Reduced Testing Frequency for Glycated Hemoglobin, HbA_{1c}, Is Associated With Deteriorating Diabetes Control

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Diabetes Care 2014;37:2731–2737 | DOI: 10.2337/dc14-0297

OBJECTIVE

We previously showed that in patients with diabetes mellitus, glycated hemoglobin (HbA_{1c}) monitoring outside international guidance on testing frequency is widespread. Here we examined the relationship between testing frequency and diabetes control to test the hypothesis that retest interval is linked to change in HbA_{1c} level.

RESEARCH DESIGN AND METHODS

We examined repeat HbA_{1c} tests (400,497 tests in 79,409 patients, 2008–2011) processed by three U.K. clinical laboratories. We examined the relationship between retest interval and *1*) percentage change in HbA_{1c} and *2*) proportion of cases showing a significant HbA_{1c} rise. The effect of demographics factors on these findings was also explored.

RESULTS

Our data showed that the optimal testing frequency required to maximize the downward trajectory in HbA_{1c} was four times per year, particularly in those with an initial HbA_{1c} of ≥7% (≥53 mmol/mol), supporting international guidance. Testing 3-monthly was associated with a 3.8% reduction in HbA_{1c} compared with a 1.5% increase observed with annual testing; testing more frequently provided no additional benefit. Compared with annual monitoring, 3-monthly testing was associated with a halving of the proportion showing a significant rise in HbA_{1c} (7–10 vs. 15–20%).

CONCLUSIONS

These findings provide, in a large, multicenter data set, objective evidence that testing outside guidance on HbA_{1c} monitoring frequency is associated with a significant detrimental effect on diabetes control. To achieve the optimum downward trajectory in HbA_{1c}, monitoring frequency should be quarterly, particularly in cases with suboptimal HbA_{1c}. While this impact appears small, optimizing monitoring frequency across the diabetes population may have major implications for diabetes control and comorbidity risk.

The use of glycated hemoglobin (HbA_{1c}) to monitor control is a central part of the management of patients with diabetes mellitus. It is well recognized that poor control of diabetes is associated with poorer clinical outcomes and increased risk of complications (1). Hence many professional bodies and national health care

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Received 31 January 2014 and accepted 2 June 2014.

agencies worldwide provide recommendations on frequency of monitoring using HbA_{1c} to help maintain optimal control.

In the U.K., the National Institute for Health and Clinical Excellence (NICE) recommend HbA_{1c} testing at 2–6-monthly intervals in patients with unstable diabetes, with a measurement made at an interval of less than 3 months being used as an indicator of direction of change rather than of a new steady state (2,3). In those with stable diabetes on unchanging therapy, intervals of 6–12 months are recommended. Similar guidance is provided by the American Diabetes Association (ADA) (4). While these recommendations are well established, conformity to such monitoring program is poor and extremely variable (5–7). We previously showed that in general practice, 6–32% of HbA_{1c} tests were requested too soon relative to guidance while 9–54% of tests were requested too late.

Despite this guidance on monitoring frequency, there are few data to support the impact of testing frequency on clinical outcome. Utilizing data from laboratory information systems, we examined the link between monitoring frequency (interval between individual requests for HbA_{1c} measurement) and change in HbA_{1c} levels using data on 400,497 repeat requests for HbA_{1c} in 79,409 patients from three clinical laboratories over a 4-year period to provide evidence to support (or otherwise) recommendations on monitoring frequency for patients with diabetes.

RESEARCH DESIGN AND METHODS

Patients

Data on all HbA_{1c} test requests (n = 565,924) between January 2008 and December 2011 were extracted from the Clinical Biochemistry Laboratory Information Management System databases at the University Hospital of North Staffordshire National Health Service Trust (303,369 requests from 122,738 patients), Royal Wolverhampton National Health Service Trust (156,332 requests from 35,383 patients), and Salford Royal Hospital National Health Service Foundation Trust (106,223 requests from 31,199 patients). These centers were selected as they use different laboratory information systems (North Staffordshire, Clinisys Masterlab; Salford, iSoft Telepath; Wolverhampton, Technidata TD-Synergy) and have contrasting patient demographics (e.g., South Asian population served: North Staffordshire, 1.8%; Salford, 4%; Wolverhampton, 17.9%; South Asian ethnicity is associated with a higher risk of diabetes and poorer glycemic control [8,9]). From this data set, we concentrated on repeat requests only, leaving a core data set of 400,497 repeat requests in 79,409 patients. The characteristics of this data set are described in Table 1. During this period, there was little evidence (from clinical details supplied with requests) that HbA_{1c} was being used as a diagnostic tool, and we specifically used data collected prior to the implementation of WHO guidance on use of HbA_{1c} in diagnosis in 2011 (10).

Data Analysis

Using data on intervals between HbA_{1c} requests categorized into 1-month blocks (e.g., 0–1 month, 1–2 months), we first examined the relationship between mean change in HbA_{1c} value between tests, expressed as a percentage rise or fall, and interval between consecutive tests. We then examined the impact of patient demographics, center, and initial HbA_{1c} value on this relationship. To explore the potential impact of biological and analytical variation on these findings, we then examined the proportion of cases with a significant rise based on

$$\text{Significant difference} = \sqrt{(A^2 + B^2)} \times 2.8,$$

where A is the analytical variation and B is the biological variation.

Using this equation, assuming a local analytical coefficient of variation for HbA_{1c} of 3.0% and a biological variation of 1.9% (11), led to a 9.9% rise as representing a significant increase from the baseline measurement.

All statistical analyses were performed using Stata (version 12; College Station, TX). χ^2 tests were used to compare differences in proportions and ANOVA for differences in mean differences between categories. As in our previous work (5), we also recognized that testing intervals were not independent observations (they are clustered within patients). We therefore reanalyzed a subset of the data based on a randomly selected single interval from each patient. This analysis produced identical inferences to the complete data set (data not shown). Hence, the statistical analyses presented in the results section are based on the complete data set.

RESULTS

Patient Characteristics

Table 1 shows the demographic characteristics of the data set across the three centers. Mean ages and sex distributions were similar, though the large number of observations in each category led to statistical differences between groups (both $P < 0.001$; ANOVA for age, χ^2 tests for proportion of males). Mean initial HbA_{1c} was generally higher in the Wolverhampton group, and proportion of requests from general practice was higher in the North Staffordshire group (both $P < 0.001$; ANOVA for initial HbA_{1c}, χ^2 tests for proportion of requests from general practice). Mean interval between requests was broadly similar, though this again achieved statistical significance ($P < 0.001$; ANOVA), with the longest interval being observed in the North Staffordshire group (6.8 months) and the shortest in the Salford group (6.0 months).

Association Between Repeat Request Interval and Change in HbA_{1c}

Figure 1 shows the relationship between repeat requesting interval (categorized in 1-month intervals) and percentage change in HbA_{1c} concentration in the total data set. From 2 months onward, there was a direct relationship between retesting interval and control. A testing frequency of >6 months was associated with deterioration in control. The optimum testing frequency in order to maximize the downward trajectory in HbA_{1c} between two tests was approximately four times per year. Our data also indicate that testing more frequently than 2 months has no benefit over testing every 2–4 months. Relative to the 2–3 month category, all other categories demonstrated statistically higher mean change in HbA_{1c} (all $P < 0.001$).

We then examined whether patterns were comparable between the three centers and assessed the impact of starting HbA_{1c}. Figure 2*A* shows that similar patterns were observed for each of the three centers, with the optimum interval to improvement in overall control at ~3 months across all centers. The Royal Wolverhampton Hospital showed a generally lower increase in HbA_{1c} after 6 months, perhaps

Table 1—Patient demographics

	Salford	North Staffordshire	Wolverhampton
Number of repeat requests	73,995	208,669	117,833
Mean age ± SD (years)	63.3 ± 14.0	61.7 ± 13.7	62.9 ± 15.9
Mean initial HbA_{1c} ± SD (%)	7.3 ± 1.7	7.4 ± 1.6	7.8 ± 1.7
Mean initial HbA_{1c} ± SD (mmol/mol)	56 ± 18.5	57 ± 17.5	62 ± 18.5
Mean interval between tests ± SD (months)	6.0 ± 4.7	6.8 ± 5.6	6.4 ± 4.5
Proportion of requests in males (%)	55.1	53.2	53.1
Proportion of requests from general practice (%)	78.6	88.6	76.9

reflecting a higher overall starting HbA_{1c} concentration (Table 1). However, given the similarities, all subsequent analysis was based on the combined data set.

Figure 2*B* shows the effect of starting HbA_{1c}, categorized as <6% (<42 mmol/mol; to reflect patients who are have generally achieved their target and are on stable therapy), 6–7% (42–52 mmol/mol; intermediate group where active intervention is variable), and ≥7% (≥53 mmol/mol; to reflect those patients generally considered to have poor diabetes control). These data show that in patients with poor control, the pattern was similar to that seen in the total group, except that *1*) there was generally a more marked decrease or more modest increase in change of HbA_{1c} concentration throughout and, consequently, *2*) a downward trajectory in HbA_{1c} was observed when the interval between tests was up to 8 months, rather than the 6 months as seen in the total group. In patients with a starting HbA_{1c} of <6% (<42 mmol/mol), there was a generally linear relationship between interval and increase in HbA_{1c}, with all intervals demonstrating an upward change in mean HbA_{1c}. The intermediate group showed a similar pattern as those with a starting HbA_{1c} of <6% (<42 mmol/mol), but with a steeper slope.

Association Between Repeat Test Interval and Proportion of Patients Showing a Significant Increase in HbA_{1c}

In order to examine the potential link between monitoring frequency and the risk of major deterioration in control, we then assessed the relationship between testing interval and proportion of patients demonstrating an increase in HbA_{1c} beyond the normal biological and analytical variation in HbA_{1c} (see RESEARCH DESIGN AND METHODS for definition of *significant* in this context). Using this definition of *significant* increase as a ≥9.9% rise in subsequent HbA_{1c}, our data show that the proportion of

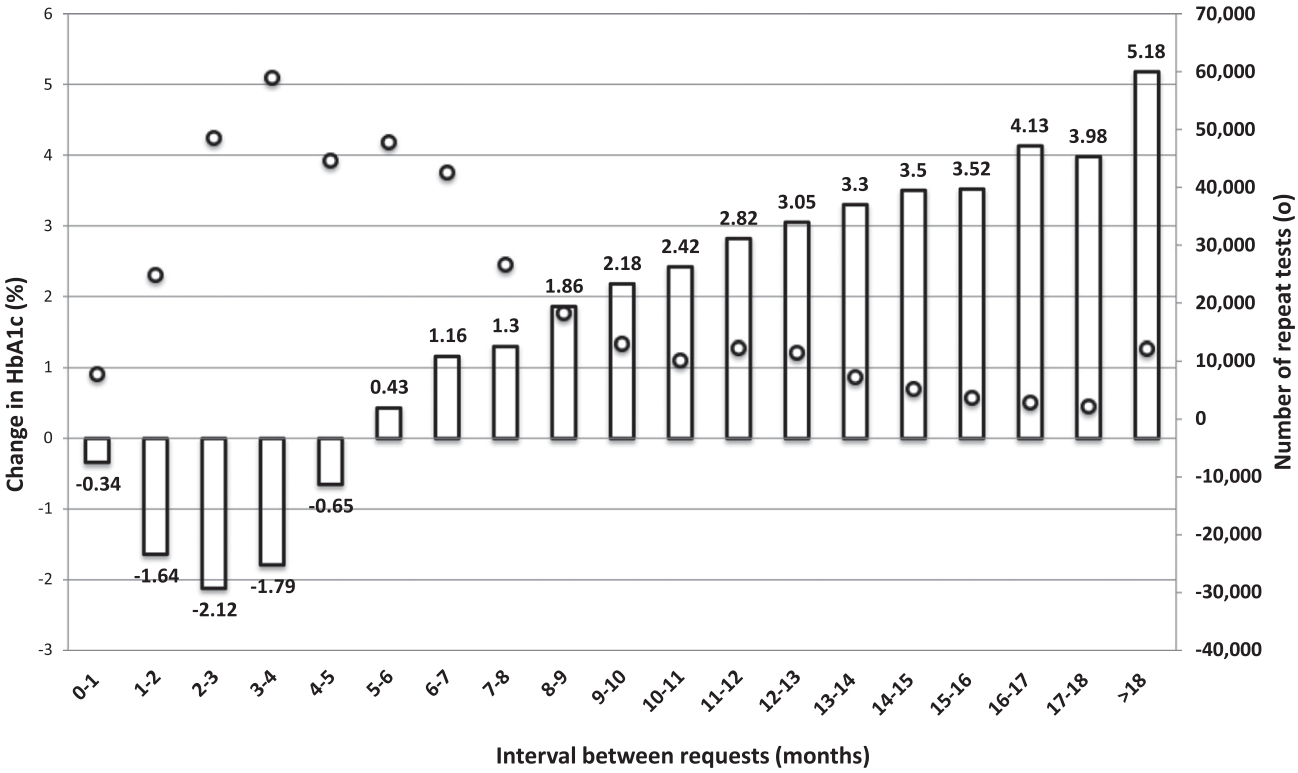

Figure 1—Relationship between HbA_{1c} testing interval and overall percentage change in HbA_{1c} concentration. Number of tests in each category is shown by the floating point (white circles) using the right-hand vertical axis.

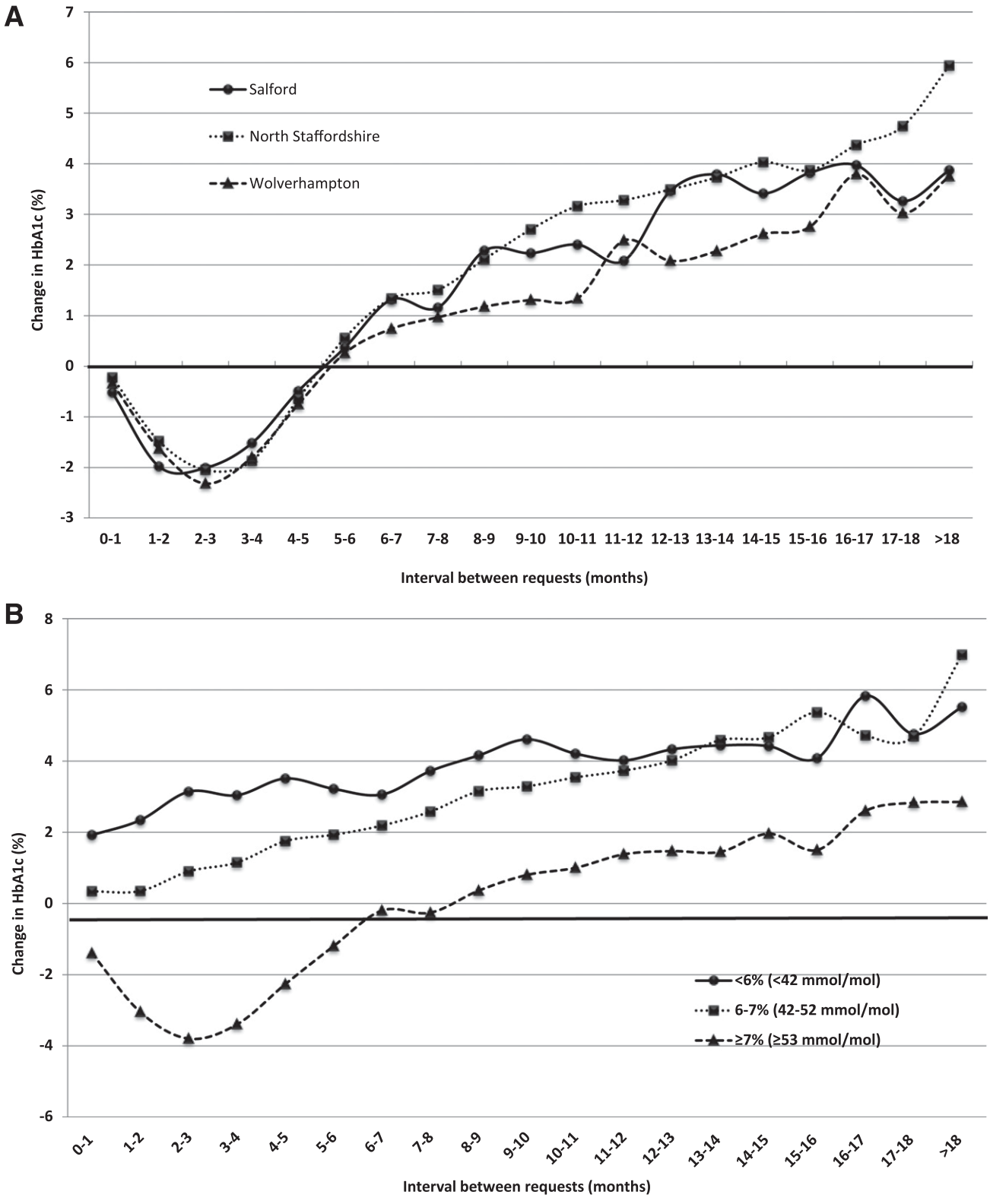

Figure 2—Relationship between HbA_{1c} testing interval and change in mean HbA_{1c} concentration (*A*) across the three centers and (*B*) in patients with poorly controlled diabetes (starting HbA_{1c} ≥7% [≥53 mmol/mol]), intermediate control (starting HbA_{1c} 6–7% [42–52 mmol/mol]), and well-controlled diabetes (starting HbA_{1c} <6% [<42 mmol/mol]).

patients showing this magnitude of rise increased month to month, with increasing intervals between tests for each of the three centers. For example, across the centers, 21–26% of cases where the interval was greater than 18 months demonstrated a significant increase in HbA_{1c} compared with 17–19% at 12–13 months, 11–13% at 6–7 months, and 7–9% at 2–3 months. Hence, testing at 2–3-monthly intervals would, at a population level, result in a

marked reduction in the proportion of cases demonstrating a significant increase compared with annual testing ($\chi^2_1 = 880$; $P < 0.0001$).

Figure 3 shows that irrespective of the baseline HbA_{1c}, there was a generally linear relationship between interval and the proportion demonstrating a significant increase in HbA_{1c}, though the slope of this relationship increased with rising initial HbA_{1c}. Interestingly, only in those cases where the interval was greater than 6 months was a higher initial HbA_{1c} associated with a marked increase in proportion showing a significant rise in HbA_{1c} compared with the other two groups.

CONCLUSIONS

This study describes the relationship between frequency of HbA_{1c} monitoring and glycemic control in patients with diabetes. The large amount of longitudinal data held in clinical laboratory information systems provides a unique opportunity to relate the patterns of requesting to outcome, though it should be recognized that laboratory records can provide limited access to clinical data.

Our data indicate that for a HbA_{1c} retest interval of more than 2 months, there was a direct relationship between retesting interval and control (Fig. 1), with a retest frequency of greater than 6 months being associated with deterioration in control. The data showed that for diabetic patients as a whole, the optimum repeat testing interval should be four times per year, particularly in those with poorer diabetes control (starting $HbA_{1c} > 7\%$ [≥53 mmol/mol]). This supports recommendations provided in worldwide guidance for patients with unstable diabetes (2–4,12). Our findings are also in keeping with those of Fu et al. (13) who identified a negative correlation between *level* of HbA_{1c} and monitoring frequency in 1,511 patients, using information on testing frequency gained from self-reported questionnaire data. They showed that the proportion of patients with an HbA_{1c} of ≥7% (≥53 mmol/mol) was significantly lower in those who had >2 tests per year compared with those who had only one HbA_{1c} measurement or those who had not had a test in the previous year. Turchin et al. (14) showed that frequent testing in patients with diabetes was associated with a shorter time to target HbA_{1c}, even after correction for potential confounding factors, including initial HbA_{1c} level. The optimum retest interval across the three centers was similar, suggesting that our findings may be unrelated to clinical laboratory factors, local policies/protocols on testing, or patient demographics.

Similar to that recommended by the ADA, U.K. guidance suggests, in stable patients on unchanging therapy, a testing frequency of 1–2 times per year (2–4). Our data showed a more linear relationship between frequency and change in HbA_{1c} in these patients. In those with a starting HbA_{1c} of <6% (<42 mmol/mol), most of whom are likely to be on unchanging therapy, the slope of the

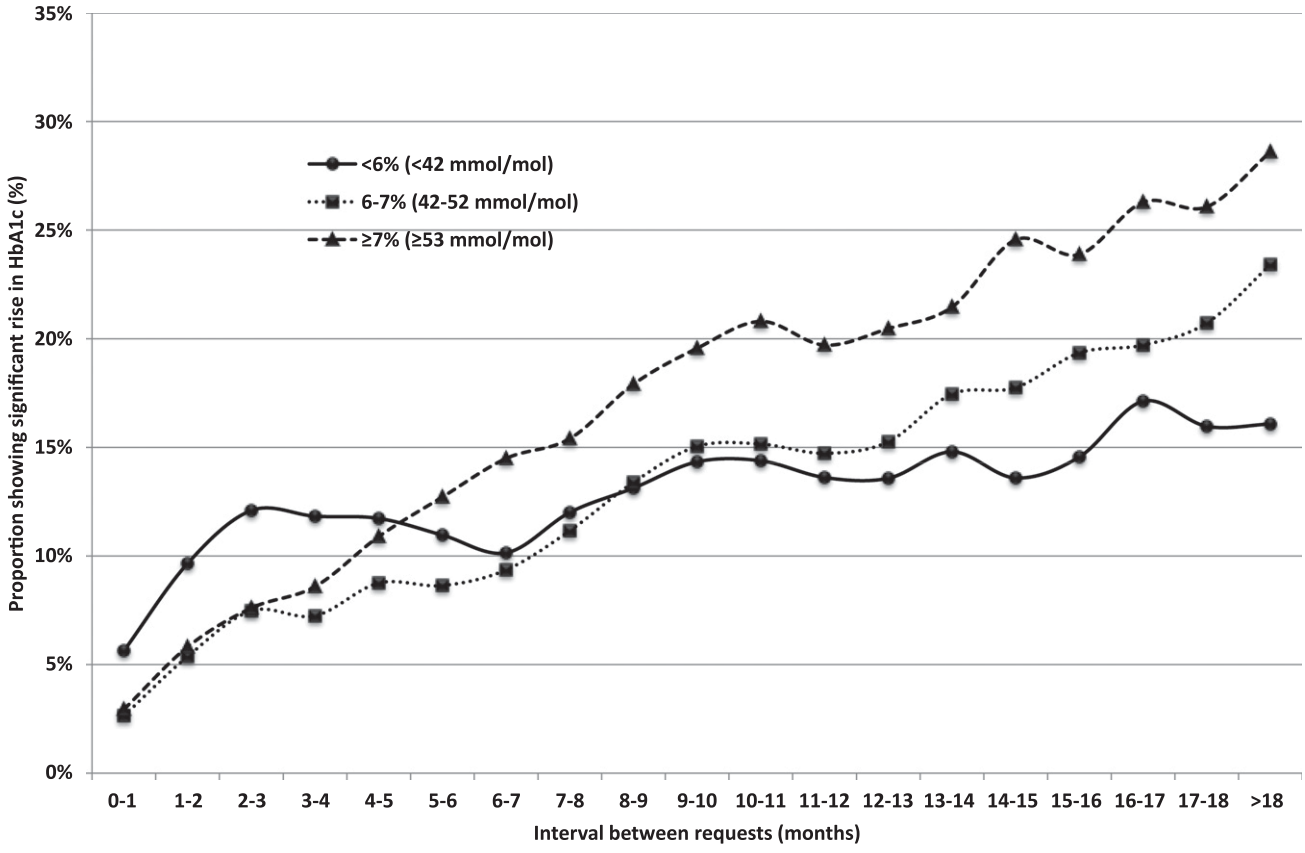

Figure 3—Relationship between HbA_{1c} test requesting interval and proportion of requests showing a significant (>9.9%) increase in HbA_{1c} concentration in patients with poorly controlled diabetes (starting $HbA_{1c} \geq 7\%$ [≥53 mmol/mol]), intermediate control (starting HbA_{1c} 6–7% [42–52 mmol/mol]), and well-controlled diabetes (starting $HbA_{1c} < 6\%$ [<42 mmol/mol]).

relationship between testing frequency and change in HbA_{1c} (4% over 12 months; equivalent to a change from 5.5 to 5.7% [37 to 38.5 mmol/mol]) is consistent with the natural history of disease progression in such patients. Heianza et al. (15) estimated the annual increase at ~0.09% (~1 mmol/mol) per year in nondiabetic patients 1–3 years prediagnosis.

Our data also suggested that testing more frequently than 2 months had no additional benefit over quarterly testing, supporting U.K. guidance (2,3). This is possibly related to red cell survival (~115–125 days [16,17]) and the analytical challenges facing detection of a biologically significant change in HbA_{1c} at intervals of less than 2 months. It is, however, complicated by the finding that erythrocyte survival is itself highly variable between individuals and by suggestions that it is reduced in patients with poor glycemic control (estimated at a reduction in survival of ~7 days per 1% [11 mmol/mol] rise in HbA_{1c} in one study [16]), though data on this link between survival and glycemic control are inconsistent (17,18).

We also found a linear relationship between testing frequency and proportion of patients showing a biologically significant increase in HbA_{1c}. This finding illustrates the benefits of frequent testing, at least in patients with a starting HbA_{1c} of ≥7% (≥53 mmol/mol). In ostensibly well-controlled patients (initial HbA_{1c} 6–7% [42–52 mmol/mol]), this is perhaps at odds with NICE guidance. Previous data from our and other groups on requesting patterns indicated that relatively few patients in general practice were tested annually (5,6). The U.K. Quality and Outcomes Framework, a voluntary incentive scheme for general practices in the U.K. that rewards them for how well they care for patients, requires that the practices provide information on "the percentage of patients with diabetes in whom the last [International Federation of Clinical Chemistry and Laboratory Medicine]-HbA_{1c} is 59 mmol/mol (equivalent to HbA_{1c} of 7.5% in [Diabetes Control and Complications Trial] values) or less (or equivalent test/reference range depending on local laboratory) in the preceding 15 months" (19). This could be achieved using a testing frequency significantly lower than that that suggested by NICE, ADA, and others and certainly less than the 3-monthly interval implied by our data. These findings strongly suggest that U.K. Quality and Outcomes Framework indicators should be reviewed if maximum benefit to patients is to be achieved.

While this study indicates the overall optimum testing frequency for HbA_{1c} in a large population of patients with diabetes across three centers, there are a number of limitations to the study. We have not examined the impact of this at a doctor or patient level (though subanalysis selecting a single sequential pair of tests from each patient showed the same results), and we were not able, from laboratory data, to differentiate between type 1 and type 2 diabetes (or indeed gestational diabetes) or account for treatment/lifestyle interventions following testing. Similarly, it does not provide data on the reason for the interval between tests. We have previously shown that a range of patient and systemic factors, as well as those associated with health care professionals, can influence testing frequency (20). Furthermore, our findings are associative and do not imply causality, though they do indicate an area of study warranting further investigation. The 5.8% difference in change in HbA_{1c} between 3- and 15-monthly testing may appear small (equivalent to a change in HbA_{1c} of 7.3 to 6.9% [56 to 52 mmol/L]). However, extrapolating from the UK Prospective Diabetes Study data (1), this reduction in mean HbA_{1c} would be associated with reductions in risk of 7% for diabetes-related mortality, 11% for cardiovascular comorbidity (stroke, myocardial infarction, heart failure), and 12% for microvascular complications (1), irrespective of the starting HbA_{1c}. These data indicate that at the population level, lack of conformity to the monitoring frequency for HbA_{1c} recommended in national guidance, whatever the underlying cause, is associated with suboptimal diabetes control and hence potentially increased risk of comorbidities and poorer patient outcomes. The role of monitoring frequency in this important area therefore requires further study.

Importantly, the study has two wider implications: first, it illustrates the power (and limitations) of using existing laboratory data sets to address key clinical questions and, second, while we have concentrated on HbA_{1c}, this approach provides a model that is applicable to the use of other monitoring tests in a range of other chronic diseases.

Acknowledgments. The authors are grateful to the members of Diabetes UK (North Staffordshire Branch) and Stoke-on-Trent Community Health Voice for advice and feedback on the patient aspects of the study.

Funding. This study was supported by a National Institute for Health Research Healthcare Scientist Fellowship award to O.J.D. (HCS/08/011), supervised by A.A.F., and the Health Foundation Shine Award to A.A.F. and O.J.D.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. O.J.D. wrote the manuscript, performed the data analysis, and provided clinical advice and critique from a clinical laboratory scientist perspective. D.H. performed the data analysis. J.L.W., J.J.S., and M.T. performed the data extraction from the three centers. C.F. provided clinical advice and critique from a clinical laboratory scientist perspective. A.H. and F.W.H. provided clinical advice and critique from a clinical diabetologist perspective. P.W.J. supervised the statistical analysis. R.J.P., as a Diabetes UK expert patient, provided a patient perspective and ensured the team had a patient-centered focus. A.A.F. wrote the manuscript and provided clinical advice and critique from a clinical laboratory scientist perspective. All authors reviewed and edited the manuscript. A.A.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. The initial findings of this study were presented at FOCUS, the Association for Clinical Biochemistry National Meeting, York, U.K., 14–18 April 2013 (Ann Clin Biochem 2013;50[Suppl. 1]:68).

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