The CKD Classification System in the Precision Medicine Era

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Introduction
“Tonight, I’m launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes—and to give all of us access to the personalized information we need to keep ourselves and our families healthier” (President Barack Obama, State of the Union Address, January 20, 2015).

The underlying concept behind the Precision Medicine Initiative is that disease prevention and treatment strategies must take individual variability into account (1). Here, we argue that the current CKD classification system is antithetical to this burgeoning initiative.

Imprecision: The New Reality
It was a typical bustling morning at an urban academic ambulatory clinic, with the nephrology attending awaiting the onrush of fellows and residents, hoping that she would soon hear the trainees efficiently establishing a tailored diagnostic and treatment plan to address each patient’s kidney disease. “My patient has stage 3 CKD,” reported the first fellow as he moved through a checklist of metabolic abnormalities associated with renal tubular dysfunction. “My patient has CKD 4,” declared another trainee as she sought guidance for managing her patient’s anemia. Iterations of CKD after CKD followed all morning.

Noble Intent
In 2002, the nephrology community awoke to a new classification for kidney diseases. The National Kidney Foundation-sponsored Kidney Disease Outcomes Quality Initiative (KDOQI) Working Group had just published a set of guidelines regarding the definition, classification, and evaluation of CKD (2). No longer would we sift through poorly defined and nonspecific terms, such as chronic renal failure, renal insufficiency, renal dysfunction, or chronic renal disease (3). We now had a unifying classification scheme that categorized chronic diseases of the kidneys into five stages on the basis of the eGFR.

Indeed, the ability to describe with some precision, irrespective of patient or provider influences, the extent of an illness or condition can provide a foundation from which to develop therapeutic strategies and implement action plans. Dissemination of the initial KDOQI guidelines and the subsequent Kidney Disease Improving Global Outcomes revised guidelines in 2012 (4) generated substantial optimism for spreading awareness and facilitating communication about kidney diseases among the nephrology community, other health care providers, and the general public. Importantly, CKD classification paved the way for critical insight into the incidence and prevalence of kidney diseases in the United States and abroad (5,6). Moreover, as evidenced by increases in kidney disease awareness (from 4.7% to 9.2% among persons with CKD stages 3 and 4 in the United States), the nephrology community had established a solid platform from which to message the public on the risk factors, manifestations, prevention, and treatment of kidney diseases (7). Clinically, the KDOQI staging system formed the basis of a revised classification that integrated eGFR and proteinuria (the strongest determinants of progression to ESRD) and provided clinicians with an important framework to anticipate complications, such as anemia and mineral and bone disorders, and consider education and planning for ESRD treatment (2,8). Introduction of the CKD terminology further provided a means to compare processes and outcomes across diverse populations and health systems, including data collected from routine clinical care, cohort studies, and clinical trials (3,9). Through such collaboration, for example, we learned about the important associations of kidney diseases and cardiovascular risk (10). We further moved from descriptive studies to predictive models that provided accurate estimates of the risks of progressing to ESRD (11).

Chronic Renal Confusion
Unfortunately, confusion and questions about the utility of the CKD classification system in caring for individual patients are growing (3). Almost from the outset, several thoughtful voices in nephrology had expressed concerns about the conceptual foundations of the CKD classification system (12–15). Now, a deluge of ever–evolving GFR–estimating equations and conflicting declarations of the size of a CKD epidemic have confused policymakers, medical professionals, and patients alike (16–19). In particular, the absence of age adjustments has cultivated growing frustration...
among clinicians about how best to advise their older patients—most with modest, stable reductions in eGFR—about their kidney disease (20). This has led some to ask the question, “Why are we even thinking about this as a disease?” (21). Confusion among patients and care providers has been augmented by revisions to CKD classification that now do not fully count stages 1 and 2 CKD as CKD.

**CKD in the Precision Medicine Era**

Although useful for epidemiology, lumping all kidney diseases together irrespective of etiology simply makes little sense for optimizing clinical care, something that every clinician knows intuitively. We illustrate four hypothetical case scenarios (Figure 1)—an otherwise healthy elderly woman; a young man with refractory hypertension who, on genotyping, is homozygous for apolipoprotein L1 (APOL1) risk alleles; a middle-aged woman with type 2 diabetes mellitus and multiple comorbidities; and a young man with biopsy–proven membranous nephropathy and severe nephrosis. Each would be classified as having stage 3 CKD with approximately the same eGFR, but it is patently obvious that virtually every aspect of clinical decision-making—such as ordering appropriate diagnostic tests, assessing prognosis, use of targeted therapeutics, frequency of required follow-up, and supportive testing—would greatly differ in caring for these four individuals. Additionally, if we had kidney tissue available to examine using modern molecular techniques, it would be abundantly clear that there is heterogeneity of disease mechanisms along with heterogeneous clinical presentations. We fool ourselves by lumping these scenarios into the same disease category, and we sell ourselves short to the rest of the medical community by suggesting that care for highly complex patients can be reduced to simple one–or two–dimensional algorithms.

**Limitations from a Reductionist Approach**

Chronic diseases of the kidney range from rare inherited disorders, such as Fabry disease, to more common acquired entities, such as diabetic kidney disease. Despite the myriad clinical phenotypes and histopathologic subtypes, even within, for example, diabetic kidney disease, this diverse collective is viewed similarly when estimates of glomerular filtration align. Contrast this approach with that of multiple myeloma, a diagnosis that prompts routine cytogenetic studies, such as fluorescent in situ hybridization, to guide additional diagnostics, therapeutics, and research. Classifying kidney diseases on the basis of eGFR further ignores the complexities of renal function. Unique transporters and cell structure of each nephron segment work in concert to maintain homeostasis (22). Moreover, eGFR is a poor correlate for the concentrations of a broad range of uremic retention solutes (23,24). Marked albuminuria and severe glomerular lesions can also develop in the absence of reductions in eGFR, most notably in diabetes mellitus but also in a broad range of glomerular diseases, such as minimal change disease, membranous nephropathy, and FSGS (25,26). Nearly three decades ago, Bohle et al. (25) astutely observed that “this paradoxical observation”—lack of serum creatinine elevations in the setting of severe glomerular lesions—occurred when “the post-glomerular capillary bed was not compromised.” Few in our field now remember such nuanced observations.

Let us also remember the lessons that we learned from great renal physiologists, like James Shannon and Homer Smith, who taught us that the kidney is not just a simple excretory organ that eliminates waste products but is the organ primarily responsible for maintaining metabolic homeostasis or the milieu interior for the entire organism. We need to go back to embracing the beauty and complexity encompassed in the structure and function of the entire mammalian kidney, including a multitude of different cell types and an incredibly complex and beautiful architecture, and appreciate how the kidney integrates a multitude of transporters with known and unknown function to maintain homeostasis.

Although we lament our scientific community’s paucity of clinical trials and breakthrough studies compared with other disciplines, such as cardiology and oncology (27), we remain steadfast with our reductionist approach. Whether the all–encompassing term CKD now impoverishes our profession and frustrates development of a deeper understanding of kidney function in health and disease is a question that the nephrology community needs to consider. We now frequently ignore the diverse etiologies and types of kidney diseases in favor of the CKD terminology to the extent that many professionals now believe that CKD represents an actual diagnosis. Perhaps our patients know better: kidney disease awareness among persons with moderately or severely reduced eGFR (<60 ml/min per 1.73 m²) remains remarkably low (9.6%) compared with awareness of associated conditions, such as hypertension (74%) and diabetes mellitus (70%), during the same period.

To better serve our unique patients, reinvigorate interest in our profession, and innovate strategies to address the myriad of kidney diseases that we encounter in daily practice, the time has arrived to reconsider our approach. As the eminent physiologist Claude Bernard noted, “It is what we think we know already that often prevents us from learning.”

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**Figure 1. Hypothetical CKD case scenarios that illustrate clinical heterogeneity not captured by the CKD classification system.** These four individuals have similar eGFR and CKD classifications but differ widely in prognosis and appropriate treatment recommendations.
Disclosures
None.

References

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