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

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

50 **Software Packages and Tools for the Analysis of Continuous**

51 **Glucose Monitoring Data**

52

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61 **Running title:** Software packages for CGM data analysis

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63

64 **Keywords:** CGM, glycemic variability, diabetes, toolbox, software application, graphical

65 user interface.

## 66 **Abstract**

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

## 91 **Introduction**

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

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

116 CGM devices manufacturers; however, international consensus on CGM data analysis and  
117 standard metrics that should be computed for clinical care has been reached only recently<sup>17,18</sup>.

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

## 127 **Comparison of Available Software Packages and Tools in terms of Main** 128 **Characteristics and Preprocessing Procedures**

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

### 132 **GlyCulator**

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

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

### 147 **EasyGV**

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

### 157 **CGM-GUIDE<sup>®</sup>**

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

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

### 171 **GVAP**

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

### 184 **Tidepool**

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



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

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

## 213 **CGManalyzer**

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

## 232 **cgmanalysis**

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

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

## 249 **GLU**

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

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

### 273 **CGMStatsAnalyser**

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

288 trace of glucose with respect to time represented by the median value and the 5<sup>th</sup> and 95<sup>th</sup>  
289 percentiles. Interactive visualization of metrics can be displayed using violin plots, with the  
290 possibility to observe the different distributions according to a specified grouping variable.  
291 Moreover, a heatmap of the correlation between the computed metrics can be displayed and  
292 by clicking on the colored dot representing a specific pair of metrics, the value of the  
293 correlation coefficient and  $-\log_{10}(\text{p-value})$  will be visualized.

## 294 **iglu**

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

### 311 **rGV**

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

### 321 **cgmquantify**

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

## 332 **Comparison of Available Software Packages and Tools in Terms of** 333 **Computed Metrics**

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

### 343 **GlyCulator**

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

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

### 360 **EasyGV**

361 Computable metrics in EasyGV are: mean, SD, CV, the continuous overall net glycemic  
362 action (CONGA<sup>44</sup>) with the possibility to define the time window length (default value is 60  
363 min), Lability Index (LI<sup>45</sup>) with the possibility to define the interval (default value is 60 min),  
364 J-index, LBGI, HBGI, GRADE (also with the computation of the relative contribution of  
365 hypo-, eu- and hyperglycaemia to the GRADE risk score, expressed in percentage), MAGE  
366 (with the possibility to compute a modified version, MAGE-CGM, for peak-to-trough or  
367 trough-to-peak identification<sup>46</sup>, more suitable for CGM readings; default is 0=off but turning  
368 it on it additionally eliminates short term fluctuations due to sensor inaccuracy using a fuzzy-  
369 logic algorithm), the mean of daily differences in glucose (MODD<sup>47</sup>), average daily risk range  
370 (ADRR<sup>42</sup>), mean absolute glucose (MAG<sup>48,49</sup>), M-value with the possibility to set the  
371 reference ideal glucose value (IGV, default is 120 leading to M-120 index), index of glycemic  
372 control (IGC<sup>50</sup>), personal glycemic state (PGS<sup>51</sup>), glycemic variability percentage (GVP<sup>52</sup>),  
373 %TIR, percentage of time spent in ranges at risk (%TBR and %TAR), and also ranges defined  
374 by customizable thresholds.

### 375 **CGM-GUIDE<sup>©</sup>**

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



## 382 **GVAP**

383 Computable metrics in GVAP are average area below/above under curve (being AUC-  
384 high/low divided by time in min), customizable %TBR and %TAR, CONGA (with a fixed  
385 time window of 60 min), MODD, and a slightly modified version of an existing MAGE  
386 algorithm, that also separately considers the mean of the upward excursions (MAGE+), or  
387 downward excursion (MAGE-)<sup>54</sup> and from which the metric Excursion frequency (EF) is also  
388 obtained. Possible settings include the meaningful excursions value, which can be set within  
389 30-500 mg·dl<sup>-1</sup> and the target range, which can be set within 50-240 mg·dl<sup>-1</sup>. For the  
390 calculation of Avg. AUC-high/low, %TBR/%TAR and MAGE, the program uses all the  
391 available data, but for CONGA and MODD only result from days with measurements  
392 available for the whole day can be included.

## 393 **Tidepool**

394 Metrics computed in Tidepool are time in ranges (%TBR, %TAR, % TIR), mean, sensor usage  
395 (percentage of expected CGM readings), GMI, minimum (min), maximum (max), SD, and  
396 CV; default thresholds are the recommended 54, 70, 180 and 250 mg·dl<sup>-1</sup>, and for the central  
397 range, representing the target range (i.e., between 70 and 180 mg·dl<sup>-1</sup>), thresholds can be  
398 customized.

## 399 **CGManalyzer**

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

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

#### 410 **cgmanalysis**

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

#### 421 **GLU**

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

## 432 **CGMStatsAnalyser**

433 In CGMStatsAnalyser, computable metrics are subdivided into main, secondary, and other  
434 CGM indices and can be selected from those available in the respective sections. The “Main  
435 CGM indices” section calculates six metrics; these are the mean blood glucose (MBG,  
436 corresponding to mean), MAGE<sup>40</sup>, J-index, SD, CONGA for the indicated n hours; the AUC-  
437 high is elaborated as “Secondary CGM indices” and computed with the option of selecting 10  
438 mmol·l<sup>-1</sup> or 15 mmol·l<sup>-1</sup> as threshold. Moreover, through the section “Other CGM indices”  
439 the user could choose to compute also the following metrics: primary glycemic variability  
440 (CV), percentage of time in level 2 hypoglycemic range, percentage of time in level 1  
441 hypoglycemic range, percentage of time in target range, percentage of time in level 1  
442 hyperglycemic range, percentage of time in level 2 hyperglycemic range, corresponding to  
443 the %TIR, %TAR, %TBR computed using the thresholds recommended in the consensus<sup>17</sup>,  
444 eA1C<sup>59</sup>, HBGI and LBGI.

## 445 **iglu**

446 In iglu, CGM data are processed to derive metrics that can be diversified into time-  
447 independent and time-dependent metrics. Time-dependent metrics requires evenly spaced  
448 data between glucose values. Therefore, to create a grid of equidistant glucose measurements,  
449 the CGMS2daybyday() function is used. The Active Percent (percentage of expected CGM  
450 readings) is automatically provided as part of the standardized output of the Ambulatory  
451 Glucose Profile (AGP) and can also be obtained directly by calling the active\_percent()  
452 function. The computed metrics are AUC, ADRR, CV, CONGA (with specifiable time  
453 window), continuous glucose monitoring index (COGI<sup>60</sup>), eA1c<sup>56</sup>, GMI, GVP, GRADE,  
454 HBGI, LBGI, hyperglycemia index (Hyper Index)<sup>50</sup>, hypoglycemia index (Hypo Index)<sup>50</sup>,  
455 index of glycemic control (IGC<sup>50</sup>), interquartile range (IQR), J-index, mean absolute glucose  
456 change per unit time (MAG), MAD (computed as  $1.4826 * \text{median}(|g1 - \text{median}(g1)|)$ ), MAGE<sup>40</sup>

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

#### 462 **rGV**

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

#### 470 **Cgmquantify**

471 The metrics that can be computed by cgmquantify are SD, CV, CONGA24 (with n fixed to  
472 24 hours), GMI, HBGI, LBGI, ADRR, J-index, MAGE<sup>40</sup>, mean of glucose outside range  
473 (MGE<sup>46</sup>, default range is 1SD of mean), mean of glucose inside range (MGN, default range  
474 is 1SD of mean), MODD, eA1c, mean, median, min, max, Q1, Q3, Percentage of time spent  
475 outside range (POR, also given in minutes), Percentage of time spent inside range (PIR, also  
476 given in minutes). The computation of the POR and PIR is done considering the sum of time  
477 spent inside or outside a specifiable multiple of SD<sup>63</sup>. In addition to the computation of SD  
478 and CV considering the entire CGM trace, cgmquantify provides values of the aforementioned  
479 metrics separately for each day and computes the mean, median and standard deviation of all  
480 the SD and CV obtained for each separate day.

## 481 **Discussion**

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

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

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

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

531 iglu package provides a rather faithful reproduction of this display mode, similarly to all the  
532 proprietary software solutions. In particular, the stacked bar charts for the representation of  
533 the time in range, also part of the AGP report, have shown to be an advantageous  
534 representation as they are compact and simple in performing comparisons<sup>67</sup>. The software  
535 solutions Glyculator, Tidepool and iglu provide time in range visualization as option;  
536 however, in none of them the display option of time in range is automatically adjusted to  
537 account for different thresholds in different categories of patients (i.e., older patients, pregnant  
538 women and different diabetes type). While clinicians may be more interested in solutions that  
539 offer standardized metrics, on the other hand, researchers may be interested in all the metrics  
540 and display options that best meet the needs of the analyses, depending on the research  
541 question they want to address. In the case of advanced statistical analysis, i.e., applying  
542 machine learning methods, having a high number of computable metrics could be desirable;  
543 in this regard, iglu provides a total of 39 metrics, a very high number compared to the  
544 proprietary solutions, and the highest among the non-commercial ones. Thus, incorporating  
545 in the software packages metrics that are continuously coming out would allow the evaluation  
546 of their properties and limitations, evaluating possible correlations with existent ones and their  
547 usefulness in characterizing glycemic control. For instance, software authors should consider  
548 including metrics such as COGI (that uses TIR, TBR and CV) - now available in iglu - and  
549 the more recent Glycemia Risk Index (GRI)<sup>68</sup>, a composite metric that uses both level 1 and  
550 2 of TBR and TAR in its computation. It can be observed that, currently, not all the software  
551 solutions are able to provide at the same time breakout by level 1 and level 2, which would  
552 be required for computation of GRI. If the software provides the possibility to set  
553 customizable thresholds, the information related to breakout by the two levels can be still  
554 obtained “off-line”, by using a two-step running and then computing difference between the

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

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

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



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

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

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

## 610 **Conclusions**

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

## 615 **Author contributions**

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

## 623 **Conflicts of Interest**

624 Nothing to disclose.

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825 **Figure legends**

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

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828 **Tables**

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

Name	Glycylator	EasyGV	CGM-GUIDE	GVAP	Tidepool	CGManalyzer	cgmanalysis	GLU	CGMStatsAnalyzer	iglu	rGV	cgquantify
<b>Year analysed version</b>	oct-21	oct-20	dec-11	apr-15	sep-15	gen-18	oct-19	feb-20	gen-21	apr-21	jul-21	aug-21
<b>GUI</b>	yes	yes	yes	yes	yes	no	no	no	yes	yes	yes	no
<b>Available</b>	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	yes
<b>Open source</b>	no‡	no	no	yes	yes	yes	yes	yes	no	yes	no	yes
<b>Citations</b>	68	221	24	19	29	17	23	4	0	5	0	1
<b>Programming Language#</b>	R	Mi	Mat 2008b	Mat 2010b	JS	R	R	R	app	R	R	R, Py
<b>Supported devices§</b>	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*
<b>Data format</b>	csv, txt, xls, xlsx	xlsm	xls	xls	d.s.	d.s.	csv	csv	csv	csv	csv	csv
<b>Data frame</b>	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
<b>Input units</b>	mg ·dl <sup>-1</sup> , mmol ·l <sup>-1</sup>	mmol ·l <sup>-1</sup>	mg ·dl <sup>-1</sup>	mg ·dl <sup>-1</sup>	mg ·dl <sup>-1</sup> , mmol ·l <sup>-1</sup>	mg ·dl <sup>-1</sup> , mmol ·l <sup>-1</sup>	mg ·dl <sup>-1</sup>	mmol ·l <sup>-1</sup>	mmol ·l <sup>-1</sup>	mg ·dl <sup>-1</sup>	mg ·dl <sup>-1</sup>	mg ·dl <sup>-1</sup>
<b>Complexity for data upload</b>	low	low	-	med.	-	high	med.	med.	med.	med.	med.	med.
<b>Download reports/data extraction</b>	yes	yes	-	no	yes	yes	yes	yes	yes	yes	yes	yes
<b>Units conversion</b>	yes	to mmol ·l <sup>-1</sup>	no	no	yes	no	no	no	no	n.a.	no	yes
<b>Documentation</b>	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	yes
<b>Updating</b>	yes	yes	no	no	yes	yes	yes	yes	new	yes	new	new
<b>Toy example</b>	yes	yes	no	yes	yes	yes	yes	yes	no	yes	no	yes
<b>Video tutorial</b>	yes	no	no	no	yes	no	no	no	no	no	no	no

830 Number of citations provided is based on Scopus (latest search May 2022).  
 831 \* any device is accepted after conversion to a general format;  
 832 # Programming languages: R, Microsoft (Mi), Matlab (Mat), Javascript (JS), Java (J), Python (Py), Ruby (Ru);  
 833 § Supported devices: Abbott FreeStyle Libre (AbbF), Glutalor (Glut), Dexcom (Dex), Medtronic (Med), Diasend (Dia), Carelink (CL),  
 834 Abbott FreeStyle Libre Pro (AbbP);  
 835 - not available information;  
 836 ‡ Glycylator source code available only for the previous versions;  
 837 d.s.: device specific;  
 838 n.a.: not available;  
 839 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 <sup>56,59</sup>
%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 <sup>42</sup>
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 <sup>60</sup>
CONGA	Continuous overall net glycemic action <sup>44</sup>
CV†‡	Coefficient of variation of glucose trace (sometimes given in %)
daytime	Number of all sensor glucose values during specified daytime hours <sup>30</sup>
Distance Travelled	The sum of the absolute difference in glucose levels for one day of consecutive CGM readings <sup>61</sup>
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 <sup>30</sup>
Fasting Proxy	Measure of fasting glucose levels computed as the mean of the six lowest consecutive glucose values occurring during night <sup>31</sup>
FD	Fractal dimension <sup>76</sup>
GMI‡	Glucose management indicator <sup>41</sup>
GRADE	Glycemic risk assessment in diabetes equation <sup>43</sup>
GVP	Glycemic variability percentage <sup>52</sup>
HBGI/LBGI†	High blood glucose index/ low blood glucose index <sup>42,62</sup>
Hyper/Hypo Index	Hyperglycemia/hypoglycemia index <sup>50</sup>
IGC	Index of glycemic control, equal to the sum of hyper index and hypo index <sup>50</sup>
IQR	Interquartile range of glucose
J-index	Measure of both the mean level and variability of glycemia <sup>39</sup>
LI	Libality Index <sup>45</sup>
MAD	Mean absolute deviation
MAG	Mean absolute glucose change per unit time <sup>48</sup>
MAGE	Mean amplitude of glucose excursions (default = 1SD) <sup>40,46,53,54</sup>
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) <sup>46</sup>
MGN	Mean of glucose inside range (default = 1SD) <sup>34</sup>
min	Minimum glucose over all days
MODD	Mean of daily differences in glucose <sup>47</sup>
MSE	Multiscale sample entropy <sup>28</sup>
M-value	Measure of variation of glucose values around a reference value <sup>38</sup>
nighttime	Number of all sensor glucose values during specified nighttime hours <sup>30</sup>
Number of days CGM worn†‡	Number of days the device was worn
number of episodes per day	Number of episodes (below 54 mg·dl <sup>-1</sup> and above 70 mg·dl <sup>-1</sup> ) 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 <sup>51</sup>
PIR	Percent of time spent inside range specified as multiple of SD (also in minutes), default = 1SD <sup>63</sup>
POR	Percent of time spent outside range specified as multiple of SD (also in minutes), default = 1SD <sup>63</sup>
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 <sup>57</sup>
Post-event time to peak	The number of minutes between the meal and the subsequent glucose peak value <sup>57</sup>
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 <sup>58</sup>

Please note that in the original software name of the metric may slightly differ from the one here reported.

† Key metrics for CGM data analysis recommended by the 2017 international consensus on use of CGM<sup>17</sup>;

‡ Standardized CGM metrics for clinical care recommended by the 2019 international consensus on time in range<sup>18</sup>.

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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	egmanalysis	GLU	CGMStats Analyser	iglu	rGV	egmquantify
<b>Tool version used</b>	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
<b>Metrics</b>												
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 <sup>-1</sup>						6.2 ·(10 <sup>4</sup> )* mmol·l <sup>-1</sup> ·min	10.7 mmol·l <sup>-1</sup>		10.7* mmol·l <sup>-1</sup>	1.5 ·(10 <sup>4</sup> )* mmol·l <sup>-1</sup> ·min 24h AUC	
AUC-high/low‡			-	2.4 /0.1* mmol·l <sup>-1</sup>					133.0 ·(10 <sup>2</sup> ) /- mmol·l <sup>-1</sup> ·min			
COGI (%)										36*		
CONGA1 (mmol·l <sup>-1</sup> )		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 <sup>-1</sup> )											215.9*	
EF (count)				20								
Excursions over/under (count)							7/3					
Fasting proxy (mmol·l <sup>-1</sup> )								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 <sup>-1</sup> )										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 <sup>-1</sup> )						4.9†		3.5		3.3*		
MAG (mmol·l <sup>-1</sup> )		2.3								2.2	2.3	
MAGE‡ (mmol·l <sup>-1</sup> )	8.7	12.4	-	9.0*			8.1*		8.6	12.5*	not present	soon

MAGE+/ MAGE-‡ (mmol·l <sup>-1</sup> )				<b>9.1/ 8.9*</b>						<b>12.6/ 12.5*</b>	not present	
max/min (mmol·l <sup>-1</sup> )					-	<b>22.2/ 2.2</b>	<b>22.2/ 2.2*</b>			<b>22.2/ 2.2*</b>		<b>22.2/ 2.2*</b>
mean (mmol·l <sup>-1</sup> )	<b>10.7</b>	<b>10.7</b>	-	<b>10.7*</b>	-	<b>10.7</b>	<b>10.7*</b>		<b>10.7</b>	<b>10.7*</b>	<b>10.7*</b>	<b>10.7*</b>
median (mmol·l <sup>-1</sup> )	<b>9.9</b>					<b>9.9</b>	<b>9.9*</b>			<b>9.9*</b>		<b>9.9*</b>
MGE (mmol·l <sup>-1</sup> )												<b>11.7*</b>
MGN (mmol·l <sup>-1</sup> )												10.7 <sup>^*</sup>
MODD (mmol·l <sup>-1</sup> )		<b>4.4</b>	-	-1.0§		0.9§	<b>4.4*</b>			<b>4.4*</b>	<b>4.4*</b>	soon
MSE (d.n.)						array						
M-value (d.n.)	294.8 <sup>^</sup>	<b>47.5</b>								<b>47.5</b>	65.5 <sup>†</sup>	
number of days CGM worn	<b>4</b>						<b>4</b>			<b>4</b>		
number of episodes per day											<b>0.5</b>	
number of missing values		<b>0</b>				<b>0</b>						
PGS (d.n.)		<b>26.99</b>										
PIR (%)												not present
POR (%)												<b>33</b>
Post-event AUC								no event				
Post-event time to peak (min)								no event				
Q1/Q3 (mmol·l <sup>-1</sup> )						<b>7.2/ 13.9</b>	<b>7.2/ 13.9*</b>			<b>7.2/ 13.9*</b>		<b>7.2/ 13.9*</b>
Range (mmol·l <sup>-1</sup> )										<b>20.0*</b>		
ROC (mmol·l <sup>-1</sup> min <sup>-1</sup> )										array		
SD (mmol·l <sup>-1</sup> )	<b>5.1</b>	<b>5.1</b>	-	<b>5.1*</b>	-	<b>5.1</b>	<b>5.1*</b>		<b>5.1</b>	<b>5.1*</b>	<b>5.1*</b>	<b>5.1*</b>
SD of ROC (mmol·l <sup>-1</sup> min <sup>-1</sup> )										<b>0.05*</b>		
sGVP (%)								<b>0.022</b>				
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

846 Grey-color cells indicate consensus metrics (2017 and 2019); settings for the metrics are as follows: n=1 for CONGA, LLTR  
847 = 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.  
848 stands for dimensionless number; “not present” indicates that the metric was not given as output when using the tool; “no  
849 event” indicates that the metric cannot be computed when event information is absent (as in the present case); “soon” means  
850 that the metric is only available in the Python-based version and, as declared by the software authors, will be made soon  
851 available in the R version (the one here used).

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

854 Error/warning flags:

855 <sup>^</sup> error in the computation;

856 <sup>§</sup> warning on the code;

857 <sup>¶</sup> warning on identified difference for no apparent reason that can be detected by the authors.

858 Note flags:

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

860 <sup>||</sup> difference due to inclusion/not inclusion of level 2 values as part of level 1 (>180 mg·dl<sup>-1</sup> or 181-250 mg·dl<sup>-1</sup> for TAR-level  
861 1 and <70 mg·dl<sup>-1</sup> or 54-69 mg·dl<sup>-1</sup> for TBR-level 1);

862 <sup>†</sup> difference in the interpretation;

863 <sup>\*</sup> conversion from mg·dl<sup>-1</sup> to mmol·l<sup>-1</sup> using 18 as conversion factor;

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

866 <sup>\*</sup> not directly provided as percentage by the software;

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

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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



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<b>Link to product documentation*</b>	<a href="https://www.medtronicdiabetes.com/customer-support/carelink-software-support/carelink-reports">https://www.medtronicdiabetes.com/customer-support/carelink-software-support/carelink-reports</a>	<a href="https://provider.dexcom.com/education-research/cgm-education-use/product-information">https://provider.dexcom.com/education-research/cgm-education-use/product-information</a>	<a href="https://pro.libreview.io/">https://pro.libreview.io/</a>	<a href="https://global.eversensediabates.com/patient-education/everense-user-guides">https://global.eversensediabates.com/patient-education/everense-user-guides</a>	<a href="https://support.glooko.com/hc/en-us/articles/360001498269-Glooko-for-Personal-Use-Quick-Start-Guide">https://support.glooko.com/hc/en-us/articles/360001498269-Glooko-for-Personal-Use-Quick-Start-Guide</a>	<a href="http://www.agp-report.org/agp/research">http://www.agp-report.org/agp/research</a>
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\*accessed 2022/07