The use of albumin measurement in urine as a marker of end-stage renal disease and cardiovascular disease (CVD) is well established, in particular for the diabetic population (1). Increased urine albumin is a predictor of renal failure, type 1 and type 2 diabetes, and cardiovascular events (2–4). It is now recognized that albuminuria reflects generalized vascular endothelial damage (5). The prevalence of diabetes, hypertension, obesity, and chronic kidney disease is rising markedly in many developing countries, and all of them contribute to cardiovascular disease. By 2020, it is predicted that 80% of the global burden of CVD will be borne by developing countries (6).

The use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers may reduce microalbuminuria in individuals with and without diabetes, reduce progressive renal injury, and reduce cardiovascular events (7–9). These benefits appear to be partially independent of their antihypertensive effects. Control of dysglycemia and lipids, physical activity, and dietary protein restriction have been shown to reduce protein in urine and to have beneficial effects (8–10). Testing for albumin in urine has an identified role in secondary prevention, to establish treatment interventions and monitor progress and response to treatment. In primary prevention, it may have a role in reducing the burden of these chronic vascular diseases, but its practicality has not yet been fully defined by clinical studies.

The measurement of albumin in urine is not standardized. The ongoing problems with analytical performance will probably continue to be an issue in the absence of both a reference material and a reference system for urine albumin measurement. Data from external quality assessment schemes show large between-laboratory and between-method variations for estimation of albumin in urine. Clinical laboratories have poor data available for intrindividual biological variation, and we use a wide range of nonstandardized measurement procedures for urine albumin. Furthermore, there is inconsistency between laboratories regarding sample type, units of reporting, and reference intervals or cut points.

Although clinical laboratories place great emphasis on analytical variation, it has not yet been adequately addressed for urine albumin. Clinical laboratories place less emphasis on the control of preanalytical factors and almost none relating to how laboratory test results are requested, interpreted, and then applied in clinical practice. An innovative study in this issue of Clinical Chemistry (11) addresses the challenge in the postanalytical phase. The authors mailed a case history–based questionnaire to primary care physicians in 10 European countries and Australia and received 2298 responses. The questionnaire model has been validated and used in a similar interventional survey relating to the application and interpretation of blood glucose and glycohemoglobin tests. The case history was developed around a patient with known diabetes, since this was probably the clinical situation most extensively identified for the measurement of urine albumin.

Guidelines for urine albumin measurement have been issued in many countries and by international organizations. The authors of this study (11) concluded that guideline recommendations were not being followed and that there was marked variation in whether to use random or spot, early or first-morning urine samples. Timed samples were used extensively in some countries but not in others, and many physicians did not follow up on a positive test result with a repeat test for confirmation. In different countries, the prevalence of in-office testing varied, with a wide range of systems to test for albumin/creatinine ratio and quantitative and semiquantitative albumin. The study was not designed to draw conclusions about the comparative merits of the different measurement systems or the impact of the content of guidelines on clinical interpretation. However, one of the most fascinating aspects of this study is the attempt to quantify general practitioners’ perception of a minimal difference between 2 consecutive results—a difference that assures them of a true increase or decrease in urine albumin concentration. Approximately 30% of physicians did not estimate a clinically important change, and the remaining 70% had a wide range for their significant differences, with variations in the percentages quoted for incremental and decremental changes.

What lessons can laboratory medicine learn from this study? The first would be to recognize the challenges faced by primary care physicians, and the second to examine how clinical laboratories may have contributed to the less-than-ideal findings. There should be no smugness concerning the physicians’ varying assess-
ment of the critical difference between consecutive results when measuring low concentrations of urine albumin. How many of us would have readily available recall of intraindividual biological variation, analytical bias, and imprecision to answer a similar clinical scenario questionnaire and declare the true critical difference? Nevertheless, guidance as to how to do this has long been available to us (12–14). Would we be able to respond to a further challenge as to what is the clinical significance of that critical difference, and whether it justifies a change in management of an individual patient? In daily clinical practice, the primary care physician is faced with a large number of challenges, only some of which are related to clinical laboratory tests. It is unlikely that even if the data were available, any one individual could retain all the information relevant for every laboratory test. The limited time available for each clinical consultation does not facilitate complex data-searching procedures. Does this represent an opportunity for laboratory professionals to search for, or conduct, the relevant studies that would allow us to incorporate the appropriate data into our laboratory information system, which could simply calculate and report for each patient result the range of minimal significant difference?

Primary care physicians are inundated with clinical guidelines, recommendations, and position statements. It is not surprising that the individual physician struggles to implement recommendations when those recommendations differ. If testing for albumin in urine is not performed, or is performed inadequately, it affects the public by being an obstacle to early identification of disease, with a subsequent late diagnosis and intervention.

Confusing reporting methods make education difficult for the users of laboratory services. The necessity to understand clinically significant changes in quantities is also highlighted by the fact that urine albumin is a continuous risk factor (15). There is a clear need for greater involvement of laboratory scientists and physicians in collaboration with clinical colleagues in the creation, promotion, and maintenance of the laboratory components of clinical guidelines. The goal of such involvement must be to make them more consistent and more easily understood. The potential for laboratory involvement in the postanalytical application of laboratory tests has been demonstrated in a number of studies, including this report from primary care (11).

Some confusion clearly exists in clinical practice in a number of areas, demonstrated in this postanalytical external quality assessment of urine albumin conducted in multiple European countries. It is highly unlikely that the findings would have been any different with North American participation. Currently, there is discussion as to whether albuminuria can be used in therapeutic trials as a surrogate marker for a clinically meaningful end point and whether it would predict the effect of therapy. It would be desirable to have such a surrogate marker, but it is unlikely to be achieved without significant effort directed by us toward improvement in the current measurement and reporting of urine albumin, particularly as this marker is relevant and useful for an increasingly large number of the world’s population.

We must be prepared to learn from the fact that a measurement procedure, performed many millions of times throughout the world and of great clinical relevance, should be so ill understood by the clinical laboratory and poorly applied by community physicians. The authors of this study (11) are to be commended for developing and validating a study design that reliably allows us to assess how a test is conducted and to implement the results in a specific clinical practice setting. It has highlighted areas for clinical and laboratory investigation and collaboration toward improving the clinical utility of testing for small quantities of albumin in urine.

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