Analytical Goals for Point-of-Care Testing Used for Diabetes Management in Australian Health Care Settings Outside The Laboratory

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Abstract: Diabetes mellitus is a major global health problem. Pathology testing for hemoglobin A1c (HbA1c), lipids, and urine albumin/creatinine ratio (ACR) has an important role in the management of diabetes patients. Each of these markers can be performed by point-of-care testing (POCT). This article focuses on setting analytical goals (quality specifications) for the imprecision, bias, and total allowable error of these selected POC tests in the public health environment in Australia. The article reviews published data on analytical goal setting for laboratory tests, considers the factors that set POCT apart from the laboratory, compares laboratory-based analytical goals with state-of-the-art performance, and then sets analytical goals that are designed to be relevant for nonlaboratory POCT environment. The desirable analytical goals for imprecision are the following: HbA1c, 3%; cholesterol, 3%; triglyceride, 5%; high-density lipoprotein cholesterol, 4%; low-density lipoprotein cholesterol, 4%; urine albumin, 10%; urine creatinine, 6%; and urine ACR, 12%. The analytical goals for total allowable error are the following: HbA1c, 4%; cholesterol, 10%; triglyceride, 15%; high-density lipoprotein cholesterol, 15%; low-density lipoprotein cholesterol, 15%; urine albumin, 12.5%; urine creatinine, 7.5%; and urine ACR, 15%. The recommended analytical goals are designed to be flexible and refinable as more data, particularly from clinical outcome studies, become available. They have the potential to be adopted by countries outside Australia, given the limited published data on analytical goals specifically for the nonlaboratory POCT sector.

Key Words: analytical goals, point-of-care testing, diabetes management, non laboratory setting

Diabetes mellitus is a major global health problem that has reached epidemic proportions in many parts of the world. It was estimated that there were 160 million people with diabetes worldwide in the year 2000, and this figure was predicted to climb to more than 280 million by the year 2025, the majority of whom will have type 2 diabetes.1,2 Diabetes causes significant morbidity and mortality among people with this disease, primarily from the cardiovascular and renal complications and retinopathy arising from the disease. In the United States, diabetes-related costs account for approximately 12% of the national health budget.2

In Australia, the number of adults with diabetes has trebled since 1981. A major recent study (the Australian Diabetes, Obesity and Lifestyle Study) reported a prevalence rate of 7.5% in people older than 25 years. In addition, the rate of impaired glucose metabolism was 16%, and it was estimated that for every known case of diabetes, there was 1 undiagnosed case.2 In Australia’s indigenous population, prevalence rates of diabetes are of particular concern, being 2 to 3 times that of non-Aboriginal Australians.3

Pathology testing has an important role in the management of patients with established diabetes and in the monitoring of complications of the disease. Hemoglobin A1c (HbA1c) and urine albumin/creatinine ratio (ACR) are well-established biochemical tests that form part of a patient’s regular diabetes review, as is the lipid profile of tests (total cholesterol, high- and low-density lipoproteins [HDL and LDL, respectively] cholesterol, and triglyceride). Hemoglobin A1c provides a long-term measure of a patient’s glycemic control, urine ACR can detect early stages of diabetic nephropathy, whereas dyslipidemia characterized by high plasma triglyceride and low HDL cholesterol concentrations is common in type 2 diabetes. Each of these markers can readily be performed by point-of-care testing (POCT). During the past 7 years in particular, there has been considerable uptake of POCT for diabetes management in Australian public health care settings outside the laboratory, particularly in Aboriginal medical services, country hospitals, and, more recently, general practice.4-9 There has been also been an increase in the number of POC instruments available in the diagnostic market place offering the ability to conduct tests in public health care settings. When selecting a POC instrument for use outside the laboratory, it is crucial to consider its analytical performance and to be aware of analytical concepts such as precision, accuracy, and total error (refer to Glossary of Key Terms). It is therefore also crucial that analytical goals are set to critically assess the competency of POCT instruments being used for clinical decision making for diabetes management in settings outside the laboratory in Australia.

This article therefore focuses on setting analytical goals (or analytical quality specifications) for the performance of
HbA1c, urine ACR, and lipid POC tests used for diabetes management in Australia. The article describes current approaches used to set analytical goals for laboratory methods, discusses the relevance of these approaches to POCT, reviews available published data on analytical goals for the candidate tests and how these goals relate to current state-of-the-art performance in Australia, and makes recommendations on analytical goals for these tests that are relevant and appropriate for the POCT public health environment in Australia. Goals have been set for the imprecision, bias (inaccuracy), and total allowable error for each POC test (refer to Glossary of Key Terms). Many of the analytical goals recommended in this article have been adopted for use by the Australian Government’s Department of Health and Ageing in a major new trial of POCT in General Practice in Australia (see accompanying article in this issue).10

Approaches Used to Set Analytical Performance Standards in Laboratories

There is an internationally accepted, 5-tiered hierarchical model for the setting of analytical goals for the imprecision, bias, and total allowable error of laboratory tests (Table 1).11–15 Where data are available from more than 1 approach, models higher in the hierarchy are considered to hold greater weighting than those from lower levels.

The highest quality standard is required when analytical quality has a direct effect on medical decision making in a specific clinical situation. As described later, HbA1c is an example of a test where this standard should be applied. Analytical goals for broader clinical need can be derived from biological variability or from clinical survey on how clinicians use test results. Biological variation data (both within individual and between individuals) are now available on more than 300 analytes.14,15

Three classes of analytical goals (minimal, desirable, and optimal), based on fractions of within-individual biological variation, have also been developed for the imprecision of commonly measured tests.12–15 The desirable analytical goal for most biochemical analytes is that the analytical imprecision (coefficient of variation, CVa) should be less than one half of the average within-person biological variation (0.5 CVw).12 However, for those analytes for which the desirable goals derived using this formula are readily achievable with current methodology, it is recommended that an optimal analytical goal be used, based on the formula CVa < 0.25 CVw.12 For those analytes for which desirable goals are not readily attainable using current methodology, a minimum analytical goal is recommended, based on the formula CVa < 0.75 CVw.12

Many national and international groups have also set profession-defined analytical goals (eg, the recommendations of the National Cholesterol Education Program [NCEP] in the United States, which have been widely used to set goals for lipid analyses).

Government or external quality assurance program organizers also set analytical quality specifications. In Australia, the Royal College of Pathologists of Australasia (RCPA) Quality Assurance Programs Pty Ltd Chemical Pathology Group is the major provider of external quality assurance (proficiency testing) programs for clinical chemistry laboratories. This group sets analytical goals for total allowable error (which they call “allowable limits of performance”) for all biochemical tests offered through their programs.16

How Relevant Are Laboratory-defined Analytical Goals for POCT Settings Outside the Laboratory?

As an overarching principle, analytical goals for POCT should be equivalent to those used for laboratories to ensure the use of POCT does not compromise standards of patient care and clinical decision making. Fraser has stated that the internationally accepted hierarchical approach to setting analytical goals should be adopted in, and is appropriate for, all settings in which laboratory medicine is practiced, including POCT.17

However, it is important to acknowledge that the POCT environment, particularly in rural and remote Australia, is often very different to the laboratory setting. First, long-term retention of staff as POCT operators is an ever-present problem for rural and remote health services, creating difficulties in sustaining not only POCT but other health programs in general. For many rural and remote health services using POCT, refrigerator space, efficient and timely delivery of reagents and quality products, regular power fluctuations, poor lighting, heat, dust, and humidity within the working environment are all real issues that can impact on the ability to deliver and sustain a quality POCT service. Second, there needs to be a balanced approached to goal setting. There is limited value in setting analytical goals that are too stringent and which current POCT (and/or laboratory) instruments cannot achieve. On the other hand, there is a clinical imperative to ensure that excessive analytical noise from POCT methods does not mask clinically significant changes in patient results. Minimum analytical goals for the imprecision of nonlaboratory-based POCT should be set (along with desired and optimal goals) where sufficient data are available with the proviso that performance outside the minimum goal should be investigated and acted upon by the clinician responsible for clinical governance of POCT and the POCT site operator. Third, when assessing analytical performance in POCT environments against published literature, it should be noted that the majority of published

| TABLE 1. Hierarchical Approach for Procedures to Set Analytical Goals |
|-----------------|-----------------|-----------------|
| Level | Approach | Procedure |
| 1 | Specific clinical need | Clinical outcome studies |
| 2 | Broad clinical need | Biological variation; Clinical survey |
| 3 | Profession defined | Experts panels; National/international guidelines |
| 4 | Proficiency testing | Specifications from external quality assurance organizers or regulation |
| 5 | State of the art | Published data from external quality assessment schemes or literature |
evaluations of POCT instruments have been conducted in the laboratory setting (ie, away from the field site where the POCT instrument is to be used) by trained laboratory staff (rather than the staff who would normally be required to perform POCT in the field). Analytical goals may also vary depending upon the intended purpose of the test. For example, different goals may be needed for diagnosis versus monitoring of test results and for monitoring an individual patient at 1 health service compared with different sites. The analytical goals recommended in this article are for goals for patient management within a given health service. 

HEMOGLOBIN A1C

Goals for Imprecision

Results from clinical outcome studies such as the Diabetes Control and Complication Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have firmly established the importance of tight glycemic control in reducing the complications of diabetes.18,19 In the DCCT study, for example, 1441 patients with type 1 diabetes were randomly allocated to either an intensively treated or a conventionally treated group. The intensively treated group had a mean HbA1c level of 7.2% during a 6.5-year period, whereas the conventionally treated group had a mean HbA1c of 9.1%. The risks of developing retinopathy, microalbuminuria, and neuropathy (all complications of diabetes) were reduced by 76%, 39%, and 60%, respectively, in the intensively treated group.18 In the UKPDS study, 3867 patients with type 2 diabetes were randomly assigned to intensive and conventionally treated groups. Over 10 years, the mean HbA1c level was 7.0% in the intensively treated group and 7.9% in the conventionally treated group. Although the difference in mean HbA1c levels was not as striking as in the DCCT trial, there was still a 21% and 34% reduction in retinopathy and microalbuminuria end points in the intensively treated group from the UKPDS trial.19 From 1997 to 2002, the American Diabetes Association (ADA) recommended a target HbA1c of less than 7% for optimal glycemic control, whereas treatment with more intensive therapy was recommended for HbA1c levels of greater than 8%.20 More recently, the ADA have recommended the optimal HbA1c target for individual patients should be as close as possible to normal (HbA1c, <6%) without significant hypoglycemia.21 Collectively, the DCCT and UKPDS clinical outcome studies and the ADA recommendations concerning glycemic targets emphasize the critical requirement for low imprecision in monitoring serial HbA1c measurements in the individual patient with diabetes.

This has led professional bodies and expert groups to recommend a general tightening of analytical goals for imprecision of HbA1c assays during the past decade. The National Glycohemoglobin Standardization Program in America requires that an HbA1c method must have a total (between-run) imprecision of 4% or less to achieve National Glycohemoglobin Standardization Program certification.22 Many expert groups representing clinical and chemical pathology organizations from the United States, United Kingdom, and Australia have recommended imprecision goals of 3% (within laboratory) and 5% (between laboratory) for HbA1c.23-26 More recently, an international workshop representing distinguished bodies including the International Diabetes Federation, the International Federation of Clinical Chemistry (IFCC), and the ADA produced a consensus statement advocating an optimal imprecision goal for HbA1c of 2%.27,28

Only methods with an analytical imprecision, or coefficient of variation (CV%), of 3% or less can distinguish statistically between HbA1c treatment goals of 7% and 8%29; coefficient of variation is a statistical measure of imprecision, calculated as the SD divided by the mean of replicate measurements and expressed as a percentage. At the ADA target of 7% HbA1c, an analytical CV% of 3% equates to an SD of 0.21. Thus, the true result has a 95% probability of lying within the range of 6.58% to 7.42% HbA1c (+2 SD). At an HbA1c of 8%, the level formerly recommended by ADA for a change in therapy, an analytical CV% of 3% equates to an SD of 0.24. Here, the true result has a 95% probability of lying within the range of 7.52% to 8.48% HbA1c. For methods with an analytical imprecision greater than 3%, there will be an increasing degree of overlap in these values. Further, 2 serial HbA1c results must differ by greater than 2.77 SD for there to be at least a 95% probability that they are analytically different.14 For an HbA1c assay with a CV% of 5%, this means that the 2 HbA1c results would need to differ by >1.0% (at a level of 7%) for the physician to be confident that a clinically significant change has occurred in the patient. For methods with CV%≥s of 4% and 3%, results would need to differ by more than 0.8% and more than 0.6%, respectively, to be confident there has been a clinically significant change in glycemic status.

Data on biological variation of HbA1c is limited. Early published estimates list the within-person biological variation of glycated hemoglobin in blood as 5.6, from which a desirable imprecision goal of 2.8% can be derived.13,14 However, more recent estimates indicate the within-person biological variation of HbA1c is 1.9%, leading to a tighter desirable goal of 1.0%.15,30,31 Clearly, an imprecision goal of less than 3% is the desirable analytical goal for laboratory HbA1c methods, based on clinical requirement, with an optimal imprecision goal of 2% now being recommended by leading professional groups.

Can these analytical goals be achieved in Australia by laboratory (and POCT) methods? The average imprecision (CV%) recorded by the top 20%, 50% (median), and 90% of laboratories participating in the 2005 RCPA Quality Assurance Programs Glycohemoglobin Program was 1.9%, 2.7%, and 5.1%, respectively (Table 2). Only approximately 55% of analytical systems used in Australia achieved a precision of less than 3%, most of which are high-performance liquid chromatography (HPLC)–based methods. The main POCT device used by laboratories in Australia (the DCA 2000; Bayer, Tarrytown, NY) recorded a CV% of 2.9% in this program during 2005.32 State-of-the-art data on POCT HbA1c testing outside the laboratory are available through the national Quality Assurance for Aboriginal Medical Services (QAAMS) Program. The Bayer DCA 2000 recorded a median
CV% of 3.2% for quality assurance testing in the QAAMS Program during 2005. A recent comparison of 4 POCT devices for HbA1c in the hands of hospital nursing staff revealed that only the Bayer DCA 2000 was able to achieve a within-batch CV% of less than 3%.

With many laboratory systems currently unable to attain the desirable analytical goal of 3% for HbA1c testing, it would therefore seem inappropriate to impose this goal on POCT devices measuring HbA1c outside the laboratory. It is therefore recommended that a minimum imprecision goal of 4% for POCT HbA1c testing be set for this analyte, along with a desirable goal of 3% and an optimal goal of 2%.

**Goals for Bias**

Routine laboratory methods for HbA1c are based on 3 different analytical principles: those that measure HbA1c by difference in charge (eg, cation exchange HPLC), structure (affinity chromatography) or antigenicity (immunoassay). Methods based on these principles measure slightly different glycation products and hence generate slightly different HbA1c results. Some methods may also be subject to interference by fetal hemoglobin, abnormal hemoglobin variants, and uremia seen in renal patients (as a result of carbamylation of hemoglobin from urea-derived isocyanate) or in patients on long term-saliclycylate therapy.

From a clinical perspective, the use of glycemic targets for assessing management and therapy dictates that there should be no difference between the accuracy of analytical methods. This clinical requirement has led to a pressing need among clinical biochemists to standardize (or harmonize) all HbA1c methods globally. There has been considerable work devoted to this task during the past decade by the IFCC Working Group on HbA1c Standardization. The preparation of pure HbA1c calibration material, the establishment of international reference methods, and a reference system is well under way and should lead not only to a minimization of analytical bias between methods but also a reduction in between-method imprecision. With the new reference system close to being implemented globally, the analytical goal for both laboratory and POCT HbA1c methods should be to have zero bias.

**Goals for Total Allowable Error**

In Australia, the RCPA Quality Assurance Programs Chemical Pathology Group has set an analytical goal (“allowable limit of performance”) for HbA1c measurement of ±0.5 at HbA1c concentrations of 10.0% or less and ±5% at HbA1c concentrations of more than 10.0% for their laboratory-based glycohemoglobin program. A goal for total allowable error of HbA1c analysis of 2.7% can also be derived from recent biological variation data. However, given the goal for accuracy is to have no bias and the clinical imperative for HbA1c to have minimal analytical imprecision, it is recommended that the goals for total allowable error for HbA1c POCT measurement should be the same as those set for imprecision.

Although the Bayer DCA 2000, which is the most widely used POCT instrument in Australia, can achieve performance close to the desired goals, many other current POCT analysers will unquestionably have difficulty achieving the recommended analytical goals. However, the clinical requirement for precise and accurate results dictates that stringent goals need to be set for POCT HbA1c testing to ensure patient management is not compromised.

### LIPIDS

**Goals for Imprecision**

Most of the data concerning analytical goals for laboratory lipid analysis comes from biological variation studies or is profession derived.

Minimum, desirable, and optimal imprecision goals for lipid testing based on biological variation data are available from several sources and are summarized in Table 3.

**Table 2. Imprecision Observed in 2005 by Laboratories Participating in Quality Assurance Programs Administered by the RCPA Quality Assurance Programs Chemical Pathology Group**

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Program</th>
<th>2005 Cycle Number</th>
<th>2005 Cycle Period</th>
<th>Top 20% of Laboratories CV%</th>
<th>50% of Laboratories CV%</th>
<th>90% of Laboratories CV%</th>
<th>Concentration Range in Quality Assurance Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>Glycohemoglobin</td>
<td>22</td>
<td>Jan-Jun</td>
<td>1.9</td>
<td>2.5</td>
<td>5.1</td>
<td>5.3–13.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23</td>
<td>Jul-Dec</td>
<td>1.7</td>
<td>2.6</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Special lipids</td>
<td>28</td>
<td>Jan-Jun</td>
<td>1.5</td>
<td>2.3</td>
<td>5.7</td>
<td>2.5–10.5 mmol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>29</td>
<td>Jul-Dec</td>
<td>1.7</td>
<td>2.1</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Triglyceride</td>
<td>Special lipids</td>
<td>28</td>
<td>Jan-Jun</td>
<td>1.9</td>
<td>2.8</td>
<td>5.1</td>
<td>0.5–3.2 mmol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>29</td>
<td>Jul-Dec</td>
<td>1.7</td>
<td>2.3</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>Special lipids</td>
<td>28</td>
<td>Jan-Jun</td>
<td>1.7</td>
<td>5.6</td>
<td>10.0</td>
<td>0.7–2.2 mmol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>29</td>
<td>Jul-Dec</td>
<td>3.5</td>
<td>4.7</td>
<td>7.7</td>
<td></td>
</tr>
<tr>
<td>Urine albumin</td>
<td>General urine chemistry</td>
<td>41</td>
<td>Jan-Jun</td>
<td>3.4</td>
<td>5.8</td>
<td>12.6</td>
<td>10–130 mg/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>42</td>
<td>Jul-Dec</td>
<td>3.6</td>
<td>5.7</td>
<td>12.6</td>
<td></td>
</tr>
<tr>
<td>Urine creatinine</td>
<td>General urine chemistry</td>
<td>41</td>
<td>Jan-Jun</td>
<td>2.0</td>
<td>3.3</td>
<td>7.2</td>
<td>2.4–22 mmol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>42</td>
<td>Jul-Dec</td>
<td>2.0</td>
<td>3.1</td>
<td>7.4</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented for the two 6-monthly testing cycles completed by laboratories during 2005.

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Control and Prevention (CDC) through its CDC–National Heart, Lung, and Blood Institute Lipid Standardization Program and the NCEP. The CDC-National Heart, Lung, and Blood Institute Lipid Standardization Program arose in the late 1980s out of a desire to improve the analytical performance of specialist lipid laboratories around the world. The CDC analytical goals are complex because they are concentration dependent and couched mainly in SD rather than CV% terms. The NCEP have been reporting analytical goals for imprecision, bias, and total allowable error for cholesterol since 1988 and for triglyceride, HDL cholesterol, and LDL cholesterol since 1995. Goals recommended by the NCEP for the imprecision of lipid analyses is shown in Table 3.

For total cholesterol, an imprecision goal of 3% is the desirable specification for laboratory methods. Is this goal achievable by laboratories in Australia? The average imprecision (CV%) recorded by the top 20%, 50% (median), and 90% of laboratories participating in the RCPA Quality Assurance Programs Special Lipid Program was 1.6%, 2.2%, and 4.7%, respectively, in 2005 (Table 2). Most, but not all of the current laboratory analytical systems, achieved the desirable imprecision goal. For POCT outside the laboratory in Australia, a minimum imprecision goal of 5%, based on rounded biological variation, is therefore recommended. An optimal goal of 2% can also be set based on the current performance base achieved by the better Australian laboratories.

For triglyceride, the desirable goal for imprecision derived from biological variation (10.5%) is twice that recommended by the NCEP (5%) because triglyceride exhibits a large degree of within-person biological variation (21%). The average imprecision (CV%) recorded by the top 20%, 50% (median), and 90% of laboratories participating in the 2005 RCPA Quality Assurance Programs Special Lipid Program was 1.8%, 2.6%, and 4.9%, respectively, in 2005 (Table 2). It is therefore recommended that the NCEP-derived desirable imprecision goal of 5% is more appropriate for this analyte than the corresponding goal from biological variation. A minimum imprecision goal of 7.5% for POCT outside the laboratory, which represents the approximate midpoint between goals of 10.5% from biological variation and 5% from the NCEP is also recommended and should readily be achievable in the nonlaboratory environment. An optimal goal of 2% can also be set based on the current performance base achieved by the top 20% of Australian laboratories.

For HDL cholesterol, an imprecision goal of 4% is the desirable performance standard from both NCEP and biological variation data. However, the average imprecision (CV%) recorded by the top 20%, 50% (median), and 90% of laboratories participating in the RCPA Quality Assurance Programs Special Lipid Program was 3.7%, 5.2%, and 8.9%, respectively, in 2005 (Table 2). These data indicate that current laboratory methods struggle to meet the desirable goal and this goal is too tight to be imposed on POCT HDL cholesterol testing outside the laboratory. Historically, HDL cholesterol has been a technically demanding and time-consuming assay in the laboratory environment, and the fact that HDL cholesterol can be performed by POCT at all is quite a remarkable technological feat. In Australia, HDL cholesterol concentrations are also generally reported to 1 decimal place. For these reasons, it is recommended that a minimum goal for imprecision of POCT HDL cholesterol testing be set at 6% (which is slightly higher than the minimum goal derived for biological variation). An optimal goal of 3.5% can also be set based on the current performance base achieved by the top 20% of Australian laboratories.

LDL cholesterol is not measured directly by routine laboratory or POCT lipid analysers, rather it is a calculated value based on the Friedewald formula. This formula provides an adequate surrogate measurement of LDL cholesterol only when the sample has a triglyceride concentration less than 4.5 mmol/L and is free of chylomicrons. Analytical errors in each of the tests measured in calculating the formula (total cholesterol, HDL cholesterol, and triglyceride) are additive. It is therefore recommended that a minimum imprecision goal of 6% (from biological variation) and a desirable imprecision goal of 4% (from both biological variation and NCEP recommendations), respectively, be set for LDL cholesterol. An optimal goal of 3.5% can be set from biological variation but would be extremely difficult to achieve with laboratory, let alone, POCT methods.

For HDL cholesterol, an imprecision goal of 4% is the desirable performance standard from both NCEP and biological variation data. However, the average imprecision (CV%) recorded by the top 20%, 50% (median), and 90% of laboratories participating in the RCPA Quality Assurance Programs Special Lipid Program was 3.7%, 5.2%, and 8.9%, respectively, in 2005 (Table 2). These data indicate that current laboratory methods struggle to meet the desirable goal and this goal is too tight to be imposed on POCT HDL cholesterol testing outside the laboratory. Historically, HDL cholesterol has been a technically demanding and time-consuming assay in the laboratory environment, and the fact that HDL cholesterol can be performed by POCT at all is quite a remarkable technological feat. In Australia, HDL cholesterol concentrations are also generally reported to 1 decimal place. For these reasons, it is recommended that a minimum goal for imprecision of POCT HDL cholesterol testing be set at 6% (which is slightly higher than the minimum goal derived for biological variation). An optimal goal of 3.5% can also be set based on the current performance base achieved by the top 20% of Australian laboratories.

### Goals for Bias

The following goals can be derived from biological variation data and NCEP recommendations: total cholesterol, 4.0% and 3%, respectively; triglyceride, 10.7% and 5%, respectively; HDL cholesterol, 5.2% and 5%, respectively; LDL cholesterol, 6.8% and 4%, respectively. However, the profession-driven NCEP recommendations would seem more appropriate to apply to laboratory and POCT methods.

### Goals for Total Allowable Error

A comparison of goals for total allowable error derived from biological variation and the recommendations of the

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**TABLE 3.** Goals for Imprecision of Lipid Testing Derived from Biological Variation and the Recommendations of the NCEP

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Biological Variation (CV%)</th>
<th>Derived Imprecision Goal (CV%)</th>
<th>Imprecision Goal from NCEP (CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>6.0</td>
<td>Minimum 4.5</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Desirable 3.0</td>
<td>Optimal 1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.0 (CV%)</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>21.0</td>
<td>Minimum 15.8</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Desirable 10.5</td>
<td>Optimal 5.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.0 (CV%)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>7.1</td>
<td>Minimum 5.3</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Desirable 3.6</td>
<td>Optimal 1.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.0 (CV%)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>8.3</td>
<td>Minimum 6.2</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Desirable 4.2</td>
<td>Optimal 3.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.0 (CV%)</td>
</tr>
</tbody>
</table>
NCEP and the RCPA Quality Assurance Programs are shown in Table 4.

Using the first 2 approaches, goals for total allowable error are generally comparable for cholesterol (approximately 9%), HDL cholesterol (12%), and LDL cholesterol (13%). For triglyceride, the goal from biological variation is influenced by large within- and between-person variation and is therefore much wider than the NCEP goal. Given that most current methods for triglyceride (including POCT) are of good quality, the NCEP goal for total allowable error of 15% is considered most appropriate. To allow for the vagaries of the nonlaboratory POCT environment outlined in the introduction, recommended total allowable error goals have been rounded to 10% for total cholesterol and 15% for both HDL and LDL cholesterol.

### URINE ACR

Microalbuminuria can be defined in terms of either a urine ACR in a first morning urine, a urine albumin excretion rate (AER) in a timed (overnight) urine sample or urinary albumin excretion per day. The measurement of urine ACR on a first morning sample has proven clinically popular in Australia because it is convenient for the patient and does not require a timed collection or measurement of urine volume.

### Goals for Imprecision

The following minimum, desirable, and optimal imprecision goals for urine albumin and creatinine can be derived from biological variation data: 27%, 18% and 9% for urine albumin and 18%, 12%, and 6% for urine creatinine.14,15

Given the wide within-person biological variation observed with urine albumin, the National Academy of Clinical Biochemistry (NACB) has argued that a lesser degree of precision is required for this analyte. They have recommended that “the analytical imprecision (CV%) of methods to measure microalbuminuria should be <15%.”16

From state-of-the-art laboratory data, the average imprecision (CV%) recorded by the top 20%, 50% (median), and 90% of laboratories participating in the 2005 General Urine Chemistry Program run by the RCPA Quality Assurance Programs Chemical Pathology Group was 3.5%, 5.8%, and 12.6%, respectively (Table 2). All but a small minority of infrequently used methods achieved the profession-based NACB goal.

In the national QAAMS Program for urine ACR POCT on the Bayer DCA 2000 in Australian Aboriginal medical services, participating services (n = 30) achieved an average imprecision of 8.3% for urine albumin (as well as 4.6% for urine creatinine and 4.4% for urine ACR) during the past 3 years.32

These 2 sets of data indicate the goal for urine albumin proposed by the NACB can readily be achieved using current laboratory and POCT methodology. It is therefore recommended that the desirable goal be set at 10%, closer to the optimal goal derived from biological variation data.

For urine creatinine, the desirable imprecision goal from biological variation data is 12%. However, once again, current Australian laboratories can readily achieve this goal. The average imprecision (CV%) recorded by the top 20%, 50% (median), and 90% of laboratories participating in the 2005 RCPA Quality Assurance Programs General Urine Chemistry Program was 2.0%, 3.2%, and 7.3%, respectively (Table 2). As mentioned above, the average imprecision for POC urine creatinine testing in the national QAAMS Program for urine ACR was 4.6%. It is therefore recommended that the desirable imprecision goal for POCT urine creatinine be set at 6%, consistent with the optimal goal derived from biological variation data.

To calculate the desirable imprecision goal for the urine ACR, it is necessary to add the recommended goals for urine albumin (10%) and creatinine (6%) according to the following formula:

\[
\text{Total CV}\%\text{ for ACR} = (CV_{\text{Alb}}^2 + CV_{\text{Creat}}^2)^{1/2}
\]

Thus, the calculated desired goal for imprecision for urine ACR is 12%. This was readily achieved by the DCA 2000 POCT instrument in the QAAMS Program, but detailed data on the performance of other POCT microalbumin analysers is not available in Australia as yet.

### Goals for Bias

There is only extremely limited data available on accuracy goals. Goals calculated from biological variation data appear to be too wide to be of practical or clinical use (urine albumin, 16.4%; urine creatinine, 8.6%).

Traditionally, almost all laboratories have used immunochemical methods to measure urine albumin. However, the recent reporting of a previously unrecognized nonimmuno-reactive form of urine albumin in diabetes patients separated...
The IFCC has now formed a working group on the standardization of the microalbumin assay in urine. Their charter is to establish a reference procedure and reference methods for the measurement of urine (micro)albumin, to undertake a chemical and immunochemical characterization of the various forms of albumin in urine, and to decide upon the optimum analyte for the assessment of microalbuminuria.

Goals for Total Allowable Error

Analytical goals for total allowable error derived from biological variation data are too wide and of limited clinical relevance (urine albumin, 46%; urine creatinine, 28%).

In the RCPA Quality Assurance Programs’ General Urine Chemistry Program, “allowable limits of performance” of ±4 for concentrations of up to 20 mg/L and ±20% at concentrations greater than 20 mg/L have been set for urine albumin and ±0.5 at 5 mmol/L or less and ±10% at concentrations greater than 5 mmol/L for urine creatinine.

In the QAAMS urine ACR Program, goals for total allowable error of 12.5% for urine albumin, 7.5% for urine creatinine, and 15% for urine ACR have been set by the program organizers. They would seem relevant, appropriate, and readily achievable for the POCT environment.

DISCUSSION

This article focuses on setting analytical goals for the performance of selected common POCT tests used for diabetes management in Australia. The article reviews the current data on analytical goal setting in laboratories, addresses the factors that set POCT apart from the laboratory environment, compares laboratory-derived analytical goals with current state-of-the-art performance, and then sets goals for POCT conducted in the nonlaboratory environment. The analytical goals recommended in this article are summarized in Table 5. They aim to be appropriate and achievable for diabetes management in the nonlaboratory POCT setting in Australia and ensure that the quality of patient care is not compromised. Analytical goals have been set for the imprecision, bias, and total allowable error for each POCT test where sufficient data are available. A minimum imprecision goal has been recommended for each blood analyte. Point-of-care testing methods that are unable to achieve these minimum goals should be used with caution.

The goals for analytes such as triglyceride and urine albumin should be readily achievable by most POCT analysers. At the other extreme, the goals for HbA1c will undoubtedly present a challenge for POCT manufacturers to develop more innovative and advanced technological and methodological systems to meet the clinical imperative to minimize total analytical error. Diagnostic companies will need to pay particular attention to the automation and quality management of manufacturing processes to ensure within- and between-batch variation in reagents is minimized. The tight goals for HbA1c will also demand that nonlaboratory POCT operators have continuous access to on-going education and training for POCT HbA1c testing to ensure competency standards and skills are maintained at optimal levels.

The analytical goals recommended for POCT in this article should be regarded as a starting point for further profession-based discussion, with the goals needing to be flexible and continually reviewed and refined as further relevant data (particularly from clinical outcome studies) become available. The current Australian Point-of-Care Testing Trial in General Practice will provide a suitable environment in which to rigorously assess the validity and appropriateness of the goals recommended by this article. While the purpose of this article was to recommend goals for POCT conducted in the nonlaboratory setting in Australia, it is also envisaged that the promulgated goals will be broadly applicable and relevant for countries conducting POCT in the public health care setting outside Australia.

GLOSSARY OF KEY TERMS

Accuracy The closeness of the agreement between the measured value and the true value of an analyte.

Analyte The pathology test that fulfills its stated or implied purpose. The terms analytical goals, analytical quality specifications, and allowable limits of performance are used interchangeably in this article.

Between-person biological variation The difference between the homeostatic setting points of individuals.

Bias (or inaccuracy) The numerical difference between the measured value and the true value of an analyte.

Coefficient of variation (CV%) A statistical measure of imprecision, calculated as the standard deviation divided by the mean of replicate measurements and expressed as a percentage. Thus, CV% = (SD/mean) * 100.

CVa Analytical coefficient of variation.

CVw Within-person biological coefficient of variation.

Imprecision (or analytical imprecision) The standard deviation or coefficient of variation of the results in a set of replicate measurements of an analyte.

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Goal for Imprecision (CV%)</th>
<th>Goal for Total Allowable Error</th>
</tr>
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<tbody>
<tr>
<td>HbA1c</td>
<td>Minimum (%)</td>
<td>Desirable (%)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>7.5</td>
<td>5</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Urine albumin</td>
<td>—</td>
<td>10</td>
</tr>
<tr>
<td>Urine creatinine</td>
<td>—</td>
<td>6</td>
</tr>
<tr>
<td>Urine ACR</td>
<td>—</td>
<td>12</td>
</tr>
</tbody>
</table>

by size-exclusion HPLC has raised considerable global debate among clinical biochemists about the accuracy of urine albumin measurements. The IFCC has now formed a working group on the standardization of the microalbumin assay in urine. Their charter is to establish a reference procedure and reference methods for the measurement of urine (micro)albumin, to undertake a chemical and immunochemical characterization of the various forms of albumin in urine, and to decide upon the optimum analyte for the assessment of microalbuminuria.
Point-of-care testing Pathology testing that is performed by or on behalf of the requesting clinician at the time of consultation with the patient, allowing the test result to be used to make immediate, informed decisions (in the context of this article) about patient management.

Precision The closeness of agreement between replicate measurements on the same analyte under specified conditions; precision is also often referred to as the reproducibility, repeatability, or scatter of a set of replicate measurements.

Standard deviation A statistical measure of imprecision (or the dispersion of replicate measurements on the same analyte), calculated as the square root of the sum of the squares of the difference between each data point and the mean divided by the total number of data points minus 1.

Total (analytical) error The sum of the bias and imprecision, usually defined by the formula $TE = [\text{bias}] + 1.65 * \text{precision}$, where bias does not have a sign.

Total allowable error The analytical goal or quality specification for total error.

Within-person biological variation The inherent biological variation of an analyte around the homeostatic setting point for that individual.

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REFERENCES


