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Percentiles of estimating glomerular filtration rate: a new personalized tool for detection of chronic kidney disease

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Detection of chronic kidney disease is based on estimated glomerular filtration rate and urine albumin-to-creatinine ratio. The latter is significantly underused, even in high-risk populations. As previously suggested, the fixed estimated glomerular filtration rate threshold of 60 ml/min per 1.73 m^2 is potentially misleading. In this issue of *Kidney International*, Yang *et al.* used age- and sex-adjusted estimated glomerular filtration rate percentiles to more accurately identify individuals at high risk for kidney failure and death. By enhancing albumin-to-creatinine ratio testing, this approach could improve chronic kidney disease detection.

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Chronic kidney disease (CKD) affects between 5% and 10% of the population, though these figures can vary according to the populations and definitions considered. In the vast majority of cases, CKD is a silent disease, with symptoms appearing only at the (very) late stages. It is a truism that, by the time renal failure occurs, it is too late for prevention. In this context, CKD early detection relies primarily on biological parameters. Among these, serum creatinine (mainly used in equations to calculate the estimated glomerular filtration rate [eGFR]) and urine albumin excretion (most often measured as the urine albumin-to-creatinine ratio [ACR]) are simple, analytically robust, and inexpensive markers. It is of paramount importance to test and interpret these 2 variables in conjunction.[1] However, ACR is underused, whereas eGFR interpretation might be currently oversimplified. The debate about systematic detection of CKD in the general population using ACR and eGFR remains unresolved, but there is little doubt about the value of testing these 2 parameters in high-risk populations such as individuals with hypertension, diabetes, or a family history of kidney disease.[1,2] Here, we will discuss how and how often CKD screening is realized rather than an in-depth examination of the appropriate target population.

ACR is still underused

As a matter of fact, ACR is, however, tested far too infrequently, even in high-risk populations. Recent data on US type 2 diabetic patients reveal that only 50% of these patients are tested annually for albuminuria.[3] In the current issue of *Kidney International*, Yang *et al.*[4] present compelling epidemiological data from Stockholm in Sweden, that is, the Stockholm CREAtinine Measurements (SCREAM) project. Of note, clinical chemistry, especially nephrology-oriented, is indebted to this country, as Otto Folin was a pioneer in measuring serum creatinine, and Ander Grubb discovered cystatin C. Sweden is a high-income country with an excellent health system, also recognized for the quality of its registers and epidemiological data (as it is for the SCREAM project). Despite this favorable environment, only 39% of individuals with CKD (defined according to the Kidney Disease Improving Global Outcomes [KDIGO] guidelines by an eGFR below 60 ml/min per 1.73 m^2) have been tested for ACR within 1 year before or after GFR estimation in SCREAM. Testing rate was higher in CKD subjects with diabetes (64%) and hypertension (44%) but far from optimal, whereas in the absence of these comorbid conditions, the rate of testing was only 28%.[4] Once again, this

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relatively low testing rate is not specific to the SCREAM study, as, in many epidemiological studies on CKD, the ACR testing is frequently desperately low. We must thus question why ACR is underused, although measuring ACR is very simple, requiring just a random urine sample—in a sense, it is even easier than testing serum creatinine. The CKD staging based on ACR (into 3 stages, A1–A3) is well established, and there is little debate in the literature on this definition,[1] which is not the case for the eGFR-based CKD definition.[5,6] The association between increased ACR and outcomes is strong and linear, and a normal reference value (ACR below 30 mg/g) is unequivocally accepted.[1] Again, this is not the case for eGFR, as its association with mortality is U-shaped and the "normal" eGFR range that should be used as the reference remains debated.[6] In personalized risk scores for predicting kidney failure, such as the Kidney Failure Risk Equation, both eGFR and ACR are included, but the mathematical weight of ACR is preponderant.[7] Importantly, albuminuria is widely recognized as the most valid surrogate marker in nephrological trials for testing new drug efficacy (ACR is the primary end point), even more so than eGFR slopes that are more considered as a secondary end point. Last but not least, the 2 first-line therapies recommended to delay CKD progression—sodium-glucose cotransporter-2 inhibitors and renin-angiotensin system inhibitors—are particularly efficient in patients with high albuminuria, whereas the level of evidence for kidney protection is lower in the absence of pathologic albuminuria. Beyond the fact that ACR measurement is clearly still not implemented in the practice of non-nephrologists (and it is always difficult to change habits), there are some problems slowing down the wider use of ACR. Indeed, if KDIGO guidelines insist on ACR measurement, this measurement is not standardized and not available and/or reimbursed in every country. Proteinuria measurement or albuminuria estimation with urinary strips is then a valid alternative, but this might also be viewed as a bit confusing, especially by non-nephrologists. If ACR on a random urine sample is valid and adequately promoted by recommendations, there are sometimes false-positive and -negative results. To simplify the message to non-nephrologists, it can be stated that abnormal test results must be systematically confirmed by a second quantitative measurement. In case of uncertainty, the patient should be referred to a nephrologist, who will make the final decision based on the interpretation of the first-morning urine sample or, still better, on the 24-hour urine collection.[1]

Patients with CKD are better identified with percentiles

At this juncture, we can briefly summarize the current discussion in the literature regarding the GFR threshold that should be used to define CKD. Until now, KDIGO guidelines have considered all patients with eGFR below 60 ml/min per 1.73 m^2 as having CKD.[1] Proponents of an age-adapted definition argue that GFR physiologically declines with age and that a fixed threshold will artificially increase the number of CKD diagnoses in older individuals while decreasing detection in younger people.[5,6] This concept is effectively illustrated by Yang *et al.*,[4] who established percentiles of eGFR in their population. One might object that the SCREAM population was not strictly healthy. However, the authors used statistical tools (they account for the inverse probability of being tested) to make their sample more representative of the general population. Moreover, the percentiles they describe were very similar to those established in a more strictly defined healthy European population, recently published in *Kidney International* (and in which SCREAM data were included).[8] Although minor variations in eGFR percentiles are observed between males and females and across different eGFR equations, the overall trend remains consistent: GFR percentiles decline with aging. This observation has significant implications for CKD diagnosis. Indeed, in many subjects around 40 years of age (and also in subjects younger than 40 years who have been excluded from the analysis), individuals whose eGFR falls below the 10th percentile (P10) may still have an eGFR exceeding 60 ml/min per 1.73 m^2. This suggests that the current fixed threshold definition may underestimate the true prevalence of CKD in this younger population. Conversely, many subjects older than 60 or 65 years with an eGFR below 60 ml/min per 1.73 m^2 remain well above the corresponding P10 of their age category, implying that the fixed threshold potentially overestimates the real CKD prevalence in older individuals.[4,8] Moving from a fixed GFR threshold to an age-adapted or percentile-adapted threshold will thus impact CKD prevalence, as this has been illustrated, notably in *Kidney International*.[9] Crucially, Yang *et al.*[4] also showed that subjects in the lower percentiles (under P25 and even more under P5) have a significantly higher risk of kidney failure with replacement therapy and death. Using percentiles for CKD definition better reflects the physiological behavior of GFR with aging, while simultaneously identifying individuals with a higher risk of worse outcomes.[4,6]

A new strategy to detect CKD?

The work of Yang *et al.* could pave the way for a new strategy in CKD detection and prevention. We should take advantage that eGFR is frequently tested in the general population to enhance albuminuria testing: in the SCREAM project, 40% of the Stockholm population had at least 1 creatinine measurement per year, and 80% of the population was represented at least once during the study period (2006–2021).[4] We now have all the necessary tools to determine a patient's eGFR percentile according to their age and sex, as such data are available on every continent with different eGFR (or even measured GFR) methods.[6] In 2026, with the help of a laboratory system, the argument of the percentile complexity no longer holds up. One can easily imagine that laboratories

automatically join a percentile result to the eGFR estimation and could add an alert such as follows: "Your patient's eGFR is at XXth percentile for his/her age and sex, which is under P25. We suggest testing ACR." Indeed, thanks to Yang's work, we know that the risk of worse outcomes is significant once eGFR falls below P25. Keeping in mind that, once again, only 26% of subjects with eGFR below the P25 have been tested for albuminuria, the authors also showed that they have a higher rate of pathologic albuminuria (A2 or A3 stage).[4] This could be a justifiable reason to measure ACR in these subjects to better clarify the relative risk compared with the healthy population and certainly to evaluate the personalized absolute risk with scores like Kidney Failure Risk Equation (this score could also be automatically calculated by laboratories, once ACR and creatinine are available!). Based on the eGFR and ACR results, the decision on whether to initiate first-line therapies can be made (or not). For the moment, we still do not know whether P25 is too liberal, or whether a threshold closer to P10 or P5 would be more effective, notably in terms of abnormal albuminuria detection. Future studies are necessary to evaluate the efficacy and cost-effectiveness of such new strategies. Indeed, the current *status quo* regarding the detection and prevention of CKD is unsatisfactory, especially because we now have the tools for both personalized detection and management.

DISCLOSURE

PD is a consultant for Nephrolyx. The other author declared no competing interests.

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The expanding role of complement inhibitors in the treatment of IgA nephropathy

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Complement activation has emerged as a key driver of IgA nephropathy, catalyzing the rapid expansion of complement-targeted therapies. Barbour *et al.* reported promising phase 2 results of sefaxersen, an antisense inhibitor of Factor B, showing reduced proteinuria, improved hematuria, and sustained alternative-pathway inhibition. Nonetheless, as the therapeutic landscape expands, advancing precision medicine in IgA nephropathy will require defining appropriate patient profiles and predictors of therapeutic response to guide individualized treatment.

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Over the past decade, the therapeutic landscape for IgA nephropathy (IgAN) has undergone substantial evolution, with the emergence of novel therapies providing renewed optimism for enhanced patient outcomes. This progress has been driven by major advances in our understanding of IgAN pathogenesis and, in particular, the central role of complement activation as a mediator of kidney injury.[1,2] The current "4-hit" model describes how galactose-deficient IgA1 (gd-IgA1), anti–gd-IgA1 autoantibodies, and circulating immune complexes ultimately deposit in the mesangium to trigger downstream inflammation. Yet deposition alone does not fully explain the variable clinical trajectories observed in IgAN. It is the subsequent engagement of innate immune pathways, particularly the complement system, that amplifies tissue injury and determines progression for many patients.

Complement activation in IgAN is complex and involves both the

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