

## Glucose and Glycated Haemoglobin Point-of-care Testing and Early Diagnosis of Diabetes and Pre-diabetes

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### Abstract

The number of individuals with impaired glucose metabolism ('pre-diabetes') and type 2 diabetes is reaching epidemic proportions. This increase is associated with higher cardiovascular morbidity and mortality. Early screening for diabetes and pre-diabetes (i.e. elevated glucose and/or glycated haemoglobin [HbA<sub>1c</sub>]) may aid in the reduction of diabetes-related complications. Point-of-care testing, defined as testing at or near the site of the patient, is able to bring diagnostic tests and its associated therapeutic actions immediately to the patient and may aid in the detection of diabetes and the reduction of complications. However, the majority of available point-of-care testing devices for glucose and HbA<sub>1c</sub> do not meet generally accepted analytical performance criteria and may underestimate the true risk of diabetes. Until these analytical performance issues have been addressed properly, caution should be exercised in the use of point-of-care testing of glucose and HbA<sub>1c</sub> in the diagnosis of and screening for pre-diabetes and diabetes.

### Keywords

Point-of-care testing, oral glucose tolerance test, glucose, glycated haemoglobin (HbA<sub>1c</sub>), pre-diabetes, diabetes, diagnosis, sensitivity, specificity, performance, quality assurance

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Over the last few decades the prevalence of diabetes has reached epidemic proportions in western societies and is even higher in developing countries,<sup>1–4</sup> mainly due to population growth, ageing and obesity.<sup>15</sup> The World Health Organization (WHO) has estimated that the global prevalence of diabetes will increase from 2.8% in 2000 to 4.4% by 2030.<sup>6</sup> The increases in both obesity and diabetes will have a profound impact on diabetes- and obesity-related complications,<sup>7</sup> the use of healthcare resources<sup>8</sup> and the quality of life of affected patients.<sup>9</sup>

Diabetes comprises a group of metabolic diseases characterised by elevated blood glucose levels, and the diagnosis is based on increased fasting and/or post-load (after an oral glucose tolerance test [OGTT]) plasma glucose values (see *Table 1*).<sup>10–12</sup> Type 2 diabetes, which accounts for 90–95% of all diabetes cases, is characterised by inappropriate insulin secretion due to a decline in  $\beta$ -cell function and the presence of (obesity-related) insulin resistance,<sup>13,14</sup> resulting, among other metabolic disturbances, in fasting and post-prandial hyperglycaemia. Glycaemic control, as reflected by glycated haemoglobin (HbA<sub>1c</sub>), is common practice in the management of diabetes to adjust therapy regimens and to aid in patient education.

Recently, the American Diabetes Association (ADA) has advocated the use of HbA<sub>1c</sub> in the diagnosis of diabetes<sup>15,16</sup> as a result of the global standardisation of the HbA<sub>1c</sub> assay with associated improvement of the analytical performance of the assay.<sup>17–20</sup> However, the WHO and the International Diabetes Federation (IDF) recommend against the use of HbA<sub>1c</sub> in the diagnosis of diabetes in their 2006 consensus report.<sup>12</sup>

Individuals with type 2 diabetes have an increased risk of developing macrovascular and/or microvascular complications and mortality,<sup>21,22</sup> and the risk of developing these complications may increase if good glycaemic control is not adequately maintained. Studies such as the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) have supported the notion that adequate glycaemic control in the general patient population may aid in the prevention or reduction of the risk of developing diabetes-related vascular complications.<sup>23–26</sup> Early detection of high-risk patients with elevated glucose levels may aid in the prevention or reduction of diabetes-related complications. This could be achieved by screening individuals who are at high risk of developing diabetes by for example capillary glucose testing by point-of-care testing.

This article focuses on the potential role of point-of-care testing of glucose and HbA<sub>1c</sub> in the diagnosis of pre-diabetes and diabetes. It gives an overview of the principles, pitfalls and analytical performance of glucose and HbA<sub>1c</sub> point-of-care testing and summarises the studies that have applied point-of-care testing of glucose and HbA<sub>1c</sub> in the diagnosis of (pre-) diabetes. Finally, the article concludes with the authors' recommendations on the applicability of point-of-care testing of glucose and HbA<sub>1c</sub> in the diagnosis of diabetes.

### Point-of-care Testing of Glucose and Glycated Haemoglobin – Principles, Practice and Pitfalls Principles of Point-of-care Testing

Point-of-care or near-patient testing can be defined as diagnostic testing at or near the site of the patient and is able to bring the

diagnostic test and its associated therapeutic actions immediately to the patient.<sup>27</sup> This could lead to improvement of patient care, given that appropriate quality assurance systems in point-of-care testing have been implemented.<sup>27,28</sup> The application of point-of-care testing of glucose and HbA<sub>1c</sub> in the management of diabetes has been introduced and is regarded as standard care. Indeed, evidence is suggesting that point-of-care testing of glucose may improve glycaemic control,<sup>29</sup> whereas point-of-care testing of HbA<sub>1c</sub> was shown to be effective in the improvement of glycaemic control in some but not all studies depending on the HbA<sub>1c</sub> targets.<sup>30-32</sup> The applicability of point-of-care testing of glucose and HbA<sub>1c</sub> in the diagnosis of diabetes and pre-diabetes is less evident and still under debate, mainly due to analytical performance issues of the devices and the definition of optimal cut-off values.<sup>33-36</sup>

### Developments in Glucose Point-of-care Testing Devices

Over the last four to five decades the principles of point-of-care testing of glucose have changed considerably.<sup>37,38</sup> The first-generation quantitative point-of-care testing devices for glucose included a modified dipstick originally designed for detecting glucose in urine that is based on an enzymatic reaction with a change of colour of the pad of the dipstick. A blood sample was applied to the strip and whipped off. Subsequently, the change in colour intensity was measured and compared with an internal calibration and translated to a quantitative result. The second-generation point-of-care glucose testing devices provided automatic timing and no need for wiping off the strip, which considerably improved the performance of the device. The latest point-of-care glucose testing devices are based on enzymatic methods (glucose dehydrogenase and glucose oxidase) and electrochemical sensors instead of colorimetric assays.<sup>39-41</sup> These technical advances have led to an improved performance with respect to operation and sample handling and to improvement of the analytical performance of these devices. However, even state-of-the-art devices can still be improved.

### Developments in Glycated Haemoglobin Point-of-care Testing Devices

Laboratory analysers for HbA<sub>1c</sub> utilise technologies that are based on either charge differences (high-pressure liquid chromatography) or structure (boronate affinity or immunoassay combined with general chemistry). In the last five to 10 years these technologies have been incorporated into point-of-care testing devices, allowing for immediate availability of HbA<sub>1c</sub> measurements.<sup>42-44</sup> The first HbA<sub>1c</sub> point-of-care devices needed several manual handlings, while the newly developed devices are easy to use and are provided with tools to make it possible to be connected with other information systems.

### Practice and Pitfalls of Point-of-care Testing of Glucose and Glycated Haemoglobin

Point-of-care testing for glucose has been used in a variety of settings, including hospitalised patients with diabetes, self-management of patients with diabetes, outpatient diabetes clinics, emergency departments, general practitioners' offices and pharmacies,<sup>45-47</sup> whereas the use of point-of-care testing of HbA<sub>1c</sub> is less common in clinical practice. In The Netherlands, HbA<sub>1c</sub> point-of-care devices are mainly used in paediatric diabetes centres in children with type 1 diabetes. The major advantages of point-of-care testing include portability, small sample volume (whole blood) and immediate result with appropriate therapeutic action.<sup>27</sup> However, in general

**Table 1: Diagnostic Criteria for Diabetes and Pre-diabetes**

	American Diabetes Association <sup>15</sup>	World Health Organization/IDF <sup>12</sup>
<b>Diabetes</b>		
Fasting plasma glucose <sup>§</sup>	≥7.0mmol/l (or)	≥7.0mmol/l (or)
Post-load plasma glucose*	≥11.1mmol/l	≥11.1mmol/l
HbA <sub>1c</sub> **	≥6.5%	Not recommended
<b>Impaired Fasting Glucose</b>		
Fasting plasma glucose	5.6–6.9mmol/l	6.1–6.9mmol/l (and)
Post-load plasma glucose	<7.8mmol/l (and)	<7.8mmol/l
HbA <sub>1c</sub>	5.7–6.4%	Not recommended
<b>Impaired Glucose Tolerance</b>		
Fasting plasma glucose	<7.0mmol/l (and)	<7.0mmol/l (and)
Post-load plasma glucose	≥7.8 and <11.1mmol/l	≥7.8 and <11.1 mmol/l
HbA <sub>1c</sub>	5.7–6.4%	Not recommended

HbA<sub>1c</sub> = glycated haemoglobin; IDF = International Diabetes Federation.

<sup>§</sup>Diagnostic testing should be repeated, unless patient presents with symptoms of hyperglycaemia or hyperglycaemic crisis or random plasma glucose of ≥11.1 mmol/l;

\*Venous plasma glucose two hours after an oral glucose tolerance test (75g) and after no caloric intake for at least eight hours. \*\*Based on a National Glycohaemoglobin Standardisation Program (NGSP)-certified method and standardised to the Diabetes Control and Complications Trial (DCCT) assay.

point-of-care testing of glucose is still more expensive than the laboratory reference method and higher analytical variability has been reported. In addition, quality assurance issues should be addressed properly.<sup>27,28</sup>

Although the performance of glucose point-of-care testing devices has improved, some pitfalls in point-of-care testing should still be acknowledged. The operators should be properly trained and certified to obtain an optimal whole-blood sample and to apply the correct amount of blood volume on the point-of-care testing device.<sup>48,49</sup> Furthermore, patient characteristics that may adversely influence the result should be noted, including haematocrit levels,<sup>50,51</sup> interfering drugs<sup>52</sup> and metabolic disorders (e.g. uraemia, hyperlipidaemia).<sup>53,54</sup> Low (<0.35) and high (>0.55) haematocrit levels may significantly influence the result of glucose measurement by point-of-care devices as illustrated in *Figure 1*, and should be evaluated in patients in whom the point-of-care devices are to be applied. Finally, factors that might adversely affect the operation of the devices and the performance of the strips such as temperature, humidity and high altitude should be taken into account.<sup>55-57</sup> Although the use of point-of-care testing of HbA<sub>1c</sub> is less common than that of glucose, similar limitations and pitfalls of point-of-care testing of HbA<sub>1c</sub> may apply. In addition, immunoassay-based HbA<sub>1c</sub> point-of-care devices may interfere with haemoglobin variants, which is not the case with affinity-based point-of-care testing devices.<sup>58,59</sup>

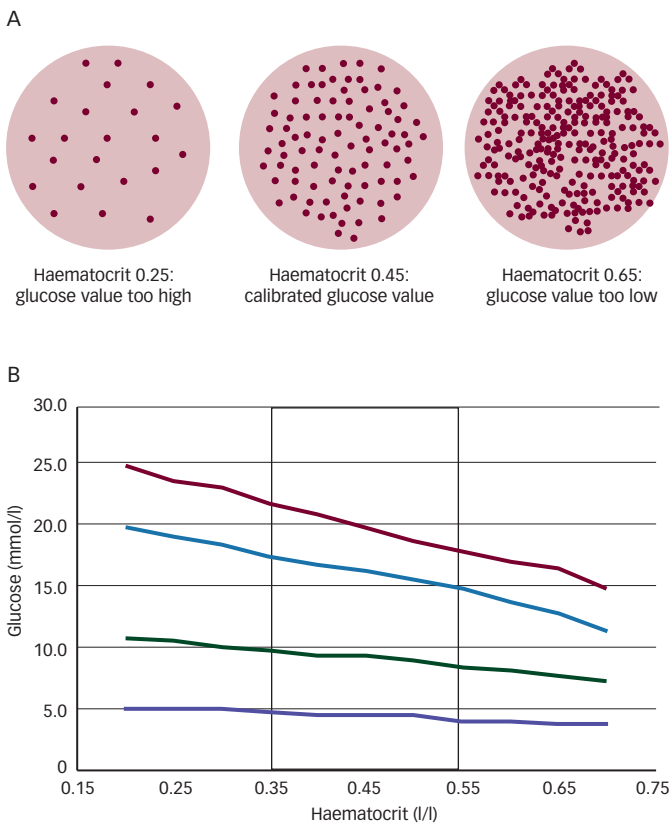
Although the technical specifications of the point-of-care devices have improved considerably, pre-analytical, analytical and post-analytical issues should still be acknowledged and quality assurance systems should be implemented.

### Analytical Performance of Point-of-care Testing of Glucose and Glycated Haemoglobin Regulations and Guidelines

Although glucose point-of-care testing devices can provide immediate results, these results may not be equivalent to the results produced by laboratory analysers.<sup>60,61</sup> Over the past few years various regulatory affairs bodies have issued guidelines for the analytical performance of

# Blood Glucose Testing

**Figure 1: Effect of Haematocrit on Point-of-care Testing for Glucose**



Point-of-care testing devices for glucose are calibrated at normal haematocrit levels (e.g. 0.35–0.55l/l; panel A). A whole blood sample with a low haematocrit (i.e. 0.25l/l) has a relative excess of plasma and the measurement will yield a value that will be incorrectly too high. The opposite will be the case if the haematocrit is high. The influence of haematocrit levels at various glucose levels is depicted in Panel B.

**Table 2: Minimal Performance Criteria of Point-of-care Testing Devices for Glucose Based on TNO Guidelines<sup>67</sup>**

Criterion	Comment
Accuracy	Max. 15% deviation from hexokinase method
Reproducibility	Max. coefficient of variation of 10%
Haematocrit dependency (range: 0.35–0.55)	Max. coefficient of variation of 10% for glucose values >6.5 mol/l or 1 mmol/l for glucose values <6.5 mmol/l
Underfilling protection	Max. 10% deviation from result at minimal volume or error mark

TNO = Netherlands Organisation for Applied Scientific Research.

glucose point-of-care testing devices. The US Food and Drug Administration (FDA) has cleared over 200 point-of-care testing devices for medical use based on the review of clinical and laboratory evidence provided by the manufacturer.<sup>62,63</sup> A systematic review in 2007 concluded that none of the included reports on the evaluation of glucose point-of-care devices followed generally accepted recommendations of performing these evaluation studies and the authors concluded that these limitations may have affected the conclusions of these evaluation reports.<sup>64</sup> The Clinical and Laboratory Standards Institute (CLSI)/National Committee on Clinical Laboratory Standards (NCCLS) guideline states that >95% of the results should be within  $\pm 20\%$  or 0.8mmol/l (whichever is greater) of the laboratory value.<sup>65</sup> The International Organisation for Standardisation (ISO) recommends an agreement of  $\pm 20\%$  for levels above 4.2mmol/l or within  $\pm 0.83\text{mmol/l}$  for glucose levels less than 4.2mmol/l (ISO 15197).<sup>66</sup>

The Dutch guideline issued by the Netherlands Organisation for Applied Scientific Research (TNO) Centre for Medical Technology recommends a maximum of  $\pm 15\%$  average deviation from a hexokinase laboratory value >6.5mmol/l and within 1mmol/l for values <6.5mmol/l.<sup>67</sup> Finally, the ADA has proposed the most stringent guidelines and recommends an agreement within  $\pm 10\%$  of a laboratory method, with an eventual goal of <5% deviation.<sup>68</sup> Based on the TNO guidelines, an overview of the current minimal criteria for assessment of the performance of point-of-care glucose devices is presented in Table 2.

As yet, there is no consensus on what should be considered the maximum deviation of the point-of-care devices. Currently, the ISO 15197 guideline is under revision and a maximum deviation of 15% in point-of-care testing devices for home use versus a reference method is proposed. In our view, for point-of-care testing devices for clinical uses a lower deviation should be implemented (<10%).

## Performance of Glucose and Glycated Haemoglobin Point-of-care Testing Devices

Slingerland and co-workers found that only 60% of 30 available point-of-care testing devices available in The Netherlands complied with the TNO guidelines (15% deviation). If all criteria as set out in the TNO guidelines were tested, including reproducibility (maximum coefficient of variation of 10%), haematocrit dependency and under-filling protection, only 20% of the devices would comply with the TNO guideline.<sup>69</sup> HbA<sub>1c</sub> point-of-care testing devices have been made available over the last few years and only a number of validation studies have been published. One of the most extensive validation studies was performed by Lenters-Westra and Slingerland. They reported that the majority of HbA<sub>1c</sub> point-of-care testing devices do not comply with the generally accepted performance criteria,<sup>70</sup> and these results imply that these devices should be used with caution in the screening of diabetes and pre-diabetes.<sup>71</sup> Unfortunately, the most stringent ADA criteria may not be met by most glucose point-of-care testing devices. In addition, the majority of HbA<sub>1c</sub> point-of-care devices do not meet generally accepted analytical performance criteria.

## Point-of-care Testing of Glucose and Glycated Haemoglobin in the Diagnosis of Diabetes and Pre-diabetes

### Diagnosis of Pre-diabetes with Point-of-care Testing of Glucose

The diagnosis of diabetes and pre-diabetes (impaired fasting glucose and/or impaired glucose tolerance) is based on elevated fasting plasma glucose and/or post-load (after a 75g OGTT) glucose levels and/or hyperglycaemia related symptoms (see Table 1). The OGTT is regarded as the gold standard in the diagnosis of diabetes, and is preferably performed on two separate occasions. The reproducibility of the OGTT is relatively low (95% of the random test and re-test differences were less than 15% with fasting glucose and 46% with post-load glucose), mainly due to intra-individual biological variability and, to a lesser extent, to analytical variability if glucose is measured in venous plasma with a laboratory reference method with low analytical co-efficients of variation (<2%).<sup>72–74</sup> Indeed, an analysis of the DCCT data demonstrated that the biological variation was higher than the variation of the glucose measurements.<sup>75</sup>

The co-efficients of variation of glucose measured by point-of-care testing devices may be considerably higher and therefore may contribute to further lowering the reproducibility of the OGTT.

**Table 3: Overview of Studies Assessing the Value of Point-of-care Testing of Glucose in the Diagnosis of Diabetes**

Author(s), Year	Cohort/ Population	n	Diagnostic Criteria	Reference	(Pre-) Diabetes n (%)	Sensitivity/ Specificity	AUC	Authors' Conclusion
Rush et al., 2008 <sup>33</sup>	Te Wai o Rona	3,225	WHO 2006	Single OGTT	NDM 161 (5.0%) IFG 115 (3.6%) IGT 299 (9.3%)	NDM 57%/ 98%	NDM 0.88	POCT cannot be recommended as a means of screening for (pre-) diabetes
Zhou et al., 2010 <sup>35</sup>	Qingdao	2,332	WHO 1999	Single OGTT	NDM 278 (11.9%) IFG/IGT 689 (29.55%)	Not reported	Not reported	POCT of glucose, as a screening tool for diabetes and pre-diabetes, performed better than HbA <sub>1c</sub>
Kruiskoop, 2004 <sup>36</sup>	CoDAM	350	WHO 1999	Single OGTT	NDM 97 (27.7%) IGT 77 (22.0%)	NDM 84%/ 98%	Not reported	Cost-effective inclusion schemes for epidemiological studies
Marley, 2007 <sup>34</sup>	Australian cohort	200	Glucose $\geq 11.1$	Fasting or non-fasting venous glucose	Not reported	NDM 83.3%/ 99.3%	Not reported	Can be used in the process of diagnosis or excluding diabetes using locally established reference values

AUC = area under curve; HbA<sub>1c</sub> = glycated haemoglobin; IFG = impaired fasting glycaemia; IGT = impaired glucose tolerance; OGTT = oral glucose tolerance test; NDM = newly detected diabetes mellitus; POCT = point-of-care testing; WHO = World Health Organization.

Indeed, a number of studies that compared venous plasma glucose assessed by a laboratory reference method with glucose measured in capillary whole blood by point-of-care devices showed an acceptable correlation between both values, but significantly higher co-efficients of variation in the point-of-care-measured glucose values.

To date, only a limited number of studies have addressed the applicability of point-of-care glucose testing in the diagnosis of diabetes and pre-diabetes (see Table 3). Rush and co-workers studied the performance of glucose point-of-care testing in an outpatient setting for the diagnosis of diabetes and pre-diabetes.<sup>33</sup> An OGGT was performed in more than 3,000 individuals with a laboratory-based glucose reference method and with point-of-care glucose testing to assess the comparability of the two methods. The glucose levels as measured by the point-of-care device were significantly lower compared with the laboratory reference method, and the authors recommended against the use of point-of-care glucose testing for the diagnosis of diabetes and pre-diabetes.<sup>33</sup> By contrast, based on their study of 200 participants in an area of Western Australia, Marley and co-workers concluded that point-of-care glucose testing could be used in the diagnosis and exclusion of diabetes if based on locally established reference values.<sup>34</sup> A recently published study conducted by Zhou and co-workers compared HbA<sub>1c</sub> (laboratory reference method) with point-of-care glucose testing with plasma glucose values after an OGTT to diagnose diabetes and pre-diabetes. The authors concluded that point-of-care glucose testing performed significantly better than HbA<sub>1c</sub> for the diagnosis of diabetes and/or pre-diabetes. Unfortunately, the authors did not present data on the comparability of point-of-care-derived glucose values with the plasma glucose values of the reference method at diagnostic values (i.e.  $\geq 7.0$  mmol/l). Overall, the reported areas under the receiver operating characteristics curve were less than 0.81 and 0.68 for detecting diabetes and pre-diabetes, respectively.<sup>35</sup> Kruiskoop and co-workers studied the applicability of glucose point-of-care testing in epidemiological studies in a subset (350 subjects) of the CoDAM study, a population-based cohort study. The concordance between capillary and venous glucose measurements was 78%.<sup>36</sup> The authors concluded that use of point-of-care glucose measurement is reliable and cost-effective in epidemiological settings.

Based on these studies it can be concluded that the performance of point-of-care glucose testing may suffice for epidemiological studies in the screening of diabetes and pre-diabetes, and that local cut-off values of point-of-care glucose testing may, to some extent, enhance the performance of point-of-care glucose testing. However, in screening and diagnosis of individual patients the performance of point-of-care testing of glucose may lead to a significant misclassification of patients.

### Diagnosis of (Pre-) Diabetes with Point-of-care Testing of Glycated Haemoglobin

An elegant alternative to fasting and post-glucose testing in the diagnosis of diabetes and pre-diabetes is the use of HbA<sub>1c</sub>. The patient does not need to fast or to undergo an OGTT, which can be associated with some discomfort. Instead, a non-fasting blood sample can be drawn to measure HbA<sub>1c</sub>, which has an overall lower analytical variability than glucose measurements (either capillary or venous plasma). Recently, the ADA has proposed the use of HbA<sub>1c</sub> in the diagnosis of diabetes.<sup>15</sup> However, the applicability of HbA<sub>1c</sub> and the optimal cut-off value ( $\geq 6.5\%$  as proposed by the ADA) in diagnosing diabetes seem to depend on ethnicity, age, sex and diabetes prevalence,<sup>76</sup> and therefore other HbA<sub>1c</sub> cut-off values have been proposed. Furthermore, the life span of the erythrocyte should be taken into account, which may differ between individuals and may influence HbA<sub>1c</sub>.<sup>77</sup> In addition, recent studies that applied the cut-off value of  $\geq 6.5\%$  reported low sensitivity and specificity of HbA<sub>1c</sub> in the diagnosis of diabetes.<sup>78-81</sup>

To the best of our knowledge, no studies that used point-of-care HbA<sub>1c</sub> testing in the diagnosis of diabetes and pre-diabetes have been published to date. Given the recent observation that the majority of point-of-care HbA<sub>1c</sub> devices performed poorly with respect to generally accepted analytical performance criteria, the applicability of these point-of-care testing devices in the diagnosis of diabetes and pre-diabetes may be very limited or may even be discouraged until these performance issues have been properly addressed.

Based on these observations with respect to HbA<sub>1c</sub> testing in the diagnosis of diabetes and pre-diabetes, we can conclude that HbA<sub>1c</sub> assessed by reference laboratory methods may underestimate

or overestimate the prevalence of undiagnosed diabetes and pre-diabetes. Given the low analytical performance of point-of-care HbA<sub>1c</sub> devices, their use in diagnosing diabetes and pre-diabetes is not recommended.

## Conclusions

The number of patients with type 2 diabetes is reaching epidemic proportions and this increase is associated with an increase in cardiovascular morbidity and mortality. Early screening of patients with undetected diabetes and pre-diabetes (i.e. elevated glucose and/or HbA<sub>1c</sub>) may eventually lead to a reduction in diabetes-related complications. Point-of-care testing of glucose and HbA<sub>1c</sub> have been introduced and could lead to improvement of patient care. However, currently the majority of available point-of-care testing devices for glucose and HbA<sub>1c</sub> do not meet generally accepted analytical performance criteria, and may therefore underestimate or overestimate the risk of diabetes. Until these analytical performance issues have been addressed properly, we recommend against the use of point-of-care testing of glucose and HbA<sub>1c</sub> in the diagnosis and screening of pre-diabetes and diabetes. ■

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Robbert J Slingerland is a Clinical Chemist and Manager of the Clinical Chemistry Laboratory at the Isala klinieken in Zwolle, one of the largest hospitals in The Netherlands, where he is responsible for clinical chemistry. His responsibilities includes special chemistry, quality assurance, diabetes investigations and point-of-care testing. He is member of the committee for Point-of-care Testing of the Dutch Society of Clinical Chemistry.

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