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Q&A

Optimal Use of Biomarkers for Chronic Kidney Disease

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The primary laboratory tests for diagnosis of chronic kidney disease (CKD)[9] are serum/plasma/blood creatinine with calculation of estimated glomerular filtration rate (eGFR) and urine albumin–creatinine ratio (UACR). Cystatin C is becoming a secondary test for estimating eGFR in some clinical situations. Urine total protein and the protein–creatinine ratio are also used to monitor patients with more advanced CKD. The US Renal Data System 2018 reports that data from the National Health and Nutrition Examination Survey provide an estimate that 15% of the US population meet the laboratory criteria for CKD based on the Kidney Disease Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline definition of GFR <60 mL/min/1.73 m^2 or UACR >30 mg/g (3 mg/mmol).

In the years from 2010 to 2018, 80%–90% of laboratories in the US have reported eGFR along with creatinine, yet patient awareness of having CKD continues to be poor. In the 2013–2016 US National Health and Nutrition Examination Survey data, only 8% of people with eGFR <60 mL/min/1.73 m^2 were aware of having CKD, and 28% of people with eGFR <60 mL/min/1.73 m^2 and UACR >30 mg/g (3 mg/mmol) were aware of having CKD.

In this Q&A, a panel of experts in laboratory medicine and in nephrology examine laboratory ordering, testing, and reporting practices and recommend how those practices can be improved to better serve patients with CKD.

What is a kidney profile and when should it be ordered?

Joseph Vassalotti: The American Diabetes Association, KDIGO, and the National Kidney Foundation (NKF)'s

Kidney Disease Outcomes Quality Initiative recommend eGFR and UACR as the tests for CKD targeted for the major risk groups, including diabetes and hypertension. The combination of eGFR and UACR guides therapeutic interventions and predicts risk for CKD progression as well as cardiovascular events, and mortality. The UACR is particularly underutilized in the US, with data for 2016 showing 41.8% and 49.0% testing for diabetes compared to 6.6% and 7.1% UACR assessment for hypertension in the Medicare 5% sample and commercial insurance (Optum Clinformatics™) populations, respectively. Undertesting of risk groups contributes to clinician underdiagnosis and low patient awareness of CKD. The Laboratory Advisory group convened by the NKF in 2016 recommends implementation of the kidney profile, $eGFR_{creatinine}$, using the CKD-EPI equation plus UACR, but allows for flexibility in how this test is offered by the laboratory or ordered by the clinician. Thus, the kidney profile could be ordered individually or combined with frequently used panels at the discretion of the laboratory and ordering clinician. Panels that include serum creatinine for eGFR calculation commonly used in the US are the basic metabolic panel, comprehensive metabolic panel, and renal function panel. The kidney profile should not be used for mass or general population screening, but rather for targeted testing of risk groups.

A growing number of clinical laboratory professional societies and active laboratories are collaborating with NKF to implement the following 6 laboratory engage-

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[9] Nonstandard abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urine albumin-creatinine ratio; KDIGO Kidney Disease Improving Global Outcomes; NKF, National Kidney Foundation; IDMS, isotope dilution mass spectrometry; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CPT, Common Procedural Terminology.

ment priorities (https://www.kidney.org/CKDintercept/laboratoryengagement):

1. Harmonize the descriptive language and reporting of the random or spot UACR as "albumin-creatinine ratio, urine" as an alias to the "microalbumin" test, reported in milligram per gram.
2. Standardize the use of the CKD-EPI $eGFR_{creatinine}$ equation.
3. Implement the "kidney profile" with the clinical laboratory community.
4. Develop a professional education campaign to ensure that clinicians appropriately order and interpret CKD tests for their at-risk patients.
5. Develop a public education campaign for people with and at risk for CKD to understand their CKD test results and what they can do to preserve their kidney health.
6. Measure the effect of "kidney profile" use on population health.

The NKF seeks additional collaborating organizations to advance the availability of the kidney profile and effect of the laboratory tests on CKD population health. The diagnosis and monitoring of CKD depend entirely on the clinical laboratory professionals who in turn have an opportunity to become engaged in population health and quality improvement.

Lesley Inker: A kidney profile should be ordered for patients at risk for CKD, for example, patients with hypertension, diabetes, cardiovascular disease, rheumatic conditions, or who have a family history of CKD. A kidney profile is also useful for patients with known CKD to evaluate the progression, which is defined as the change in GFR over time. In addition, the kidney profile is useful for patients with large amounts of UACR who were put on medications that block the renin angiotensin system to evaluate their response to therapy.

Graham Jones: The combination of eGFR (based on serum creatinine) and a UACR is part of the definition of CKD and the staging criteria. The promotion of the "kidney profile" makes sense to ensure both tests are available to be able to make this diagnosis, especially as an abnormality in either test may be the first sign of kidney damage. Of course, different regulatory requirements in different locations can affect good advice. For example, in Australia, under our national Medicare system, only agreed test groups are allowed, and "kidney profile" is

currently not one of them. Having said that, Kidney Health Australia promotes the Kidney Health Check consisting of these 2 tests and a blood pressure check. The combination of serum creatinine with eGFR and urine albumin should be requested whenever CKD is being considered as a possible diagnosis and for monitoring of progression. Of course, serum creatinine also has important roles in other settings, especially when considering acute kidney injury or for making drug-dosing decisions. In these settings the addition of urine albumin is not required.

An additional advantage of the profile would be the easier process of applying an interpretive comment to the pathology report. An example of such a comment could be as follows: "RENAL PANEL INTERPRETATION: Results for eGFR of 33 mL/min/1.73m^2 and for UACR of 55 mg/g are consistent with CKD stage G4A2. Please note that persistence of this condition for at least 3 months is required to confirm the diagnosis." The process of adding an interpretive comment is facilitated by ensuring both results are included in the same laboratory episode. Similarly searching for previous results to include in the logic for the comment is also facilitated if the eGFR and UACR are corequested.

How does a kidney profile differ in use from a renal function panel that typically includes serum glucose, creatinine, urea or urea nitrogen, calcium, phosphorus, albumin, sodium, chloride, potassium, carbon dioxide, and anion gap?

Joris Delanghe: As many diabetics are unaware about their condition, the determination of serum or plasma glucose might be informative. The more complete renal function panel (e.g., calcium phosphate product) provides information about additional complications in advanced renal failure.

Lesley Inker: The kidney profile includes only tests to detect CKD and to stage it based on severity. The diagnosis of CKD is made if the patient has a GFR <60 mL/min/1.73 m^2 or if the patient has markers of kidney damage, the most common of which is albuminuria. The

severity of CKD staging is based on the amounts of GFR and albuminuria. A renal function panel can be used to detect complications of CKD, such as abnormalities of mineral metabolism, nutrition status, hyperkalemia, or acidosis. A renal function panel can also be used to evaluate side effects of medications such as hyponatremia, hypokalemia, or metabolic alkalosis from diuretics. Glucose concentrations are important as hyperglycemia can cause acute kidney injury and risk factors for CKD progression.

Joseph Vassalotti: The kidney profile could be combined with the renal function panel for monitoring of patients with established CKD, because the renal function panel is intended for monitoring patients who have low eGFR. For example, abnormalities in serum phosphorus, specifically hyperphosphatemia, typically develop when the eGFR falls below 30 mL/min/1.73m^2, although obtaining a baseline phosphorus concentration for future trending is worth considering at higher levels of kidney function. Other laboratory panels, such as the basic metabolic panel and comprehensive metabolic panel, are more appropriate tests to consider in combination with the kidney profile when screening for incident CKD in the at-risk population.

What is the preferred equation to estimate eGFR from serum/plasma/blood creatinine?

Lorin Bachmann: Reporting the eGFR identifies patients with CKD earlier in their disease, at a point in time when therapy is most effective for preventing disease progression, compared to reporting the creatinine concentration alone with a single reference interval. All laboratories should use creatinine measurement procedures that are traceable to an isotope dilution mass spectrometry (IDMS) reference measurement procedure and eGFR equations that are appropriate for IDMS-traceable creatinine measurements. The preferred equations are the IDMS-traceable Modification of Diet in Renal Disease (MDRD) Study equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Both equations are valid for patients over the age of 18 and contain variables that adjust the eGFR to account for creatinine differences due to age, sex, and African American vs non-African American ethnicity. Use of these variables improves agreement of the calculated eGFR with GFR measured using iothalamate or iohexol clearance studies.

The IDMS-traceable MDRD Study and CKD-EPI equations agree well with each other and with the measured GFR when eGFR is $<$60 mL/min/1.73 m^2. However, the IDMS-traceable MDRD Study equation underestimates GFR when values are equal to or exceed 60 mL/min/1.73 m^2; therefore, values above this threshold should be reported as $\geq$60 mL/min/1.73m^2 if using the IDMS-traceable MDRD Study equation. The CKD-EPI equation is more accurate vs measured GFR when eGFR is 60–120 mL/min/1.73 m^2. Multiple studies have shown that an increased risk of progression of CKD exists when GFR is only mildly decreased in the interval 60–89 mL/min/1.73 m^2 or when GFR is normal ($\geq$90 mL/min/1.73 m^2) in the presence of albuminuria as defined as a urine albumin to creatinine ratio of $>$30 mg/g (3 mg/mmol). Because the CKD-EPI equation can be used to report eGFR $\geq$60 mL/min/1.73 m^2, the NKF and KDIGO recommend the CKD-EPI equation to enable identification of patients at a point earlier during kidney disease progression.

Joris Delanghe: In a practical setting (when only serum creatinine is available), the CKD-EPI equation is preferred because of its extended range of quantitative results. The influence of imprecision of creatinine assays on the uncertainty of an eGFR value is greater at higher eGFR values and should be considered when determining the highest eGFR value to report. On the other hand, the IDMS-traceable MDRD Study equation has proven its value for eGFR $<$60 mL/min/1.73m^2. In children, the "Bedside" Schwartz formula can be used (in combination with an enzymatic creatinine). In the aged, eGFR estimations are difficult because the formulas have not been validated for older ages.

Lesley Inker: The CKD-EPI equation has been shown to be the most accurate compared to measured GFR of several equations developed over the years. It has also been shown to best predict future adverse outcomes compared to other equations, in particular the IDMS-traceable MDRD Study equation. Consequently, the CKD-EPI is the preferred equation to estimate GFR from creatinine. Unlike the IDMS-traceable MDRD Study equation, there is no increase in error at higher levels of GFR, and therefore, the CKD-EPI creatinine can be reported throughout the range of GFR. It is important to remember that all estimating equations have errors relative to measured GFR. The 2002 Kidney Disease Outcomes Quality Initiative guidelines concluded that an eGFR within 30% of a measured GFR was satisfactory for clinical interpretation. Errors will be greater for people who have non-GFR determinants that are different than the populations in which the equations were derived, for example vegetarians or bodybuilders.

Graham Jones: There are several factors related to the choice of a formula for eGFR reporting, and it is likely

that some compromises may be necessary in selecting the formula for use. The simple answer may be "the most accurate formula for my patient population." However, I believe an equally important factor is uniformity between different laboratories in a city, state, or country. Confidence in the laboratory system is compromised when a patient may have a diagnosis of CKD in one laboratory but does not have the condition when tested at another laboratory. Consistent results are clearly vital when monitoring disease progression.

Just as there is a need for creatinine assay traceability, I believe there is a strong need to harmonize the formula and the result reporting for eGFR. I strongly support the advice of the KDIGO 2012 guideline to use the CKD-EPI equation unless there is evidence of a better formula. A key aspect here is to assess the quality of the evidence. For example, any formula will always work best in the data set used to establish the formula. For this reason, 1 or more large, high-quality independent validations is absolutely mandatory before considering the use of a formula. To achieve harmonization, the group recommending a formula should represent the laboratories and clinicians who will report and use the results. A potential risk of wide-scale harmonization is inertia and lack of on-going development.

Joseph Vassalotti: The 2 common $eGFR_{creatinine}$ equations used in the US are the IDMS-traceable MDRD Study and the CKD-EPI equations. The CKD-EPI equation is substantially more accurate and less biased than the IDMS-traceable MDRD Study equation in the population with eGFR near and above 60 mL/min/1.73 m^2. Observational studies comparing the 2 widely used equations show the CKD-EPI creatinine equation more accurately predicts adverse kidney, cardiovascular, and mortality outcomes for people with CKD. An important caveat for the clinical laboratory is that the latter preferred equation is dependent on IDMS-traceable creatinine methods. Major laboratories in the US have reported $eGFR_{creatinine}$ using the CKD-EPI equation since 2010. In practical terms, by using the CKD-EPI equation consistently, clinical laboratories will help clinicians appropriately interpret trends in eGFR when the results are reported from different laboratories.

Should enzymatic methods replace Jaffe-based methods for measuring creatinine?

Lorin Bachmann: The National Kidney Disease Education Program recommends that laboratories should use creatinine measurement procedures that are traceable to an IDMS reference measurement procedure. Use of IDMS-traceable creatinine measurement procedures reduces measurement variability among laboratories and improves accuracy of eGFR calculated with IDMS-traceable equations. In general, Jaffe creatinine measurement procedures are influenced to a greater degree by interferences from many substances including glucose, acetoacetate, acetone, ascorbate, pyruvate, protein abnormalities, dobutamine, and cephalosporins compared to enzymatic creatinine measurement procedures. In addition, eGFR results calculated with IDMS-traceable enzymatic creatinine methods tend to agree more closely with measured GFR in patients with diabetes compared to Jaffe creatinine methods. However, some enzymatic methods do suffer from interferences, particularly from hemoglobin and bilirubin, that need to be considered.

Joris Delanghe: Because of their better specificity, enzymatic creatinine methods are analytically superior to Jaffe-based methods. Therefore, enzymatic creatinine methods are recommended. Enzymatic creatinine methods have largely eliminated the analytical interferences caused by pseudochromogens (e.g., plasma proteins, glucose, cephalosporins, and other drugs). With Jaffe methods, these pseudochromogen-induced positive analytical errors more or less counteracted the overestimation of glomerular filtration rate that was due to the tubular secretion of creatinine. In particular, in infants and children (in which reference values for serum creatinine are low and the tubular secretion error is relatively large compared to adults) these effects were of importance for estimating eGFR. Removing the effect of pseudochromogens by enzymatic methods implies that the effect of tubular secretion on the plasma creatinine result is less counteracted. In consequence, creatinine clearance based on enzymatic assay might overestimate GFR in young children and infants. On the other hand, the lower reference interval for proteins in young children and infants is quite challenging for compensated Jaffe methods because these methods use fixed compensation factors for both adults and children causing overcompensation, or negative bias, of the error caused by pseudochromogens in children. Because of the low cost of Jaffe-based reagents, economic arguments are preventing a switch to enzymatic methods in many parts of the world.

Graham Jones: As a general statement, there are 3 reasons for different methods to give different results. These are bias (systematic error), imprecision (random error), and analytical specificity. Enzymatic assays can differ from Jaffe assays in all 3 aspects. Most discussion has focused on specificity both for common noncreatinine chromogens such as glucose or protein and patient-specific factors such as drug interferences. However, the other factors may be just as relevant. In an in-house study from 2014, we ran over 10 000 serial creatinine requests in parallel using an enzymatic assay and a so-called "compensated Jaffe" assay from the same manufacturer. With regard to bias, the percentage of samples with an eGFR

<60 mL/min/1.73 m^2 fell from 27% to 24% when enzymatic creatinine was used. The differences due to random and patient-specific factors were particularly seen at low creatinine concentrations with over 20% of samples below 0.56 mg/dL (50 μmol/L) showing between method differences of >20%. By contrast, the number of major differences, for example, due to identified drug interferences, was very low. The enzymatic assay had reduced intermediate imprecision based on quality-control values that did not translate into a smaller reference change value because the analytical imprecision of either assay type was small relative to the within-individual biological variation.

In summary, laboratories should use enzymatic assays when possible for improvements in all aspects of assay performance. This is particularly important in pediatric samples and is formally recommended in Australian Guidelines. However, in resource-limited settings, the use of a Jaffe assay is acceptable, but most importantly, attention should be given to ensure IDMS traceability (a shorthand for traceability to Reference Materials, Methods, and Laboratories listed on the Joint Committee for Traceability in Laboratory Medicine database) and also selection of an assay with other good performance characteristics.

When should cystatin C be ordered?

Joris Delanghe: Cystatin C is an alternative filtration marker with stronger and more linear risk relationships than creatinine. Addition of cystatin C results to creatinine results when calculating eGFR improves the risk classification for cardiovascular disease, end-stage renal disease, and death. However, current cystatin C testing is too expensive to justify a systematic replacement of creatinine by cystatin C.

Cystatin C should be ordered in those conditions for which creatinine production of the human body is abnormally low, for example, in sarcopenia, in patients with low muscle mass, limb amputation, or abnormally high muscle mass such as bodybuilders or elite athletes. Cystatin C is superior to serum creatinine as a marker of kidney function in the detection of early renal failure and in various patient groups (e.g., patients with liver cirrhosis, diabetes, spine injuries, muscle wasting cancer, children, and the elderly).

Even when using enzymatic creatinine methods, analytical interferences can never be excluded. Bilirubin, hemoglobin, and homogentisic acid may interfere with enzymatic methods. In these situations, cystatin C determinations can be helpful.

Lesley Inker: A confirmatory test for $eGFR_{creatinine}$ should be considered when an accurate level of GFR is needed for clinical decisions. Decisions include administration or dosing of toxic medications cleared by the kidneys such as cisplatin, carboplatin, several antibiotics, or contrast agents; determination of GFR before decisions for kidney donation; or determination of GFR before decision for heart or liver transplant alone or simultaneous with kidneys. Estimated GFR from cystatin C is 1 confirmatory test. Others are measured GFR using exogenous filtration markers or measured creatinine clearance. In patients with traumatic amputations or in otherwise healthy people with reduced muscle mass, $eGFR_{cystatin}$ is clearly better than $eGFR_{creatinine}$. However, in most populations, several studies have now clearly demonstrated that it is the combination of creatinine and cystatin that provides the most accurate estimates (i.e., $eGFR_{creatcyst}$). Even in the chronically ill, when one might have expected that $eGFR_{creatinine}$ would substantially underestimate the GFR, data show that $eGFR_{cystatin}$ is not necessarily more accurate than $eGFR_{creatinine}$. It is therefore recommended to use $eGFR_{creatcyst}$ as a confirmatory test. However, for some patients, there might still be questions about the accuracy even of $eGFR_{creatcyst}$ and in such circumstances, it is recommended to perform a measured GFR using exogenous filtration markers or measured creatinine clearance.

Graham Jones: The uptake of routinely available cystatin C testing in Australia is very low and it does not appear in any current national guidelines. Having said that, there are a number of circumstances in which creatinine-based eGFR values are likely to be erroneous and cystatin C testing is useful. These circumstances are generally when muscle mass is markedly different from that of participants enrolled in the trials in which the CKD-EPI formula was established and has been validated. For example, transplant patients and other patients with chronic debilitating diseases typically have low muscle mass. A local case noted a rise in creatinine in a patient recently started on trimethoprim, which was shown not to be a fall in GFR by use of cystatin C measurements.

Joseph Vassalotti: Currently, cystatin C is occasionally used in special circumstances by nephrologists but should not be ordered routinely. Use of serum cystatin C avoids the limitations related to both diet and muscle mass that affect serum creatinine. Whereas cystatin C is produced by all nucleated cells, creatinine is a product of the muscle metabolism of creatine and is therefore influenced by diet, particularly extremes of red meat intake, and muscle mass. Some studies have reported that estimating equations based on serum concentrations of cystatin C, either alone or especially in combination with serum creatinine, may be more predictive of outcomes compared to $eGFR_{creatinine}$, but there is variable performance among populations. These equations need to be extensively val-

idated before use in routine clinical practice. In addition, widespread use of estimating equations that incorporate cystatin C requires standardized calibration of serum cystatin C assays to the certified reference material ERM-DA 471/IFCC Human Serum (cystatin C) introduced in 2010.

The 2012 KDIGO CKD guideline recommends assessment of cystatin C in persons with $eGFR_{creatinine}$ 45–59 mL/min/1.73 m^2 without albuminuria on the basis of data showing that $eGFR_{creatinine}$ may misclassify CKD. Studies show that GFR estimates using cystatin C alone or in combination with creatinine improve classification of CKD based on measured GFR. Persons with $eGFR_{creatinine}$ 45–59 mL/min/1.73 m^2 without albuminuria and whose $eGFR_{creatcyst}$ or $eGFR_{cystatin}$ values are above 60 mL/min/1.73 m^2 have a very low risk for CKD complications. These persons could be considered not to have CKD. In addition, cystatin C may also be useful for persons with extremes in muscle mass and diet, including amputees, paraplegics, bodybuilders, people with a neuromuscular disorder, and those with malnutrition, on a vegetarian diet, on a high red meat diet, or taking creatine supplements.

When should urine albumin and/or urine total protein be measured in patients with CKD?

Joris Delanghe: Whereas serum creatinine is a measure of the number of functional nephrons, albuminuria allows assessment of the quality of the glomerular membrane. Albuminuria is useful for screening and monitoring nephropathy in patients with diabetes, arterial hypertension, cardiovascular disease, relatives of patients with end-stage renal disease, systemic vasculitis, recurrent urinary tract infections, and in patients with a history of chronic nonsteroidal antiinflammatory drugs intake.

Determination of proteinuria is recommended for patients with monoclonal gammopathy of undetermined significance, pregnant women (preeclampsia), and autoimmune diseases. In patients with tubulo-interstitial nephropathy, a dissociation between total proteinuria and albuminuria may indicate loss of tubular proteins.

Lesley Inker: For glomerular disease, urine albumin should be approximately 60%–70% of urine total protein. Most kidney diseases, such as diabetes, affect the glomerulus. As such, for most causes of kidney disease, theoretically both albumin and protein can provide similar information about kidney disease. However, because assays for albumin are more accurate and can detect lower concentrations, it is recommended that urine albumin be used as the primary method to detect CKD. However, there are conditions in which it is important to detect the presence of nonalbumin proteins. The most important of these are immunoglobulins that could indicate myeloma or, more generally, monoclonal gammopathy of renal significance. Thus, both total protein and albumin should be ordered when clinicians are concerned about these diseases. A total protein concentration more than 30% greater than the urine albumin concentration can indicate nonalbumin proteins in the urine and a need for further diagnostic tests.

Joseph Vassalotti: Urine albumin and urine total protein tests are often used interchangeably in practice. The UACR is a more sensitive and specific measure of kidney damage. Moreover, only the urine albumin is currently being standardized, whereas the urine total protein will probably never be standardized. For these reasons, albuminuria is the preferred test for routine screening targeted to risk groups. Because total protein includes nonalbumin proteins, both tests may be useful to distinguish the subtypes of proteinuria including nonselective glomerular (typically about 60%–70% albumin), selective glomerular (mostly albumin), tubular (little or no albumin), and overflow (little or no albumin). Selective glomerular proteinuria may be observed with minimal change disease and early diabetic kidney disease. Tubular and overflow types can be distinguished by the quantity because tubular proteinuria rarely exceeds 1000 mg/g creatinine, whereas overflow may be nephrotic range or >3000 mg/g creatinine caused by paraproteinuria associated with multiple myeloma, amyloid, and related disorders. Urine protein electrophoresis is a specialized test that will distinguish the types of proteinuria when necessary in selected cases.

How should urine albumin and the albumin-creatinine ratio (or urine total protein and protein-creatinine ratio) be reported?

Lorin Bachmann: Historically, the urine albumin excretion rate calculated from a 24-h urine collection was the gold standard test used for assessment of albuminuria. Owing to the frequent inaccuracies in collecting 24 h urine specimens, the UACR, expressed as mg/g (or mg/mmol) and preferably measured from a first morning void specimen, has become the recommended marker for albuminuria by most practice guidelines. Inclusion of creatinine normalizes for hydration, therefore reporting of albumin concentration alone is not recommended.

There is confusion regarding how to report the UACR when urine albumin values exceed the upper limit of the analytical measuring range for the measurement procedure. To further complicate the situation, the instructions for use for many manufacturers' urine albumin assays lack dilution protocols to enable extension of the measuring interval. If the manufacturer's instructions lack a procedure for dilution, laboratories should validate their own dilution protocols according to recommenda-

tions published in the Clinical and Laboratory Standards Institute guideline EP34 and report UACR results when albumin values are within the validated extended measuring interval. If a result is obtained that exceeds the extended measuring interval, a result for the UACR should be reported as "greater than" the maximum value that would be obtained for the upper limit of the extended measuring interval. For example, if measured urine albumin exceeds an extended measuring interval limit for an assay determined to be 2000 mg/L and measured urine creatinine is 0.8 g/L (7.1 mmol/L), then the UACR result should be reported as >(2000 mg/L divided by 0.8 g/L) or >2500 mg/g (>282 mg/mmol).

Graham Jones: The key factor for any reporting is that it provides clear, unambiguous transfer of information. Many doctors and patients obtain results from different laboratories; consequently, uniformity of formatting, including units, is of great importance. A current issue in Australia is the development of a national electronic health record in which patients and their treating doctors will have access to pathology reports. This development creates an even more urgent need for uniformity to avoid unnecessary confusion.

Joseph Vassalotti: Perhaps the semantic morass is best summed up by my anecdotal experience of having trainees in nephrology and internal medicine use the oxymoron "the patient has macro microalbuminuria." Ideally, the UACR would be called albumin-creatinine ratio, urine with uniform reporting in mg/g. In addition to the crucial nature of laboratory methodology and accuracy, nomenclature and reporting units are also important as there is confusion among clinicians regarding what is currently called the "microalbumin with creatinine" test. The current Common Procedural Terminology (CPT®) code used in the US for the microalbumin test (CPT 82043) is used to report the concentration of urinary albumin alone. Some laboratories in the US only report urine albumin concentration to thresholds of, for example, >97 mg/dL or >300 mg/L, which obviously does not permit accurate calculation of the UACR. Moreover, clinicians who are familiar with UACR thresholds may misinterpret the albumin concentration in the urine when reported in isolation by using the UACR thresholds.

When the UACR is reported, the laboratory must perform and report both urinary albumin, misnamed microalbumin (CPT 82043), and urinary creatinine (CPT 82570). When UACR is reported, the units for albumin and creatinine concentrations are not uniform across laboratories. In addition, to add to the confusion and complexity, there is another, less-sensitive urinary albumin assay with a corresponding CPT code (82042) that is not appropriate for routine evaluation of the population at risk for CKD. The terms "microalbumin" and "macroalbumin" also cause confusion, because practitioners may incorrectly conceptualize that microalbumin is testing for excretion of a small albumin molecule rather than an intermediate level of urinary albumin excretion. The current terms were derived from the detection limits of specific urine dipstick tests and have caused widespread use of arbitrary decision points that do not reflect the continuously variable cardiovascular and kidney outcomes risk associated with progression of UACR levels. Recent clinical practice guidelines have recommended that the "microalbumin" term be replaced with "albuminuria" for the reasons noted above.

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