A New Look at Screening and Diagnosing Diabetes Mellitus

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Objective: Diabetes is underdiagnosed. About one third of people with diabetes do not know they have it, and the average lag between onset and diagnosis is 7 yr. This report reconsiders the criteria for diagnosing diabetes and recommends screening criteria to make case finding easier for clinicians and patients.

Participants: R.M.B. invited experts in the area of diagnosis, monitoring, and management of diabetes to form a panel to review the literature and develop consensus regarding the screening and diagnosis of diabetes with particular reference to the use of hemoglobin A1c (HbA1c). Participants met in open session and by E-mail thereafter. Metrika, Inc. sponsored the meeting.

Evidence: A literature search was performed using standard search engines.

Consensus Process: The panel heard each member’s discussion of the issues, reviewing evidence prior to drafting conclusions. Principal conclusions were agreed on, and then specific cut points were discussed in an iterative consensus process.

Conclusions: The main factors in support of using HbA1c as a screening and diagnostic test include: 1) HbA1c does not require patients to be fasting; 2) HbA1c reflects longer-term glycemia than does plasma glucose; 3) HbA1c laboratory methods are now well standardized and reliable; and 4) errors caused by nonglycemic factors affecting HbA1c such as hemoglobinopathies are infrequent and can be minimized by confirming the diagnosis of diabetes with a plasma glucose (PG)-specific test. Specific recommendations include: 1) screening standards should be established that prompt further testing and closer follow-up, including fasting PG of 100 mg/dl or greater, random PG of 130 mg/dl or greater, or HbA1c greater than 6.0%; 2) HbA1c of 6.5–6.9% or greater, confirmed by a PG-specific test (fasting plasma glucose or oral glucose tolerance test), should establish the diagnosis of diabetes; and 3) HbA1c of 7% or greater, confirmed by another HbA1c- or a PG-specific test (fasting plasma glucose or oral glucose tolerance test) should establish the diagnosis of diabetes. The recommendations are offered for consideration of the clinical community and interested associations and societies. (J Clin Endocrinol Metab 93: 2447–2453, 2008)
the actual onset and the diagnosis of type 2 diabetes (1–3). It is also now established that microvascular and macrovascular complications are sometimes present, even in prediabetes ([impaired fasting glucose (IFG) or impaired glucose tolerance] (4–13). Early detection of diabetes, in addition to its potential for identifying retinopathy (5), could also find peripheral neuropathy (6) and microalbuminuria (7) as well as the markedly increased risk of macrovascular disease (8–13).

These realities support the critical need to identify diabetes and its precursors more efficiently and earlier.

Several barriers impede the effort to diagnose diabetes in timely fashion. First, screening for diabetes in asymptomatic people is now recommended only by questionnaires to evaluate risk or by fasting plasma glucose (FPG) or oral glucose tolerance test (OGTT), both of which require that the patient be fasting. Criteria defining a positive screen do not differ from those used to diagnose diabetes (14). The World Health Organization in 2002, however, recommended trials of screening approaches (http://www.who.int/diabetes/publications/en/screening_mnc03.pdf).

Current recommendations of the American Diabetes Association were made a decade ago (15, 16). They reject the use of hemoglobin A1c (HbA1c) as a diagnostic tool, largely because it was considered at the time to be inadequately standardized and insensitive. The issue has been discussed before and since that 1997 expert committee report (17–28), but the recommendations were not substantively changed in the 2003 update (16).

Given more recent evidence and the increasingly recognized need to make the diagnosis of diabetes efficiently, a panel considered the data related to current diabetes screening and diagnostic approaches, and in particular, the possible utility of HbA1c. The panel was made up of people with varying backgrounds, including an academic clinical pathologist (D.B.S.), a general internist (D.E.), an expert in diabetes cost-effectiveness analysis (W.H.H.), and three academic diabetologists (C.D.S., R.M.B., M.B.D.). In this report, we describe the issues reviewed and the result of our deliberations.

The following specific questions were addressed: what practical issues surround the use of HbA1c in the screening and diagnosis of diabetes? What are the accuracy, sensitivity and specificity of HbA1c in screening for and diagnosing diabetes? How would confounders and effect modifiers of HbA1c affect results? Will changes in the reference anchor for HbA1c affect its use in screening for and diagnosing diabetes? Should HbA1c be accepted as a diagnostic criterion for diabetes? What evidence supports the specific HbA1c diagnostic recommendation? Should criteria be established for screening for diabetes, and if so, should they include HbA1c? Finally, should a random, or casual, plasma glucose be used in screening for diabetes?

What practical issues surround the use of HbA1c in the screening and diagnosis of diabetes?

A series of practical considerations favor the use of HbA1c in screening for and diagnosing diabetes. First, both the OGTT and FPG require that the patient fast for at least 8 h, but the measurement of HbA1c does not. Unless the patient is severely hyperglycemic and overtly symptomatic, the diagnosis cannot be made in most patients coming for afternoon appointments or if they are before a morning appointment. This need for a fasting sample cuts into the opportunity to diagnose diabetes. The American Diabetes Association Expert Committee report discussed extensively the challenges of performing the OGTT and specifically recommended FPG in routine clinical settings (15, 16). They did not, however, emphasize that HbA1c is even simpler to obtain than FPG, requiring only venous blood or, with point of care testing, a capillary sample without regard to time since last meal (29).

Second, HbA1c level is not affected by short-term lifestyle changes. Whereas a few days or weeks of dieting or increased exercise in preparation for a doctor visit can significantly affect FPG and OGTT, HbA1c accurately reflects longer-term glycemia (30).

Third, established diagnostic criteria for diabetes are not followed in the community. Ealovega et al. (31) found that 95% of opportunistic screening was done by random plasma glucose alone, the least sensitive test. In their survey, only 3% of screenings used FPG, 2% used HbA1c, and less than 1% used OGTT. Furthermore, a survey of a convenience sample of 258 physician respondents was conducted by an independent survey company at the 2005 annual meeting of the American College of Physicians. Of physicians surveyed, 93.4% reported that they routinely screen for diabetes, and 49% reported using HbA1c for screening and 58% for diagnosis of diabetes. Forty-nine percent also thought HbA1c was an approved test for screening. Anecdotally, HbA1c is frequently assessed in patients not known to have diabetes, further suggesting its widespread use in the community as a screening tool.

Fourth, whereas HbA1c is only a surrogate measure for average blood glucose, the major trials that relate glycemic control to diabetic microvascular complications uniformly use HbA1c as the measure of glycemia (32–34). It is therefore the measurement best proven to correlate with at least diabetic retinopathy, nephropathy and neuropathy.

Finally, HbA1c is familiar to clinicians, widely used as the basis of assessing glycemic control in established diabetes (35).

The lack of availability of HbA1c in more remote or underserved areas of the world, and the cost of the test are legitimate concerns. Point-of-care testing could be used in settings without easy laboratory access (29). No doubt, blood glucose measurement is the most widely available test, but including HbA1c among accepted diagnostic criteria would not adversely affect centers that cannot perform the test. They would simply maintain current practice.

What are the accuracy, sensitivity, and specificity of HbA1c in screening for and diagnosing diabetes?

Under the leadership of the National Glycohemoglobin Standardization Program (NGSP), remarkable strides have been taken in standardizing HbA1c assays in many nations worldwide (36, 37). Presently more than 99% of laboratories measuring HbA1c in the United States use NGSP-certified methods (http://www.ngsp.org/). The NGSP is in the process of tightening certification criteria. Effective in September 2007, to obtain NGSP certification, manufacturers have to meet a bias criterion in

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which 95% confidence intervals of the differences are within ± 0.85%.

FPG itself is neither perfectly stable nor free of laboratory variability. Petersen et al. (38) found FPG variance from day to day to be 12–15%, whereas the variance of HbA1c was only 1.9%. Ollerton et al. (39) reported that the biological variability (2 sd) of FPG was 14%. By contrast, Sacks et al. (40) reported that the day-to-day variance of HbA1c is less than 2%, whereas laboratory variability of FPG was 4%. This, in addition to the estimated 13.7% biological variability, yielded 95% confidence interval for FPG measured at 126 to be 103–149 mg/dl (40).

Bennett et al. (41) recently published a systematic review of reports describing the accuracy of HbA1c for the detection of type 2 diabetes, with the OGTT as the reference standard. Of 63 papers identified from a search, nine primary cross-sectional studies, published between 1998 and 2004, met criteria for inclusion. Receiver operating characteristic (ROC) analysis was used in seven of these primary studies to identify a useful cut point for diabetes. The review found no evidence to suggest that FPG is superior to HbA1c in screening for diabetes, with OGTT as the gold standard. HbA1c had a slightly higher specificity and slightly lower sensitivity, than FPG for the detection of diabetes. The HbA1c cut points in the analyses by Bennett et al. (6.1–6.2%) are similar to those proposed by other investigators (42, 43).

Rohlfing et al. (42) in 2002 analyzed the Third National Health and Nutrition Examination Survey (NHANES III) for the sensitivity and specificity of HbA1c in the diagnosis of diabetes based on FPG. They concluded that HbA1c provided a specific and convenient approach to screening for diabetes and suggested a value of 6.1% or greater, 2 sd above the mean in the normal NHANES III population.

Buell et al. (43) recently completed a similar analysis based on the 1999–2004 NHANES data. The diagnosis of diabetes was considered established if FPG was 126 mg/dl or greater. Using a ROC analysis, they found that HbA1c of 5.8% or greater is the point that yielded the highest sum of sensitivity (86%) and specificity (92%). They concluded that HbA1c of 5.8% would be an appropriate cut point above which to proceed to further evaluation (43).

Nakagami et al. (44) also recently assessed HbA1c vs. FPG in the diagnosis of diabetes. In a cross-sectional study of 1904 Japanese people in one town, aged 35–89 yr, they found that the area of the ROC for HbA1c was almost the same as that for FPG (0.856 vs. 0.902, respectively), suggesting that each is a good diagnostic test.

Perry et al. (45), doing OGTTs on people with FPG 100–125 mg/dl, found that FPG was insensitive in the detection of OGTT-defined diabetes. The addition of HbA1c greater than 6.1% to FPG greater than 100 mg/dl improved the sensitivity of screening substantially, from 45% to 61%.

Selvin et al. (46) evaluated NHANES III data with repeated measurements of FPG, 2-h plasma glucose (PG), and HbA1c in 685 fasting participants without the diagnosis of diabetes. They found that 2-h PG had the greatest within-person variability (coefficient of variation 16.7%), and FPG and HbA1c had coefficient of variation 5.7 and 3.6%, respectively. Their conclusion was that both the 2-h and FPG measurements had high variability relative to HbA1c (46). They noted that their results confirm prior reports of HbA1c being more stable over time than FPG (47–49).

Finally, three studies tested the use of HbA1c in predicting new onset rather than only prevalent diabetes. Edelman et al. (50) followed up 1253 patients in the Department of Veterans Affairs Medical Center for over 3 yr and found that using a multivariate logistic regression model, baseline HbA1c was strongest predictor of new clinically defined diabetes. Droumaguet et al. (51) in the Data Epidemiological Study on the Insulin Resistance Syndrome, a French cohort study of 2820 people, found that FPG-defined diabetes risk increased exponentially with baseline HbA1c, with a sensitivity of 64% and specificity of 77% using a cut point of 5.9%. Analysis of the data by Inoue et al. (52), also studying type 2 diabetes in Japan, found that baseline HbA1c of 5.8% or greater (the upper limit of normal for their assay), regardless of FPG, imposed a 10-fold increase in diagnosed diabetes over 7 yr.

How would confounders and effect modifiers of HbA1c affect results?

There are certain well-known confounders and effect modifiers that influence the clinical use of HbA1c (35), including relatively common hemoglobinopathies. Hemoglobin S trait interferes with some assay methods (53–55), but only 14% of labs currently use methods with clinically significant hemoglobin S interference, and this is expected to come down to 5% by mid-2008 with the modification of a widely used method. About 11% of laboratories currently have interference from hemoglobin C, but this will also drop to about 5% by mid-2008. No data are available at present for interference by hemoglobin E.

Racial disparities in HbA1c may exist that are independent of blood glucose. The Diabetes Prevention Program and the ADOPT Study Group found that African-Americans had an HbA1c 0.4–0.7% greater than Caucasians, (56, 57). The extent of these disparities clearly needs further research.

Uncommonly, high-dose salicylates, vitamins C and E, and severe iron deficiency have been reported to be interfering substances (35). A case report suggests that dapsone lowers HbA1c (58).

Considering effect modifiers, any condition that shortens erythrocyte survival, such as hemolytic anemia, will proportionally decrease HbA1c because the hemoglobin in younger red cells has less exposure to the ambient glycemia. Active bleeding, with increased reticulocyte production, will reduce the age of the average erythrocyte and thereby lower HbA1c. Conversely, any condition that increases average circulating erythrocyte age, such as splenectomy (which slows red cell clearance) or aplastic anemia (in which reticulocyte production is impaired), will increase the concentration of HbA1c independent of glycemia.

Thus, confounders and effect modifiers can significantly affect the accuracy of HbA1c when used to screen for or diagnose diabetes. Three approaches could minimize the impact of these factors. First, the use of HbA1c could be considered invalid in the setting of anemia. (By analogy, glycemic criteria are now considered invalid in the unstable clinical state.) Second, if a diag-
nostic threshold for diabetes based on HbA1c is equivocal, this could require validation (see below). (By analogy, any PG dependent diagnosis must now be confirmed by a second FPG unless there is symptomatic hyperglycemia.) Third, the specific methodology used to test HbA1c could be made appropriate for the population being screened (for example, methods that are not affected by abnormal hemoglobins should be used in areas with high rates of hemoglobinopathies).

Will changes in the reference anchor for HbA1c affect its use in screening for and diagnosing diabetes?

The analytic method that serves as anchor for HbA1c assessment worldwide is in the process of changing to a mass spectrometry-based assay (59–61). A consensus panel recommended reporting the HbA1c-derived estimated average glucose together with both the NGSP-standardized HbA1c result and millimoles of glycated hemoglobin (62). However results are reported, the new anchor will have no practical impact on the clinical use of HbA1c. Laboratory methods currently approved to measure HbA1c will continue to be used. If anything, the diabetic public will have a more meaningful translation of the HbA1c result into its corresponding average glucose. HbA1c will continue to be a pivotal test in the management of diabetes, and the confusion that could have been caused by changing HbA1c reference range (63) will be avoided. Most importantly for this discussion, there will be no effect on the utility of HbA1c in screening for or diagnosing diabetes.

Should HbA1c be accepted as a diagnostic criterion for diabetes?

After careful discussion of the above issues and others, the panel determined that the HbA1c 6.5% or greater should be accepted as a criterion for diagnosing diabetes (Table 1). The rationale for this cutoff is presented below, although it is recognized that precise cut points are a matter of judgment and are inevitably arbitrary. A single elevated HbA1c would not suffice to establish the diagnosis, but would require a second test. If the first test HbA1c is unequivocally elevated (≥7.0%), this could be confirmed with a second HbA1c because interference with the assay is unlikely; if the first A1c is 6.5–6.9, it should be confirmed with a plasma glucose-specific test (FPG or 2 h OGTT). This should provide adequate protection against misinterpreting a HbA1c that is slightly elevated due to nonglycemic factors. HbA1c would not be considered valid in the setting of anemia or known confounders. These caveats are no more burdensome than the current requirement that PG criteria be repeated on another day and be done with the person in a stable clinical state. Indeed, HbA1c and a PG could be done on the same day, establishing the diagnosis without repeat testing.

What evidence supports the specific HbA1c diagnostic recommendation?

The existing glycemic criteria for diagnosing diabetes, FPG 126 mg/dl or greater, random or 2-h post-OGTT PG 200 mg/dl or greater (64), were not reconsidered by this panel. They were established based on an expert committee’s evaluation of levels of glycemia that associate with diabetic retinopathy (15). This report presented data (their Fig. 2), suggesting that the relationship between glycaemia and retinopathy is just as strong for HbA1c as for FPG and 2-h PG (25).

In choosing a HbA1c cut point to recommend for the diagnosis of diabetes, we started with the population average and SD for HbA1c from NHANES III, which was 5.17%, SD 0.45% (27). HbA1c of 6.5% is just under 3 SD above the mean. Measured against accepted glycemic criteria that define diabetes, this HbA1c would yield a specificity of 99.6% and sensitivity of 43–44%, based on NHANES III and 1999–2004 NHANES data, respectively (27, 43). Table 2 compares diagnostic sensitivity/specificity data for these two analyses over a range of potential HbA1c cut points. The panel thus chose a level of HbA1c on a statistical basis (3 SD above the mean). This value is highly specific for, and reasonably sensitive for, the diagnosis of diabetes based on FPG or OGTT. We thus do not reassess the validity of glycemic criteria for diagnosis or for treatment.

Should specific criteria be established to screen for diabetes, and if so, should they include HbA1c?

Engelgau et al. (65) discussed the theory of screening as distinguished from diagnostic testing, and Zhang et al. (66) studied the efficiency of screening for diabetes. Screening tests are gen-

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**TABLE 1.** Proposed criteria for screening and diagnosis of diabetes

<table>
<thead>
<tr>
<th>Screening*</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG ≥ 100 mg/dl</td>
<td>FPG ≥ 126 mg/dl</td>
</tr>
<tr>
<td>A1c &gt; 6.0%</td>
<td>A1c ≥ 6.5%*</td>
</tr>
<tr>
<td>RPG ≥ 130 mg/dl</td>
<td>RPG ≥ 200 mg/dl</td>
</tr>
<tr>
<td>If screening result is negative, screen again in 3 yr.</td>
<td>2-h OGTT ≥ 200 mg/dl</td>
</tr>
<tr>
<td>If screening result is positive but below the diagnostic threshold, do another test for diagnosis, using a different method.</td>
<td>Diagnosis requires confirmation unless unequivocal symptoms of hyperglycemia are present.</td>
</tr>
<tr>
<td>If screening result is above the diagnostic threshold but a second test does not reach the threshold, test again in 1 yr.</td>
<td>Diagnosis based on HbA1c requires confirmation using a glucose-dependent test (FPG or OGTT) or, if first HbA1c is ≥7.0%, by a second HbA1c ≥ 6.5%.*</td>
</tr>
</tbody>
</table>

*Denotes criteria that are proposed additions to currently accepted criteria.
should be done (and, implicitly, reimbursed) (16).

The purpose of screening is to identify people who, on further testing, have the disease or are at high risk for developing it. Screening focuses the attention of these people, their caregivers, and payers on preventive action and closer follow-up. IFG and impaired glucose tolerance (so-called prediabetes) have been defined on the basis of increased risk for diabetes, and their treatment is directed toward reducing that risk (67). A person with formally defined IGT by the gold standard OGTT should be followed at a later date. But IFG is therefore a reasonable glycemic criterion to consider as a positive screen for diabetes, given especially the considerable day-to-day variability of IFG. In most cases, a FPG, not a full OGTT, would be done to screen for diabetes. If pursued with further diagnostic testing, many of those with IFG would in fact meet criteria for diabetes when retested either by FPG, OGTT, or HbA1c, and those who do not should be followed up closely for conversion to diabetes.

The panel therefore agreed that it would be a net health benefit to establish specific criteria as screening tests for diabetes, distinct from those used to establish the diagnosis, and that HbA1c would be a useful in screening test. HbA1c greater than 6.0%, which is 2 s above the population mean, is suggested as a positive screen (Table 1). Based on the two NHANES data sets, HbA1c greater than 6.0% alone would yield reasonable (63–67%) sensitivity, with specificity adequately high (97–98%) to avoid an undue burden of false-positive tests (Table 2). This is in accordance with the recent Health Technology Assessment report by Waugh et al. (http://www.hta.ac.uk/fullmono/mon1117pdf, p.12), which concludes that "glycated hemoglobin does not require fasting and may be the best compromise (to screen for IGT)."

**Should random, or casual, plasma glucose be used in screening for diabetes?**

A casual plasma glucose [more commonly called random plasma glucose (RPG)] 200 mg/dl or greater, together with symptoms, is an established diagnostic criterion for diabetes (15), but it is very insensitive, requiring diabetes to be in poor glycemic control. There is a range of RPG extending well less than 200 mg/dl that does not cause symptoms but if further pursued would establish the diagnosis of diabetes. The above-mentioned practical issues suggest that including a RPG screening value well less than 200 mg/dl might be useful in screening for diabetes.

Observational data found that RPG is the most frequently performed measure of glycemia (13). Ealovega et al. (13) analyzed data from a large health system, noting that nearly 70% of nondiabetic patients 45 yr of age or older had measures of glycemias performed at least once over a 3-yr period. As noted above, 95% of all tests were RPG, with only 3% tested using FPG, and fewer than 1% with OGTT. It is likely, therefore, that in a large proportion of these tests, RPG was used as part of routine chemistry profiles and that the results could be used to screen for diabetes.

RPG has in fact been validated as a screening test for diabetes (68). Table 3 shows the performance of various RPG cut points, using OGTT as the gold standard for diagnosis of diabetes (68). A RPG of 130 mg/dl or greater provides reasonable sensitivity and specificity as a screening test for diabetes, at 63 and 87% respectively (Table 3). Johnson et al. (69) also ran simulations to estimate the number of false-positive and false-negative tests that would be found using various levels of RPG and various screening intervals. The RPG of 130 mg/dl or greater provides good yield and minimizes false positives when used at 3-yr intervals.

The interpretation of RPG as a screening test for diabetes is improved by a knowledge of the number of hours since the last food or caloric drink (70), although this may be difficult to obtain accurately on a routine basis. Analysis of data from a population sample of persons having RPG tests and, on a separate day, OGTTs demonstrated that only 5% of random glucose tests were fasting (postprandial time ≥ 8 h) and most (65%) were within 3 h of eating (68). In general, as expected, RPG levels are highest 1–3 h postprandially and decrease thereafter.

For these reasons, the panel recommends that RPG 130–199

| Table 2. Comparison of sensitivity and specificity achieved for the diagnosis of diabetes based on FPG, at various levels of HbA1c, from NHANES III (27) and 1999–2004 NHANES (43) |
|-----------------------------|-----------------------------|-----------------------------|
| **HbA1c** | **Sensitivity, %** | **Specificity, %** |
| **NHANES III** | **NHANES, 1999–2004** | **NHANES III** | **NHANES, 1999–2004** |
| 5.6% | 83.4 | 88.6 | 84.4 | 80.3 |
| 6.1% | 63.2 | 66.6 | 97.4 | 98.0 |
| 6.5% | 42.8 | 44.3 | 99.6 | 99.6 |
| 7.0% | 28.3 | 25.3 | 99.9 | 99.9 |

* Data presented for 6.1% because in NHANES III, data were only given at those cut points, based on ±1 SD above the mean.

| Table 3. Sensitivity and specificity of achieved in screening for diabetes based on random plasma glucose of various levels (70) |
|-----------------------------|-----------------------------|-----------------------------|
| **Random plasma glucose (mg/dl)** | **Sensitivity (%)** | **Specificity (%)** |
| ≥110 | 84 | 65 |
| ≥120 | 76 | 77 |
| ≥130 | 63 | 87 |
| ≥140 | 55 | 92 |
| ≥150 | 50 | 95 |
| ≥160 | 44 | 96 |
| ≥170 | 42 | 97 |
| ≥180 | 39 | 98 |
mg/dl be considered a positive screening test for diabetes (Table 1). Although not meeting criteria to diagnose diabetes, this range of RPG would be worthy of further diagnostic testing.

Conclusions
There are serious deficiencies in the current criteria for diagnosing diabetes, including the requirement that the patient be fasting, and the lack of agreed-on screening criteria. These deficiencies make it unnecessarily inconvenient for clinicians to diagnose diabetes, thereby delaying the diagnosis and contributing to avoidable morbidity and mortality. The panel conclusions can be summarized by the following three recommendations:

- Incorporate the long-established and universally accepted recommendations:
  - The A1c Screening Review Panel meeting was sponsored by a grant from Metrika, Inc.
  - Disclosure Statement: The panel deliberations and manuscript preparation were independent of the sponsor.

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