Variations in Managing Chronic Kidney Disease Associated With Type 2 Diabetes Across the United States and Validation of the FINE-CKD Model for Future Health Technology Assessments of Finerenone

HIGHLIGHTS

› Validation of the FINE-CKD Model for Future Health Technology Assessments for Finerenone in Patients With Chronic Kidney Disease Associated With Type 2 Diabetes

› Geographical Variation in Kidney Function Testing and Associations With Health Care Costs Among Patients With Chronic Kidney Disease and Type 2 Diabetes
Variations in Managing Chronic Kidney Disease Associated With Type 2 Diabetes Across the United States and Validation of the FINE-CKD Model for Future Health Technology Assessments of Finerenone

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Variations in Managing Chronic Kidney Disease Associated With Type 2 Diabetes Across the United States and Validation of the FINE-CKD Model for Future Health Technology Assessments of Finerenone

**OVERVIEW**

This supplement to *The American Journal of Managed Care®* describes the internal and external validation of the FINE-CKD model for estimating the cost-effectiveness of finerenone therapy in patients with chronic kidney disease and type 2 diabetes. Also described is an assessment of the adequacy of estimated glomerular filtration rate and urine albumin creatinine ratio testing to evaluate the risk of kidney and heart disease in affected patients across the United States.

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Validation of the FINE-CKD Model for Future Health Technology Assessments for Finerenone in Patients With Chronic Kidney Disease And Type 2 Diabetes

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Chronic kidney disease (CKD) is progressive and irreversible, causing gradual loss of kidney function that may lead to kidney failure (end-stage kidney disease [ESKD]). CKD is often associated with type 2 diabetes (T2D), which causes gradual and irreversible loss of kidney function that substantially impacts both mortality and morbidity. The key morbidity burden in these patients is associated with progression to ESKD and risk of cardiovascular (CV) events. These risks increase with kidney function loss, albuminuria and particularly both biomarker findings and are associated with increased mortality, and reduced quality of life. The international Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for CKD Evaluation and Management, endorsed in the United States by the Kidney Disease Outcomes Quality Initiative, describe a cause-glomerular filtration rate-albuminuria (C-G-A) CKD definition and classification to detect CKD and stratify risk based on the estimated glomerular filtration rate (eGFR) and urine albumin-creatinine ratio (uACR).

The current treatment (referred to as background therapy, BT) of patients with CKD associated with T2D includes lifestyle modifications and pharmacotherapy, focusing on slowing progression of the disease, preventing ESKD, and reducing the risk of CV events and mortality. Nonetheless, there are residual risks and an unmet clinical need. Finerenone is a new, selective, nonsteroidal mineralocorticoid receptor antagonist (MRA) with higher antagonistic potency for mineralocorticoid receptor (MR) and lower relative affinity for other steroid hormone receptors than noted with other steroidal MRAs. It can be used independently of BT normally used in the treatment of hyperglycemia or hypertension. Finerenone slows CKD progression and reduces CV morbidity and mortality in patients with CKD associated with T2D.

Two complementary randomized clinical trials, FIDELIO-Diabetic Kidney Disease (FIDELIO-DKD) and FIGARO-DKD, examined the impact of finerenone therapy on kidney and CV outcomes in patients with T2D associated with CKD in different, but overlapping, populations across various disease severity. The FIDELITY analysis was based on a prespecified pooling of these trials to provide robust estimates of the safety and efficacy of finerenone compared with

ABSTRACT

BACKGROUND: The FINE-CKD model was developed to estimate the cost-effectiveness of finerenone in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D).

OBJECTIVE: To perform internal and external validation by comparing the model estimates with trial results and outcomes from other models.

METHODS: Incidence rates from trials were compared with the model predictions. Statistical tests were then performed to assess whether modeled event rates aligned with trial observations. A cross-validation was also performed using the online version of the SHARP CKD-Cardiovascular Disease [SHARP CKD-CVD] model, with population characteristics from the finerenone trials analyzed. Where no finerenone data were available, the default SHARP CKD-CVD values were used. Comparison of the results considered the ranges from both models.

RESULTS: The outcomes of the FINE-CKD model reflect the event rates observed in the trials. Based on the results of the statistical tests, the hypothesis of no difference between observed and modeled events cannot be rejected for any of the outcomes. The results of the FINE-CKD model are within the ranges from the SHARP CKD-CVD model. Disease progressions align across the models; however, incident kidney failure events in the SHARP CKD-CVD model were higher. This can be explained by simulation of more severely affected patients in the SHARP CKD-CVD model.

CONCLUSIONS: This study demonstrates that the FINE-CKD model adequately reflects the clinical data and provides reliable extrapolation relative to the existing predictive tools while also being conservative in its approach.

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For author information and disclosures, see end of text.
placebo. Based on the FIDELITY results, on top of the maximum tolerated renin–angiotensin system inhibitor (RASi) treatment, finerenone showed substantial benefits for a range of CV and renal outcomes. The FINE-CKD model was developed to estimate the cost-effectiveness of finerenone in patients with CKD and T2D using data from FIDELIO-DKD. Use of finerenone in this population is intended to reduce the rate of kidney disease progression and the risk of CV mortality and morbidity. The FINE-CKD model was adapted to apply data from the FIDELITY analysis and use the full data set to compare outcomes of finerenone with those of placebo. The objective of this manuscript was to assess this model by presenting results of internal and external validation exercises comparing the FINE-CKD model estimates with trial results and outcomes from other models. The structure of the FINE-CKD model and a systematic literature review of existing economic models for CKD was described in detail elsewhere.

Methods
The FINE-CKD Model
The FINE-CKD model used a Markov modeling approach; the structure is presented in Figure 1. Justification of the chosen approach and the model structure can be found elsewhere.

Model health states were defined according to the stage of CKD and history of CV events. Four stages of CKD, defined according to the estimated glomerular filtration rate (eGFR) as per the KDIGO guidelines, were considered: CKD stage 1/2, CKD stage 3, CKD stage 4, and CKD stage 5 without renal replacement therapy (RRT). Additionally, 2 stages of ESKD were considered: dialysis and transplant. Patients could start the model in 1 of the CKD stages without CV events. Patients could remain in the same CKD stage or move to more/less advanced CKD stages and/or experience a first modeled CV event (nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure) or death.

Patients’ characteristics, probabilities of a first modeled CV event, other nonfatal and fatal events, and CKD progression for the BT arm were modeled based upon events observed in the placebo group of the FIDELITY analysis. BT probabilities were varied between CKD stages and computed as an average rate per 4-month cycle to align with the cycle length used in the FINE-CKD model. Hazard ratios (HRs) concerning treatment efficacy of finerenone together with BT relative to BT alone were calculated based on FIDELITY data for a range of outcomes comprising onset of eGFR decrease to less than 15 mL/min, progression to dialysis, CV mortality, renal mortality, first and subsequent CV events, hyperkalemia, sustained eGFR decrease of at least 40% from baseline, and new onset of atrial fibrillation/atrial flutter. Each of these was defined according to FIDELITY. These HRs then were used to determine probabilities for the finerenone arm.

External Validation With the FIDELITY Analysis
The objective of the external validation was to test the reliability of the model by ensuring alignment between the outcomes predicted by the model and the FIDELITY results. The incidence of first modeled CV events and CV deaths, as well as the number of patients undergoing dialysis, were compared with those of the model predictions. For each of the outcomes, a Kaplan-Meier curve of the observed cumulative event-free survival (EFS) was plotted against a cumulative EFS curve generated by the predictions of the model.

To test the null hypothesis of no difference between observed and predicted survival curves, Guyot’s algorithm was used to produce...
patient-level data from survival probabilities given by the model. To assess whether the modeled survival coincided with that observed in FIDELITY, investigators performed these statistical tests:

- log-rank test (using tests from survival and coin packages in R statistical software version 4.2.0),
- Gehan-Breslow test

External Validation With Existing Economic Models for CKD
Development of the FINE-CKD model was supported with a systematic literature review of existing economic models for CKD. Comparison of the FINE-CKD model with other published economic evaluations was performed. The objective of the cross-validation was to understand whether the FINE-CKD model is similar in terms of methodological approach, inputs, and outcomes. Two of the main challenges encountered during the cross-validation were the different model structures and the underlying assumptions; in addition, there was insufficient published information to align the base case or to compare results with the FINE-CKD model. Overall, the challenges meant that most identified models could not be sufficiently harmonized to adequately perform a validation check. The exception was the SHARP CKD-CVD model, a Markov model described by Schlackow et al. For cross-validation purposes, however, the online version of the SHARP CKD-CVD model was used. This was appropriate, because the publication did not present results for T2D patients, the population for whom finerenone is indicated.

In the SHARP CKD-CVD model, transitions between CKD stages, individualized renal and CV events, and CVD risks were estimated using 5-year follow-up data of the 9270 patients with CKD in the SHARP dataset and multivariate parametric survival analysis. The model includes a CKD submodel that simulates progression of CKD and a CVD submodel that simulates experience of fatal and nonfatal CV events and nonvascular death. A cohort simulation with annual cycles was used to evaluate the outcomes. Modeling focused on CV events and CKD progression according to patient history. Albuminuria was identified as a predictor of CKD progression and had an impact on the risk of CV events; however, as in the case of the FINE-CKD model, it was not explicitly included in the model structure. Health states considered by the model were CKD stage 3B, CKD stage 4, ESKD, need for dialysis, kidney transplant, CV events, and death. For each participant, the annual risk of CV events was estimated in the SHARP CKD-CVD model using survival risk equations with a range of baseline characteristics. Age, time since CKD diagnosis, CVD history, and CKD status were updated annually. In each year, participants not on RRT could progress to, or remain in, any CKD category; transition probabilities were estimated using multivariate multinomial logistic regression. For participants on dialysis, the probability of receiving a kidney transplant was estimated using logistic regression.

As stated by the authors, the SHARP CKD-CVD model was validated internally, in several external datasets, and against existing risk scores. The following clinical outcomes were chosen for the comparison: CV events or CV death, CV death, and initiation of RRT (dialysis and transplantation). Differences in outcomes were defined between models (Figure 2).

For cross-validation purposes, the patient baseline characteristics from FIDELITY were entered into the SHARP CKD-CVD model. When there were no data available from FIDELITY, default values from the SHARP CKD-CVD model were used. It was not possible to source all the parameters needed for the SHARP CKD-CVD model from data available in FIDELITY. For the validation, we reported results as the base case value, with ranges corresponding to minimum and
maximum values of each outcome that could be obtained in the SHARP CKD-CVD model after checking all possible values for the model’s parameters (Table 1).

For the purposes of this validation, the results of the FINE-CKD model were presented as cumulative event probabilities (of major CV event or CV death, initiation of RRT, and CV death) per 1000 participants at the end of years 5 and 10. These were calculated using the Kaplan-Meier product.

The results of 2 models with different inputs were compared considering the ranges of estimates that could be obtained using the SHARP CKD-CVD model and confidence intervals (CIs) from the probabilistic sensitivity analysis run in the FINE-DKD model.

**Results**

**External Validation With the FIDELITY Analysis**

The outcomes predicted by the FINE-CKD model reflect the incidence of the first modeled CV event observed in the FIDELITY trial. The model estimations for BT are within the range of the FIDELITY CIs (Figure 3). Similar findings have been obtained for model estimates of CV deaths (Figure 4) as well as the number of patients starting dialysis (Figure 5). The outcomes of the FINE-CKD model for the time to first modeled CV event (Figure 6), CV death (Figure 7), and the start of dialysis (Figure 8) for finerenone plus BT vs BT alone correspond well with the observations from the FIDELITY analysis. This is further supported by the CIs that are determined by applying the lower and higher bounds of the HRs of FIDELITY to the probabilities used in the model; they also align with the CIs sourced directly from the event frequencies in the study. Based on the results of the statistical tests, the null hypothesis of no difference between observed and modeled curves cannot be rejected. The estimated P values are presented in the Table 2.

As reflected in the FIDELITY analysis, there were no observations of patients initiating dialysis within the first year of either FIDELIO-DKD or FIGARO-DKD. In the FINE-CKD model, the per-cycle rate of dialysis was calculated as an average across the entire follow-up of the FIDELITY analysis; this was consistent with the approach used involving all transition probabilities in the Markov model. However, to better reflect the reality of FIDELITY, FINE-CKD was able to omit transitions to dialysis for up to 1 year from the start of the model. The validation results reported here were generated assuming no dialysis in the model in the first year.

**External Validation With Existing Economic Models for CKD**

Results of the comparison with the SHARP CKD-CVD model are presented in Table 3 for patients given standard of care alone (ie, BT arm in the FINE-CKD model).

CKD progression and CV events were assessed in the SHARP CKD-CVD model using risk equations, and they varied in each cycle; therefore, ranges for the estimates were generated using validation of base case inputs and testing of the following parameters:

- smoking status (current smoker, former smoker)
- body mass index (BMI) (25-29 kg/m²)
- albumin level (< 3.9 or ≥ 4.2 g/dL)
- hemoglobin level (< 11.6 or ≥ 13 g/dL)
- phosphate level (< 3.7 or ≥ 4.6 mg/dL)
- urine albumin-to-creatinine ratio (< 30 or 30-300 mg/g)
- renal diagnosis (other known or unknown cause)
FIGURE 3. Time to First Modeled CV Event for BT: Model vs FIDELITY Results

FIGURE 4. Time to CV Death for BT: Model vs FIDELITY Results

FIGURE 5. Time to Dialysis for BT: Model vs FIDELITY Results

FIGURE 6. Time to First Modeled CV Event for Finerenone + BT: Model vs FIDELITY Results

FIGURE 7. Time to CV Death for Finerenone + BT: Model vs FIDELITY Results

FIGURE 8. Time to Dialysis for Finerenone Plus BT: Model vs FIDELITY Results

FIGURE 9. Time to First Modeled CV Event for Finerenone + BT With CIs for HR: Model vs FIDELITY Results

FIGURE 10. Time to CV Death for: Finerenone + BT With CIs for HR: Model vs FIDELITY Results

FIGURE 11. Time to Dialysis for: Finerenone + BT With CIs for HR: Model vs FIDELITY Results

BT, background therapy; CV, cardiovascular.
The application of a Markov framework appropriately allows for the modeling of the impact of finerenone on CKD outcomes is inherently complex, a range of simplifications were applied, including omission of including albuminuria as a modelled health state. These simplifications have been undertaken in the FINE-CKD model for practical reasons, and their impact on model results was assessed via sensitivity or subgroup analysis. None of the simplifications applied hindered the ability to determine the cost-effectiveness of finerenone in this indication. Differences in both model structure and underlying assumptions, along with published information that proved insufficient for alignment with the models’ base case or adequate comparison of results, made cross-validation with other published models challenging. Nonetheless, the FINE-CKD model was compared with the SHARP CKD-CVD model due to the online availability of version of the latter, which specifically considered a subgroup of patients with T2D.

The SHARP CKD-CVD model was highly flexible, but differences complicated the ability to obtain the same results as in FINE-CKD for some outcomes. For example, the SHARP CKD-CVD model predicted higher incidence of renal events. This indicates that the FINE-CKD model estimates are more conservative from a cost-effectiveness perspective, because a higher baseline risk of such events with an advantageous treatment benefit relative to standard of care would translate into a greater scope to offer value through treatment.

In general, however, the clinical progression modeled by the FINE-CKD model appears to be well-aligned with the results of the SHARP CKD-CVD model. The alignment was more precise for CV outcomes, although the number of patients estimated to start RRT by the FINE-CKD model was within the possible ranges of scenario analyses using the SHARP CKD-CVD model.

Despite the positive results of the cross-validation, some uncertainty remains, as shown by the SHARP CKD-CVD model yielding wide ranges and being the only identified model sufficient for cross-validation. Nevertheless, the results of the FINE-CKD model are at the lower end of the reference range in terms of initiation of RRT.
Estimates of the FINE-CKD model, therefore, can be considered conservative in the context of the model being used for cost-effectiveness assessment.

Conclusions

Following recommendations from ISPOR, a model should be declared “valid” only in the context of its future applications. The FINE-CKD model is the first de novo model deemed suitable for future health technology assessments of finerenone in patients with CKD associated with T2D. In this context, the most important requirements of the model are transparency and an ability to adequately reflect the available clinical data. Together, these provide a basis for reliable extrapolation relative to the existing predictive tools.

The results of this study demonstrated that the FINE-CKD model meets these requirements, as it uses a potentially conservative approach. Nevertheless, in the case of any model, some level of uncertainty remains—and FINE-CKD is not an exception. This uncertainty must be addressed in future health technology assessments via a comprehensive and exhaustive set of scenario and sensitivity analyses.

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Introduction

Diagnosis and staging of chronic kidney disease (CKD) in patients with diabetes should be assessed using estimated glomerular filtration rate (eGFR) and urine albumin-creatinine ratio (uACR), according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease.1 The results of eGFR testing characterize glomerular filtration functioning and have long been used to define the 5 CKD GFR (G) stages (ie, G1 [normal or high], eGFR ≥ 90 mL/min/1.73 m²; G2 [mildly decreased], 60 to 89 mL/min/1.73 m²; G3 [moderately decreased], 45 to 59 mL/min/1.73 m²; G4 [severely decreased], 15 to 29 mL/min/1.73 m²; and G5 [kidney failure], < 15 mL/min/1.73 m²).2 The uACR measures patients’ level of albuminuria, a sensitive indicator of morphological kidney damage or endothelial inflammation; it has also been used in defining the 3 CKD albuminuria (A) stages (ie, A1 [normal to mildly increased], uACR < 30 mg/g; A2 [moderately increased], 30-300 mg/g; A3 [severely increased], > 300 mg/g).3 The uACR is an important laboratory indicator of morphological kidney damage or endothelial inflammation; it has also been used in defining the 3 CKD albuminuria (A) stages (ie, A1 [normal to mildly increased], uACR < 30 mg/g; A2 [moderately increased], 30-300 mg/g; A3 [severely increased], > 300 mg/g). The uACR is an important laboratory indicator of CKD, as it reflects underlying kidney injury at an early stage in patients with T2D, even if eGFR initially remains unaffected.5-7 Thus, it is important to use both eGFR and uACR measurements to identify CKD and characterize disease severity.

Patients with type 2 diabetes (T2D) are at higher risk of developing CKD. In the United States, there were 37 million patients with diabetes in 2019, and 90% to 95% of the cases were T2D.11 Approximately 1 of 3 patients with diabetes have kidney disease, and 20% to 30% of patients with T2D have moderate-to-severe CKD (ie, CKD G stages 3-5, defined as an eGFR < 60 mL/min/1.73 m²).4,12,13 These national statistics suggest that 6 million to 10 million people in the United States have both CKD and T2D.

CKD substantially increases the risks of cardiovascular events and mortality in the general population and those with comorbid T2D.2-10 In addition, a high economic burden has been observed among patients with both CKD and T2D. About 4.6% of Medicare enrollees had both CKD and diabetes, but treatment of these individuals accounted for 7.4% of Medicare’s total expenditures.19 In addition, a large electronic medical records study observed...
that patients with both CKD and T2D had more than double the annual mean medical costs than that of patients with CKD alone ($17,333 vs $7,374, respectively, during 2016-2017); hospitalization was the major driver of expenditures.20 In 2019, the mean annual all-cause health care costs for patients with CKD and T2D in this study escalated with rising CKD G stage, totaling $10,783 at stage G3a, $15,075 at stage G3b, $27,020 at stage G4, and $62,853 at stage G5.20 Similarly, a US claims database analysis reported that patients with T2D and CKD incurred escalating annual health care costs and higher hospitalization rates that correlated with more severe stages of CKD according to both CKD G and CKD A stages.21

The high prevalence and massive health care and economic burdens associated with CKD and T2D emphasize the importance of early detection, adequate monitoring, and effective disease management. Thus, a major treatment goal is the prevention of disease progression by forestalling additional loss of kidney function and/or slowing albuminuria progression to reduce complications and costs.22 The American Diabetes Association, American Society of Nephrology, KDIGO, and the Kidney Disease Outcomes Quality Initiative advocate targeted screening of eGFR and albuminuria in high-risk populations, including patients with diabetes.1,2,23-26 After diagnosis, timely testing and adequate monitoring are needed to guide effective interventions that improve clinical outcomes and reduce health care costs by slowing CKD progression.22,24-26 For these reasons, clinical practice guidelines recommend that both eGFR and albuminuria be measured at least annually in patients with CKD and more frequently in those at advanced stages of the disease.5,25

Despite the importance of identifying and managing albuminuria, insufficient testing of uACR has been noted in patients with T2D.7,20-21 However, this has not been well evaluated in patients with CKD and T2D, in whom albuminuria is prevalent. In addition, neither variations in testing adequacy across the United States in T2D and CKD nor the economic burdens associated with inadequate testing have been studied. To address these knowledge gaps and inform clinical practice and health care resource allocation, the geographical variations in uACR and eGFR testing and the associated all-cause health care costs were evaluated among patients with CKD and T2D in the United States.

**Methods**

**Data Source**

This retrospective cohort study used anonymized patient-level data from the Optum Clinformatics database spanning January 2015 to December 2019. This claims database is a single-payer source of administrative health claims from enrollees across all of the United States; it includes over 51 million commercial health plan beneficiaries and Medicare Advantage enrollees. Administrative claims contained comprehensive, longitudinal information from verified and adjudicated medical and pharmacy claims. As the data were de-identified, no institutional board review was required.

**TAKEAWAY POINTS**

This study assessed testing adequacy of estimated glomerular filtration rate (eGFR) and urine albumin-creatinine ratio (uACR) in patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D) in the United States.

- Despite the recommendation of annual testing for eGFR and uACR in patients with CKD and T2D per clinical guidelines, uACR undertesting was common nationally and across states, with large geographical variations in testing rates.
- Lower uACR testing rates were associated with higher health care costs at the state level.
- The lack of sufficient uACR testing raises concerns about CKD management in this population.

**Study Population**

The study population was composed of adults (age on the index date [defined below], ≥ 18 years) with CKD and T2D between January 2015 to December 2019. Patients with T2D were identified using diagnostic codes and medications for T2D (eAppendix Table 1 [eAppendix available at ajmc.com]) based on a modified version of the Electronic Medical Records and Genomics algorithm.24 Patients with diagnosis codes for type 1 and other categories of diabetes were excluded. Patients with CKD were defined as those with at least 1 inpatient or at least 2 outpatient claims on distinct dates with diagnosis codes for CKD (eAppendix Table 1).

The study period was the 1-year span after the first (index) date when both the CKD and T2D definitions were met. Patients eligible for inclusion were required to have full continuous insurance enrollment during the 1-year study period. Patients with end-stage kidney disease (ESKD; on dialysis or prior kidney transplantation) before the index date or during the study period were excluded from the study sample, as their testing requirements differed from those of patients with CKD stages G1 to G5.

**Testing for eGFR and uACR**

The eGFR tests were identified using serum creatinine laboratory tests, and uACR tests were identified using urine albumin tests and urine creatinine tests obtained on the same day (test codes are listed in eAppendix Table 1). Testing rate (ie, the proportion of patients who received ≥ 1 test during the 1-year follow-up period), testing frequency, and monitoring adequacy (ie, the proportion of patients who had adequacy testing per CKD G stage) during the 1-year study period were assessed.

Adequate monitoring was defined by CKD G stage, which was derived based on the KDIGO clinical guidelines.1 Specifically, on an annual basis, at least 1 measurement of eGFR and at least 1 measurement of uACR are recommended for CKD stages G1 and G2, at least 2 measurements of eGFR and at least 2 measurements of uACR are...
recommended for CKD stage G3, at least 3 measurements of eGFR and at least 3 measurements of uACR are recommended for CKD stage G4, and at least 4 measurements of eGFR and at least 4 measurements of uACR are recommended for CKD stage G5. Testing performed less frequently than recommended by the most recent KDIGO clinical guidelines\(^3\) for the CKD stage were considered inadequate.

**Total Health Care Costs**

Total health care costs, including medical (ie, inpatient, outpatient, emergency department visits, and other costs) and pharmacy expenditures, were assessed for each state during the study period. All costs were calculated based on a US payer’s perspective and were inflated to 2020 US dollars using the medical care component of the Consumer Price Index.\(^35\)

**Statistical Analyses**

Descriptive analyses were performed for patient characteristics (ie, age, race/ethnicity, and CKD G stage) as well as uACR and eGFR annual testing rates (ie, proportion of patients undergoing ≥ 1 test), annual testing frequencies, annual monitoring adequacy, and the annual total all-cause health care costs by state. Means and standard deviations (SD) were presented for continuous variables, and frequency counts and percentages were reported for categorical variables. Subgroup analyses were conducted by age group (< 55 years, 55 to < 65 years, 65 to < 75 years, and ≥ 75 years), race/ethnicity group (White, Black, Asian, and Hispanic patients), and CKD G stages. Heat maps were generated to demonstrate the variation in testing rate, monitoring adequacy, and annual total health care costs across states. A Pearson correlation (\(r\)) was estimated for the cost-uACR testing rates association at the state level. States contributing less than 200 patients were excluded from the state-level cost analyses. A \(P\) value of less than .05 indicated statistical significance.

SAS version 9.4 (SAS Institute Inc) was used for all statistical analyses. The heat maps were generated in R software version 3.6.3 (The R Foundation).

**Results**

**Patient Characteristics**

A total of 101,057 US adults with both CKD and T2D were included in the study (Figure 1). Patient baseline characteristics are listed in Table 1. The majority of patients in the sample were aged at least 65 years (80.1%), and 55.8% were White individuals. At the index date, 78.8% (\(n = 79,624\)) of patients had a diagnosis record indicating their CKD G stage. Among them, 5.1% were in CKD stage G1, 20.9% were in stage G2, 68.6% were in stage G3, and 5.4% were in stage G4 or G5.

**Testing Patterns**

National patterns. During the 1-year study period, the eGFR testing rate (ie, the proportion of patients with ≥ 1 test over a 1-year follow-up

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<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>No. (%)(^a) of patients with CKD and T2D ((N = 101,057))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
</tr>
<tr>
<td>&lt; 55</td>
<td>5,942 [5.9]</td>
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<tr>
<td>55 to &lt; 65</td>
<td>14,100 [14.0]</td>
</tr>
<tr>
<td>65 to &lt; 75</td>
<td>42,780 [42.3]</td>
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<td>≥ 75</td>
<td>38,235 [37.8]</td>
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<tr>
<td>Race/Ethnicity</td>
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<tr>
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<tr>
<td>Black</td>
<td>16,807 [16.6]</td>
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<tr>
<td>Asian</td>
<td>3088 [3.1]</td>
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<tr>
<td>Hispanic</td>
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<tr>
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<tr>
<td>CKD G stage</td>
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</tr>
<tr>
<td>Stage 1</td>
<td>4070 [4.0]</td>
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<tr>
<td>Stage 2</td>
<td>16,616 [16.4]</td>
</tr>
<tr>
<td>Stage 3</td>
<td>54,609 [54.0]</td>
</tr>
<tr>
<td>Stage 4</td>
<td>4087 [4.0]</td>
</tr>
<tr>
<td>Stage 5</td>
<td>242 [0.2]</td>
</tr>
<tr>
<td>Unknown</td>
<td>21,433 [21.2]</td>
</tr>
</tbody>
</table>

\(\%\) may not add up to 100% due to rounding.

---

\(\) CKD, chronic kidney disease; G, glomerular filtration rate category; T2D, type 2 diabetes; y, year(s).
period) was 94.1% (n = 95,101), and the average annual testing frequency was 4.2 (SD, 4.0) tests. The proportion of patients with adequate eGFR monitoring was 86.6% (n = 68,937). For uACR, the testing rate was 38.7% (n = 39,092), and the average annual testing frequency was 0.6 (SD, 0.9) tests. Only 20.3% (n = 16,161) of patients had adequate uACR monitoring.

Patterns by age, racial group, and CKD stage. The subgroup analyses were generally consistent with the national results, with high eGFR and low uACR testing rates observed across age and racial/ethnic subgroups (eAppendix Table 2). The eGFR testing rates were consistently high across CKD G stages (eAppendix Table 3), whereas the proportion of patients with adequate eGFR monitoring based on KDIGO guidelines was lower among patients with higher CKD G stages (58.3% in stage G5) compared with those with less advanced stages (90.0% in stage G1), as higher stages required more frequent monitoring. The uACR testing rates were generally very low across all CKD G stages. Particularly, substantially lower proportions of adequate uACR monitoring were observed among patients with higher CKD G stages (stage G4, 5.8%; stage G5, 2.5%).

State-level patterns. The eGFR and uACR testing rates and monitoring adequacy by state are displayed as heat maps in Figure 2 (eGFR) and Figure 3 (uACR). Overall, the eGFR testing rates were high across states, ranging from 79.5% (Colorado) to 97.3% (Alabama); monitoring adequacy was highest in southeastern states and lowest in midwestern states. Conversely, the uACR testing rates were much lower and displayed larger variations. The 3 states with the highest uACR testing rates were Hawaii (58.9%), Utah (53.1%), and Washington (52.6%); the states with the lowest uACR testing rates were Maine (14.0%), Arkansas (19.8%), and Minnesota (20.1%). Overall, the central and midwestern states had the lowest uACR testing rates. The proportion of patients with adequate testing for uACR was lowest in Minnesota (7.1%) and highest in Florida (30.9%).

Economic Burden
Among the 101,057 patients with CKD and T2D, the average annual health care costs were $28,636. Costs increased with CKD severity, from $20,122 in stage 1 (n = 4070) to $38,072 in stage 5 (n = 242, excluding patients with ESKD). The high health care costs were largely driven by inpatient costs ($12,032), which accounted for 42% of the total annual health care costs, followed by outpatient costs ($9923) and pharmacy costs ($5391).

Large geographical variations in health care costs were observed across states (Figure 4A). After excluding states with small sample sizes (ie, n < 200), the 3 states with the highest health care costs were Illinois ($35,995), Kentucky ($34,245), and Oklahoma ($33,557);
the states with the lowest health care costs were Hawaii ($21,003), Arizona ($22,052), and Utah ($22,631). No clear relationship between costs and eGFR testing rates was observed (Pearson $r = 0.27; P = .09$), whereas higher costs were correlated with lower uACR testing rates (Pearson $r = –0.55; P < .01$) (Figure 4B).

**Discussion**

Using real-world data from patients with CKD and T2D in a large US administrative claims database, this study characterized uACR and eGFR testing patterns nationally and across US states; it also delved into the relationship between testing rates and all-cause health care costs. Nationally, eGFR testing rates were high for this patient population—94.1% received at least 1 test, and 86.6% received adequate testing—with moderate variation noted across states (79.5%–97.3%). In contrast with the eGFR testing patterns, the rates for uACR testing were low nationally (38.7% had ≥ 1 test) and had larger variations between states (14.0%–58.9%).

Albuminuria, measured by the uACR tests, plays an important role in the management of patients with CKD associated with T2D. An elevated uACR is an independent predictor of poor cardiovascular outcomes and is associated with higher morbidity and risk of mortality. However, despite the importance of controlling albuminuria in patients with CKD associated with T2D, inadequate uACR testing was ubiquitous. Previous studies have reported low rates of uACR screening or testing among patients with T2D who are at risk of developing, but who have not yet received a diagnosis of, CKD. Other investigations assessing CKD monitoring in a T2D population with a previous CKD diagnosis also found that uACR was largely undertested despite clinical practice guideline recommendations. The severe undertesting of uACR observed in this study and others raises concerns about management of these patients, especially when the observed association between a low uACR testing rate and higher state-level health care costs are considered.

As changes in albuminuria are predictive for CKD progression, treatment decisions made in the absence of uACR testing data may delay proper treatment and, in turn, lead to higher health care costs due to CKD progression. On the other hand, timely initiation of treatments that control elevated albuminuria can improve disease outcomes and potentially lower downstream health care costs. Recent clinical practice guidelines recommend reduction in albuminuria as a therapeutic target. For example, angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers yield significant kidney and cardiovascular protective effects, reducing the risk of ESKD and costly dialysis or kidney transplantation in patients with CKD, albuminuria, and T2D. Finerenone and SGLT2 inhibitors also demonstrate clinical benefits in preventing cardiovascular
FIGURE 4. Average Total Annual Health Care Costs (a) Across US States and (b) Relative to uACR Testing Rates (2020 USD)

A. Average annual health care costs across states

B. Average annual health care costs relative to uACR testing rates across states

uACR, urine albumin-creatinine ratio; USD, United States dollars.
*States with less than 200 patients, which were not included due to small sample size.
events, slowing the progression of kidney disease, and reducing risk of death in patients with CKD and T2D. The present findings emphasize the need to monitor patients with CKD adequately to reduce health care costs and improve patient outcomes through early detection of progression and prompt treatment initiation.

Furthermore, the low rates of uACR testing in the United States suggest that there may be barriers to adequate testing. Unlike eGFR, which is calculated using serum creatinine level included in the basic metabolic panel for blood tests, uACR results are specific to kidney disease and found via a urine test. Therefore, the low uACR testing rate could be due to infrequent visits to a nephrologist or low awareness of the importance of urine testing and uACR among patients and clinicians of other specialties. Inadequate testing of albuminuria in T2D may lead to underdiagnosis of CKD, consequently limiting patient awareness of CKD. According to a survey of US adults with CKD by Dharmarajan et al, only 15% of individuals with diabetes reported being aware of their CKD status. Of note, the present study observed lower uACR testing rates in the central, and predominantly rural, United States. As reported in a study by Naylor et al, individuals in these regions may have relatively lower access to health care resources, and particularly to specialists, when compared with those in the rest of the United States.

This study benefits from several strengths. First, a large US claims database (Optum Clininformatics) was used to assess the testing patterns and health care costs for patients with CKD and T2D. The extensive dataset permitted both a large study sample covering all US geographical regions and the construction of subgroups for more detailed analyses. Second, in addition to eGFR testing, this study evaluated the patterns and adequacy of uACR testing in the CKD and T2D population across US states, which is an understudied area. The results suggested unmet needs in the management and monitoring of this patient population, which could inform clinical practice. Finally, we characterized the economic burden of CKD across US states and its association with both eGFR and uACR testing, which could inform health care resource allocation or promote costs savings by increasing awareness.

Limitations

Despite these strengths, the results of this study should be considered in the light of its limitations. First, as with all claims database analyses, medical services and laboratory tests obtained outside a patient’s plan were not captured. Further, coding inaccuracy and errors may have led to classifications of patients identified based on diagnostic codes; in particular, this may pertain to information on CKD G stage. Similarly, kidney function tests identified based on test codes may be subject to nondifferential measurement error. To address this limitation, 2 outpatient CKD diagnoses were required to reduce potential errors. Second, the study excluded patients with ESKD (dialysis or had kidney transplantation), whereas a small group of patients (n = 242) with CKD stage G5 who did not have evidence of ESKD were included. Thus, this may not be a representative sample of all patients with CKD stage G5. Third, because of the ecological study design, potential confounding may exist and mitigate findings, particularly for the relationship between kidney function testing patterns and economic outcomes. Finally, the study results cannot be used to directly infer the underlying reasons for inadequate uACR testing. To improve CKD management and awareness of ideal patient monitoring, future studies are warranted to assess contributing factors to low rates of uACR testing and to inform policy-making.

Conclusions

Among US patients with both CKD and T2D, severe undertesting for uACR was observed nationally and across all states, and large geographical variations in testing rates were revealed. Lower uACR testing rates were associated with higher state-level health care costs. This lack of sufficient uACR testing raises concerns about the management of CKD in patients with T2D.

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Data sharing statement: The study was conducted using commercially licensed de-identified individual patient level data. Data used in this study are not available for public access.

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Author Disclosures: Dr Betts, Dr Song, and Dr Wu are employed by and report institutional conflicts of interest with Analysis Group, Inc, which received consulting fees from Bayer US, LLC for this work. Dr Elliott was employed by Bayer US, LLC at the time of the study and owns stock in Bayer US, LLC. Farej, Dr Singh, and Dr Warmock are employed by and report institutional conflicts of interest with Bayer US, LLC, such as US and EU approval of a product for chronic kidney disease in type 2 diabetes.

Authorship Information: Concept and design (KAB, JS, JE, NW, RF, AW, RS); acquisition of data (RS); analysis and interpretation of data (KAB, JS, JE, RF, AW, RS); drafting of the manuscript (KAB, NW, AW); critical revision of the manuscript for important intellectual content (KAB, JS, JE, RF, AW, RS); statistical analysis (JS, AW); administrative, technical, or logistic support (RF, RS); and supervision (KAB, JS, RS).

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REFERENCES

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eAppendix: Geographical Variation in Kidney Function Testing and Associations With Health Care Costs Among Patients With Chronic Kidney Disease and Type 2 Diabetes
Keith A. Betts, PhD; Jinlin Song, PhD; Jay Elliott, PhD; Neil Warnock, MD, MS, CHCQM; Ryan Farej, BS; Aozhou Wu, PhD; and Rakesh Singh, PhD

From a supplement to The American Journal of Managed Care®: “Variations in Managing Chronic Kidney Disease Associated With Type 2 Diabetes Across the United States and Validation of the FINE-CKD Model for Future Health Technology Assessments of Finerenone.”

eAppendix Table 1. Diagnostic Codes and Test Codes Used in the Study

<table>
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<th>Diagnostic codes</th>
<th>ICD-9-CM^a</th>
<th>ICD-10-CM^a</th>
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<tr>
<td>Type 2 diabetes</td>
<td>250.x0, 250.x2 (excluding 250.10 and 250.12)</td>
<td>E11 (excluding E11.1)</td>
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<td>Other types of diabetes (for exclusion)</td>
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<tr>
<td>Type 1 diabetes</td>
<td>250.x1, 250.x3</td>
<td>E10</td>
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<tr>
<td>Diabetes due to underlying conditions</td>
<td>249</td>
<td>E08</td>
</tr>
<tr>
<td>Chemical induced diabetes</td>
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<td>E09</td>
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<tr>
<td>Other specified diabetes</td>
<td></td>
<td>E13</td>
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<tr>
<td>Chronic kidney disease (CKD)</td>
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<td></td>
</tr>
<tr>
<td>Stage G1</td>
<td>585.1</td>
<td>N18.1</td>
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<td>Stage G5</td>
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<td>Unspecified</td>
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<td>Anemia in CKD</td>
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<td>D63.1</td>
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<td>Test codes</td>
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<tr>
<td>CPT</td>
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</tr>
<tr>
<td>82565 Creatinine, serum; eGFR calculation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80053 Comprehensive metabolic panel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80048 Basic metabolic panel (calcium, total)</td>
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<tr>
<td>80069 Renal function panel</td>
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<tr>
<td>80047 Basic metabolic panel (calcium, ionized)</td>
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<td>82575 Creatinine, clearance</td>
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<td>82043 Albumin: urine, microalbumin, quantitative</td>
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<td>Urine albumin</td>
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<td>Urine creatinine</td>
<td>82575 Creatinine, clearance</td>
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**eAppendix: Geographical Variation in Kidney Function Testing and Associations With Health Care Costs Among Patients With Chronic Kidney Disease and Type 2 Diabetes**

From a supplement to *The American Journal of Managed Care*®: “Variations in Managing Chronic Kidney Disease Associated With Type 2 Diabetes Across the United States and Validation of the FINE-CKD Model for Future Health Technology Assessments of Finerenone.”

**eAppendix Table 2. eGFR and uACR Testing Rates, Testing Frequency, and Monitoring Adequacy Among Age and Race/Ethnicity Subgroups**

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>No. of patients (%)</th>
<th>Patients having eGFR testing</th>
<th>Patients having uACR testing</th>
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<td></td>
<td></td>
<td>≥ 1 test, n (%)</td>
<td>Annual test frequency, mean (SD)</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td><strong>N = 101,057</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 55</td>
<td>5,942 (5.9)</td>
<td>5,257 (88.5)</td>
<td>3.5 (4.4)</td>
</tr>
<tr>
<td>55 to &lt; 65</td>
<td>14,100 (14.0)</td>
<td>13,019 (92.3)</td>
<td>4.0 (4.2)</td>
</tr>
<tr>
<td>65 to &lt; 75</td>
<td>42,780 (42.3)</td>
<td>40,623 (95.0)</td>
<td>4.2 (3.8)</td>
</tr>
<tr>
<td>≥ 75</td>
<td>38,235 (37.8)</td>
<td>36,202 (94.7)</td>
<td>4.3 (3.9)</td>
</tr>
<tr>
<td><strong>Race/Ethnicity&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td><strong>N = 88,485</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>56,372 (63.7)</td>
<td>53,346 (94.6)</td>
<td>4.2 (4.1)</td>
</tr>
<tr>
<td>Black</td>
<td>16,807 (19.0)</td>
<td>15,980 (95.1)</td>
<td>4.3 (4.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>3,088 (3.5)</td>
<td>2,863 (92.7)</td>
<td>3.5 (3.5)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>12,218 (13.8)</td>
<td>10,846 (88.8)</td>
<td>3.5 (3.4)</td>
</tr>
</tbody>
</table>

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SD, standard deviation; uACR, urine albumin-to-creatinine ratio; y, year(s).

<sup>a</sup>Monitoring adequacy was assessed only among patients with known CKD stages (n = 79,624 in the age subgroup analysis and n = 69,232 in the race/ethnicity subgroup analysis).

<sup>b</sup>Patients with missing race (n = 12,572 [12.4%]) were not included in the analysis.
eAppendix: Geographical Variation in Kidney Function Testing and Associations With Health Care Costs Among Patients With Chronic Kidney Disease and Type 2 Diabetes

From a supplement to *The American Journal of Managed Care*: “Variations in Managing Chronic Kidney Disease Associated With Type 2 Diabetes Across the United States and Validation of the FINE-CKD Model for Future Health Technology Assessments of Finerenone.”

**eAppendix Table 3. eGFR and uACR Testing Rates, Testing Frequency, and Monitoring Adequacy by CKD G Stage**

<table>
<thead>
<tr>
<th>Kidney function test</th>
<th>T2D + CKD</th>
<th>T2D + CKD stage G1</th>
<th>T2D + CKD stage G2</th>
<th>T2D + CKD stage G3</th>
<th>T2D + CKD stage G4</th>
<th>T2D + CKD stage G5a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 101,057</td>
<td>n = 4,070</td>
<td>n = 16,616</td>
<td>n = 54,609</td>
<td>n = 4,087</td>
<td>n = 242</td>
</tr>
<tr>
<td><strong>eGFR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of ≥ 1 eGFR test, n (%)</td>
<td>95,101 (94.1)</td>
<td>3,662 (90.0)</td>
<td>15,474 (93.1)</td>
<td>52,128 (95.5)</td>
<td>3,957 (96.8)</td>
<td>229 (94.6)</td>
</tr>
<tr>
<td>Annual eGFR test frequency, mean (SD)</td>
<td>4.2 (4.0)</td>
<td>3.3 (3.5)</td>
<td>3.7 (3.5)</td>
<td>4.5 (4.1)</td>
<td>5.7 (5.0)</td>
<td>5.2 (4.1)</td>
</tr>
<tr>
<td>Adequate eGFR monitoring, n (%) b</td>
<td>68,937 (86.6)</td>
<td>3,662 (90.0)</td>
<td>15,474 (93.1)</td>
<td>46,419 (85.0)</td>
<td>3,241 (79.3)</td>
<td>141 (58.3)</td>
</tr>
<tr>
<td><strong>uACR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of ≥ 1 uACR test, n (%)</td>
<td>39,092 (38.7)</td>
<td>1,693 (41.6)</td>
<td>6,947 (41.8)</td>
<td>21,829 (40.0)</td>
<td>1,427 (34.9)</td>
<td>67 (27.7)</td>
</tr>
<tr>
<td>Annual uACR test frequency, mean (SD)</td>
<td>0.6 (0.9)</td>
<td>0.6 (0.9)</td>
<td>0.6 (0.9)</td>
<td>0.6 (0.9)</td>
<td>0.6 (1.0)</td>
<td>0.5 (1.0)</td>
</tr>
<tr>
<td>Adequate uACR monitoring, n (%) b</td>
<td>16,161 (20.3)</td>
<td>1,693 (41.6)</td>
<td>6,947 (41.8)</td>
<td>7,279 (13.3)</td>
<td>236 (5.8)</td>
<td>6 (2.5)</td>
</tr>
</tbody>
</table>

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; G stage, glomerular filtrate rate category; SD, standard deviation; T2D, type 2 diabetes, uACR, urine albumin-to-creatinine ratio.

aPatients with end-stage kidney disease, including those who were on dialysis or who had kidney transplant, were excluded from the study.

bMonitoring adequacy was assessed only among patients with known CKD G stages.