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ORIGINAL ARTICLES

A Cause-and-Effect-Based Mathematical Curvilinear Model That Predicts the Effects of Self-Monitoring of Blood Glucose Frequency on Hemoglobin A1c and Is Suitable for Statistical Correlations

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Abstract

Background:
Previous studies have shown an association between the frequency of self-monitored blood glucose (SMBG) and hemoglobin A1c. Randomized controlled trials (RCTs) have shown this to be a causal correlation for insulin-using patients. Several studies have used linear regression, but a straight line will descend into negative hemoglobin A1c values (an impossibility). This study developed a cause-and-effect-based nonlinear model to predict the outcome of RCTs on this subject, tested this model with clinical data, and offered this model in place of linear regression, especially for the still-debated case of noninsulin-using patients.

Method:
The model was developed from cause-and-effect principles. The clinical study utilized retrospective data from patient histories of a large endocrine practice. Data sets were obtained for five treatment regimens: continuous subcutaneous insulin infusion (CSII), subcutaneous insulin (SC), no insulin (NI), oral medication (OM), and no medication (NM). OM and NM are subgroups of NI. The model was fitted to each group using nonlinear least-squares methods. Each group was ordered by SMBG tests per day (BGpd) and was divided in half; *t* tests were run between the A1C's of the two halves.

Results:
Self-monitored blood glucose readings from 1255 subjects were analyzed (CSII, $N = 417$; SC, $N = 286$; NI, $N = 552$; OM, $N = 505$; NM, $N = 47$). The CSII, SC, NI, and OM groups showed the expected declining statistically fitted curve and a significant association of BGpd with hemoglobin A1c ($P < 0.004$). The NM group showed insignificant results.

Conclusions:
The nonlinear model is based on cause-and-effect principles and mathematics. It yields a prediction that RCTs will be able to reveal that higher SMBG frequency causes lower hemoglobin A1c.

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Abbreviations: (BGpd) blood glucose tests per day, (CSII) continuous subcutaneous insulin infusion, (*n*) blood glucose tests per day, (*N*) number of patients, (NI) no insulin, (NM) no medication, (OM) oral medication, (RCTs) randomized controlled trials, (SC) subcutaneous insulin, (SEM) standard errors of the mean, (SMBG) self-monitoring of blood glucose

Keywords: blood glucose, blood glucose self-monitoring, SMBG

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Introduction

A growing body of research supports the benefit of regular self-monitoring of blood glucose (SMBG) for improving glycemic control. A cause-and-effect relationship has been shown by randomized controlled trials (RCTs)[1–3] in insulin-using patients. Significant associations have been shown by longitudinal studies[4,5] and retrospective studies with all treatment regimens. Of particular interest are those studying noninsulin-using patients,[4–7] including one[7] that studied long-term morbidity and mortality rather than hemoglobin A1c.

The remaining disputed area is the need to show that more frequent SMBG directly causes a significant lowering of hemoglobin A1c in noninsulin-treated patients. RCTs on noninsulin-treated patients have been the subject of meta-analyses[2,8,9] and reviews.[1] Three meta-analyses[2,8,9] maintain that frequent SMBG plus training plus SMBG-based clinical decisions and feedback is a significant cause of lower hemoglobin A1c in noninsulin-treated patients; one meta-analysis[9] cautiously reported significance for SMBG alone. Two studies reporting significance[10,11] are often cited by reviewers and meta-analysts. The first[10] of these is cited for achieving significance, but only with extra training of the SMBG group. The second[11] of these also achieved significance but is criticized for its high (>40% for both groups) dropout rate. The majority of opinions among reviewers and meta-analysts is that further studies are necessary.

Several researchers have accompanied their analyses by linear regressions,[12,13] but correlated declining straight lines for hemoglobin A1c will cross the SMBG frequency axis into the region of negative hemoglobin A1c, an impossibility. The present model satisfies the intuitive expectation of a declining curve that flattens as it declines toward a lower hemoglobin A1c value that it never crosses. To our knowledge, a nonlinear regression model for SMBG data has not yet been published.

The purpose of this study was twofold: (1) to develop a curvilinear mathematical model that explains the effect of SMBG frequency on hemoglobin A1c and is suitable for curve fitting and (2) to utilize retrospective data to test the model and to statistically investigate the nature of the relationship. The resulting model is based on cause and effect, which shows that it supports the efforts of RCTs to demonstrate that SMBG is a significant cause of low hemoglobin A1c.

Research Methods

Subject Data

This retrospective study utilized data obtained from patient records of a large endocrine practice (Atlanta Diabetes Associates, Atlanta, GA). The frequency of SMBG per day (BGpd) was calculated from meter downloads. Data sets were obtained for five treatment regimens: continuous subcutaneous insulin infusion (CSII), subcutaneous insulin (SC), no insulin (NI), orally medicated (OM), and no medications (NM). The OM and NM groups are subgroups of the NI group. The brand of meter used by each patient was recorded but was not considered relevant to the study at hand.

Study Site

The routine at the study site for regular patients is as follows: All meters are downloaded. The BG of all patients is tested simultaneously using the laboratory test device and by the patients using their own meters. The medical assistant observes and can correct any procedural errors by the patient. Hemoglobin A1c is tested unless the previous hemoglobin A1c is less than 60 days old. Medical personnel provide customized training to each patient, asking questions as well as imparting information. There are very few patients without meters. In short, the study site practice provides training, feedback, and SMBG data usage as a matter of routine. Since this study is a retrospective analysis of the practice's records, all patients in the study received the same standard of routine treatment and training.

Mathematical Model

The model developed in this study is based on the premise that higher BGpd affects hemoglobin A1c through two causal pathways: (1) patients have more opportunities for corrective action and (2) practitioners have more data available for use in providing feedback and adjusting patient regimens. These two model-development pathways arrived at the same model independently.

1. Model-development pathway based on corrective action in response to high glucose "cue"

For insulin-treated patients, a high blood glucose value is the cue to take insulin as a corrective action.

For noninsulin-treated patients, a high glucose value is often the cue to reduce the carbohydrate content of the next meal, exercise, increase their oral medication, and/or

contact the practitioner. Because the effects of these corrective actions may not be as immediate or as large as the effects of insulin, it is reasonable to expect the correlation of BGpd to hemoglobin A1c for NI regimens to be less well defined, but detectable nonetheless.

Inverse Relationship between Frequency and Magnitude

Given that an insulin-using patient needs a certain amount of insulin each day, it can be said that if the patient increases BGpd, then the average size of the corrective insulin doses will become smaller. In other words, low-frequency BGpd may lead to a small number of large corrections, whereas high BGpd may lead to a large number of small corrections. This concept holds equally well for noninsulin-treated patients. For example, a patient may exercise in response to an elevated BG for a duration proportional to the initial BG level, so that infrequent BG testing may result in infrequent but long-duration exercise sessions, whereas frequent testing may result in more numerous exercise sessions but for a shorter duration each time. Also, meal-related testing allows the patient to adjust the carbohydrate content of the upcoming meal in proportion to the elevation of the BG. Testing before four meals will allow four smaller adjustments than testing for only one meal per day.

This concept can be reduced to a simple principle applicable to both types of treatment. In this principle, the correction magnitude is represented by BG – Target. If a comparison is made between 2 days in which all independent variables remain the same except BGpd, then the sum of the values of all the correction magnitudes will remain constant for small changes in BGpd.

The following equation illustrates this principle by calculating the impact of a change of one test per day. BGpd is represented temporarily by a lowercase n. The equation represents two versions of the same day, with n BG values in the day shown on the left and $n + 1$ BG values in the day on the right.

$$\sum_{i=1}^{n}\left(\mathrm{BG}_{(n,i)}-\mathrm{Target}\right)=\sum_{i=1}^{n+1}\left(\mathrm{BG}_{(n+1,i)}-\mathrm{Target}\right)$$

In the equation, each BG is a function of the number of tests per day in the regimen (n or $n + 1$) and also has its own index number (i), where $i = 1$ for the first BG of the day, $i = 2$ for the second, and so on up to the last BG of the day, which will be $i = n$ or $n + 1$. The corrections (BG – Target) are summed for both days. According to the principle, the sums are equal. Recalling the definition of a mean, the equation can be rewritten as follows:

$$n \times [\mathrm{BGmean}_{(n)} - \mathrm{Target}] = [n + 1] \times [\mathrm{BGmean}_{(n+1)} - \mathrm{Target}].$$

Further, the equation may be rearranged to obtain

$$n \times [\mathrm{BGmean}_{(n)} - \mathrm{BGmean}_{(n+1)}] = \mathrm{BGmean}_{(n+1)} - \mathrm{Target}.$$

The equation may also be written in terms of $(n – 1)$:

$$(n - 1) \times [\mathrm{BGmean}_{(n-1)} - \mathrm{BGmean}_{(n)}] = \mathrm{BGmean}_{(n)} - \mathrm{Target}.$$

Next, these last two equations are averaged. Several terms cancel, leading to

$$n \times [\mathrm{BGmean}_{(n-1)} - \mathrm{BGmean}_{(n+1)}]/2 - [\mathrm{BGmean}_{(n-1)} - \mathrm{BGmean}_{(n)}]/2 = [\mathrm{BGmean}_{(n+1)} + \mathrm{BGmean}_{(n)} - 2 \times \mathrm{Target}]/2.$$

Further simplification yields

$$[\mathrm{BGmean}_{(n+1)} - \mathrm{BGmean}_{(n-1)}]/2 = -([\mathrm{BGmean}_{(n+1)} + \mathrm{BGmean}_{(n-1)}]/2 - \mathrm{Target})/n.$$

The left side of the equation can be recognized as the derivative of BGmean over two increments of n. The right side is an average and equals the value at the center point, which is then divided by n:

$$\frac{d\mathrm{BGmean}_{(n)}}{dn} = \frac{-\left[\mathrm{BGmean}_{(n)} - \mathrm{Target}\right]}{\mathrm{n}}$$

This is a first-order linear differential equation. It may be solved to obtain

$$\mathrm{BGmean}_{(n)} = \mathrm{Target} + \mathrm{C2}/n.$$

The model for hemoglobin A1c is similar. The notation is shifted back from "n" to "BGpd":

$$\mathrm{Hemoglobin\ A1c} = \mathrm{C1} + \frac{\mathrm{C2}}{(\mathrm{BGpd} + \mathrm{C3})}$$

C3 is introduced because the actual parameter hemoglobin A1c has a maximum, i.e., an intercept of the vertical hemoglobin A1c axis and does not go to infinity when BGpd = 0. C3 is needed to ensure that this happens and to prevent the expression from going to infinity.

2. Model-development pathway based on standard error of the mean (SEM) in practitioner's data

Practitioners often adjust patient regimens based on average BG values. Errors in practitioner adjustment are therefore proportional to errors of these averages, otherwise

known as SEM, which are proportional to 1/BGpd. When patients apply these readjustments to their own regimens, variations fall on both sides of their glucose targets. However, most low blood glucose values are not tolerated by patients and are corrected with increased carbohydrate intake. As a result, some low values are overtreated to become high values, joining the other high values that are tolerated more leniently. This, in turn, causes the patient's hemoglobin A1c level to rise proportionally to 1/BGpd. This approximate proportionality is formed into a model by inclusion of a proportionality constant (C2), a baseline (C1), and once again (C3) for the same reasons mentioned earlier. This mathematical model is the same as the first.

The aforementioned model, derived by either pathway, describes a cause-and-effect relationship. The existence of this descriptive causative model lends credence to the efforts by researchers to verify a causal relationship.

Statistical Methods

Data for each treatment regimen were divided in half, based on BGpd. *t* tests were run between the high BGpd half and the low BGpd half. The mathematical model was statistically fitted to data in each treatment regimen group using nonlinear least-squares methods, except the NM group, which had a nonsignificant *t* test.

Results

Self-monitored blood glucose readings from 1255 subjects were analyzed in this report: 417 treated with continuous subcutaneous insulin infusion; 286 treated with subcutaneous insulin; and 552 noninsulin treated, including 505 orally treated and 47 treated with no medication, including patients on diet and exercise.

A *t* test was performed between hemoglobin A1c values in the low BGpd half versus the high BGpd half of each group. Results showed that improved glycemic control was significantly associated with higher BGpd in all treatment groups except NM (**Table 1**).

To the eye, scatter charts of all treatment groups showed a declining curve that flattened as BGpd increased (**Figures 1–3**), and the curvilinear model was fitted successfully to the CSII, SC, NI, and OM groups but not the NM group because of its insignificant *t* test.

CSII group results: $N = 417$. Average hemoglobin A1c = 7.3%. Average BGpd = 4.0, the highest testing frequency of all the groups (**Figure 2**).

$$\text{Correlation curve: hemoglobin A1c} = 5.65 + \frac{10.29}{(\text{BGpd} + 2.84)}$$

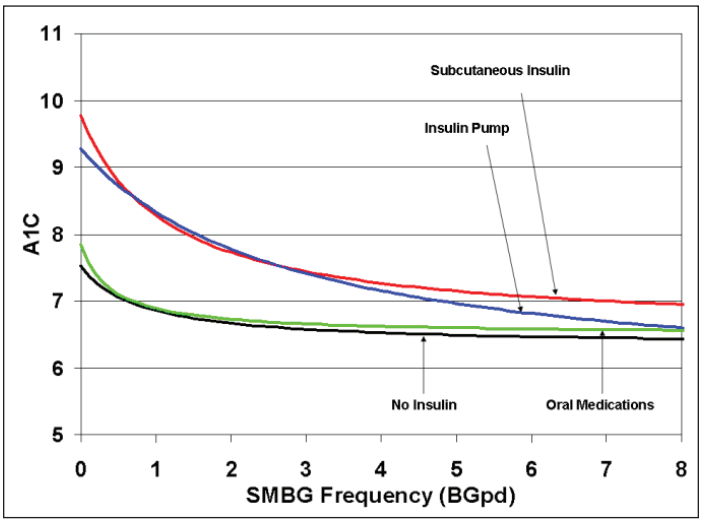

Figure 1. Superimposed curves. Pump patients benefit the most from the high frequency of testing. The OM group was created by removing the low-lying NM group from the NI group. The resulting OM curve increased slightly.

Table 1.
Results of *t* Tests [a]

		Average BGpd		Average hemoglobin A1c		
Regimen	*N*	Lower BGpd half	Higher BGpd half	Lower BGpd half	*t* test	Higher BGpd half
Insulin pump (CSII)	417	2.63	5.38	7.63	$P < 0.001$	6.90
SC insulin (SC)	286	1.01	3.54	8.38	$P < 0.001$	7.43
No insulin (NI)	552	0.45	1.7	7.17	$P < 0.004$	6.7
Oral medication (OM)	505	0.46	1.7	7.2	$P < 0.0001$	6.8
No medication (NM)	47	0.32	1.69	6.5	$P < 0.14$	6.1

[a] Data were sorted by BGpd before dividing into halves. All groups show a significantly lower average hemoglobin A1C for higher BGpd except the NM group.

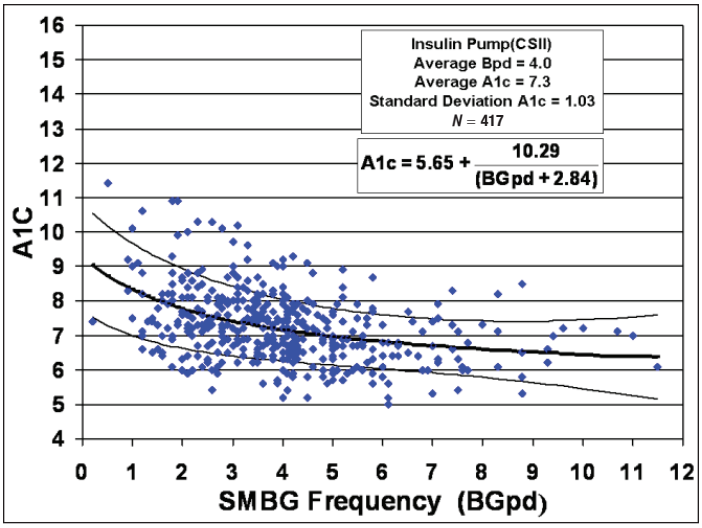

Figure 2. Patients following insulin pump (CSII) regimens. The average BGpd is higher than the other groups. Very few patients test less than once per day.

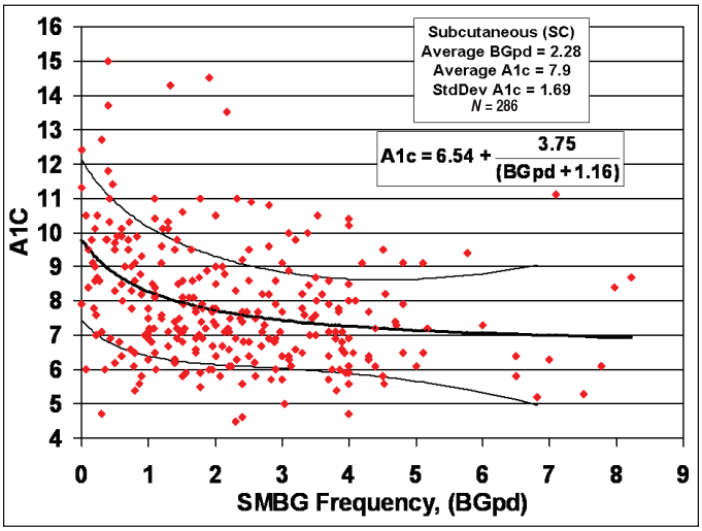

Figure 3. Patients following subcutaneous insulin (SC) regimens. Data are more to the left than the CSII patients.

SC group results: $N = 286$. Average hemoglobin A1c = 7.9%. Average BGpd = 2.3 (**Figure 3**).

$$\text{Correlation curve: hemoglobin A1c} = 6.54 + \frac{3.75}{(\text{BGpd} + 1.16)}$$

NI group results: $N = 552$. Average hemoglobin A1c = 6.9%, the lowest of all the groups. Average BGpd = 1.1, lower than the insulin-using patients. The NI group is composed of two subgroups, the OM and NM groups.

$$\text{Correlation curve: hemoglobin A1c} = 6.36 + \frac{0.96}{(\text{BGpd} + 0.8)}$$

OM group results: The OM group is a subgroup (comprising 91%) of the NI group. $N = 505$. Average hemoglobin A1c = 7.0. Average BGpd = 1.1. The correlation curve (not shown) was slightly higher than the NI group because of the absence of the other subgroup, the lower-lying NM group. The OM group showed a slightly more significant association between BGpd and hemoglobin A1c ($P = 0.00011$) than the NI group as a whole ($P = 0.0031$).

$$\text{Correlation curve: hemoglobin A1c} = 6.5 + \frac{0.55}{(\text{BGpd} + 0.41)}$$

NM group results: $N = 47$. The NM group was clustered at the low end of each axis. Average hemoglobin A1c = 6.3. Average BGpd = 0.87. Because the t test did not show a significant result, no correlation was attempted.

Discussion

The cause-based nonlinear model is supported by the result that the curvilinear model fitted data smoothly in all patient groups (except the NM group, which had sparse data).

A statistically significant association was found between hemoglobin A1c and frequency of SMBG in all groups except the NM group. This result for a retrospective study is not a first. A discussion of the typical problems this study shares with other retrospective studies is given next.

Curvilinear Statistical Association

Two possible causes were identified for this statistical association, and the two are indistinguishable:

1. The first possible cause is the direct causative link, predicted by the model. This has been sought in many studies; it says that frequent SMBG provides more opportunities for corrective action by the patient and/or provides more information to the practitioner, both of which may result in improved hemoglobin A1c. It produces a declining curve.

2. The second possible cause is that frequent monitoring may only be indicative of strict adherence to the prescribed treatment regimen and not causative of improved hemoglobin A1c (i.e., frequent monitoring and low hemoglobin A1c may both be effects of a common cause). The graph would appear similar to the direct causative link.

An Interfering Effect, Patient Motivation

The effects of patient motivation run contrary to the two effects just given. Hemoglobin A1c test results motivate a patient to change his or her SMBG frequency, in a reversal of cause and effect.

1. Patients with only moderate deficiencies in endogenous insulin secretion and/or insulin sensitivity

Hemoglobin A1c values are low. Therefore, motivation to increase SMBG frequency is lacking, and patients' data points appear at the lower left of the scatter chart. In this study, the NI group, particularly its subgroup, the NM group, contains patients like this. The slightly lower *P* value for the OM group shows that the OM group may be easier to correlate in an RCT than the NI group. This is a good reason for future RCTs to focus on the OM group.

2. Patients with large deficiencies in endogenous insulin secretion and/or insulin sensitivity

The news of high hemoglobin A1c may subsequently motivate the patients to test more frequently.[1,5,14] This may result in an ascending curve if *previous* hemoglobin A1c is plotted against BGpd. However, increased testing and good medical care may bring the hemoglobin A1c down. In the current study, few data points appeared to follow this trend. This can be attributed to the fact that data analyzed in the study were *current* hemoglobin A1c, not *previous* hemoglobin A1c. In addition, the absence of this effect suggests that the medical care provided at the study site was reducing hemoglobin A1c levels rapidly with minimal lingering at high levels, demonstrating that the effect can be minimized by the timing of data collection.

Lack of Consensus Issues

Much of the interest in these studies is due to efforts to justify reimbursement for strip usage to noninsulin users. Three meta-analyses[2,8,9] call for an additional RCT. It would be helpful if the researchers knew in advance what kind of study is preferred by the reimbursement policy makers. A sampling of the literature shows some lack of consensus issues that need resolving before additional large and expensive studies are undertaken.

In published RCTs, there is a lack of consensus about whether and to what degree the practitioners in the studies should use SMBG to make clinical decisions about the subject's regimen; for instance, in one study trial[15] (currently underway), the two experimental groups are followed primarily by nurses who "manage" patient care based on blood glucose data, but changes in medication are made by a medical doctor based on hemoglobin A1c levels. The practitioner is notified if SMBG results are consistently >270 mg/dl (15 mmol/liter). Thus, it is conceivable that patients will receive no changes in their medication regimens even when their blood glucose levels, particularly postprandial glucose, are well above targets established by recognized diabetes organizations.[16–18] There is a similar lack of consensus about providing SMBG-based feedback to the patients.

There is a third lack of consensus issue about the nature of the training that should be provided to the SMBG group and to the control group. The authors of review articles and meta-analyses[1,2,8,9] have reported a wide variety of training protocols.

The approaches to these three issues by RCTs may be sorted loosely into two "approaches." These apply to all three lack of consensus issues, but listing all the combinations ($2 \times 2 \times 2 = 8$) would require too much space. For brevity, only the training approaches are shown; the other issues usually follow suit.

1. Special training for the SMBG group and average or minimum training for the control group

This approach does not differentiate the effect of the SMBG from the effect of the training. Significance is easiest to achieve using this approach, as evidenced by the significant results of studies[10,19] and the results of a small ($n = 26$) study[20] that showed a greater improvement for the SMBG group over the control group but did not achieve significance. The result of Schwedes and coworkers[10] is sufficient proof that SMBG plus improved training plus use of SMBG for feedback and clinical decisions causes improved glycemic control. If this approach is accepted by the reimbursement policy makers, the question of implementation arises: Will documented proof of attendance at an approved training program be a prerequisite for reimbursement for strips? This creates more paperwork and slows down the clinical process.

2. Deliberately equal standardized training for both groups

This approach maintains that SMBG alone must be demonstrated as a significant cause of improved glycemic control. A special case is to provide no training to either group and no SMBG data usage for clinical decisions or feedback. Significance is difficult to achieve, as evidenced by the negative results of a study[21] that used minimum SMBG-based feedback and clinical decisions, and another study[12] that used maximum SMBG-based feedback and clinical decisions.

Another special case is to provide maximum training to both groups. This approach has not been studied. The two groups would receive identical training of a type that would be suitable for the SMBG group alone. The control group would be an *infrequent SMBG* group. They would be given only a few test strips (e.g., enough for 3/week) to use whenever they like. The *frequent SMBG* group would have an unlimited supply. SMBG-based feedback and clinical decisions would be allowed. This approach is similar to Fontbonne and colleagues,[12] but uses maximum training. Maximum training would give the frequent SMBG group an advantage; consequently, statistical significance would be easier to achieve. If proved successfully, the implementation of this approach requires no additional paperwork to document training.

Summary

This article provided a cause-and-effect-based mathematical explanation of the effect of SMBG frequency on hemoglobin A1c. Understanding the effect is half of proving it. The other half is observing it experimentally in RCTs.

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