Risk Factors for CKD Progression
Overview of Findings from the CRIC Study

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Abstract
The Chronic Renal Insufficiency Cohort (CRIC) Study is an ongoing, multicenter, longitudinal study of nearly 5500 adults with CKD in the United States. Over the past 10 years, the CRIC Study has made significant contributions to the understanding of factors associated with CKD progression. This review summarizes findings from longitudinal studies evaluating risk factors associated with CKD progression in the CRIC Study, grouped into the following six thematic categories: (1) sociodemographic and economic (sex, race/ethnicity, and nephrology care); (2) behavioral (healthy lifestyle, diet, and sleep); (3) genetic (apoL1, genome-wide association study, and renin-angiotensin-aldosterone system pathway genes); (4) cardiovascular (atrial fibrillation, hypertension, and vascular stiffness); (5) metabolic (fibroblast growth factor 23 and urinary oxalate); and (6) novel factors (AKI and biomarkers of kidney injury). Additionally, we highlight areas where future research is needed, and opportunities for interdisciplinary collaboration.

Introduction
CKD is a growing public health problem worldwide (1), with an estimated prevalence of 14% in the United States (2). In response to the rising epidemic of CKD, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) established the Chronic Renal Insufficiency Cohort (CRIC) Study in 2001. Since its inception, the CRIC Study has enrolled nearly 5500 participants with the purpose of identifying factors that contribute to kidney and cardiovascular disease progression, and morbidity and mortality in persons with CKD (3,4).

The CRIC Study uses the tools of clinical epidemiology to evaluate both diabetic and nondiabetic CKD. With its large and diverse population, recruited from seven clinical centers, the study addresses research questions concerning etiology, prognosis, therapy, utilization of health care services, and quality of life pertinent to CKD. CRIC is a unique resource for examining risk factors for CKD progression. In this overview, we present a more comprehensive synthesis of recent findings from the CRIC Study, specifically focusing on factors associated with CKD progression. We also discuss clinical implications and highlight directions for future research.

The CRIC Study is an ongoing, multicenter, prospective cohort study of individuals with CKD in the United States who have been followed through annual in-person visits, as previously described (3,4). The CRIC Research Network designed the study in 2001. During the first phase, which occurred between 2003 and 2008, a cohort of 3939 adults with CKD, aged 21–74 years and with an eGFR of 20–70 ml/min per 1.73 m², was successfully recruited and characterized (46% women, 42% non-Hispanic White, 42% non-Hispanic Black, and 13% Hispanic). At baseline, 86% of participants had hypertension and 47% had diabetes. During the second phase of the study, which was completed in 2013, annual follow-up of participants continued with data collection and measurements at predetermined intervals (5). During the third phase of the study, >1500 adults with less severe CKD (eGFR of 45–70 ml/min per 1.73 m²) were recruited. In the current, fourth phase, which began in 2018, the CRIC Study is increasing the diversity of the cohort by recruiting 500 American Indian and 126 Hispanic adults, while focusing data collection by incorporating novel mobile technologies to remotely collect kidney and cardiovascular data from the participants’ homes (Figure 1).

We conducted a thorough review of the literature by using the CRIC Study website publications list (www.cristudy.org), and by searching PubMed with relevant Medical Subject Heading terms, to find all publications from the CRIC Study that evaluated factors associated with CKD progression. We identified 44 articles, in which 54 factors were examined. These factors are summarized in Table 1 and are grouped into the following exposure categories: (1) sociodemographic and economic, (2) behavioral, (3) genetic, (4) cardiovascular, (5) metabolic, and (6) novel factors. Below, we present a more in-depth discussion of select publications and their contributions to the field.

Sociodemographic and Economic Factors
Sex Disparities
Sex-related disparities in CKD are well established. According to the United States Renal Data System, the...
prevalence of kidney failure is higher among men, despite a higher prevalence of CKD among women (6), suggesting that women may have slower kidney function decline compared with men, or that women are more likely to die before progressing to kidney failure. The extensive data collection in the CRIC Study afforded the opportunity to examine potential explanations for these disparities. At baseline, compared with men, women were more likely to have adverse risk factors, including lower socioeconomic status; higher body mass index and waist circumference; lower physical activity; higher serum phosphate, fibroblast growth factor 23 (FGF23), and LDL cholesterol levels; and lower HDL cholesterol and eGFR. Furthermore, women were less likely to report the use of cardioprotective medications. However, women experience lower rates of kidney failure (defined as receipt of dialysis or kidney transplant) than men (3.1 versus 3.8 per 100 person-years). In regression analysis, women had a 28% lower risk of kidney failure compared with men, or that women are more likely to die before progressing to kidney failure. The extensive data collection in the CRIC Study afforded the opportunity to examine potential explanations for these disparities. The protective effect of endogenous estrogens has been proposed as a potential explanation for these disparities (8).

Racial/Ethnic Disparities
Racial/ethnic minority populations in the United States are more likely to experience CKD progression compared with White individuals (6). CRIC provides an opportunity to evaluate health disparities in CKD outcomes in greater depth. During a median follow-up of 6.6 years, Hispanic and non-Hispanic Black individuals experienced an almost two-fold higher rate of kidney failure compared with non-Hispanic White individuals (9). In multivariable analyses using death as a competing risk, the risk of kidney failure was similar in Hispanic compared with non-Hispanic White individuals (hazard ratio [HR], 1.32; 95% confidence interval [95% CI], 0.96 to 1.81), and in Hispanic compared with non-Hispanic Black individuals (HR, 0.94; 95% CI, 0.71 to 1.25) after adjustment for sociodemographic (e.g., age, sex, education, income) and clinical characteristics (e.g., BP, diabetes, eGFR, and proteinuria). These findings have important clinical implications because the disparity in CKD progression among these racial/ethnic minority populations is explained, in part, by potentially modifiable risk factors. As detailed below, the APOL1 gene plays an important role in CKD progression among individuals with African ancestry.

Nephrology Care
CRIC Study participants undergo extensive data collection regarding health insurance and access to health care, and there is ongoing work evaluating the role of these factors in CKD progression (defined as 50% decline in eGFR from baseline or kidney failure). Not surprisingly, the two thirds of individuals who reported nephrology care were more likely to be on renin-angiotensin-aldosterone system (RAAS) blockers. However, prior nephrology care was not associated with lower CKD progression (10). Potential reasons for this finding include the overall high achievement of guideline-recommended treatment goals among CRIC participants (making significant differences between patients with and without nephrology care difficult to appreciate), or other factors such as medication copayment or transportation, which were not measured.

Behavioral Factors
Healthy Lifestyle
Ricardo et al. (11) evaluated how healthy behaviors (i.e., not smoking, healthy diet, regular physical activity, and healthy weight) influence CKD progression. Having previously or never having smoked was associated with reduced risk of CKD progression compared with current smoking; however, there was no significant association with self-reported healthy diet (11). Physical activity was not associated with lower CKD progression, but those individuals who met the American Heart Association (AHA)–recommended physical activity guidelines had lower risk of death. A greater emphasis on lifestyle counseling for individuals with CKD has the potential of improving outcomes in this population. Paradoxically, individuals with a body mass index of ≥25 kg/m² had lower risk of CKD progression (11). Reasons for this finding are not clear, but similar observations have been reported by others (12).

Diet
Observational studies and clinical trials have documented that high dietary sodium and low potassium intake are associated with elevated BP (13,14). However, data on the effects of these nutrients on the risk of CKD progression are sparse and inconsistent. He et al. (15) evaluated the effect of dietary sodium and potassium on CKD progression using 24-hour urine measurements. Individuals in the highest quartile of urinary sodium excretion (≥195 mmol per 24 hours) were more likely to experience CKD progression compared with those in the lowest quartile (<117 mmol per 24 hours). High urinary potassium excretion (≥67 versus <39.4 mmol per 24 hours) was also associated with higher
Table 1. Summary of studies evaluating risk factors for kidney failure or CKD progression in the CRIC Study

<table>
<thead>
<tr>
<th>First Author</th>
<th>Risk Factor</th>
<th>Follow-Up (yr)</th>
<th>n</th>
<th>Association with Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographic and economic factors</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ricardo et al. (7)</td>
<td>Sex (women versus men)</td>
<td>6.9</td>
<td>3939</td>
<td>↓ Kidney failure risk in women versus men</td>
</tr>
<tr>
<td>Fischer et al. (9)</td>
<td>Hispanic ethnicity</td>
<td>5.1</td>
<td>3785</td>
<td>Similar kidney failure risk in Hispanic versus non-Hispanic White individuals</td>
</tr>
<tr>
<td>Ricardo et al. (10)</td>
<td>Nephrologist care</td>
<td>6.6</td>
<td>3855</td>
<td>No significant association</td>
</tr>
<tr>
<td><strong>Behavioral factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ricardo et al. (11)</td>
<td>Healthy diet, regular physical activity BMI &gt;25 kg/m², past /never smoker</td>
<td>4</td>
<td>3006</td>
<td>No significant association</td>
</tr>
<tr>
<td>He et al. (15)</td>
<td>↑ Urinary Na+, K+</td>
<td>15,807 p-y</td>
<td>3939</td>
<td>↓ CKD progression risk</td>
</tr>
<tr>
<td>Hu et al. (20)</td>
<td>Dietary patterns (DASH, aMED, HEI)</td>
<td>7</td>
<td>2403</td>
<td>↓ CKD progression risk in least versus most adherent tertile</td>
</tr>
<tr>
<td>Richard et al. (65)</td>
<td>Obese/ sedentary pattern in adults &lt;3 to &gt;5 with diabetes</td>
<td></td>
<td>5499</td>
<td>↑ CKD progression risk</td>
</tr>
<tr>
<td>Porter et al. (66)</td>
<td>↓ Healthy beverage score</td>
<td>7</td>
<td>2283</td>
<td>↓ CKD progression risk with higher scores</td>
</tr>
<tr>
<td>Schrauben et al. (65)</td>
<td>↑ Sleep fragmentation</td>
<td>4.4</td>
<td>431</td>
<td>↑ eGFR decline and kidney failure risk</td>
</tr>
<tr>
<td>Schrauben et al. (68)</td>
<td>Self-management behaviors (smoking, poor diet, physical inactivity, and uncontrolled BP)</td>
<td>3</td>
<td>3939</td>
<td>↑ CKD progression risk</td>
</tr>
<tr>
<td><strong>Genetic factors</strong></td>
<td></td>
<td></td>
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<tr>
<td>Parsa et al. (26)</td>
<td>APOL1 gene variants</td>
<td>4.4</td>
<td>2955</td>
<td>↑ eGFR decline and CKD progression risk</td>
</tr>
<tr>
<td>Parsa et al. (28)</td>
<td>SNPs in LINC00923 (RNA gene expressed in the kidney)</td>
<td>—</td>
<td>3074</td>
<td>↑ eGFR decline and kidney failure risk</td>
</tr>
<tr>
<td>Wing et al. (69)</td>
<td>DNA methylation pattern</td>
<td>—</td>
<td>40</td>
<td>No significant association</td>
</tr>
<tr>
<td>Kelly et al. (29)</td>
<td>Renin-angiotensin-aldosterone system genes</td>
<td>—</td>
<td>3013</td>
<td>↑ eGFR decline and CKD progression risk</td>
</tr>
<tr>
<td><strong>Cardiovascular factors</strong></td>
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<tr>
<td>Bansal et al. (33)</td>
<td>Atrial fibrillation</td>
<td>5.9</td>
<td>3091</td>
<td>↑ Kidney failure risk</td>
</tr>
<tr>
<td>Anderson et al. (37)</td>
<td>Time-updated ↑ systolic BP</td>
<td>5.7</td>
<td>3708</td>
<td>↑ Kidney failure risk</td>
</tr>
<tr>
<td>Thomas et al. (70)</td>
<td>Treatment-resistant HTN</td>
<td>5</td>
<td>3367</td>
<td>↑ CKD progression risk</td>
</tr>
<tr>
<td>Townsend et al. (45)</td>
<td>↑ Aortic pulse wave velocity</td>
<td>4.1</td>
<td>2795</td>
<td>↑ Kidney failure risk</td>
</tr>
<tr>
<td>Grunwald et al. (71)</td>
<td>Baseline retinopathy</td>
<td>2.3</td>
<td>1852</td>
<td>No significant association</td>
</tr>
<tr>
<td>Grunwald et al. (72)</td>
<td>Progression of retinopathy</td>
<td>3.5</td>
<td>1936</td>
<td>No significant association</td>
</tr>
<tr>
<td>Kurella Tamura et al. (73)</td>
<td>Cognitive impairment</td>
<td>6.1</td>
<td>3883</td>
<td>No significant association</td>
</tr>
<tr>
<td>Rahman et al. (74)</td>
<td>Self-reported cardiovascular disease</td>
<td>6.63</td>
<td>3939</td>
<td>No significant association</td>
</tr>
<tr>
<td>Rahman et al. (75)</td>
<td>Self-reported congestive heart failure</td>
<td>6.63</td>
<td>3939</td>
<td>↑ CKD progression risk</td>
</tr>
<tr>
<td>Rahman et al. (80)</td>
<td>Lipids</td>
<td>4.1</td>
<td>3939</td>
<td>No significant association</td>
</tr>
<tr>
<td><strong>Metabolic factors</strong></td>
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<tr>
<td>Isakov et al. (48)</td>
<td>↑ FGF23</td>
<td>3.5</td>
<td>3879</td>
<td>↑ Kidney failure risk (depending on baseline stage of CKD)</td>
</tr>
<tr>
<td>Dobre et al. (76)</td>
<td>↑ Serum bicarbonate</td>
<td>3.9</td>
<td>3939</td>
<td>↑ CKD progression risk</td>
</tr>
<tr>
<td>Scialla et al. (77)</td>
<td>↑ Net acid excretion</td>
<td>6</td>
<td>980</td>
<td>↑ CKD progression risk</td>
</tr>
<tr>
<td>Waikan et al. (50)</td>
<td>↑ Urinary oxalate</td>
<td>22,318 p-y</td>
<td>3123</td>
<td>↑ CKD progression risk</td>
</tr>
<tr>
<td>Coye et al. (78)</td>
<td>Absence of albuminuria in people with diabetes</td>
<td>6.3</td>
<td>1908</td>
<td>↑ CKD progression risk versus those with albuminuria and diabetes</td>
</tr>
<tr>
<td>Bansal et al. (79)</td>
<td>Body composition by BIA</td>
<td>7</td>
<td>3751</td>
<td>No significant association</td>
</tr>
<tr>
<td>Srivastava et al. (80)</td>
<td>↑ Uric acid</td>
<td>7.9</td>
<td>3885</td>
<td>↑ Kidney failure risk</td>
</tr>
<tr>
<td><strong>Novel factors</strong></td>
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<tr>
<td>Ashihhina et al. (81)</td>
<td>AA metabolites: 20-HETE, LOX, CYP450 metabolic pathways</td>
<td>10</td>
<td>300</td>
<td>↑ Kidney failure risk (20-HETE)</td>
</tr>
<tr>
<td>Rhee et al. (82)</td>
<td>Amino acid metabolites, acylcarnitines, dipeptides, nucleotides, and other cationic polar metabolites</td>
<td>—</td>
<td>400</td>
<td>Nominally associated with rapid CKD progression</td>
</tr>
<tr>
<td>Foster et al. (83)</td>
<td>Serum BTP and B2M</td>
<td>6</td>
<td>3613</td>
<td>↑ Kidney failure risk</td>
</tr>
<tr>
<td>Inker et al. (84)</td>
<td>BTP and B2M</td>
<td>13</td>
<td>3938</td>
<td>No significant association</td>
</tr>
<tr>
<td>Bishop et al. (85)</td>
<td>↓ Serum IGF-1</td>
<td>7.5</td>
<td>3895</td>
<td>↑ eGFR decline and kidney failure risk</td>
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</table>
risk for CKD progression (15). These findings are in contrast with previous epidemiologic studies and clinical trials documenting an inverse association between dietary potassium intake and BP in general populations (14,16), suggesting this association is more complex in the setting of CKD because of abnormal potassium homeostasis and the effect of RAAS blockers.

Healthy dietary patterns have been shown to reduce risk of incident CKD in general populations (17–19), but there is less evidence of an association with CKD progression. Using food frequency questionnaires, Hu et al. (20) calculated the Healthy Eating Index 2015, Alternate Mediterranean Diet, and Dietary Approaches to Stop Hypertension diet scores for 2403 CRIC participants. They observed an inverse association between healthy dietary scores and risk of CKD progression, with the strongest association for the Alternate Mediterranean Diet (20). In addition, a healthy beverage score—consistent with higher consumption of low-fat milk, coffee, tea; moderate alcohol; and lower consumption of 100% fruit juice, whole-fat milk, artificially sweetened beverages, and sugar-sweetened beverages—was also associated with lower risk of CKD progression (21). These findings suggest that, in addition to managing single nutrients, nutritional counseling for individuals with CKD should include assessment of, and recommendations for, overall food-based dietary patterns.

Sleep
There is increased recognition of the effect of sleep on health outcomes. Ricardo et al. (22) evaluated habitual sleep using wrist actigraphy in 431 individuals and found higher sleep fragmentation to be associated with higher risk for kidney failure. In addition, higher sleep fragmentation and shorter sleep duration were each associated with steeper decline in eGFR and increase in proteinuria over time (22). These findings suggest impaired sleep is a clinically significant, but unrecognized, risk factor for CKD progression that should be assessed by providers of patients with CKD. The deleterious effects of poor-quality sleep that might be responsible for these associations include acute increases in BP and heart rate, activation of the sympathetic nervous system, increased salt retention, and alterations of glucose metabolism (23). Future work is needed to evaluate interventions to improve sleep habits in patients with CKD and assess whether the observed association with CKD progression is causal.

Genetic Factors
The APOL1 gene has been implicated in the higher risk of CKD progression observed among African American individuals (24,25). Parsa et al. (26) examined the effects of two common sequence variants (G1 and G2) in the gene encoding APOL1 on CKD progression, using data from the CRIC Study and the African American Study of Kidney Disease and Hypertension. Black individuals in the APOL1 high-risk group had more rapid eGFR decline and higher risk of the composite kidney outcome than did White individuals, independent of diabetes status or BP level (26). Findings from this seminal study helped stimulate expansion of basic and translational research in this area. The National Institutes of Health (NIH)—sponsored, ongoing, multicenter APOLLO (APOL1 Long-Term Kidney Transplantation Outcomes Network) study will prospectively assess the effects of APOL1 nephropathy risk variants in kidney donors and recipients (27), and may define the clinical role of APOL1 testing.

A genome-wide association study performed among CRIC participants reported that four single-nucleotide

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<th>Table 1. (Continued)</th>
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<tr>
<td>First Author</td>
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<tr>
<td>Amdur et al. (85)</td>
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<tr>
<td>Liu et al. (55)</td>
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<td>Hsu et al. (56)</td>
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<tr>
<td>Hsu et al. (54)</td>
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<tr>
<td>Orlandi et al. (86)</td>
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<tr>
<td>Zhan et al. (87)</td>
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<tr>
<td>Anderson et al. (88)</td>
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</table>

CRIC, Chronic Renal Insufficiency Cohort; BMI, body mass index; Na+, sodium ion; K+, potassium ion; p-y, person years; DASH, Dietary Approaches to Stop Hypertension; aMED, Alternate Mediterranean Diet; HEI, Healthy Eating Index; SNP, single-nucleotide polymorphism; HTN, hypertension; FGF23, fibroblast growth factor 23; BIA, bioelectrical impedance analysis; AA, amino acid; 20-HETE, 20-hydroxyeicosatetraenoic acid; CYP450, cytochrome P450; B2M, β2 microglobulin; NGAL, neutrophil gelatinase-associated lipocalin; KIM-1, kidney injury molecule 1; NAG, N-acetyl-β-D-glucosaminidase; FABP, liver fatty acid binding protein; NSAID, nonsteroidal anti-inflammatory drug; CXCL12, inflammatory chemokine; NTproBNP, N-terminal pro-B-type natriuretic peptide; hsTnT, high-sensitivity troponin T.

*Kidney failure defined as receipt of RRT (dialysis or kidney transplant).

aCKD progression defined as kidney failure of 50% reduction of eGFR from baseline.
polymorphisms with a minor allele frequency of >0.03 were significantly associated with progression at the genome-wide threshold of \( P \leq 5 \times 10^{-8} \), and 14 gene regions reached nominal significance \( (P < 10^{-6}) \). In particular, they identified that LINC00923, an RNA gene expressed in glomeruli and endothelial cells of the kidney, was associated with CKD progression in participants without diabetes (28). In another study, the AGT and RENBP genes involved in the RAAS, and the entire RAAS pathway, were associated with CKD progression \( (P < 1.00 \times 10^{-6} \text{ for each}) \) (29). Future replication and validation studies will continue to move the field toward the goal of personalizing care for individuals with CKD.

Cardiovascular Factors

Atrial Fibrillation

Atrial fibrillation is highly prevalent among adults with CKD and is associated with adverse cardiovascular outcomes (30–32). However, the link between atrial fibrillation and kidney failure has not been fully elucidated. Bansal et al. (33) examined the risk of kidney failure among CRIC participants who developed atrial fibrillation during up to 9 years of follow-up, using marginal structural models with inverse probability weighting to accommodate for the bidirectional relationship between atrial fibrillation and kidney failure. Incident atrial fibrillation was associated with a three-fold higher risk of kidney failure, particularly among non-Hispanic White individuals. Potential explanations for the findings include the altered cardiac hemodynamics caused by atrial fibrillation over time (34,35), which may lead to a decline in kidney function. This study highlights the clinical importance of identifying atrial fibrillation in adults with CKD. Although there is strong evidence supporting the benefit of anticoagulation for atrial fibrillation in non-CrD populations, the clinical benefit among patients with CrD is less clear (36). Therefore, studies designed to address this clinical question are needed.

Hypertension

There is great controversy regarding the optimal BP target to prevent CKD progression. Anderson et al. (37) used marginal structural analysis to evaluate the association between time-updated systolic BP and CKD progression. The findings suggested a systolic BP of >130 mm Hg was associated with higher risk of kidney failure, which is consistent with AHA recommending a BP target of <130/80 mm Hg in individuals with CKD (38). This article furthered our understanding of this important association, which was stronger than that previously reported on the basis of systolic BP measured only at one time point (37).

Vascular Stiffness

Prior studies have shown that arterial stiffness contributes to death and heart failure events in CKD (39,40). It has been hypothesized that increased aortic pulse pressure can lead to microvascular kidney damage, resulting in albuminuria (41). However, the role of aortic stiffness in CKD progression has not been thoroughly investigated, and findings from previous studies have been inconsistent (42,43). Aortic stiffness is estimated from the pulse wave velocity (PWV) traveling along the aorta, in which the carotid and femoral artery sites are used to capture the wave forms (44). Townsend et al. (45) measured aortic stiffness by PWV in >2500 CRIC participants and found that, compared with individuals in the lowest tertile of PWV (<7.9 m/s), those in the highest tertile (>10.3 m/s) were at 37% higher risk for kidney failure (HR, 1.37; 95% CI, 1.05 to 1.80), independent of brachial BP. These findings suggest PWV may play a role in risk stratification, and future interventional trials focused on reducing vascular stiffness are needed.

Metabolic Factors

FGF23

Mineral and bone disorder is a well-recognized complication of CKD, but less is known about its influence on the natural history of CKD. FGF23 induces phosphaturia by decreasing phosphate reabsorption in the proximal tubule (46). In cross-sectional analyses, elevated FGF23 was found to be a common manifestation of CKD that develops earlier than increases in serum phosphate or parathyroid hormone (47). Isakov et al. (48) expanded this area of knowledge with the identification of FGF23 as a risk factor for CKD progression among individuals with an eGFR of ≥30 ml/min per 1.73 m², but not those with an eGFR of <30 ml/min per 1.73 m², suggesting FGF23 testing might help in risk stratification. Furthermore, these findings led to the design of the COMBINE (CKD Optimal Management with Binders and Nicotinamide) trial that evaluated the effects of lanthanum carbonate and/or nicotinamide on serum phosphate and FGF23 among adults with stage 3b/4 CKD (49). The study showed that neither treatment significantly lowered serum phosphate or FGF23 over 12 months; therefore, reducing phosphate and FGF23 in patients with CKD will require new approaches.

Urinary Oxalate

Waikar et al. (50) examined urinary oxalate as a potential novel predictor of CKD progression. The main sources of urinary oxalate are hepatic synthesis, breakdown of ascorbic acid, and diet (51). Oxalate nephropathy is a well-known complication of rare genetic disorders, and oxalate overabsorption and calcium oxalate crystal deposition in parenchyma of the kidney can cause tissue injury and inflammation (52). Among 3123 CRIC participants, Waikar et al. (50) found that higher 24-hour urinary oxalate excretion was associated with a 45% higher risk of kidney failure in the highest versus lowest quintile. Whether dietary and pharmacologic interventions to lower urinary oxalate excretion have an effect on CKD progression needs to be evaluated.

Novel Factors

AKI

The relationship between AKI and CKD progression is being increasingly recognized (53). In an analysis of pooled data from CRIC and the Assessment, Serial Evaluation, and Subsequent Sequelae of AKI Study, AKI
was independently associated with an increase in urine protein-creatinine ratio in individuals with CKD (54).

An ongoing study by Hsu et al. (Available at: https://projectreporter.nih.gov/project_info_description.cfm?aid=10149875&icde=52121974&ddparam=&ddvalue=&ddsub=&cr=3&csb=default&cs=ASC&pball=), designed to systemically evaluate the severity of hospitalized AKI in CRIC, will shed additional light onto this association. In addition, during the current phase of CRIC, eligible participants are performing monthly finger-stick creatinine testing, with additional weekly tests during two of the 12 testing months, to examine longitudinal patterns of CKD progression and intraindividual variability in kidney function, and occurrence of episodes of outpatient AKI.

**Biomarkers of Tubular Injury**

Several manuscripts evaluated tubular injury biomarkers as predictors of CKD progression. Liu et al. (55) reported that higher levels of 24-hour urine neutrophil gelatinase-associated lipocalin were significantly associated with CKD progression (HR, 1.70, highest to lowest quartile), independent of eGFR and proteinuria, but this biomarker did not substantially improve prediction of outcome events. Similarly, Hsu et al. (56) found that prediction of CKD progression risk with a clinical model that includes eGFR and albuminuria was not improved with the addition of kidney tubular injury biomarkers (i.e., neutrophil gelatinase-associated lipocalin, urinary kidney injury molecule-1, N-acetyl-β-D-glucosaminidase, and liver fatty acid binding protein). These findings underscore the high predictive-performance value of traditional biomarkers, such as eGFR and albuminuria (in addition to readily available clinical parameters), and the fact that measurement of tubular injury biomarkers does not provide additional information for risk prediction of CKD progression. However, CKD biomarkers may provide important pathophysiologic insight that can then lead to novel therapeutic targets or better understanding of drug toxicity (56).

**Contributions to Statistical Methodology for Cohort Studies of CKD**

In addition to the contributions to the medical field outlined above, CRIC Study investigators published several manuscripts addressing methodologic issues relevant to the cohort, including statistical methods for modeling time-updated exposures in cohort studies of CKD (57), survival analysis in the setting of competing risks (58), prediction modeling (59), recurrent event analysis (60), definition of kidney disease outcomes to identify risk factors for CKD progression (61), and repeated measures of eGFR (62). In these feature articles, mixed-effects, Poisson-regression, and survival models are illustrated by analyzing CRIC data to identify risk factors for different outcomes, and novel statistical approaches are compared with standard analyses.

**Clinical Implications and Limitations of CRIC Study Findings**

Over the years, the CRIC Study has made substantial contributions to our understanding of risk factors for CKD progression. The study has evaluated a broad array of factors addressed in a theoretic model developed by Norton et al. (63), which illustrates the complex interplay between biologic/clinical factors and social determinants of health in CKD progression (Figure 2). In particular, the CRIC findings regarding modifiable lifestyle factors have important implications for clinical practice (Table 2). As discussed in detail above, study findings can be used by clinicians to make recommendations to patients regarding smoking abstinence, diet, physical activity, and sleep habits. We acknowledge that, given the observational study design of CRIC, statements regarding causal inference should not be made. In addition, findings might not
of patients (3).

Future Directions

In the summer of 2018, the CRIC Study embarked on its fourth phase to continue to examine key outstanding research questions (Table 3). During this phase, the study protocol has incorporated several innovative, remote data-collection activities that include monthly monitoring of kidney function with finger- stick creatinine testing and urine albumin measurements. Other home-based testing include an assessment of integrated heart rate and activity (Zephyr BioPatch; Medtronic Corporation), arrhythmias (ZIO XT Patch; iRhythm Technologies), and sleep-disordered breathing (Apnea-Link Air; ResMed). CRIC is also exploring innovative, integrative statistical techniques to evaluate high-dimensional data.

Developing and testing equations that yield individual risk predictions based on the individual’s values on various risk factors will be a high-priority task during CRIC phase 4. Innovative methods, such as machine learning and electronic phenotyping, and various categories of risk information will be used to derive models that address two objectives: (1) maximizing practicality of use in typical clinical situations, and (2) maximizing predictive power using all available data. Outcomes in these models will be CKD progression, cardiovascular events, and death.

The CRIC Study offers rich opportunities for collaboration with the broad scientific community, as evidenced by the active ancillary study program that includes >22 training grants, ten diversity supplements, and 45 R01 awards. In addition, in the current phase, CRIC continues to have engagement with existing CKD consortia and study groups, such as the CKD Biomarkers Consortium and the CKD Prognosis Consortium, to maximally leverage the resources and data across these groups to affect the lives of patients with CKD. Furthermore, during CRIC phase 4, NIDDK established the CRIC Opportunity Pool Program (http://cristudy.org/Chronic-Kidney-Disease/Chronic-Renal-Insufficiency-Cohort-Study/opportunity-pool), which has set aside funds of >$2.5 million to support innovative projects led by the broader scientific community, including investigators who have not previously worked on CKD epidemiology, and those from outside the field of nephrology. Moreover, the NIDDK Central Repository of CRIC Study data (https://repository.niddk.nih.gov/studies/cric/) provides additional opportunities for investigators to leverage the detailed characterization of CKD progression. Lastly, the CRIC Study has also launched a tool (CRICDataView.org) that permits researchers to query study data.

Table 3. Key outstanding research questions for CRIC phase 4

<table>
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<tr>
<th>Research Questions</th>
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<tr>
<td>Prevalence of gut microbiome dysbiosis in CKD and its contribution to CKD progression</td>
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<tr>
<td>Prognostic implications of nonlinear trajectories and short-term variations in kidney function and damage measured frequently using home-based monitoring of serum creatinine and urine albumin</td>
</tr>
<tr>
<td>Prognostic value of biometric monitoring (e.g., measurement of heart rate) in CKD to identify subgroups at highest cardiovascular risk</td>
</tr>
<tr>
<td>Significance of undiagnosed atrial fibrillation and other atrial and ventricular dysrhythmias detected using a 14-d continuous ECG monitoring</td>
</tr>
<tr>
<td>Burden of noncardiovascular morbidity in CKD (e.g., frailty, fractures, pulmonary disease, utilization of health care resources)</td>
</tr>
<tr>
<td>Usefulness of machine learning methods in electronic phenotyping and characterization of clinical states for the purposes of cohort identification, classification, and prediction</td>
</tr>
</tbody>
</table>

CRIC, Chronic Renal Insufficiency Cohort; ECG, electrocardiogram.
Disclosures

A. Anderson reports receiving grants from NIH/NIDDK during the conduct of the study; and personal fees from Kyowa Hakko Kirin, outside the submitted work. H. Feldman reports receiving grants from NIH/NIDDK during the conduct of the study. He also reports consulting for Kyowa Hakko Kirin Co., Ltd. since January 2016 and serving as editor-in-chief of American Journal of Kidney Disease since January 2017, outside the submitted work. M. Hannan is a Robert Wood Johnson Foundation Future of Nursing Scholar Postdoctoral Fellow. E. Horwitz is an employee of MetroHealth Medical Center. J. Lash reports receiving grants from NIH during the conduct of the study. N. Meza reports receiving grants from NIDDK during the conduct of the study. A. Ricardo reports receiving grants from NIH during the conduct of the study. M. Saunders reports receiving grants from NIH/NIDDK during the conduct of the study. A. Srivastava reports receiving personal fees from AstraZeneca, CVS Caremark, and Horizon Pharma PLC, outside the submitted work. T. Tali埃尔 reports employment at Glickman Urological and Kidney Institute, Cleveland Clinic. S. Waikar reports receiving an investigator-initiated grant from Allena Pharmaceuticals and personal fees for serving on academic steering committee for phase 3 trials of a drug to treat hyperoxaluria; personal fees from Barron and Budd (versus Fresenius) for being an expert witness on litigation against Fresenius for Granuflo; personal fees from Bunch and James for being an expert witness on litigation related to mercury exposure; personal fees from Cerus for being a consultant on a device for AKI prevention; personal fees from CVS for consulting on clinical programs; personal fees from GE Healthcare as expert witness on litigation related to Omniscan and nephrogenic systemic fibrosis; personal fees from GlaxoSmithKline for serving on steering committee for phase 3 trials of dapradustat (hypoxia-inducible factor stabilizer for anemia of CKD); personal fees from Harvard Clinical Research Institute (also known as Baim) for serving on clinical end-points adjudication committees; personal fees from Kantum Pharma for serving on a scientific advisory board; personal fees from JNJ for speaking at a meeting; personal fees from Mallinckrodt for serving on an expert panel meeting; personal fees from Mass Medical International for consulting on global nephrology; personal fees from Pfizer for for being a consultant on litigation related to statins and diabetes mellitus; personal fees from Public Health Advocacy Institute as an expert witness against Philip Morris for cisplatin-induced lung injury from smoking; personal fees from Roth Capital Partners for speaking to a group of investors interested in learning about oxalate-lowering therapies; personal fees from Stratac for advisory about design of trials for a device for AKI; personal fees from Takeda for serving on a steering committee for phase 3 trial of febuxostat; personal fees from Venbio for speaking to a small group of investors about therapies for CKD; and personal fees from Wolters Kluwer for UpToDate editing; outside the submitted work. M. Weir reports receiving grants from NIDDK-CRIC during the conduct of the study. He also reports receiving personal fees from Boehringer-Ingelheim, Jansen, and MSD for serving on scientific advisory boards; personal fees from Boston Scientific for serving on steering committee; and personal fees from Relypsa/Vifor for serving on the steering committee/advisory board; outside the submitted work. K. Wolfirum reports receiving grants from NIH/NIDDK, which funded the study through which this data were collected. The funds from these grants, through employment at the University of Pennsylvania while working on the CRIC study, finance her salary. All remaining authors have nothing to disclose.

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