Hemoglobin $A_1c$ ($Hb\ A_1c$)\(^2\) is a key parameter for understanding glycemic control in diabetes. It is used by both clinicians and patients to trigger adjustments in behavior and treatment. In general, clinicians understand $Hb\ A_1c$ and its limitations well, but evidence suggests that patients have difficulty understanding what $Hb\ A_1c$ means and how it relates to glucose. This situation may be particularly applicable for patients who regularly monitor their own glucose. We know a relationship may be particularly applicable for patients who undergo further reactions that lead to deglycation (3), a process that is likely to vary between individuals. Glycation potentially affects all proteins, both intracellular and extracellular, and the term “glycation gap” refers to the difference that exists between the glycation of hemoglobin and glycation of extracellular proteins (4). Glycation of extracellular proteins is generally determined simply by exposure to glucose, but in the case of hemoglobin, additional factors come into play, including the extent to which glucose enters red blood cells, the half-life of the red blood cell, and the extent of competing glycat- ing and deglycat- ing reactions. Studies of twins have shown that approximately 70% of the glycation gap is hereditary and cannot be explained by differences in average glucose concentrations (4). The authors concluded that there are gene(s) that preferentially affect erythrocyte life span, glucose, and/or nonenzymatic glycation or deglycation in the intracellular, rather than the extracellular, compartment. Variation in these genes will lead to between-individual differences in $Hb\ A_1c$ levels and the glycation gap when patients are exposed to similar glucose concentrations.

In keeping with the concept that there are important genetic determinants of $Hb\ A_1c$ levels that are independent of the glucose concentration, a number of large studies have shown $Hb\ A_1c$ differences among ethnic groups after adjusting for both fasting and postprandial glucose, as well as for other demographic and clinical features. Herman et al. assessed various measures of glycemic control in $>2000$ patients with type 2 diabetes from several racial groups (5) and found differences in $Hb\ A_1c$ levels, but not in mean plasma glucose concentrations, among racial/ethnic groups. Mean (SD) levels of $Hb\ A_1c$ were higher in Hispanics [9.4% (1.4%)], Asians [9.2% (1.4%)], and patients of other racial/ethnic groups [9.7% (1.5%)], compared with Caucasians [8.9% (1.2%)]. In the Diabetes Prevention Program, which involved $>3000$ patients with impaired glucose tolerance, the mean $Hb\ A_1c$ level in non-Hispanic whites was 5.78%, whereas the corre-
sponding values in Hispanic, Asian, American Indian, and African American individuals were 5.93%, 6.00%, 6.12%, and 6.18%, respectively, after adjustments for relevant demographic and clinical features, including both fasting and postprandial glucose (6). These data suggest that the relationship between glucose concentration and Hb $A_{1c}$ level differs between ethnic groups. If this is the case, then it is not possible to use a single equation for expressing Hb $A_{1c}$ as eAG that does not take ethnicity into account.

Additional evidence for between-individual differences in hemoglobin glycation comes from analyses of the publicly available Diabetes Control and Complications Trial (DCCT) database, which includes almost 250,000 glucose measurements obtained by analysis of 7-point capillary blood samples and >70,000 Hb $A_{1c}$ results. Regression analysis suggests that the glucose profile explains slightly >50% of the variation in Hb $A_{1c}$ levels (7). In support of the concept that the Hb $A_{1c}$ level depends on factors other than average glucose, another analysis of the DCCT data set demonstrated that the group of conventionally treated patients had consistently higher mean glucose concentrations at any given Hb $A_{1c}$ value than intensively treated patients (8).

Of course, in addition to the factors mentioned above, individuals with increased red cell turnover will have a relationship between Hb $A_{1c}$ and glucose that is different from that of individuals with a typical turnover. Therefore, individuals with renal failure, hemoglobin variants, hematologic disorders, pregnancy, or any condition influencing red cell turnover will have a different relationship of glucose to Hb $A_{1c}$, and any conversion of Hb $A_{1c}$ level to eAG will be misleading.

The ADAG study was not sufficiently comprehensive or robust to generate an equation that would allow reliable expression of Hb $A_{1c}$ as eAG in all patients. From the first point discussed above, it is clear that the whole concept of expressing Hb $A_{1c}$ as eAG is likely to be fundamentally flawed. If, however, we accept for purposes of argument that it is possible, would the results of the ADAG study provide a sufficient basis on which to do so? Certainly, the ADAG study was carefully conducted and is the best available data set from which to derive an equation describing the relationship of Hb $A_{1c}$ to glucose. Despite this fact, the ADAG study had a number of critical limitations. The study required that 90% of individuals be within 15% of the eAG value derived from the regression line relating mean glucose concentration to Hb $A_{1c}$ level. This criterion was just about achieved, and consequently almost exactly 10% of the individuals were outside the confidence interval. Table 1 shows the consequences of this finding in the UK (9); however, between-laboratory differences in Hb $A_{1c}$ measurement also must be taken into account. An eAG concentration of 10 mmol/L would be reported as 9.15 mmol/L in some laboratories and 10.85 in others. This between-laboratory difference would add to the eAG error. Considering these facts together indicates the 61% difference in Table 1 may be closer to 100% for some patients.

In addition, the ADAG study population was restricted to 700 individuals (300 with type 1 diabetes, 300 with type 2 diabetes, and 100 healthy volunteers). The vast majority were Caucasian, and the numbers in other ethnic groups were small. Individuals with renal failure, pregnancy, hemoglobin variants, and other important illnesses were excluded, as were children. In short, there are many patients with diabetes for whom the ADAG equation simply may not be valid because of the restricted nature of the study population.

The term “estimated average glucose” is likely to cause confusion to both patients and clinicians. The main rationale for expressing the Hb $A_{1c}$ level as eAG is that patients will find eAG easier to understand. Certainly, patients who monitor their own glucose become used to interpreting glucose results and have a good idea what these results mean. Many patients with type 2 diabetes do not monitor their glucose concentrations, however, and expressing Hb $A_{1c}$ values as eAG is unlikely to improve their understanding. Even for patients who do monitor their own glucose concentration, the term “estimated average glucose” may prove confusing. Many glucose meters have a function that shows an average glucose concentration based on previously measured values. This average glucose value may be very different from the eAG value the labora-

### Table 1

<table>
<thead>
<tr>
<th>'True' mean glucose values in patients with an estimated average glucose (eAG) value of 10.0 mmol/L using $A_{1c}$-derived average glucose (ADAG) study criteria, assuming a Gaussian distribution for eAG error.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 90%$ of [individuals’] ‘true’ mean glucose [concentration] must lie between 8.5 and 11.5 mmol/L</td>
</tr>
<tr>
<td>a 35% difference in [the] true mean at the same eAG [concentration]</td>
</tr>
<tr>
<td>$\geq 95%$ of [individuals’] ‘true’ mean glucose [concentration] must lie between 8.2 and 11.8 mmol/L</td>
</tr>
<tr>
<td>a 44% difference in [the] true mean at the same eAG [concentration]</td>
</tr>
<tr>
<td>$\geq 99%$ of [individuals’] ‘true’ mean glucose [concentration] must lie between 7.65 and 12.35 mmol/L</td>
</tr>
<tr>
<td>a 61% difference in [the] true mean at the same eAG [concentration]</td>
</tr>
</tbody>
</table>

* Table taken from Kilpatrick (9); table data quoted in block-quotation-like format.
tory provides to the patient, and this discrepancy will be difficult for the patient to understand. Indeed, patients may doubt the accuracy of an estimate from the laboratory when they compare it with an actual average based on their own measurements. This disparity may cause them to lose faith in the laboratory unless a careful program of education is carried out.

In the case of clinicians, the main difficulty will be in understanding the uncertainty around the conversion of the Hb A1c value to eAG, as highlighted in Table 1. Most clinicians understand the limitations of Hb A1c–based estimates of eAG and interpret eAG in parallel with actual glucose results. The danger of eAG in the hands of a poorly informed clinician would be in the misleading advice given to the patient. This hazard could be overcome by providing confidence intervals, but they would be so wide as to make eAG almost without value. There is no doubt, however, that some experienced clinicians find the concept of eAG useful in clinical practice. Whether the use of eAG actually improves patient management and understanding can be tested. One randomized trial suggests that patient education is what matters and that the use of eAG is no more effective than talking about Hb A1c (10).

In conclusion, although some clinicians would like Hb A1c to be expressed as eAG, laboratories should think very carefully before agreeing to this practice. The role of laboratories should include pointing out the scientific difficulties and problems around this issue that I have highlighted and, if possible, participating in discussions with clinicians to reach consensus on the best way ahead. In a number of countries, such discussions have led to agreement not to report Hb A1c as eAG (11).

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References