Supplementary Data

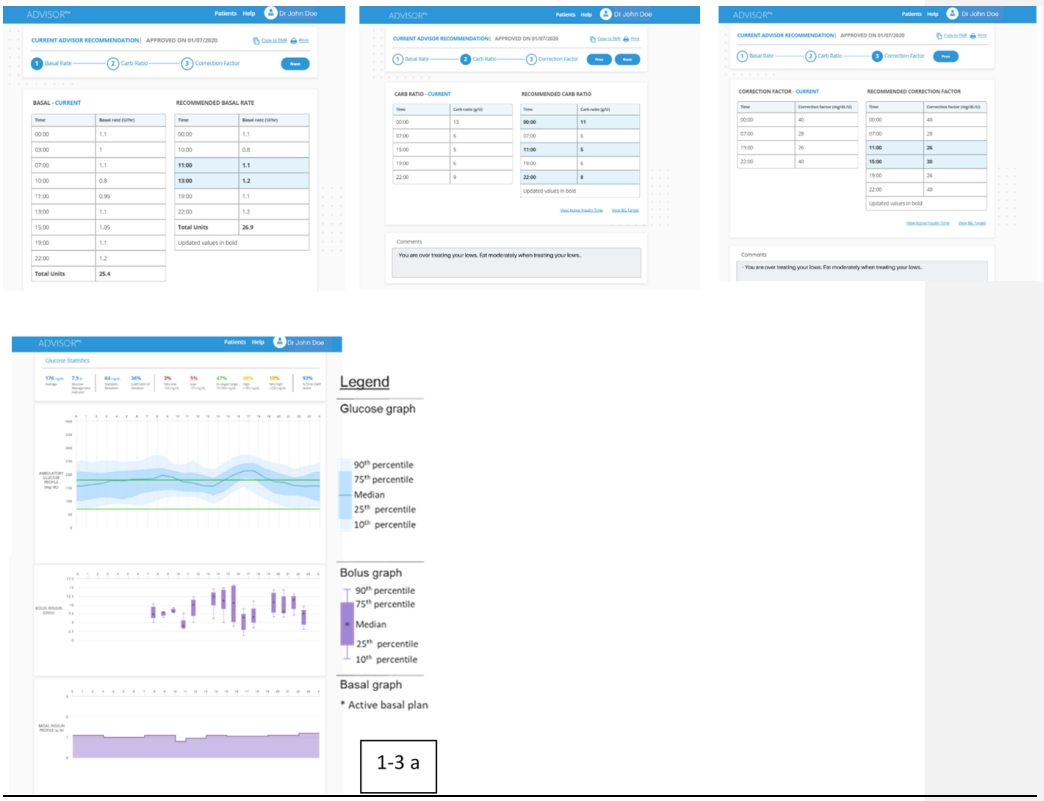
The DreaMed Advisor Pro. ("Advisor", DreaMed Diabetes Ltd., Israel)

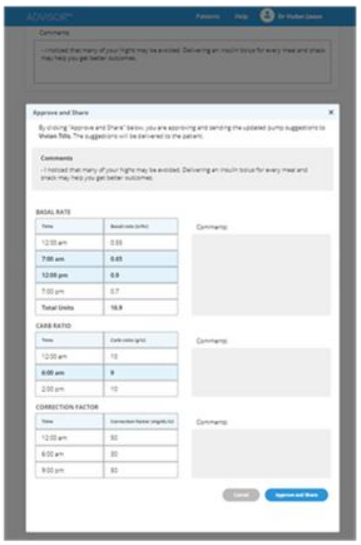
The DreaMed Advisor Pro is an FDA cleared and CE-marked artificial intelligence-based algorithm. The algorithm provides automated insulin pump dosing adjustments based on records of insulin delivery, carbohydrates intake and glucose data for health care providers who care for people with type 1 diabetes. The data is gathered from the various patient devices including the patient pump, continuous glucose monitoring and/or SMBG. The algorithm provides exact insulin pump settings adjustments including changes to insulin pump basal rate, insulin to carbohydrate ratio and insulin correction factor. In addition, the algorithm provides personalized tips regarding diabetes management and the way insulin delivery is delivered for example: "You are over treating your lows. Eat moderately when treating your lows" and "I noticed that many of your highs may be avoided. Remember to bolus before you start eating".

How does the Advisor work? Patients need to upload his/her diabetes devices to a diabetes management platform (DMP). This can be done using the Glooko DMP, where the advisor report is integrated into the platform or to Tidepool DMP as a standalone app. The Advisor Pro pulls the devices data from the DMP. The collected data contents need to meet certain minimal requirements in order to be analyzed. DreaMed Advisor Pro requires at least 12 valid days to produce recommendations (valid day defined as a day with 67% sensor data or at least 4 SMBG measurements a day that are separated from each other by at least 160 minutes). In addition, any uploaded glucose sensor data is processed to exclude data related to un-physiological sensor rate of change and drift sensor. The advisor algorithm analyzes the collected data and detects glucose patterns of hypoglycemia, hyperglycemia and patterns where glucose levels are within the desired range. Then, the Advisor assesses the cause for the glucose trend within the time frame of its occurrence. The Advisor also detects and analyzes insulin dosing events (that means any insulin bolus is analyzed in relation to the glucose levels and carbohydrate amount in case of meal bolus). The two types of analysis (the event and patterns) are then integrated to produce a personalized recommendation. The Advisor Pro has safety limitations, for example 20% change limit for the

basal rate and 30% limit for the insulin to carbohydrate ratios (CR) and the insulin correction factor (CF) from the current plan. The recommendation includes insulin pump parameters adjustments for the insulin to carbohydrate ratio, insulin correction factor and the basal rate. In the standalone app the recommendations are presented in a report for the HCP to review. The report includes the collected data presented in the AGP format (Ambulatory Glucose Profile) and as a logbook, see Figure 1S: Each page of the report displays one pump settings parameter, including current and recommended plan: 1. Basal plan 2. Carbohydrate ratio plan 3. Correction factor plan. 1-3a. The AGP is displayed at the bottom of each page in order to simplify the provider review process. 4. All categories must be reviewed and approved before the recommendations will be shared with the patient via the Advisor app or in email. 5. The recommendations delivered to the patient app

Figure 1S: Advisor Pro Report





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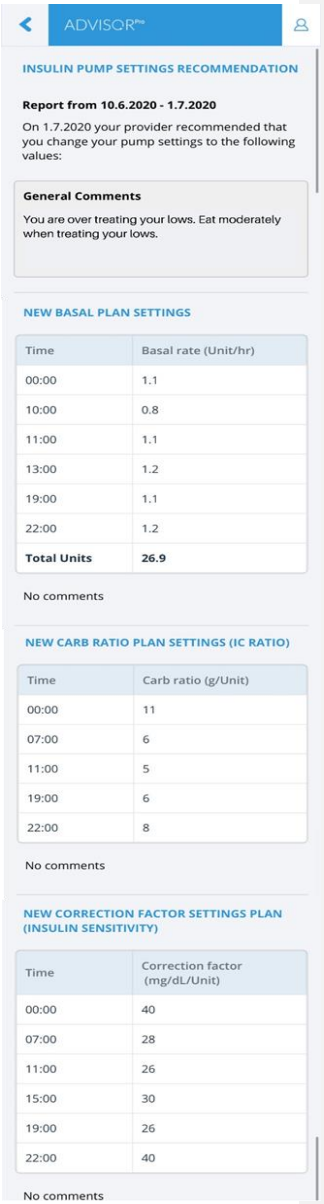

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The data in figure 1-3 and 5 related to anonymous patient data (from another study) with virtual patient name, Vivian Tills. The data in figure 4 related to different patient data set for the purpose of illustration.

Table 1S: Average Daily Blood Glucose measurements, Average Glucose, Total Daily Insulin Dose and Individual Baseline Insulin Pump Settings Parameters of the 15 Patient's Cases

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Patient #	Average BG[#]	Daily BG[#]	TDD[#]	Basal %[#]	# Basal rates in plan	Basal plan range[¥]	# CR ratios in plan	CR plan range[¥]	# CF ratios in plan	CF plan ranges[¥]
1	193.9 ± 107.5	7.9 ± 2.7	58.7 ± 16.5	0.2 ± 0.2	5	[0.43, 0.63]	3	[9, 12]	3	[20, 50]
2	204.5 ± 85.1	5.2 ± 1.8	46.6 ± 10.9	0.5 ± 0.1	2	[0.80, 0.90]	1	[10, 10]	1	[40, 40]
3	151.4 ± 75.5	6.4 ± 2.4	58.4 ± 7.3	0.6 ± 0.1	4	[1.60, 2.30]	3	[5, 6]	3	[20, 25]
4	172.2 ± 71.9	8.7 ± 3.0	32.9 ± 2.5	0.5 ± 0.0	6	[0.50, 0.75]	4	[10, 30]	3	[100, 180]
5	205.1 ± 88.8	7.1 ± 3.1	67.7 ± 13.5	0.5 ± 0.1	4	[1.10, 1.60]	1	[10, 10]	3	[30, 40]
6	185.5 ± 68.4	4.2 ± 1.7	59.8 ± 10.5	0.3 ± 0.1	5	[0.60, 1.00]	2	[10, 30]	2	[11, 170]
7	174.3 ± 108.4	6.2 ± 2.1	36.3 ± 6.6	0.5 ± 0.1	3	[0.60, 0.80]	3	[9, 15]	3	[50, 80]
8	185.4 ± 89.3	5.4 ± 1.8	57.4 ± 5.7	0.6 ± 0.1	4	[1.00, 1.70]	4	[4, 10]	3	[30, 40]
9	251.6 ± 98.3	4.6 ± 2.2	90.4 ± 18.5	0.5 ± 0.1	4	[1.50, 2.10]	1	[5, 5]	3	[20, 30]
10	179.3 ± 79.1	5.7 ± 1.5	47.0 ± 7.1	0.4 ± 0.1	6	[0.40, 1.10]	1	[7.5, 7.5]	1	[50, 50]
11	177.5 ± 68.4	8.4 ± 2.0	99.6 ± 21.5	0.4 ± 0.1	3	[1.40, 1.55]	3	[5, 12]	4	[20, 50]
12	231.3 ± 77.9	7.0 ± 2.1	30.4 ± 7.0	0.4 ± 0.1	2	[0.45, 0.60]	2	[15, 30]	3	[35, 60]
13	182.7 ± 94.6	3.8 ± 1.4	36.0 ± 6.0	0.6 ± 0.1	4	[0.45, 0.95]	2	[12, 15]	2	[30, 40]
14	137.2 ± 57.3	7.9 ± 1.9	49.5 ± 6.2	0.5 ± 0.1	7	[0.85, 1.25]	5	[8, 10]	1	[27, 27]
15	103.0 ± 27.4	6.3 ± 1.1	14.8 ± 0.9	0.6 ± 0.0	2	[0.25, 0.40]	3	[25, 30]	3	[90, 120]

[#] Presented values are in average ± STD
[¥] Presented values are in [minimum, maximum]

Data Analysis Method

The method for comparing insulin dose adjustments/changes was done on hourly basis. The pump settings: Basal, CR and CF plans were compared for every hour. For example, see the below example of basal rate plan:

Basal Plan (pump Format)			
Time of Day	00:00	07:00	19:00
Value [u/h]	0.5	1	0.8

For comparison, the day was divided into 24 hours

Basal Plan (Decision Points Format)																							
Hour	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Value [u/h]	0.5	0.5	0.5	0.5	0.5	0.5	0.5	1	1	1	1	1	1	1	1	1	1	1	1	0.8	0.8	0.8	0.8	0.8

For each hour of the day, the recommendations were compared for the relative changes (to the patient's current pump settings) in the basal, CR and CF plans between the physicians and between the physicians and the automated algorithm. Study endpoints were the percentage of comparison points for which there was full or no agreement on the direction of changes in the treatment plan.

The method for simulated SMBG based on CGM data

A comparison was made between Advisor Pro recommendations for insulin pump adjustments based on CGM data and the recommendations based on CGM simulated SMBG data points. The comparison includes the statistics on the level of agreement and disagreement as well as the progression of these parameters in correlation to the average daily SMBG simulated data points. For this comparison, 923 different data sets (21 days of pump and CGM data) were used to generate recommendations. For each of the 923 data sets, two recommendations were made, one based on CGM data and one based on simulated SMBG points. A special method was used to generate a sensor sample that will simulate an SMBG data

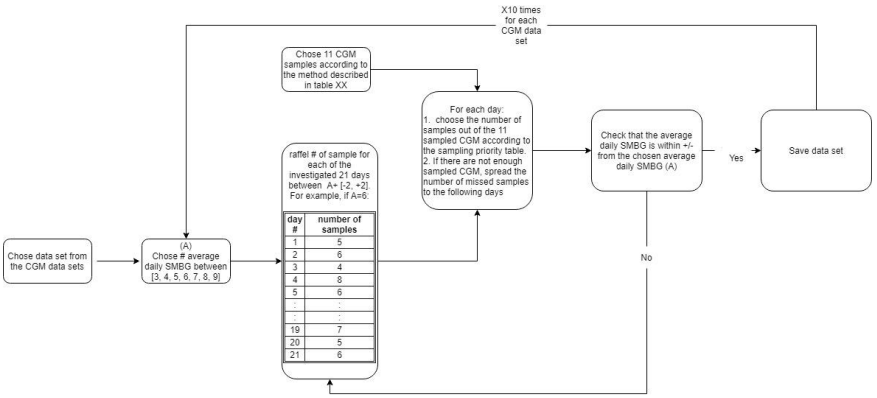
set. The method that was used to generate the SMBG samples includes the selection of 11 different daily measurements according to the following conditions:

Sample	
Sample 1: Fasting BG/ Breakfast	Taken from the CGM that was found closest to the first bolus for meal located between 6AM to 11AM. If no such bolus was found, the sample is randomly chosen from the CGM between 6AM to 11AM, unless there is a CGM measurement that is below 60 mg/dL. In that case, the chosen sample is the lowest CGM that is found between the above times.
Sample 2: Post breakfast	Taken from the CGM that was found closest to the first bolus for meal located between 1.5 to 3 hours after the time of the fasting sample. If no such meal bolus was found, the sample is randomly chosen from the CGM between the above times, unless there is a CGM measurement that is below 60 mg/dL. In that case, the chosen sample is the lowest CGM that is found between the above times. In case no fasting sample was found, the 'post breakfast' sample is randomly chosen between 10AM to 12AM unless there is a CGM measurement that is below 60 mg/dL. In that case the lowest CGM is chosen as the 'post breakfast' sample.
Sample 3: Lunch	Taken from the CGM that was found closest to the first bolus for meal located between 1 to 3 hours after the time of the post breakfast sample. If no such meal bolus was found, the sample is randomly chosen from the CGM between the above times, unless there is a CGM measurement that is below 60 mg/dL. In that case, the chosen sample is the lowest CGM that is found between the above times. In case no post breakfast sample was found, the 'lunch' sample is randomly chosen between 12AM to 2PM unless there is a CGM measurement that is below 60 mg/dL. In that case the lowest CGM is chosen as the 'lunch' sample.
Sample 4: Post lunch	Taken from the CGM that was found closest to the first bolus for meal located between 1 to 3 hours after the time of the lunch sample. If no such meal bolus was found, the sample is randomly chosen from the CGM between the above times, unless there is a CGM measurement that is below 60 mg/dL. In that case, the chosen sample is the lowest CGM that is found between the above times. In case no lunch sample was found, the 'post lunch' sample is randomly chosen between 1PM to 4PM unless there is a CGM measurement that is below 60 mg/dL. In that case the lowest CGM is chosen as the 'post lunch' sample.
Sample 5: Pre-dinner	Taken from the CGM that was found closest to the first bolus for meal located between 0.5 to 2 hours after the time of the post lunch sample. If no such meal bolus was found, the sample is randomly chosen from the CGM between the above times, unless there is a CGM measurement that is below 60 mg/dL. In that case, the chosen sample is the lowest CGM that is found between the above times.

	In case no lunch sample was found, the 'pre- diner' sample is randomly chosen between 3PM to 6PM unless there is a CGM measurement that is below 60 mg/dL. In that case the lowest CGM is chosen as the 'pre- dinner' sample.
Sample 6: Dinner	Taken from the CGM that was found closest to the first bolus for meal located between 0.5 to 3 hours after the time of the pre- dinner sample. If no such meal bolus was found, the sample is randomly chosen from the CGM between the above times, unless there is a CGM measurement that is below 60 mg/dL. In that case, the chosen SMBG is the lowest CGM that is found between the above times. In case no lunch sample was found, the 'dinner' sample is randomly chosen between 6PM to 9PM unless there is a CGM measurement that is below 60 mg/dL. In that case the lowest CGM is chosen as the 'dinner' sample.
Sample 7: Post dinner	Taken from the CGM that was found closest to the first bolus for meal located between 1.5 to 3 hours after the time of the dinner sample. If no such meal bolus was found, the sample is randomly chosen from the CGM between the above times, unless there is a CGM measurement that is below 60 mg/dL. In that case, the chosen SMBG is the lowest CGM that is found between the above times. In case no dinner sample was found, the 'post dinner' sample is randomly chosen between 8PM to 10PM unless there is a CGM measurement that is below 60 mg/dL. In that case the lowest CGM is chosen as the 'post dinner' sample.
Sample 8: Bed time	Taken from the CGM that was found closest to the first bolus for meal located between 1.5 to 3 hours after the time of the post dinner sample. If no such meal bolus was found, the sample is randomly chosen from the CGM between the above times, unless there is a CGM measurement that is below 60 mg/dL. In that case, the chosen SMBG is the lowest CGM that is found between the above times. In case no post dinner sample was found, the 'bed time' sample is randomly chosen between 9M to 11PM unless there is a CGM measurement that is below 60 mg/dL. In that case the lowest CGM is chosen as the 'bed time' sample.
Sample 9: Night	Taken from the CGM that was found closest to the first bolus located between 1.5AM to 5AM. If no such bolus was found, the sample is randomly chosen from the CGM between the above times, unless there is a CGM measurement that is below 60 mg/dL. In that case, the chosen SMBG is the lowest CGM that is found between the above times.
Sample 10: Random	After sampling the above 9 SMBG samples, the 10th sample is chosen randomly from the CGM that is at least 1 hour away from any of the above 9 samples[1].
Sample 11: Random	After sampling the above 10 SMBG samples, the 11th sample is chosen randomly from the CGM that is at least 1 hour away from any of the above 10 samples.

[1] Note that in some of the analyzed days, not all first 9 samples can be found, mainly due to the fact that there is no CGM measurement during these times. In case no CGM measurements available, the sample may be taken from the original SMBG measured by the patient.

The next step after sampling these (up to) 11 different SMBG samples was to randomly choose between X-2 to X+2 measurements for each of the investigated days (21 days). Where X is the desired average daily SMBG samples that can range from 3 to 9. The chosen samples from the above 11 samples are done according to the predefined priority (see the priority table below). This was done to create 7 different sampled data sets for each one of the 923 data sets, that will demonstrate 7 different kind of average daily SMBGs. In addition, to avoid the effect of the randomization and for creating permutations for each of the 7 data sets, the above process was done in an iterative manner, 10 times for each of the data sets and for every desired average daily SMBG measurements. See process below:



Sampling priority table

Priority	What to choose?
1	fasting BG
2	Lunch BG
3	Dinner BG
4	Bed time BG
5	Randomly chose BG between post breakfast, post lunch and post dinner BGs.
6	Randomly chose BG between post breakfast, post lunch and post dinner BGs and that was not chosen in the previous iteration
7	Randomly chose BG between post breakfast, post lunch and post dinner BGs and that was not chosen in the previous iteration
8	Randomly chose BG between the pre- dinner and night time BGs.
9	Randomly chose BG between the pre- dinner and night time BGs and that was not chosen in the previous iteration
10	Randomly chose BG between the two left random samples.

11 Randomly chose BG between the two left random samples and that was not chosen in the previous iteration.

* In case no BG is found in one of the 11 sample, the BG will be chosen from the next available priority.

The comparison and distribution to different agreement categories between the versions was done for each of the above permutations of SMBG measurements. The degree of agreement and disagreement for each data set was averaged across the 10 permutations of each data set. The final degree of agreement and disagreement between the algorithms was calculated as the average percentage of agreement and disagreement across all available data sets per average daily SMBG measurements.

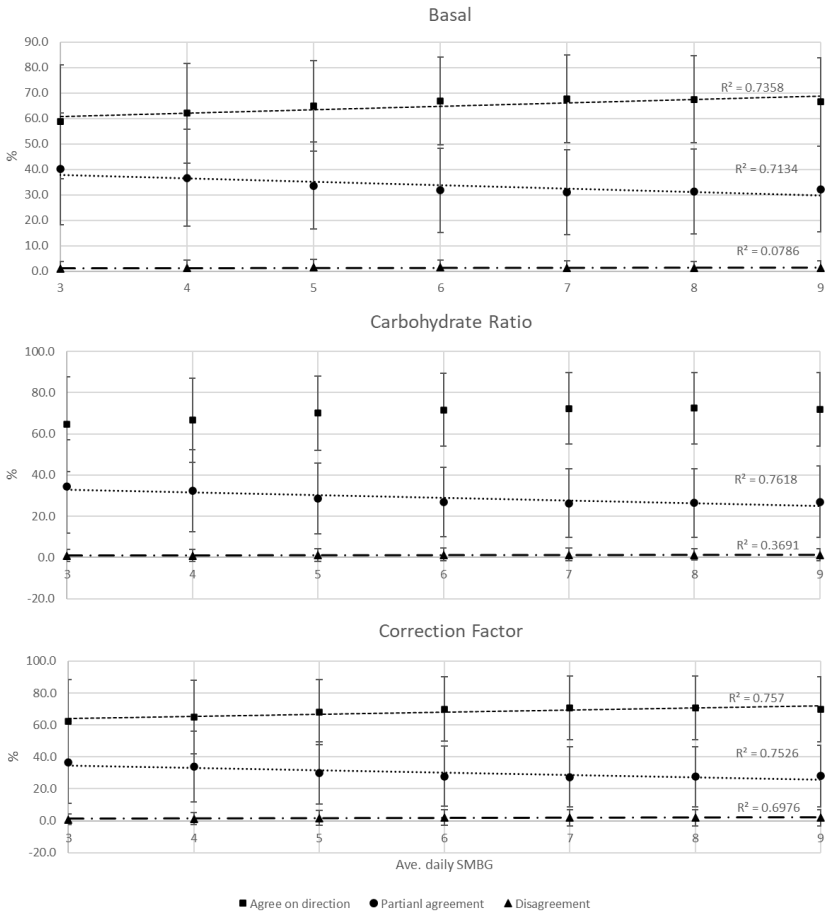
Average daily SMBG Measurements	# of available comparisons
3	923
4	923
5	923
6	921
7	919
8	917
9	914

Table 2S: Results of comparison for the level of agreement and disagreement on the direction of insulin dose adjustments between recommendations based on CGM and SMBG simulated data points

	Average between the Advisor versions (%)						
Average simulated SMBG data points / Comparison Parameter	3	4	5	6	7	8	9
Agreement on basal change direction, %	58.7±22.3	62.0±19.5	64.8±17.8	66.8±17.2	67.6±17.2	67.5±17.1	66.5±17.3
Disagreement on basal change direction, %	1.0±2.8	1.3±2.9	1.6±3.1	1.5±2.9	1.4±2.7	1.3±2.5	1.4±2.6
Agreement on CR change direction, %	64.7±22.9	66.7±20.5	70.1±18.0	71.7±17.7	72.4±17.4	72.5±17.4	71.8±17.9
Disagreement on CR change direction, %	0.8±2.9	1.0±2.9	1.2±3.1	1.3±3.4	1.2±3.3	1.1±3.2	1.1±3.3
Agreement on CF change direction, %	62.4±26.2	64.9±22.9	68.1±20.5	70.0±20.0	70.7±19.9	70.5±19.9	69.9±20.5
Disagreement on CF change direction, %	0.9±3.4	1.4±4.0	1.8±4.5	2.0±5	1.9±5.0	2.0±5.1	2.0±5.1

Abbreviations: CR, Carbohydrate to insulin ratio; CF, correction factor

Figure 2S: The percentage of the level of agreement/partial agreement/disagreement on the direction of insulin dose adjustments between Advisor Pro recommendations based on CGM data and based on 3-9 simulated SMBG data points


Basal
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
%
3
4
5
6
7
8
9
R² = 0.7358
R² = 0.7134
R² = 0.0786
Carbohydrate Ratio
100.0
80.0
60.0
40.0
20.0
0.0
-20.0
%
R² = 0.7618
R² = 0.3691
Correction Factor
100.0
80.0
60.0
40.0
20.0
0.0
-20.0
%
R² = 0.757
R² = 0.7526
R² = 0.6976
Ave. daily SMBG
Agree on direction
Partianl agreement
Disagreement