py
Supported devices§	any*	any*	any*	any*	11	AbbF, Glut, Dex, Med +any*	Dia, Dex, Med iPro 2, CL, AbbF +any*	Med iPro2, AbbF, Dex G6 +any*	Med iPro2 +any*	Dex, AbbF, AbbP, Med iPro +any*	any*	Dex, AbbF +any*
Data format	csv, txt, xls, xlsx	xlsm	xls	xls	d.s.	d.s.	csv	csv	csv	csv	csv	csv
Data frame	time, CGM	CGM	time, CGM	date, time, CGM , index	d.s.	d.s.	id, time, CGM	time, CGM	time, CGM	id, time, CGM	time, CGM	CGM, time, day
Input units	mg $\cdot dl^{-1}$, mmol $\cdot l^{-1}$	mmol $\cdot l^{-1}$	mg $\cdot dl^{-1}$	mg $\cdot dl^{-1}$	mg $\cdot dl^{-1}$, mmol $\cdot l^{-1}$	mg $\cdot dl^{-1}$, mmol $\cdot l^{-1}$	mg $\cdot dl^{-1}$	mmol $\cdot l^{-1}$	mmol $\cdot l^{-1}$	mg $\cdot dl^{-1}$	mg $\cdot dl^{-1}$	mg $\cdot dl^{-1}$
Complexity for data upload	low	low	-	med.	-	high	med.	med.	med.	med.	med.	med.
Download reports/data extraction	yes	yes	-	no	yes	yes	yes	yes	yes	yes	yes	yes
Units conversion	yes	to mmol $\cdot l^{-1}$	no	no	yes	no	no	no	no	n.a.	no	yes
Documentation	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	yes
Updating	yes	yes	no	no	yes	yes	yes	yes	new	yes	new	new
Toy example	yes	yes	no	yes	yes	yes	yes	yes	no	yes	no	yes
Video tutorial	yes	no	no	no	yes	no	no	no	no	no	no	no

Number of citations provided is based on Scopus (latest search May 2022).
* any device is accepted after conversion to a general format;
# Programming languages: R, Microsoft (Mi), Matlab (Mat), Javascript (JS), Java (J), Python (Py), Ruby (Ru);
§ Supported devices: Abbott FreeStyle Libre (AbbF), Glutalor (Glut), Dexcom (Dex), Medtronic (Med), Diasend (Dia), Carelink (CL), Abbott FreeStyle Libre Pro (AbbP);
- not available information;
‡ Glyculator source code available only for the previous versions;
d.s.: device specific;
n.a: not available;
med.: medium.

840 Table 2: Description of all the metrics that can be found in at least one of the revised software solutions.

Metric	Description
eA1c†	Estimated HbA1c[56,59]
%TAR†‡	Percentage of time spent above range (sometimes given in minutes)
%TBR†‡	Percentage of time spent below range (sometimes given in minutes)
%TIR†‡	Percent of time spent in the target range (sometimes given in minutes)
%of expected CGM readings†‡	Percentage of time the device was active with respect to the wearing time
ADRR	Average daily risk range, assessment of total daily glucose variations within risk space[42]
AUC†	Area under the glucose curve (eventually normalized to the duration of a measurement)
AUC-high/low	AUC above and below the hyper-/hypoglycemic limit
COGI	Continuous glucose monitoring index[60]
CONGA	Continuous overall net glycemic action[44]
CV†‡	Coefficient of variation of glucose trace (sometimes given in %)
daytime	Number of all sensor glucose values during specified daytime hours[30]
Distance Travelled	The sum of the absolute difference in glucose levels for one day of consecutive CGM readings[61]
EF	Excursion frequency, corresponding to the sum of all excursions
excursions_over/under	The number of local glucose peaks with an amplitude greater than a specifiable threshold [30]
Fasting Proxy	Measure of fasting glucose levels computed as the mean of the six lowest consecutive glucose values occurring during night[31]
FD	Fractal dimension[76]
GMI‡	Glucose management indicator [41]
GRADE	Glycemic risk assessment in diabetes equation[43]
GVP	Glycemic variability percentage[52]
HBGI/LBGI†	High blood glucose index/ low blood glucose index[42,62]
Hyper/Hypo Index	Hyperglycemia/hypoglycemia index[50]
IGC	Index of glycemic control, equal to the sum of hyper index and hypo index[50]
IQR	Interquartile range of glucose
J-index	Measure of both the mean level and variability of glycemia[39]
LI	Lability Index[45]
MAD	Mean absolute deviation
MAG	Mean absolute glucose change per unit time[48]
MAGE	Mean amplitude of glucose excursions (default = 1SD)[40,46,53,54]
max	Maximum glucose over all days
mean†‡	Mean glucose over all days
median	Median glucose over all days
MGE	Mean of glucose outside range (default = 1SD)[46]
MGN	Mean of glucose inside range (default = 1SD)[34]
min	Minimum glucose over all days
MODD	Mean of daily differences in glucose[47]
MSE	Multiscale sample entropy[28]
M-value	Measure of variation of glucose values around a reference value[38]
nighttime	Number of all sensor glucose values during specified nighttime hours[30]
Number of days CGM worn†‡	Number of days the device was worn
number of episodes per day	Number of episodes (below 54 mg·dl^{-1} and above 70 mg·dl-1) per day
number of missing values	Number of missing glucose readings
PGS	Personal glycemic state; composite index that assesses four domains of glycemic control: mean glucose, glycemic variability, time in range and frequency and severity of hypoglycemia[51]
PIR	Percent of time spent inside range specified as multiple of SD (also in minutes), default = 1SD[63]
POR	Percent of time spent outside range specified as multiple of SD (also in minutes), default = 1SD[63]
Post-event AUC	Mean of the blood glucose measurements applied to the 15 minutes occurring 1-hour or 2-hour after meal, medication or physical exercise events[57]
Post-event time to peak	The number of minutes between the meal and the subsequent glucose peak value[57]
Q1	First quartile glucose value over all days
Q3	Third quartile glucose value over all days
Range	Range of glucose values
ROC	Rate of change of glucose
SD†	Standard Deviation of glucose trace
SD of ROC	Standard deviation of the rate of change of glucose
sGVP	Standardized glycemic variability percentage; length of the flattened glucose trace after being standardized, which reflects the degree of trace undulation[58]

841 Please note that in the original software name of the metric may slightly differ from the one here reported.
842 † Key metrics for CGM data analysis recommended by the 2017 international consensus on use of CGM[17];
843 ‡ Standardized CGM metrics for clinical care recommended by the 2019 international consensus on time in range[18].

844 Table 3: Compendium of metrics values computed on a single standard CGM recording according to the different

845 software packages.

	Glyculator	**EasyGV**	**CGM-GUIDE**	**GVAP**	**Tidepool**	**CGManalyzer**	**cgmanalysis**	**GLU**	**CGMStats Analyser**	**iglu**	**rGV**	**cgmquantify**
Tool version used	**3.0**	**10**	**-**	**1.1**	**-**	**1.3**	**2.7.3**	**0.2.0**	**0.1.0**	**3.3.1**	**0.0.1**	**0.1.0**
Metrics												
eA1c (%)							**8.4**		**8.4**	**8.4**		**8.4**
TAR-level1‖ (%)	**49**	**49**	-	**49**#	-		**50**	**50**⁑#	**50**	**49**	**24**	
TBR-level1‖ (%)	**10**	**10**	-	**10**#	-		**10**	**10**⁑#	**4**	**10**	**4**	
TAR-level2 (%)	**25**	**25**	-	**25**#	-		**25**	**25**⁑#	**25**	**25**	**25**	
TBR-level2 (%)	**6**	**6**	-	**6**#	-		**6**	**6**⁑#	**6**	**6**	**6**	
TIR (%)	**41**	**41**	-		-		9^	**41**⁑	**41**	**41**	**41**	
Expected CGM readings (%)	**100**⁑				-		**100**§			**100**		
ADRR (d.n.)		**65.7**								54.6§	**65.7**	soon
AUC‡	**10.7** mmol·l^{-1}						**6.2 ·(10^4)*** mmol·l^{-1} ·min	**10.7** mmol·l^{-1}		**10.7*** mmol·l^{-1}	**1.5 ·(10^4)*** mmol·l^{-1} ·min 24h AUC	
AUC-high/low‡			-	**2.4 /0.1*** mmol·l^{-1}					**133.0 ·(10^2)** /- mmol·l^{-1} ·min			
COGI (%)										**36**⁑		
CONGA1 (mmol·l^{-1})		3.1¶	-	2.2*§		**2.5**	**2.5***		**2.5**	**2.5***	**2.5***	soon
%CV (%)	**48**	**48**⁑			-		**48**⁑		**48**	**48**	**48**	**48**
Distance Travelled (mmol·l^{-1})											**215.9***	
EF (count)				**20**								
Excursions over/under (count)							**7/ 3**					
Fasting proxy (mmol·l^{-1})								**5.8**				
GMI (%)	**7.9**				-		**7.9**			**7.9**	**7.9**	**7.9**
GRADE (d.n.)	**14.85**	**14.37**								**14.85**	**14.85**	
GRADE-Hypo (%)		**14**								**14**	**13**⁑	
GRADE-Eugly (%)		**3**								**3**	**3**⁑	
GRADE-Hyper (%)		**83**								**84**	**83**⁑	
GVP (%)		**29.68**								1.29†	**29.68**	
HBGI (d.n.)	**14.22**	**14.23**					17.46^		**14.26**	**14.23**	**14.23**	5.54^
Hyper/Hypo Index (d.n.)										**3.66/ 3.13**		
IGC (d.n.)		**6.78**								**6.78**		
IQR (mmol·l^{-1})										**6.7***		
J-index (d.n.)	**81.60**	**81.44**					**81.44**		**81.44**	**81.44**	**81.46**	**81.44**
LBGI (d.n.)	**2.53**	**2.54**					13.75^		**2.54**	**2.54**	**2.54**	3.60^
LI (d.n.)		**6.3**									**6.3***	
MAD (mmol·l^{-1})						4.9†		**3.5**		**3.3***		
MAG (mmol·l^{-1})		**2.3**								**2.2**	**2.3**	
MAGE‡ (mmol·l^{-1})	**8.7**	**12.4**	-	**9.0***			**8.1***		**8.6**	**12.5***	not present	soon

MAGE+/ MAGE-‡ (mmol·l^{-1})				**9.1/ 8.9***						**12.6/ 12.5***	not present	
max/min (mmol·l^{-1})					-	**22.2/ 2.2**	**22.2/ 2.2***			**22.2/ 2.2***		**22.2/ 2.2***
mean (mmol·l^{-1})	**10.7**	**10.7**	-	**10.7***	-	**10.7**	**10.7***		**10.7**	**10.7***	**10.7***	**10.7***
median (mmol·l^{-1})	**9.9**					**9.9**	**9.9***			**9.9***		**9.9***
MGE (mmol·l^{-1})												**11.7***
MGN (mmol·l^{-1})												10.7^*
MODD (mmol·l^{-1})		**4.4**	-	-1.0§		0.9§	**4.4***			**4.4***	**4.4***	soon
MSE (d.n.)						array						
M-value (d.n.)	294.8^	**47.5**								**47.5**	65.5†	
number of days CGM worn	**4**						**4**			**4**		
number of episodes per day											**0.5**	
number of missing values		**0**				**0**						
PGS (d.n.)		**26.99**										
PIR (%)												not present
POR (%)												**33**
Post-event AUC								no event				
Post-event time to peak (min)								no event				
Q1/Q3 (mmol·l^{-1})						**7.2/ 13.9**	**7.2/ 13.9***			**7.2/ 13.9***		**7.2/ 13.9***
Range (mmol·l^{-1})										20.0*		
ROC (mmol·l^{-1} min^{-1})										array		
SD (mmol·l^{-1})	**5.1**	**5.1**	-	**5.1***	-	**5.1**	**5.1***		**5.1**	**5.1***	**5.1***	**5.1***
SD of ROC (mmol·l^{-1} min^{-1})										**0.05***		
sGVP (%)								**0.022**				
Total computed metrics	19	26	11	12	11	10	23	11	15	39	28	19
Total computed standard metrics	13	9	6	5	6	1	14	6	10	14	11	6
Total error and warning/Total metrics	1/19	1/26	-	2/12	-	1/10	4/23	0/11	0/15	1/39	0/28	3/19

Grey-color cells indicate consensus metrics (2017 and 2019); settings for the metrics are as follows: n=1 for CONGA, LLTR = 80, ULTR = 140, a = 1.1, b = 2, c = 30, d = 30 for IGC, Hyper and Hypo Index, M100 is considered for the M-value; d.n. stands for dimensionless number; "not present" indicates that the metric was not given as output when using the tool; "no event" indicates that the metric cannot be computed when event information is absent (as in the present case); "soon" means that the metric is only available in the Python-based version and, as declared by the software authors, will be made soon available in the R version (the one here used).

Metric values in agreement with the expected ones are marked in bold; errors/warnings/notes are marked with flags described below (detailed explanation is provided in SupplementaryInfo.docx).

Error/warning flags:

^ error in the computation;

§ warning on the code;

¶ warning on identified difference for no apparent reason that can be detected by the authors.

Note flags:

‡ difference due to the specific algorithm used and/or the time interval considered for metric computation;

‖ difference due to inclusion/not inclusion of level 2 values as part of level 1 (>180 mg·dl^{-1} or 181-250 mg·dl^{-1} for TAR-level 1 and <70 mg·dl^{-1} or 54-69 mg·dl^{-1} for TBR-level 1);

† difference in the interpretation;

* conversion from mg·dl^{-1} to mmol·l^{-1} using 18 as conversion factor;

two-step estimation for level 1 and 2 of %TAR and %TBR; this estimation was not obtained directly from the software but off-line by the user as a result of a two-step running;

⁑ not directly provided as percentage by the software;

- no metric values can be obtained due to accessibility issues.

869 Table 4: Brief description of the characteristics of proprietary/commercial solutions.

Metrics and main features	Medtronic Carelink	Dexcom Clarity	Abbott LibreView	Senseonics Eversense	Glokoo	IDC AGP for clinical trials
eA1c				x		
mean	x	x	x	x	x	x
median		x			x	
min, max		x		x		
Q1-Q3		x				
IQR		x				
GMI	x	x	x		x	x
SD		x			x	
SD Mean		x				x
%CV	x	x	x		x	x
AUC						x
AUC high/low	x					
MODD						x
MAGE						x
Episodes avg. minutes/day						x
Episodes mean episodes/day						x
Episodes mean duration in minutes/day						x
Average daily calibrations		x		x		
Time in range	level 1 and 2	level 1 and 2	level 1 and 2	level 1 and 2	level 1 and 2	level 1 and 2
Sensor usage	% in a week	in %	in %	in %	in %	in %
Compare		compare selected data ranges				
AGP licensed partner	x	x	x	x	x	-
App	x	x	x	x	x	
Data import	uploader	app or uploader	app or USB drivers	app or uploader	app or uploader	
Data export/storage	x	x	x	x	x	x
TIR display	stacked bars charts	stacked bars charts	stacked bars charts	stacked bars charts and pie charts	stacked bars charts	stacked bars charts
Reports	AGP report; overlays of sensor glucose tracings in a 24 h timeline; episodes summary for hyper and hypoglycemia related episodes	AGP report; average glucose trend over the selected date range displayed in a 24 h timeline with hyper and hypoglycemia colored bars; overlay graph displaying 1 week of data with 7 CGM lines in a 24 h timeline; daily graphs; episodes: lows, highs, and best day	AGP report; daily glucose in a weekly summary report; episodes (highs, highs with some lows, lows) displayed in an interpretation of the AGP report	AGP report; average glucose trend over the selected date range displayed in a 24 h timeline showing maximum, minimum, 10th-90th percentiles and average glucose reading for every hour; glucose trends over a selected date range; individual glucose readings over a 24-hour period each day of the week displayed in a different color	AGP report	AGP report

Link to product documentation*	https://www.medtronicdiabetes.com/customer-support/carelink-software-support/carelink-reports	https://provider.dexcom.com/education-research/cgm-education-use/product-information	https://pro.libreview.io/	https://global.eversensediabetes.com/patient-education/eversense-user-guides	https://support.glooko.com/hc/en-us/articles/360001498269-Glooko-for-Personal-Use-Quick-Start-Guide	http://www.agpreport.org/agp/research

*accessed 2022/07