

## DISCLOSURES

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See related articles, "Postoperative Biomarkers Predict Acute Kidney Injury and Poor Outcomes after Adult Cardiac Surgery" on pages 1748–1757, and "Postoperative Biomarkers Predict Acute Kidney Injury and Poor Outcomes after Pediatric Cardiac Surgery," on pages 1737–1747.

## Screening for Proteinuria: A Tool for Predicting Rapid Declines in Kidney Function?

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The importance of chronic kidney disease (CKD) as an independent risk factor for cardiovascular disease (CVD) and mor-

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tality is supported by a substantial body of literature.<sup>1–5</sup> In addition, recent studies demonstrate the joint predictive ability of both level of kidney function and proteinuria for CVD and mortality<sup>6–9</sup> and ESRD<sup>9–14</sup> in several large populations. Although these relationships guide in the identification of individuals at high risk for adverse outcomes, it has been argued that further discrimination could be achieved by looking not only at one-time assessments of kidney function and damage, but also at changes in estimated GFR (eGFR) over time as predictors of outcome.<sup>15</sup>

Rapid decline of kidney function, defined either by absolute or annual percentage change in eGFR, can be assessed in clinical practice and in research studies. Rapid changes in eGFR clearly denote an increased risk for progression to ESRD, and several recent studies have evaluated how well such rapid declines predict CVD and mortality, as well. A loss of kidney function greater than 3 ml/min per 1.73 m<sup>2</sup>/yr among older individuals enrolled in the Cardiovascular Health Study was significantly associated with CVD and mortality even after adjustment for baseline eGFR.<sup>16,17</sup> These studies, however, did not have data on proteinuria. Additionally, in the Cardiovascular Health Study investigation that evaluated risk of CVD after rapid kidney function decline,<sup>17</sup> the relationship was strongest among those with established CKD and only of borderline significance among those without CKD at baseline. Similar findings were reported from the Atherosclerosis Risk in Communities Study, in which participants with the greatest annual percentage change in eGFR ( $\geq 5.65\%$ ) had significantly increased risk for coronary heart disease and all-cause mortality after adjustment for baseline kidney function but only among those with an initial eGFR  $< 90$  ml/min per 1.73 m<sup>2</sup>. A similar relationship was observed for all-cause mortality, but not coronary heart disease, after adjustment for multiple time-updated covariates. A report from the Heart and Estrogen/Progestin Replacement Study failed to detect an independent relationship between serum creatinine and CVD outcomes after adjustment for baseline creatinine level.<sup>18</sup> Finally, data from a Department of Veterans Affairs cohort with rheumatoid arthritis and early stage 3 CKD demonstrate an increased risk for mortality (hazard ratio, 1.54; 95% confidence interval, 1.30 to 1.82) associated with an eGFR decline  $> 4$  ml/min per 1.73 m<sup>2</sup>/yr compared with 0 to 1 ml/min per 1.73 m<sup>2</sup>/yr without adjustment for baseline kidney function or level of proteinuria.<sup>19</sup>

Few studies compare the predictive value of change in kidney function to baseline measures of kidney function and damage for predicting adverse outcomes. Two studies demonstrate that longitudinal assessments of change in kidney function are superior to baseline kidney function in predicting CVD and all-cause mortality among patients with hypertension and diabetes.<sup>20,21</sup> It is unknown, however, if time-updated adjustment for kidney function and damage perform similarly.

In this issue of *JASN*, Clark *et al.*<sup>22</sup> propose a strategy to detect those at risk for rapidly declining kidney function by

combining known clinical risk factors with screening tests for proteinuria. Among 2,574 predominantly Caucasian participants of this community-based, prospective cohort study, 8.5% had rapidly declining kidney function defined as a  $> 5\%$  annual decline from baseline eGFR. An increased risk of rapidly declining kidney function was detected for those aged  $\geq 60$  years; those with hypertension, diabetes, and a history of CVD; and those with evidence of albuminuria or proteinuria (all relative risks greater than 1.5). Compared with elevated levels of albuminuria (defined for men as  $> 17$  mg/g and for women as  $> 25$  mg/g), urine dipstick protein levels  $\geq 1$  g/L were stronger predictors of rapidly declining kidney function in this population. Use of a dipstick protein level  $\geq 1$  g/L as a screening test would detect one case of rapidly declining kidney function for every 2.6 patients followed with serial eGFR measurements. Further efficiency was gained by restricting use of the screening test to those with existing risk factors including age  $\geq 60$  years, hypertension, diabetes, and CVD. The probability of identifying rapidly declining kidney function in this high-risk population increased from 13 to 44% after implementation of the screening test, and one case would be detected for every 2.3 patients followed with annual assessments of kidney function.

Current evidence suggests that rapidly declining kidney function independently predicts CVD and mortality, especially among those with eGFR  $< 90$  ml/min per 1.73 m<sup>2</sup>. Therefore, a strategy to predict individuals likely to experience these rapid declines may be informative and beneficial.

We now ask ourselves: Does this proposed screening strategy indeed improve our ability to detect rapid progressors? Clark *et al.* report a percent agreement of 91% for a dipstick protein  $\geq 1$  g/L to identify correctly who within this population of community dwellers will experience rapidly declining kidney function. Although the authors did not report the sensitivity of using a dipstick protein level  $\geq 1$  g/L to detect rapidly declining kidney function, it was  $< 20\%$  on the basis of data presented in their paper. With such a high false-negative rate, this screening strategy does not appear to meet one of the core criteria outlined by Wilson and Jungner<sup>23</sup> for an effective screening test—namely that a suitable test be available to indicate the early phase of the disease. Additionally, in this population, the global probability of not experiencing rapid decline in kidney function is 91%. After application of the screening criteria, the negative predictive value increases only marginally to 93% despite the high level of specificity of the testing strategy at 97%. Whether or not the proposed screening strategy is more cost-effective than following all individuals with serial eGFR measurements requires a comprehensive cost-effectiveness analysis.

Despite the poor test characteristics of the screening strategy, the detection of a subset of rapid progressors could still hold clinical relevance. For example, if the majority of those identified to have rapidly declining kidney function were unlikely to otherwise be referred to a nephrologist for care, the

strategy could be cost-effective. That remains to be seen. The authors cite the widespread availability and use of dipstick protein tests as a benefit for implementing this strategy. This, in fact, is also a reason why this screening strategy may have limited clinical value. Once a primary-care physician recognizes that a patient is excreting over a gram per liter of protein in their urine, regardless of current level of kidney function or future trajectory of kidney function decline, they are likely to refer the patient to a nephrologist. This specialist care is likely to involve repeated assessments of kidney function and, importantly, therapies to reduce the risk of progressive CKD and subsequent sequelae. Even if referral to a nephrologist occurs only when eGFR falls below 90 ml/min per 1.73 m<sup>2</sup>, 74% of those who screened positive in the study by Clark *et al.* would immediately receive specialized care.

Finally, there is a paucity of studies directly comparing cross-sectional measures of kidney function and damage to longitudinal changes in kidney function to predict adverse clinical outcomes. Future studies should conduct these comparisons in the same population, in addition to exploring alternative strategies for better identifying those with rapidly declining kidney function.

One noteworthy limitation of Clark *et al.* is the definition of rapidly declining kidney function. It is well known that the Modification of Diet in Renal Disease (MDRD) equation underestimates GFR at levels greater than 60.<sup>24</sup> In addition, change in eGFR over time essentially breaks down to change in serum creatinine over time when using the simplified MDRD equation. Few studies have assessed the accuracy of eGFR slopes, but one was conducted using data from the MDRD study for both estimated and measured kidney function decline. The study demonstrated that eGFR slope tends to underestimate measured GFR slope and found that 42% of the population had absolute discrepancies between the two slopes  $\geq 2$  ml/min per 1.73 m<sup>2</sup>/yr.<sup>25</sup> In addition, it is well established that fewer eGFR measurements increase the variability of slope estimates and may cause misclassification of rapidly declining kidney function. Although Clark *et al.* only included individuals with three or more measures of eGFR in their study, it is noteworthy that the median and lower bound of the interquartile range of number of eGFR measures were 5 and 3, respectively, among those defined as having rapidly declining kidney function compared with 7 and 5 for those without rapid decline. This increased variability in slope estimates among the rapid progressors adds to the reasons why interpretation of the study's findings is difficult.

Rapidly declining kidney function holds promise as a predictor of adverse outcomes, especially among patients with eGFR <90 ml/min per 1.73 m<sup>2</sup>. Future studies should directly compare rapid declines in eGFR to joint measures of baseline kidney function and damage to evaluate their respective contributions to the prediction of outcomes. If substantiated, additional explorations into finding rapid progressors are warranted, and cost-effectiveness analyses should be performed.

## DISCLOSURES

None.

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See related article, "Dipstick Proteinuria as a Screening Strategy to Identify Rapid Renal Decline," on pages 1729–1736.

## The Rejection Barrier to Induced Pluripotent Stem Cells

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Tissue regeneration and organ development from patient-induced pluripotent stem cells (iPSCs), created through cellular reprogramming,<sup>1,2</sup> are new approaches for resolving the inadequate number of organs available for transplantation, including the kidney. Because iPSCs are derived from the patient, self-tolerance of the tissues or organs made from these cells is expected. However, recent work by Zhao *et al.*<sup>3</sup> reveals some previously unappreciated wrinkles regarding potential immunogenicity of iPSCs that raise issues regarding future use of iPSCs in the clinical setting.

Since the first successful kidney transplantation in 1954, the field of organ transplantation has prolonged many lives worldwide. However, despite the technical improvements in organ transplantation and the coordinated efforts to maximize organ donation, more than 89,000 Americans await kidney transplantation due to the paucity of available organs.<sup>4</sup> New technologies such as tissue regeneration and organ development from stem cells (from embryonic or adult sources) offer promise not only to meet the demand for organs but also to aid the repair of injured organ tissues.<sup>5–9</sup>

Patient-specific pluripotent stem cells may be one solution for innumerable medical conditions requiring cell- or tissue-based replacement therapies. Unfortunately, embryonic pluripotent stem cells (ESCs) can be derived only during a specific window of time during early development, and further, to obtain such cells without affecting the embryo has not yet been proven in humans and raises ethical concerns. Takahashi and Yamanaka, and others, have shown that expression of a transcription factor cocktail consisting of *Oct4*, *Sox2*, *Klf4*, and *Myc* can revert terminally differentiated cells to a pluripotent state, both in mice<sup>10</sup> and humans,<sup>11,12</sup> a technique called reprogramming, therefore permitting adult tissues to serve as a stem-cell source.

In the mouse, these iPSCs are similar to ESCs in gene expression profile, the ability to form all three germ layers in teratoma assays, and the ability to contribute to germline-competent chimeric mice.<sup>13</sup> Similarly, human iPSCs derived from diverse tissues also give rise to teratomas in nude mice, demonstrating the pluripotency of human iPSCs.<sup>14</sup> Although original reprogramming methods used viral

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