A conundrum addressed: the prognostic value of HbA$_{1c}$

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We read with interest the Perspectives article by Dagogo-Jack (Pitfalls in the use of HbA$_{1c}$ as a diagnostic test: the ethnic conundrum. *Nat. Rev. Endocrinol.* 6, 589–593 (2010)).[1] We fear, however, that the article may have overstated the weakness of HbA$_{1c}$ as a diagnostic test, especially in relation to fasting glucose levels.

First, although genetic differences undoubtedly contribute to variation in HbA$_{1c}$ values,[2] the clinical significance of this genetic contribution is uncertain. The prior studies mentioned by Dagogo-Jack could not exclude the possibility that heritable differences in HbA$_{1c}$ stemmed from genetic differences in glucose metabolism as opposed to genetic differences in glucose-independent processes, such as glycation tendency. In fact, the paper by Snieder *et al.*[3] found the genetic contribution to fasting glucose was nearly as large as the genetic contribution to HbA$_{1c}$ (51% versus 62%). The authors conclude "much of the variation in HbA$_{1c}$ levels between individuals is inherited"[3] and that "elevated HbA1c levels may indicate an increased familial risk of diabetic microvascular disease."[3] In individuals with diabetes mellitus, true differences in glycemia far outweigh glucose-independent mechanisms in explaining HbA$_{1c}$ variation.

Second, prior studies of racial and age-related differences in HbA$_{1c}$ levels have accounted for single measurements of fasting and 2 h post-challenge glucose, but not for integrated levels of daytime non-fasting glycemia. Older individuals and ethnic minorities might possibly have differences in diet and physical activity that influence HbA$_{1c}$ levels via real differences in nonfasting glycemia. The fact that longitudinal studies have found HbA$_{1c}$ levels equally predictive of long-term vascular and mortality risk in black and white individuals[4] supports the notion that black–white differences in HbA$_{1c}$ are 'real' (that is, due to glycemia) rather than artefactual (owing to differences in glycation tendency or other mechanisms that are independent of glucose metabolism).

Third, although we agree that, historically, important concerns were raised about many conditions that would interfere with measurement of HbA$_{1c}$, this problem has been largely solved by new assay methods. The National Glycohemoglobin Standardization Program works directly with manufacturers to certify test methods, implementing stringent requirements for accuracy and precision.[5] We certainly agree that conditions that substantially alter erythrocyte turnover can affect HbA$_{1c}$ test results, regardless of measurement methodology—HbA$_{1c}$ is definitely not perfect, but neither is glucose. The glucose assay is subject to diurnal variation, laboratory calibration problems, and preanalytical issues.[6] Additional limitations of glucose testing include participant preparation (that is, fasting) and much greater within-person variation compared with HbA$_{1c}$ levels.[7]

Fourth, judging the sensitivity and specificity of HbA$_{1c}$ against a glucose-based gold standard is misleading. Because glucose determinations are inherently more variable than HbA$_{1c}$, these convenient gold standards reduce the apparent accuracy of HbA$_{1c}$. A stronger comparison would rely on repeated glucose determinations on different days, and data suggest HbA$_{1c}$ performs extremely well when diabetes definitions that reflect those used in clinical practice are used as the gold standard.[8] An even fairer—and more clinically meaningful—gold standard might be prediction of microvascular events, vascular events and mortality. Against this unbiased standard, HbA$_{1c}$ appears at least as strong as fasting glucose.[4,9–12]

In conclusion, we recommend that the value of HbA$_{1c}$ be judged on the basis of its predictive importance, a metric that subsumes these other concerns and puts it on equal footing with the alternatives.

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Competing interests
The authors declare no competing interests.

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