Catching CKD sooner with kidney profile

Karen Titus

October 2019—Rarely (as waggish folks like to remind us) is it necessary to reinvent the wheel. Many times it's better to take existing wheels and stick them on, say, a suitcase.

Suddenly, maneuvering through airports becomes 1,000 times easier.

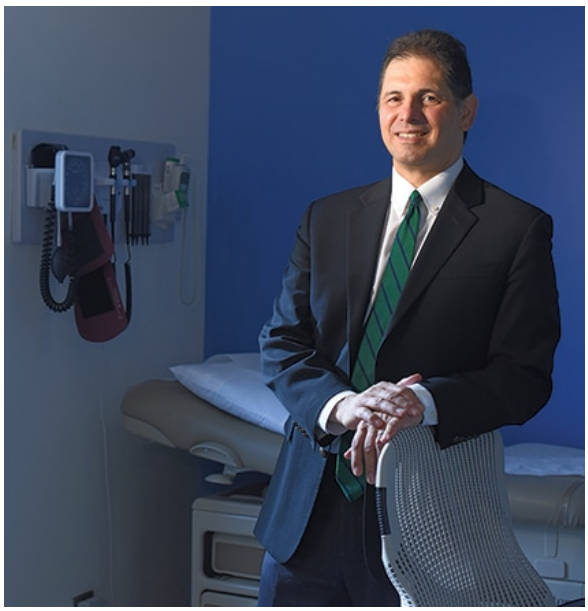
Improvement can be that simple, so obvious in retrospect. At least that's what kidney experts, both inside and outside the laboratory, are hoping as they promote use of the kidney profile lab order to diagnose and monitor chronic kidney disease.

Transformation doesn't always require the thrill of the new. While new markers are always welcome, two stalwart tests—estimated glomerular filtration rate and urine albumin-creatinine ratio—can do plenty. They're just not doing enough right now. As Joseph A. Vassalotti, MD, chief medical officer, National Kidney Foundation, and associate clinical professor, Icahn School of Medicine at Mount Sinai, New York, puts it: "There are many indications that the care of Americans with chronic kidney disease is suboptimal."

The gulf between laboratory testing and patients' awareness that they have CKD is disconcertingly wide. According to CAP Surveys data, approximately 90 percent of U.S. labs report eGFR along with serum creatinine results when creatinine is ordered, says Greg Miller, PhD, co-director of clinical chemistry, Virginia Commonwealth University Health System.

On the other hand, 2013–2016 data from the National Health and Nutrition Examination Survey showed that a mere eight percent of people with eGFR <60 mL/min/1.73 m^2 knew they had CKD; for those with that same eGFR and a uACR >30 mg/g (3 mg/mmol), only 28 percent knew they had CKD. Even among patients with CKD stage G4, only about half are aware of their condition, says Dr. Miller, who is also chair of the Laboratory Working Group of the National Kidney Disease Education Program, or NKDEP.

The misalignment feels reminiscent of an earlier era in travel, when wheeled luggage meant bunglesome efforts involving carts and bungee cords. Nice try, but no.



Dr. Joseph Vassalotti, chief medical officer of the National Kidney Foundation. "I've had so many

people tell me how frustrated they are that they didn't know sooner they had kidney disease," he says. "They wish they'd had a chance to do better." (Photo courtesy of Jennifer Altman)

The fundamental idea, Dr. Miller says, is that "instead of ordering the basic metabolic panel, and remembering also to order the urine albumin and creatinine tests, you just order the kidney profile. If the patient's at risk of kidney disease, order the kidney profile. Done. In my mind, it's a simplification process. And a convenience—convenience of memory and convenience of simplification."

To put the wheels on the suitcase, so to speak, leaders in the field are promoting the kidney profile, a term put forth roughly a year ago to encourage primary care providers to order the right tests (eGFR, uACR) on the right people (high-risk patients) at the right time (before CKD progresses).

The stakes are high. Dr. Vassalotti doesn't mince words. Using the kidney profile and acting on results "could save lives, literally. It could definitely improve lives.

"I've had so many people tell me how frustrated they are that they didn't know sooner they had kidney disease," he continues. "They wish they'd had a chance to do better."

Adds Michael Rocco, MD, MSCE: "We have over half a million people here in the United States who have end-stage kidney disease [ESKD]." The best way to treat it? "Prevent people from getting ESKD," says Dr. Rocco, who holds the Vardaman M. Buckalew Jr. chair in internal medicine/nephrology at Wake Forest School of Medicine and is chair of the NKF's Kidney Disease Outcomes Quality Initiative (KDOQI).

The basic challenge, says Dr. Miller, is that patients with CKD do not have symptoms of their disease until it's fairly advanced. The aforementioned NHANES data show that people who have CKD don't know they have it, which means, of course, that nobody is trying to prevent disease progression, says Dr. Miller. "This is the problem that's not well appreciated." Hence the drive for a convenient tool—the kidney profile—that primary caregivers can use.

Clinicians would benefit from having one box to click, Dr. Rocco says. "At my institution right now, I have to click three boxes. If you're seeing 30 patients a day, that adds up quickly."

"Both tests need to be there together," agrees James Fleming, PhD, vice president and director, Department of Science and Technology, LabCorp, which was an early adopter of the kidney profile.

The issue does not lie with the tests themselves (although there is room for improvement there, too), but rather, getting physicians to order them, says Dr. Miller. "The tests are common, and the tests have been recommended in the guidelines for years. But they're not packaged in an easy-to-order way." The destination has always been clear, in other words. But now experts are suggesting a new way through the maze.

"The real issue here," Dr. Miller adds, "is the underutilization of urine albumin and urine creatinine in high-risk patients." It might help conceptually, he says, to think of similar profiles, although there's no perfect analogy. A lipid profile for cardiovascular disease comes close, but unlike the kidney profile, that's not limited to high-risk individuals.

Among those considered high risk are patients with hypertension or diabetes mellitus, which includes about 75 million Americans, according to the Centers for Disease Control and Prevention. Multiple data, including from Medicare, the American Medical Group Association, and OptumClinformatics (a commercial insurance database), suggest that the vast majority—more than 90 percent—of patients with hypertension do not undergo uACR testing; approximately 60 percent of patients with diabetes or with both conditions go untested annually, says Dr. Vassalotti.

Similarly, he reports that a National Ambulatory Medical Care Survey (2006–2014) of more than 7,000 outpatient visits revealed that uncontrolled hypertension in the CKD population was 46 percent in 2006–2008 and 48 percent

in 2012–2014 ($P = 0.50$). Uncontrolled diabetes was present in 40 percent of the CKD population in 2012–2014. Statin use to reduce cardiovascular risk among CKD patients ages 50 and older was low and remained unchanged, from 29 percent in 2006–2008 to 31 percent in 2012–2014 ($P = 0.92$). Kidney protective angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) use decreased slightly from 40 percent to 36 percent ($P = 0.07$) (Tummalapalli SL, et al. *Clin J Am Soc Nephrol.* 2019;14[8]:1142–1150). The uACR test results inform the population with CKD that will have difficult to control diabetes and hypertension, Dr. Vassalotti notes, and guide the use of ACEi or ARB.

The laboratory is crucial not only to the diagnosis of CKD but also to risk stratification, he says. The lower the level of kidney function, the greater the risk—not only of kidney disease progressing, or for subsequent loss of kidney function over time, or of dialysis or transplant, but also for hospitalization, cardiovascular events, and all-cause and cardiovascular mortality. Elevated albuminuria (uACR) is associated with the same outcomes, he says, though perhaps less well known.

And in the hospital setting, the laboratory can help improve the diagnosis of acute kidney injury, defined as a sudden loss of kidney function, with a creatinine rise of 0.3 mg/dL or more over 48 hours, says Dr. Vassalotti.

Guidelines from groups such as the American Diabetes Association, the NKF's KDOQI, and an international organization called KDIGO (Kidney Disease Improving Global Outcomes) have long called for annual eGFR and uACR testing.

So why has it been so hard to get those wheels on the suitcase?

Education, says Dr. Fleming. "Just a lack of understanding that diabetes and cardiovascular disease are two major risk factors for chronic kidney disease. Whereas if someone has diabetes, everyone knows they should be treated preventively for cardiovascular disease."

Part of the problem is lack of clinician awareness, Dr. Vassalotti agrees. "I think laboratories can help promote testing. And clinicians can test more thoroughly—there's no question." But he suggests the two are related.

Dr. Vassalotti cautions against being overly critical of clinicians. "We want to collaborate to integrate these simple, scalable changes in their workflows."

The recent effort to promote the profile represents a sort of phase two for CKD testing. Most labs now measure eGFR, Dr. Rocco says, although "it was a struggle for 10 years. But now most labs have come around."

Dr. Miller

Ordering of urinary albumin and creatinine has lagged behind eGFR, however. "There hasn't been as much publicity around the importance of it, like there was for eGFR," says Dr. Miller. Recognizing this deficiency, the NKF began its push to package the eGFR and uACR together. In some regards, this takes a page from Amazon's playbook—an *Others who bought this item also purchased* approach that makes it easy to order both tests.

"If the tests are harmonized, are simplified, that will help stimulate clinician testing," Dr. Vassalotti says. "Also, if labs report the results in a harmonized way," that will increase clinician confidence in results that are produced in different labs—which is not an uncommon practice. Clinicians use different labs for the same patients for any number of reasons, including changes in insurance and patient convenience or preference. That can make it difficult for physicians and patients to interpret results and understand their nuances. "Sometimes the results could

be related to different reporting formats," Dr. Vassalotti says.

Even the widely used eGFR has a few rough spots in need of smoothing out. CKI-EPI is felt to be a better representation of eGFR and is the equation recommended for the kidney profile. But the isotope dilution mass spectrometry Modification of Diet in Renal Disease study and original MDRD study equations are still in use. "That, unfortunately, creates nuances in laboratory results that are related to the equation, not biology," says Dr. Vassalotti.

Dr. Fleming

The MDRD equation was initially published in the KDOQI guidelines. It had several limitations, Dr. Fleming says, including that it was not validated above a filtration value of 60 mL/minute, nor was it based on a multiethnic study. "So we had to report a result above 60 mL/min/1.73 m^2 as literally, 'The result is somewhere above 60 mL/min/1.73 m^2.' Which could represent stage two CKD classification, or be perfectly normal."

As for urine albumin, "It's not well standardized," Dr. Miller says. NKDEP's Laboratory Working Group has been working on this issue since 2010, he says, and it's closing in on having reference materials and methods available from NIST and two other U.S. sites. "We're relatively close to having the standardization tools available to the IVD industry. We're at the final stages of validating the reference measurement procedures." NIST plans to release the primary reference material later this year, he says. "So it's coming together."

Standardization is critical. Depending on what method is used, an at-risk patient might face a delay in being identified as having CKD. "The ability to discriminate around the nominal cutpoint, which is 30 milligrams of albumin per gram of creatinine, is affected by the bias among different procedures," Dr. Miller says.

Dr. Vassalotti says he's "thrilled" with the efforts of Dr. Miller and others in the Laboratory Working Group. Sooner rather than later, he hopes, urine albumin and urine creatinine will be standardized in a process analogous to what happened with serum creatinine years ago.

But even a standardized test becomes that proverbial tree in the forest if it's not ordered. "To start with," says Dr. Vassalotti, "some labs don't even offer the urine albumin-to-creatinine ratio, believe it or not." Instead, they offer total protein-to-creatinine ratio. "So of course the lab can do something there." Other labs report only the urine concentration of albumin, not the ratio. Not only is the ratio recommended by groups such as the ADA, NKF, and KDIGO, but it also has a much narrower within-individual biological CV, he says, compared with the CV for albumin alone or creatinine alone. It adjusts for differences in hydrational level of the patient, he notes, and it correlates very well with (and is less cumbersome than) the 24-hour urine. Nor "is it subject to the overcollection and undercollection of the 24-hour urine that we see in practice."

When these experts refer to the ratio, they do mean ratio. Reporting the urine albumin and the urine concentration as separate results, without calculating the ratio, is basically handing clinicians a suitcase, cart, and a bungee cord.

"Labs will often tell me things like, 'Of course it's simple to figure out—it's just division,'" Dr. Vassalotti says. No doubt. But to busy clinicians, another step—no matter how simple—can become a barrier. "We want to report the complete result uniformly to make it easier," Dr. Vassalotti says.

Based on his own experiences, Dr. Vassalotti offers another suggestion: that labs exercise caution about how they report eGFR results in the 60–90 range. It's not unusual for a patient with an eGFR of, say, 72, to be classified as

having CKD stage G2 based on that result alone. “Those patients don’t have kidney disease unless they have a marker of kidney damage,” such as albuminuria or an abnormal kidney biopsy.

“I’ve reviewed papers in the peer-reviewed literature that make this error,” reports Dr. Vassalotti, “and I also have been asked this question a lot and see patients” in similar situations. “They may just have a level of kidney function in that range, but may not have evidence of kidney disease.”

It’s also time to banish microalbumin, a test name that can trip up physicians trying to order urine albumin. Says Dr. Vassalotti: “I get calls from people: *Where is the test? I can’t find it.* They look under U for urine, they look under A for albumin. They can’t find it because it’s under microalbumin. It sounds silly, but for busy clinicians efficiency is paramount.”

The name itself is confusing. Some might think, incorrectly, that microalbumin has something to do with the size of albumin, or that it refers to a specific range (because 30–300 mg/g is sometimes called microalbuminuria). Dr. Vassalotti suggests using an alias to ensure having a legacy of the previous tests—something welcomed by many physicians.

The initial impulse for the term may have been good, Dr. Fleming says, when labs struggled to measure urine albumin. Laboratorians invented the term to account for the enhanced sensitivity needed to analyze the smaller amount of albumin found in urine versus blood. “It’s not that there’s a tiny little urine albumin molecule,” he says with a laugh. But with more sophisticated methods now in use, “We don’t need to make that designation anymore.”

The urine test is more fraught than eGFR, in part because it answers to many names. Some hospitals call it urine albumin. In some institutions physicians can simply order a urine albumin-creatinine ratio; at others, they have to order urine albumin separately from the urine creatinine. “And then there’s confusion because some people will order a urine protein instead of a urine albumin,” Dr. Vassalotti says.

As noted, there’s very little new in any of this. Much has already been published in guidelines from KDIGO and KDOQI, dating back as early as 2013.

Dr. Rocco walks back the history even further. When KDIGO refined a set of guidelines developed in 2002 by the National Kidney Foundation for the management of CKD, it built on the idea of dividing kidney disease into stages and called for assessing not only the presence of proteinuria but also its severity.

“So with today’s focus on prevention, we want to identify patients both from an eGFR standpoint as well as a urine protein standpoint, because that tells us how aggressive to be in managing these patients,” Dr. Rocco says.

It’s not that primary care providers aren’t aware of the guidelines, Dr. Rocco says. In fact, they’re probably aware of too many guidelines, from endocrinology and rheumatology to infectious disease and cardiology. “If you’re a primary care physician, you’re being bombarded.”

Most physicians know to order creatinine in patients with diabetes or hypertension, Dr. Rocco says, given that it’s part of a routinely ordered metabolic profile. “You would think it would be common sense,” he says.

Part of the problem, he adds, is that non-nephrologists aren’t always aware of when to screen or refer. Numerous studies show that patients who are referred late to a nephrologist progress faster to end-stage renal disease and tend to have worse outcome once they begin dialysis, Dr. Rocco says. There is also a fair percentage of patients who are so-called gatecrashers, who see a nephrologist only when they are at end stage.

Change, like voting habits, waxes and wanes and often requires fresh steps to revitalize—think registering voters at the DMV. Even leaders like Dr. Vassalotti struggle. At large academic systems, “we’ve had less success” trying to implement the kidney profile.

The first step might be to line up the leadership in each area, says Dr. Vassalotti—laboratory, administrative,

nephrology, and primary care leadership. All need to see that kidney disease is a problem, and helping them see that could help bring about change.

It's partly an institutional issue, Dr. Rocco agrees, citing a need for clinical pathologists to talk to hospital administrators about the need to add the kidney profile to testing menus. Beyond that, clinical pathologists and nephrologists need to educate primary care providers—physicians, physician assistants, and nurse practitioners—about the value of the profile versus a creatinine level.

Dr. Fleming says it's the laboratory's responsibility to educate physician colleagues about the CKD-CVD-diabetes triad. "I have no qualms about making that statement," he says. "It is pathologists and the laboratory who must herald that trumpet." Currently, he says, many primary care practitioners think CKD is the province of nephrologists, "that when your patient has almost no filtration left they're referred, when in fact they should be referred much earlier. You need to drive home the message that while kidney disease may not be preventable, you can certainly slow its progress."

The typical primary care provider is inundated with patients, Dr. Miller says, but if they know what tests to order, they'll order them. Providing that education about the kidney profile "is where we as laboratorians, as well as our physician colleagues, need to put more energy." He also suggests that the CAP could provide materials to help pathologists engage with colleagues on the topic—"How to go forth and do good," as he puts it. "I'd appreciate concrete guidance," he adds, conceding that while he talks regularly with nephrologists at Virginia Commonwealth about testing, he has fewer conversations with GPs and others.

"You don't need to convince nephrologists," Dr. Miller continues. But "Laboratory directors need to reach out to their primary care physician colleagues and recommend that we introduce the kidney profile," he says. The basic message is not that complicated: "If a patient is suspected of having diabetes, or has been diagnosed with diabetes, order a kidney profile. If a patient has hypertension, order a kidney profile. If a patient has a family history of kidney disease, order a kidney profile."

Dr. Vassalotti would like to see labs consider linking results to educational materials from groups such as the NKF, either on the clinical or patient awareness side.

The CDC reports that chronic kidney disease affects 15 percent of American adults. But, Dr. Vassalotti rues, that has not been a call to action in and of itself. "One of the most important things I've learned in the last two decades is that population health for kidney disease works best if the intervention is integrated into an existing but related chronic disease program. If you start talking kidney, people fall asleep. Their eyes glaze over. You have to talk about population health for diabetes and how kidney disease fits into that. Or population health for hypertension, and how kidney disease fits into that, or cardiovascular disease, or obesity."

Dr. Rocco reports good news on one front: The FDA has acknowledged (Levey AS, et al. *Am J Kidney Dis*, article in press) that change in urinary excretion of albumin could be used as a marker of risk for progression of kidney disease in clinical trials. "For the FDA to say urine albumin is important, that's really a big deal."

LabCorp has been offering a combination of eGFR and uACR for well over a decade, Dr. Fleming says. "And for every creatinine result in any panel, we automatically attach calculation for the eGFR. It's very easy to do."

LabCorp has also dropped the term "microalbumin" and replaced it with "urinary albumin," having taken the initial steps to notify clients more than a year ago. "We thought that was going to raise some eyebrows, that we'd get pushback from clients who've been so used to the term over many, many years. But I don't think we've received one call."

Dr. Miller suspects that one stumbling block may be the current lack of a CPT code for the kidney profile.

"But that shouldn't be a barrier," he continues. "We can offer order sets that include reimbursable tests. We just have to bill for each individual test. So I don't personally see this as that big of a hurdle."

Dr. Fleming agrees. The eGFR, a calculation, is not currently reimbursed. And while LabCorp is trying to address that, through its corporate coding group, “We do get paid for the tests that are performed.”

Few observers seem confident that CPT reimbursement will be forthcoming anytime soon, if at all. Perhaps it doesn’t matter. “The calculation does not have a lot of cost associated with it, but it has tremendous value in terms of patient care,” says Dr. Fleming. “We will always provide a test that has medical benefit to the patient. I think any laboratory would do that—we always attempt to improve the clinical outcome for the patient. These calculations are necessary for appropriate patient care.”

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