

# A Kidney Diagnostic's Impact on Physician Decision-making in Diabetic Kidney Disease

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**M**anagement of diabetic kidney disease (DKD) has emerged as a major public health challenge in the United States. CDC data estimate that more than 34 million (or 1 in 10) adults in the United States have diabetes, of whom approximately 90% to 95% have type 2 diabetes (T2D); further, an estimated 40% of patients with T2D have DKD.<sup>1,2</sup> DKD is a chronic, progressive disease that is associated with substantial health care costs and leads to end-stage kidney disease (ESKD), requiring dialysis and/or a kidney transplant. DKD accounted for 14% of all Medicare spending for patients 65 years and older in 2017.<sup>3</sup> It is a type of chronic kidney disease (CKD) caused by diabetes. The financial burden imposed by CKD and ESKD results in an estimated cost of \$120 billion annually, representing approximately 7.2% of overall Medicare fee-for-service reimbursed claims.<sup>3</sup> The incidence of ESKD is predicted to rise by approximately 11% to 18% from 2015 to 2030, due to changes in age and race distribution and the prevalence of obesity and diabetes.<sup>4,5</sup>

To reduce the clinical and economic burden of DKD, accurate staging and prognosis with respect to risk of progression are vital to enable appropriate interventions and referral to specialists early in the management of the disease.<sup>6</sup> The international Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for CKD Evaluation and Management<sup>7</sup> includes a cause–glomerular filtration rate (GFR)–albuminuria (C–G–A) CKD definition and classification system to optimize risk stratification of kidney disease progression based on the estimated GFR (eGFR) and urine albumin–creatinine ratio (uACR). However, the predictive ability of the combination of eGFR and uACR is limited by the underuse of uACR and of nuanced interpretation that considers both parameters in the CKD classification.<sup>8</sup> Current methods of risk stratification based on albuminuria and eGFR can be enhanced to identify which patients are more likely to experience progressive decline in kidney function, especially in earlier stages of DKD (G1–G3b). A more precise risk of progression that holistically accounts for blood-based biomarkers in combination with clinical parameters could better enable clinicians to implement appropriate interventions, such as prescription of guideline-based

## ABSTRACT

**OBJECTIVES:** Estimated glomerular filtration rate (eGFR) and albuminuria, the current standard-of-care tests that predict risk of kidney function decline in early-stage diabetic kidney disease (DKD), are only modestly useful. We evaluated the decision-making impact of an artificial intelligence–enabled prognostic test, KidneyIntelX, in the management of DKD by primary care physicians (PCPs).

**STUDY DESIGN:** This was a prospective web-based survey administered among PCPs in the United States.

**METHODS:** We used conjoint analysis with multivariable logit models to estimate PCP preferences. The survey included hypothetical patient profiles with 6 attributes: albuminuria, eGFR, age, blood pressure (BP), hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>), and KidneyIntelX result. Each PCP viewed 8 patient profiles randomly selected from 42 unique profiles having 1 level from each attribute. For each patient, PCPs were asked to indicate whether they would prescribe a sodium–glucose cotransporter-2 (SGLT2) inhibitor, increase angiotensin receptor blocker (ARB) dose, and/or refer to a nephrologist.

**RESULTS:** A total of 401 PCPs completed the survey (response rate, 8.8%). The relative importance of the top 2 attributes for each decision were HbA<sub>1c</sub> (52%) and KidneyIntelX result (23%) for prescribing SGLT2 inhibitors, BP (62%) and KidneyIntelX result (13%) for increasing ARB dose, and eGFR (42%) and KidneyIntelX result (27%) for nephrologist referral. A high-risk KidneyIntelX result was associated with significantly higher odds of PCPs prescribing SGLT2 inhibitors [odds ratio (OR), 1.64; 95% CI, 1.29–2.08], increasing ARB dose (OR, 1.49; 95% CI, 1.17–1.89), and referring to a nephrologist (OR, 2.47; 95% CI, 1.99–3.08) compared with no test.

**CONCLUSIONS:** The KidneyIntelX test had greater relative importance than albuminuria and eGFR to PCPs in making treatment decisions and was second only to eGFR for nephrologist referrals. Because of its significant impact on decision-making, KidneyIntelX has high clinical utility in DKD management.

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treatments to lower blood pressure (eg, an angiotensin-converting enzyme [ACE] inhibitor or an angiotensin II receptor blocker [ARB]), efforts to lower elevated blood glucose and hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) levels (eg, metformin and sodium-glucose cotransporter-2 [SGLT2] inhibitors), or, for high-risk patients, referral to a nephrologist.<sup>9</sup> Furthermore, such approaches to risk stratification may also avoid expensive treatments and unnecessary interventions in low-risk patients.<sup>10</sup>

In this study, we sought to evaluate the impact of a novel prognostic test that has been reported to potentially offer improved risk stratification for physician decision-making in patients with early-stage DKD.<sup>11</sup>

The test evaluated in this study, KidneyIntelX, can identify the risk of progression in early-stage DKD (stages G1-G3b, excluding G1A1 and G2A1) using a combination of blood-based biomarkers, including soluble tumor necrosis factor receptor (sTNFR)–1 and sTNFR-2, and kidney injury molecule 1 (KIM-1), and clinical factors, including eGFR, uACR, serum calcium, HbA<sub>1c</sub>, systolic blood pressure, platelets, and liver enzyme aspartate aminotransferase, derived from electronic health records. Based on previous research among primary care physicians (PCPs) eliciting unmet needs in DKD patient management,<sup>9</sup> PCPs may find the KidneyIntelX test to be a suitable alternative to current standard of care, particularly when the degree of albuminuria is uncertain, as described in a validation study.<sup>11</sup> The positive predictive value for progressive decline in kidney function in the high-risk group included in the validation study was 61% for KidneyIntelX vs 40% for the highest-risk stratum by KDIGO categorization ( $P < .001$ ). Only 10% of those scored as low risk by KidneyIntelX went on to experience progression, which represents a high negative predictive value of 90%.<sup>11</sup> Based on this performance, KidneyIntelX provides an alternate method of risk-stratifying patients with DKD, which could help simplify physicians' decision-making regarding these patients. **eAppendix A** (eAppendices available at [ajmc.com](http://ajmc.com)) shows the net reclassification from KDIGO risk strata to KidneyIntelX risk strata in derivation and validation sample. **eAppendix B** shows the treatment and patient management recommendations provided by KidneyIntelX, stratified by risk result.

In this study, we sought to address the question: Does availability of the information provided by the KidneyIntelX test affect physicians' treatment decisions compared with the information available from the standard tests recommended by KDIGO practice guidelines? To answer this question, we undertook a physician preference study assessing whether the results from a novel prognostic test such as KidneyIntelX would aid physician decision-making in the real-world setting more than current standard-of-care tests, such as those measuring albuminuria and eGFR.

## TAKEAWAY POINTS

A prognostic test, such as KidneyIntelX, that offers better risk stratification than the Kidney Disease Improving Global Outcomes classification, which is based solely on albuminuria and estimated glomerular filtration rate, would have a significant impact on physician decision-making pertaining to treatment selection and nephrologist referrals in patients with diabetic kidney disease (DKD).

- ▶ By demonstrating physician demand for a novel prognostic test like KidneyIntelX, this study makes a case for increasing patient access to this diagnostic through improved coverage.
- ▶ This study provides evidence of the KidneyIntelX test satisfying unmet physician needs in standard-of-care management of DKD. Policy makers can use these results to adopt novel tests such as the KidneyIntelX test into practice guidelines.
- ▶ As the first of its kind to evaluate a kidney diagnostic, this study challenges the current standard-of-care norms in the staging and management of kidney disease, thereby attempting to change practice patterns in the medical community, potentially leading to improved outcomes.

## METHODS

### Inclusion/Exclusion Criteria

We administered a web survey in a convenience sample of PCPs currently managing patients with DKD. The PCPs were recruited via an external recruiting agency that enlists panels of medical providers for primary research. Respondents were allowed to participate in the study if they (1) were board-certified in family medicine, primary care, or internal medicine; (2) had at least 2 years of experience managing patients; (3) managed more than 20 patients with T2D in the past 6 months; (4) tested at least 11 patients with T2D for DKD in the past 6 months; (5) spent at least 50% of their time in direct clinical care; and (6) did not reside in Maine or Vermont due to regulations in those states that limit physicians from receiving compensation for participation in market research. If respondents did not satisfy a criterion, their survey was terminated at the end of the screener. PCPs completing the survey were offered \$25 as honorarium.

### Conjoint Analysis Experimental Design

Conjoint analysis is a preference elicitation technique in which the implicit values for the outcome are derived from some overall score for a profile consisting (conjointly) of 2 or more attributes.<sup>12,13</sup> Conjoint analysis allows the investigator to measure how sensitive a respondent is to changes in the levels of 1 or more attributes relative to others. Sawtooth Software's Conjoint Value Analysis module version 3.0 was used for the experimental setup of this study.<sup>14</sup>

First, a set of attributes and levels that may affect physician decision-making in DKD treatment and management was developed based on a literature review and discussion with 2 clinical experts.<sup>15-20</sup> A total of 6 attributes were evaluated in this study: albuminuria, eGFR, age, blood pressure, HbA<sub>1c</sub>, and KidneyIntelX test result. The levels for each attribute presented in the patient profiles are displayed in **Table 1**.

Hypothetical profiles were then constructed using a combination of 1 level from each attribute. Given the number of attributes (6) and levels (5 attributes with 3 levels and 1 attribute with 4 levels),

**TABLE 1.** Attributes and Levels

Attribute	Level 1	Level 2	Level 3	Level 4
KidneyIntelX test result	No test	Low risk	Moderate risk	High risk <sup>b</sup>
Albuminuria <sup>a</sup>	Mildly increased	Moderately increased <sup>b</sup>	Severely increased	N/A
eGFR <sup>a</sup>	Mildly decreased	Mildly to moderately decreased <sup>b</sup>	Moderately to severely decreased	N/A
Age <sup>a</sup>	Younger	Middle aged <sup>b</sup>	Older	N/A
Blood pressure <sup>a</sup>	Normal	Moderately elevated <sup>b</sup>	High	N/A
HbA <sub>1c</sub> <sup>a</sup>	Normal	Moderately elevated <sup>b</sup>	Severely elevated	N/A

eGFR, estimated glomerular filtration rate; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; N/A, not applicable.

<sup>a</sup>To make the profiles realistic, for each level of the clinical attributes (excluding the KidneyIntelX test result attribute), the values presented could be 1 of 3 options, each differing by a small amount, such that 2 patient profiles having the same level for the same attribute would not have the exact same value for that attribute. Albuminuria was presented as 14, 15, or 16 mg/g (14, 15, or 16 mcg/mg) (level 1: mildly increased); 165, 175, or 185 mg/g (165, 175, or 185 mcg/g) (level 2: moderately increased); or 840, 850, or 860 mg/g (840, 850, 860 mcg/g) (level 3: severely increased). eGFR was presented as 79, 80, or 81 mL/min/1.73 m<sup>2</sup> (level 1: mildly decreased); 51, 52, or 53 mL/min/1.73 m<sup>2</sup> (level 2: mildly to moderately decreased); or 36, 37, or 38 mL/min/1.73 m<sup>2</sup> (level 3: moderately to severely decreased). Age was presented as 30, 31, or 32 years (level 1: younger); 54, 55, or 56 years (level 2: middle-aged); or 72, 73, or 74 years (level 3: older). Blood pressure was presented as 124/78, 125/78, or 126/78 mm Hg (level 1: normal); 134/85, 135/85, or 136/85 mm Hg (level 2: moderately elevated); or 144/90, 145/90, or 146/90 mm Hg (level 3: high). HbA<sub>1c</sub> was presented as 6.0%, 6.1%, or 6.2% (level 1: normal); 7.2%, 7.3%, or 7.4 % (level 2: moderately elevated); or 8.1%, 8.2%, or 8.3% (level 3: severely elevated).

<sup>b</sup>Levels included in the hold-out profiles in survey pretests.

asking respondents to review 972 profiles was not feasible. To improve response efficiency and maintain statistical precision, a balanced orthogonal design was generated with a fewer number of profiles using the Sawtooth Software. A balanced orthogonal design is one in which all attribute levels vary independently (and thus are not correlated) and each level of each attribute is represented an approximately equal number of times in the subset of profiles.<sup>12</sup> This yielded a total of 42 profiles. To reduce the burden on respondents and improve survey response rates, a random selection of 8 of the 42 profiles was shown to each respondent. The profiles were picked at random using the least fill methodology, such that each of the 42 profiles was shown an approximately equal number of times.

The outcome in the conjoint experiment was PCP decision-making, and it was operationalized using 3 binary variables. For each profile seen, PCPs were asked to select “yes” or “no” for the following 3 questions: (1) Would you prescribe an SGLT2 inhibitor with a DKD indication to this patient?; (2) Would you increase the dose of losartan from 50 mg per day to 100 mg per day in this patient?; and (3) Would you refer this patient to a nephrologist? These outcomes (decisions) are in accordance with both the 2020 KDIGO guidelines and 2021 American Diabetes Association guidelines and were validated for accuracy by clinical experts.

### Survey Instrument and Data Collection

The self-administered, anonymous, web-based survey was hosted by the recruiting agency. The survey was designed to be completed in 15 minutes. For the purposes of the survey, the KidneyIntelX test was blinded as Test X to minimize any potential biases. The full survey and the product profile shown to the respondents are presented in [eAppendices C and D](#), respectively.

The survey was pretested with 2 PCPs prior to full launch to detect ambiguities in the patient profiles or the treatment choice questions. In addition to the 8 patient profiles, the pretest survey included 2 additional profiles (hold-out profiles) that were identical in terms of the attributes and levels (Table 1) to assess for test-retest reliability (consistency). Feedback received in the pretest phase was implemented in the final survey before full launch. Full launch data from the final survey were collected between November 16, 2020, and December 3, 2020. The study was reviewed by an independent institutional review board (IRB) and deemed exempt from full review, as no sensitive or identifying information was being collected from the respondents (Sterling IRB approval number APP819).

### Data Analysis

A sample size of 400 PCPs was deemed sufficient after a preliminary multivariable logit analysis using dummy data produced standard errors that were approximately 0.10 or less.<sup>21</sup>

Analysis of impact of the KidneyIntelX test result and other attributes on PCP decision-making was conducted using a multivariable logit model for each binary outcome (prescription of SGLT2 inhibitors, dose change for losartan, and referral to a nephrologist). The output of the logit model includes preference weights (beta coefficients) for each level of each attribute. Relative attribute importance was calculated as the difference in the minimum and maximum values of relative preference weights for levels in each attribute. These values were normalized to sum to 100%. Raw relative preference weights for each level were also converted to odds ratios and 95% CIs to assess the impact of the KidneyIntelX test result on decision outcomes compared with no test.

## RESULTS

### Demographic Characteristics

A total of 401 respondents completed the survey. The sample attrition leading to the final number of respondents included in this study can be found in [eAppendix E](#).

A total of 6104 invitations to the web survey were sent out via email: 670 physicians opened the email, 540 physicians clicked the link and entered the survey, and 401 physicians qualified based on the inclusion/exclusion criteria and completed the full survey. A total of 139 physicians were excluded because they did not meet inclusion criteria for the survey. The median time taken to complete the survey was 15.2 minutes.

The characteristics of the 401 qualified respondents who completed the survey can be found in a table in [eAppendix F](#). The geographic

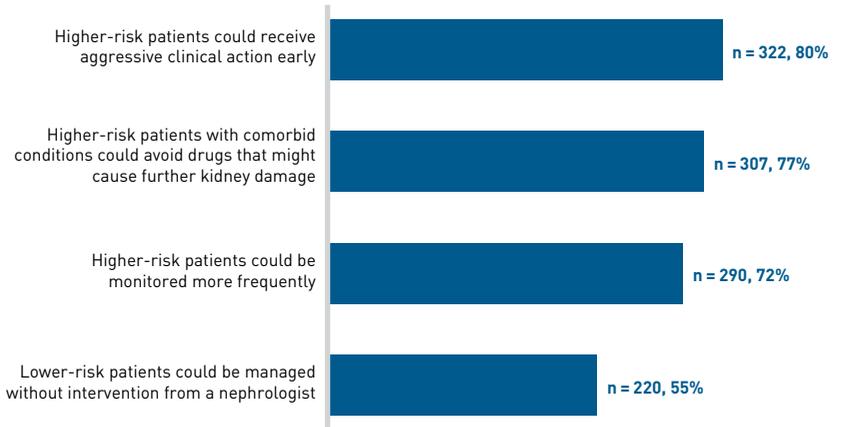
distribution of respondents was relatively even; the highest proportion of respondents was from the South (31%), followed by the Midwest (25%), which was representative of the geographic distribution in the United States.<sup>22</sup>

**Descriptive Findings**

PCPs in our study acknowledged the benefits of accurately assessing the risk of progressive decline in kidney function in both high-risk and low-risk patients with T2D (Figure 1).

PCPs reported several clinical benefits of assessing the risk of progressive kidney function decline. Approximately 80% (322/401) PCPs noted that risk assessment would support the decision to take more aggressive clinical action early in high-risk patients; 77% (307/401) suggested it would be useful to help avoid prescribing nephrotoxic drugs to high-risk patients; and 72% (290/401) indicated that with proper risk assessment, high-risk patients could be monitored more frequently. A relatively smaller yet substantial proportion (55%; 220/401) reported avoidance of unnecessary nephrologist visits in low-risk patients as a benefit. Almost 98% of PCPs in our sample indicated that they were somewhat, very, or extremely likely to order KidneyIntelX for their patients with DKD.

**FIGURE 1. Clinical Benefit of Assessing the Risk of Progressive Decline in Kidney Function in Patients With DKD<sup>a</sup>**



DKD, diabetic kidney disease.

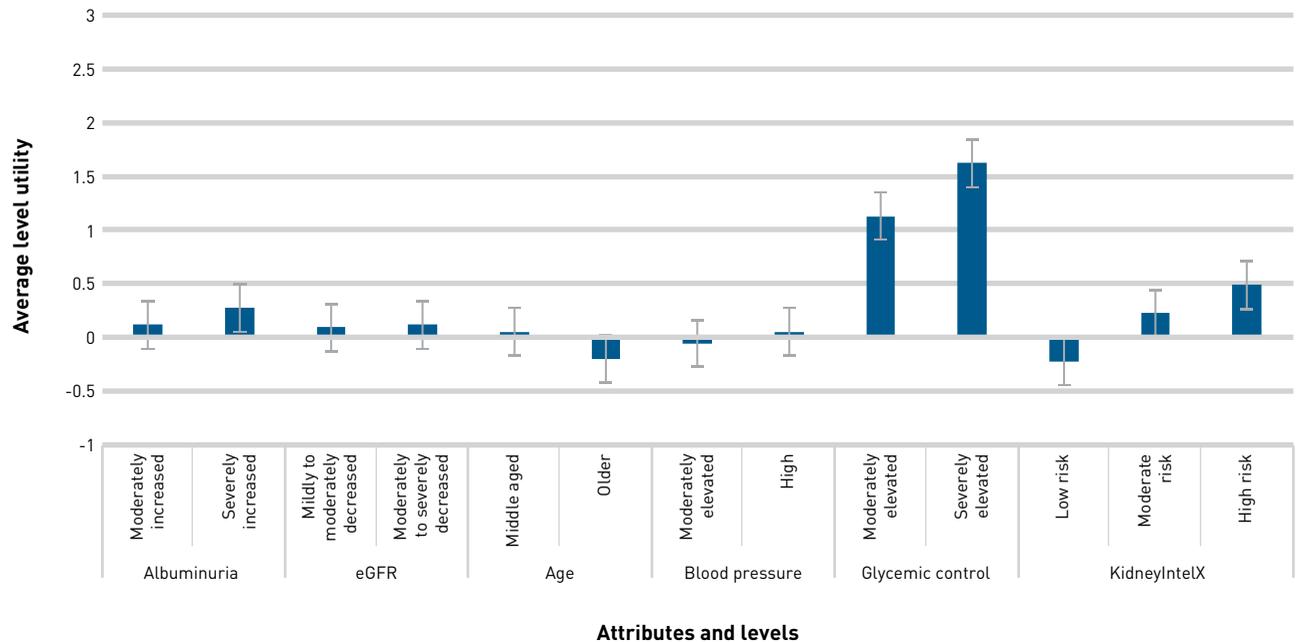
<sup>a</sup>Proportions of respondents identifying clinical benefits of accurate risk assessment are presented.

**Conjoint Analysis Findings**

The relative preference weights for each level of each patient attribute for the decisions to prescribe SGLT2 inhibitors, increase the dose of losartan, and refer patients to a nephrologist are presented in Figure 2. Severely increased albuminuria and a high-risk KidneyIntelX test

**FIGURE 2. Relative Preference Weights From Multivariable Logit Models<sup>a</sup>**

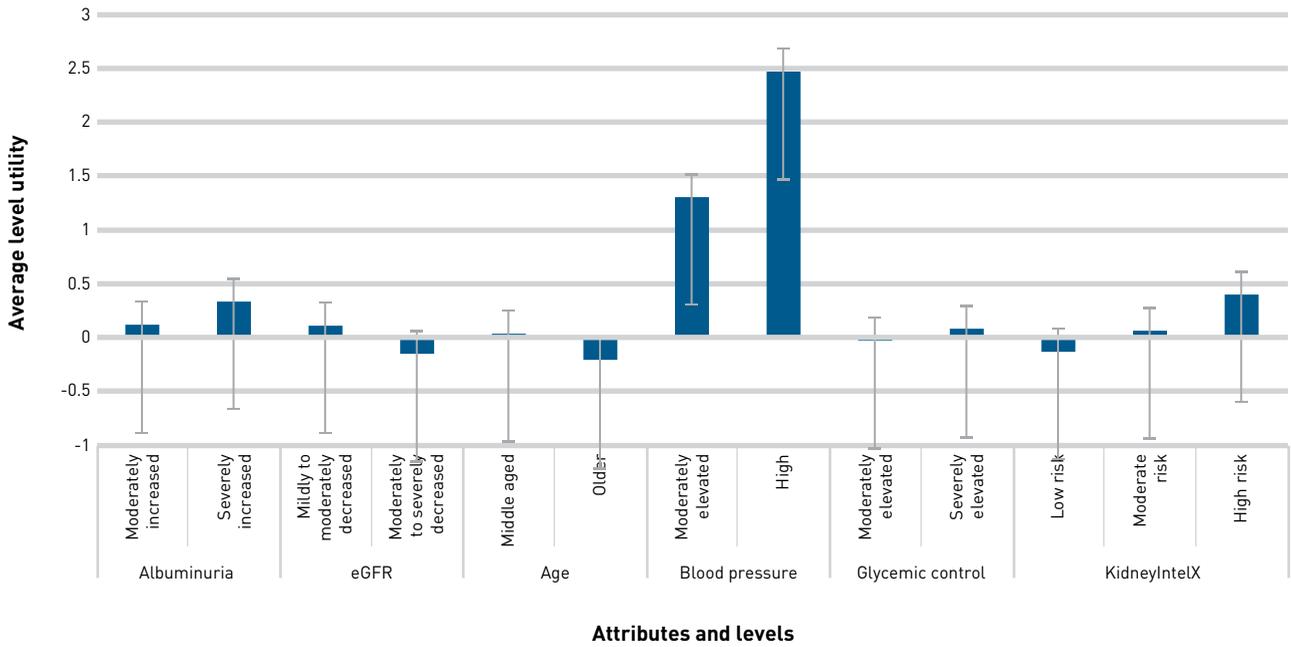
**A. Relative preference weights for SGLT2 inhibitor prescription**



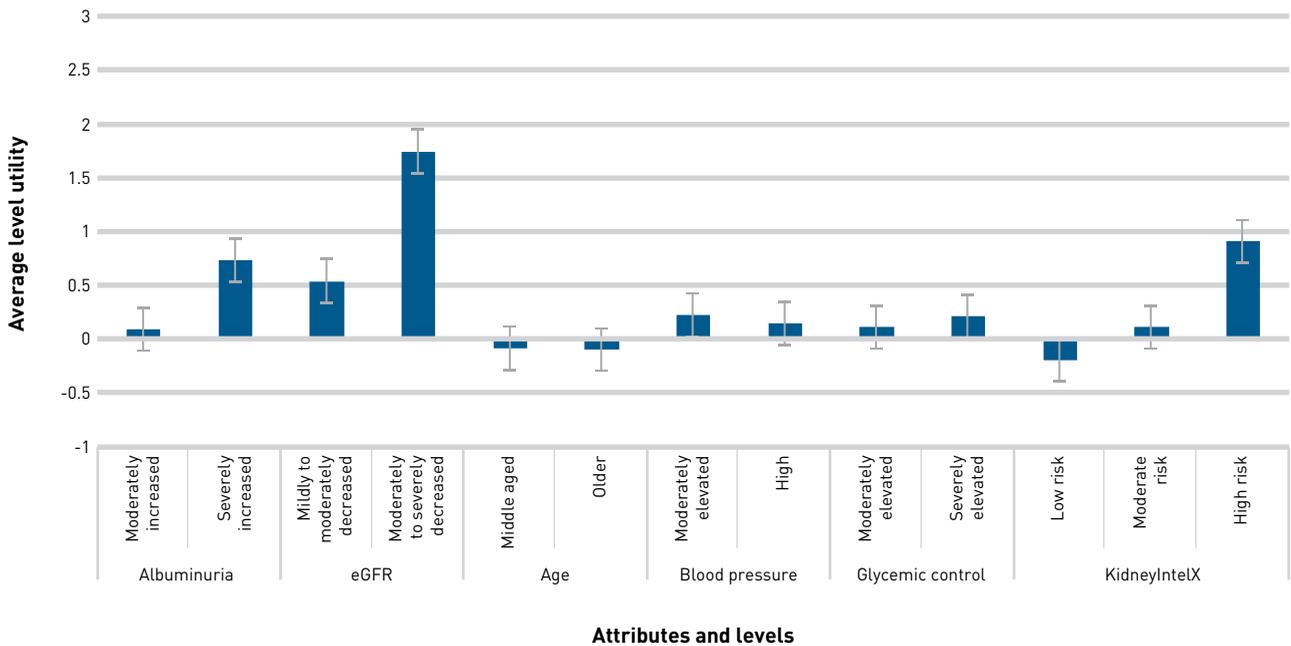
(continued)

**FIGURE 2. (Continued) Relative Preference Weights From Multivariable Logit Models<sup>a</sup>**

**B. Relative preference weights for losartan dose increase**



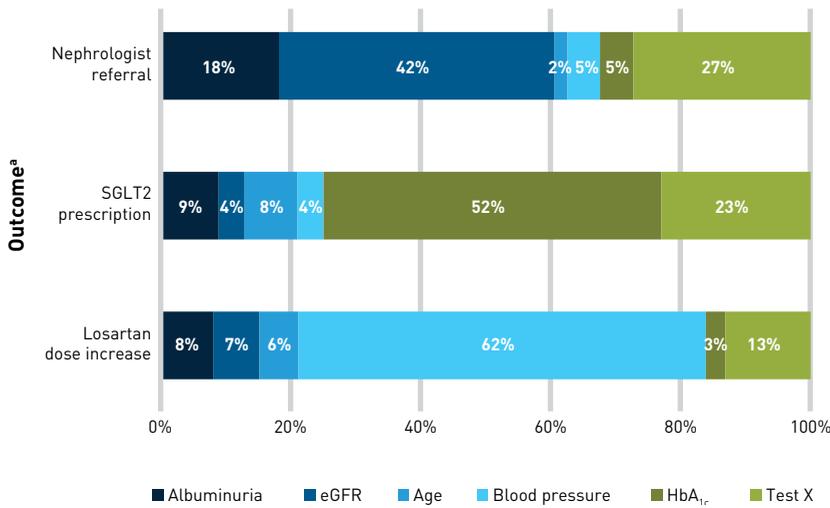
**C. Relative preference weights for nephrologist referral**



eGFR, estimated glomerular filtration rate; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; SGLT2, sodium-glucose cotransporter-2.

<sup>a</sup>Relative preference weights for levels of each attribute are presented compared with reference levels in each attribute, which include mildly increased albuminuria, mildly decreased eGFR, younger age, normal blood pressure, normal HbA<sub>1c</sub>, and no KidneyIntelX test. All preference weights presented in the figure are relative to these reference categories.

**FIGURE 3.** Relative Importance of KidneyIntelX Results and Other Attributes for Each Management Decision\*



eGFR, estimated glomerular filtration rate; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; SGLT2, sodium-glucose cotransporter-2.

\*Attribute importance values sum to 100% across attributes for each outcome assessed. The graph presents relative importance of each attribute for each outcome (physician decision-making).

result were the 2 levels that had significantly higher relative preference weights compared with their respective attribute level reference categories across all outcomes.

Figure 3 presents the overall relative importance of the attributes for the ranges of levels presented in the 3 outcomes tested in the conjoint analysis. For the decision to prescribe SGLT2 inhibitors, HbA<sub>1c</sub> was the most important attribute (relative importance, 52%), followed by the KidneyIntelX test result (23%). For the decision to increase losartan dose, blood pressure was the most important attribute (62%), followed by the KidneyIntelX test result (13%). For referral to a nephrologist, eGFR was the most important attribute (42%), followed by the KidneyIntelX test result (27%).

Table 2 displays odds ratios calculated from relative preference weights of the multivariable logit models.

A KidneyIntelX high-risk test result was associated with significantly higher odds (1.64 times) of prescribing SGLT2 inhibitors,

**TABLE 2.** ORs From Aggregate Logit Models Assessing the Impact of KidneyIntelX Test Results and Other Independent Variables on Physician Decision-making

Predictor variable	Level	Prescribing SGLT2 inhibitors with a DKD indication		Increasing losartan dose from 50 mg per day to 100 mg per day		Referral to a nephrologist	
		OR	95% CI	OR	95% CI	OR	95% CI
Albuminuria	Mildly increased	Ref	—	Ref	—	Ref	—
	Moderately increased	1.13	0.91-1.41	1.13	0.91-1.39	1.10	0.90-1.34
	Severely increased	1.32 <sup>a</sup>	1.06-1.65	1.40 <sup>a</sup>	1.13-1.73	2.08 <sup>a</sup>	1.70-2.55
eGFR	Mildly decreased	Ref	—	Ref	—	Ref	—
	Mildly to moderately decreased	1.10	0.89-1.37	1.12	0.90-1.39	1.71 <sup>a</sup>	1.40-2.10
	Moderately to severely decreased	1.13	0.90-1.41	0.86	0.69-1.07	5.73 <sup>a</sup>	4.63-7.08
Age	Younger	Ref	—	Ref	—	Ref	—
	Middle aged	1.06	0.86-1.30	1.04	0.85-1.27	0.92	0.76-1.11
	Older	0.83	0.67-1.01	0.81 <sup>a</sup>	0.66-0.99	0.91	0.75-1.09
Blood pressure	Normal	Ref	—	Ref	—	Ref	—
	Moderately elevated	0.95	0.78-1.15	3.69 <sup>a</sup>	3.07-4.43	1.25 <sup>a</sup>	1.03-1.50
	High	1.06	0.86-1.30	11.79 <sup>a</sup>	9.51-14.63	1.16	0.96-1.40
HbA <sub>1c</sub>	Normal	Ref	—	Ref	—	Ref	—
	Moderately elevated	3.09 <sup>a</sup>	2.55-3.74	0.97	0.80-1.18	1.12	0.92-1.35
	Severely elevated	5.06 <sup>a</sup>	4.12-6.22	1.08	0.89-1.32	1.24 <sup>a</sup>	1.03-1.49
KidneyIntelX risk result	No test	Ref	—	Ref	—	Ref	—
	Low risk	0.80	0.64-1.01	0.88	0.69-1.11	0.82	0.65-1.03
	Moderate risk	1.25	0.99-1.59	1.07	0.85-1.34	1.12	0.90-1.39
	High risk	1.64 <sup>a</sup>	1.29-2.08	1.49 <sup>a</sup>	1.17-1.89	2.47 <sup>a</sup>	1.99-3.08

DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; OR, odds ratio; ref, reference category; SGLT2, sodium-glucose cotransporter-2.

<sup>a</sup>Significant at  $\alpha = 0.05$ .

significantly higher odds (1.49 times) of increasing losartan dose, and significantly higher odds (2.47 times) of referring patients to a nephrologist compared with not having the test available, while controlling for other attributes. Interestingly, odds ratios for a low-risk test result were less than 1 across all outcomes when compared with no test, although these did not reach statistical significance.

## DISCUSSION

This study sought to assess the impact of a prognostic test on physician decision-making in the management of patients with DKD. The KidneyIntelX test result had a greater impact than albuminuria and eGFR in PCPs' decision to prescribe SGLT2 inhibitors and increase the dose of ARBs (losartan) and was second only to eGFR in the decision to refer patients to a nephrologist.

Timely treatment to help patients reach an HbA<sub>1c</sub> target of less than 7.0%, as well as the use of ACE inhibitors or ARBs to control their blood pressure, are beneficial in patients who are at high risk of progressive kidney function decline.<sup>23,24</sup> Despite this, data indicate that fewer than 50% of patients are treated appropriately with these agents.<sup>8</sup> Because 80% of PCPs in our study view early clinical action as a clinical benefit of assessing the risk of progressive decline in kidney function in patients with DKD, KidneyIntelX could be a very useful tool in this patient population. A major challenge to the early diagnosis and treatment of DKD is that patients with diabetes are neither routinely screened for deteriorating kidney function nor referred to nephrologists when needed.<sup>25-27</sup> This finding was corroborated in our study, with 72% of PCPs identifying the importance of frequent monitoring and 55% of PCPs emphasizing intervention by a nephrologist as a clinical need among patients with DKD. Given the shortcomings of current standard-of-care tests and high physician preference reported in our study, a prognostic test such as KidneyIntelX could address all the aforementioned needs and challenges by accurately assessing the risk of progressive decline in kidney function in patients with T2D.

Our study has 3 important findings regarding PCP decision-making for DKD patients. First, we found that the factors most associated with treatment decisions are, as expected, HbA<sub>1c</sub> for SGLT2 inhibitor prescriptions and blood pressure for losartan dose increase. This finding is not surprising, given that several preclinical studies and clinical trials of SGLT2 inhibitors, especially canagliflozin, have consistently provided evidence for reduction of albuminuria and preservation of kidney function.<sup>28,29</sup> Likewise, controlling blood pressure through the use of ACE inhibitors or ARBs is a common treatment strategy in patients with DKD because of the kidney-protective effects associated with these medications in the presence of albuminuria.<sup>30-32</sup> Clinical practice guidelines recommend that when eGFR falls below 30 mL/min/1.73 m<sup>2</sup>, patients with T2D should be referred to nephrologists.<sup>7</sup> Our study showed results that were in line with this, as eGFR was the most important attribute affecting nephrologist referrals. These findings are consistent with logical

and clinical expectations, thereby providing evidence in support of the robustness of our results.

Second, we found that routine clinical factors are not sufficient for decision-making pertaining to management of these patients. The finding that KidneyIntelX test results would affect decision-making more than albuminuria and eGFR for 2 of the 3 outcomes (ie, SGLT2 inhibitor prescription and losartan dose increase) provides strong evidence for the clinical utility of this test in the DKD management pathway. The addition of the KidneyIntelX test would significantly affect treatment and management decisions for high-risk patients based on the significantly higher odds ratios obtained for all outcomes compared with no test. Given that the model for KidneyIntelX includes uACR, eGFR, blood pressure, and HbA<sub>1c</sub>, along with blood-based protein biomarkers (sTNFR-1, sTNFR-2, and KIM-1), KidneyIntelX offers management recommendations based on more comprehensive information for physician decision-making compared with individual attributes that are currently used by PCPs to make these decisions. Moreover, clinical parameters in the KidneyIntelX test are multidimensional and additive to eGFR, which has limited predictive capability. Thus, even patients who actively manifest hyperfiltration or have a treatment-induced decline in eGFR can have a reliable and robust risk score for progression with minimal confounding by these external factors when using the KidneyIntelX test.

Third, we saw several interesting patterns in PCP decision-making based on the KidneyIntelX test results. A low-risk result was associated with lower odds of prescribing SGLT2 inhibitors, prescribing losartan, and referring patients to a nephrologist compared with no test. Although this odds ratio did not reach statistical significance, the directionality indicated that a low-risk result gave the PCPs more confidence to refrain from prescribing SGLT2 inhibitors. A similar pattern was observed for the other 2 outcomes, increasing the dose of losartan and nephrologist referral. This further demonstrates the utility of a prognostic test such as KidneyIntelX in avoiding unnecessary treatments and specialist visits in patients with low risk of progressive kidney function decline.

## Limitations

There are some limitations to this study. First, our findings are limited to the range of levels of key attributes included in this analysis and may not completely capture the scope of influence of other attributes on decision-making. However, the probability of this is very low, given that the attributes and levels included in this analysis were based on extensive secondary research and input from practicing clinical experts in the field of DKD. Second, to reduce burden, respondents were shown only a subset of the full factorial design of profiles that represented all the possible attribute and level combinations. However, the potential bias introduced from using a subset of profiles is minimal, because the 42 profiles shown to respondents (fractional factorial design) had a high D-efficiency (0.98), which is a measure of the design efficiency of the conjoint analysis (maximum possible D-efficiency = 1). Third,

this is not a real-world study measuring actual physician behavior in practice. However, whereas traditional surveys may suffer from social desirability bias, wherein survey respondents tend to answer questions in a manner that will be viewed favorably by others, our study instead uses a novel preference elicitation technique with an experimental design that assesses implicit preferences, thereby minimizing this bias to a significant degree.<sup>12</sup> Our survey also had test-retest reliability, demonstrated by the fact that both pretest participants chose the same response for the 2 hold-out cases. Finally, our study compared clinical utility of KidneyIntelX with the standard-of-care risk stratification currently being employed in practice (KDIGO risk stratification), as our goal was to derive practice-based utility. We did not test the utility of KidneyIntelX against alternative theoretical risk scores (eg, Kidney Failure Risk Equations) that predict kidney disease progression. The results of this study should be interpreted with this limitation in mind. Future studies could compare the performance and clinical utility of KidneyIntelX with other algorithms.

## CONCLUSIONS

A prognostic test such as KidneyIntelX that uses biomarkers and clinical parameters to better stratify patients by risk of kidney function decline would have a greater impact on physician decision-making than current standard-of-care tests. It addresses unmet needs identified in current practice and allows PCPs to act in the early stages of DKD progression before significant symptoms emerge. Our study shows that if tests such as KidneyIntelX were made readily accessible, PCPs would incorporate the test results into their treatment plan, ultimately making more informed decisions in the management of their patients with DKD, potentially resulting in improved outcomes. ■

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**eAppendix A. Net Reclassification from KDIGO Risk Strata to KidneyIntelX Risk Strata in Derivation and Validation Sample (Chan et al., 2021)<sup>11</sup>**

Derivation Sample		KidneyIntelX Score			Total
	KDIGO Strata	Low	Intermediate	High	
Composite Kidney Event	Moderately increased risk	15	35	20	70
	High Risk	1	17	28	46
	Very high risk	1	5	15	21
	<b>Total events</b>	<b>17</b>	<b>57</b>	<b>63</b>	<b>137</b>
No Kidney Event	Moderately Increased Risk	198	126	19	343
	High Risk	79	73	12	164
	Very high risk	13	20	9	42
	<b>Total Non-Events</b>	<b>290</b>	<b>219</b>	<b>40</b>	<b>549</b>

**Reclassified – Derivation sample**

	Higher		Lower	
	n	%	n	%
Event	83	60.6	7	5.1
Non-event	157	28.6	112	20.4

Validation Sample		KidneyIntelX Score			Total
	KDIGO Strata	Low	Intermediate	High	
Composite Kidney Event	Moderately increased risk	14	21	14	46
	High Risk	6	12	18	36
	Very high risk	0	4	15	19
	<b>Total events</b>	<b>20</b>	<b>37</b>	<b>47</b>	<b>104</b>
No Kidney Event	Moderately Increased Risk	132	80	11	223
	High Risk	53	39	13	105
	Very high risk	7	16	5	28
	<b>Total Non-Events</b>	<b>192</b>	<b>135</b>	<b>29</b>	<b>356</b>

**Reclassified – Validation sample**

	Higher		Lower	
	n	%	n	%
Event	53	51.0	10	9.6
Non-event	104	29.2	76	21.3

**eAppendix B. KidneyIntelX treatment and management recommendations by risk result**

<b>Recommendations by Test X Risk Result</b>		
<b>Low</b>	<b>Intermediate</b>	<b>High</b>
<ul style="list-style-type: none"> <li>• Monitor 1x/year</li> <li>• Maintain current level of treatment with ACEi/ARBs, antihypertensives, and anti-hyperglycemic agents</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor 2x/year</li> <li>• Medication intensification:               <ul style="list-style-type: none"> <li>○ Treat with ACEi or ARB and anti-hypertensives</li> <li>○ Consider SGLT2 inhibitors (if clinically indicated)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Monitor 3x/year</li> <li>• Medication intensification:               <ul style="list-style-type: none"> <li>○ Titrate ACEi or ARBs to maximally tolerated dose</li> <li>○ Strongly consider SGLT2 inhibitors (unless contraindicated)</li> </ul> </li> <li>• Refer patient to nephrologist</li> </ul>

## eAppendix C. Screener and Survey Questions

### SCREENER

- i. What is your main specialty? *[Randomize]*
- a. Family medicine physician *[CONTINUE]*
  - b. Primary care/internal medicine physician *[CONTINUE]*
  - c. Diabetologist **TERMINATE IMMEDIATELY**
  - d. Endocrinologist **TERMINATE IMMEDIATELY**
  - e. Gastroenterologist **TERMINATE IMMEDIATELY**
  - f. Urologist **TERMINATE IMMEDIATELY**
  - g. None of the above *[Exclusive, Anchor]* **TERMINATE IMMEDIATELY**
- ii. Are you board-certified in your specialty?
- a. Yes *[CONTINUE]*
  - b. No **TERMINATE at end of screener**
- iii. Approximately how many type 2 diabetes patients have you seen in the past 6 months?  
\_\_\_\_\_ type 2 diabetes patient(s) in the past 6 months  
**[RANGE for text box 0 – 99,999. No decimals] [TERMINATE at end of screener IF 0-20] Error message: please provide a number between 0 and 99,999**
- iv. *[If question iii is >0]* Approximately how many type 2 diabetes patients have you **tested for indications of kidney disease** in the past 6 months?  
I have tested \_\_\_\_\_ type 2 diabetes patient(s) for indications of kidney disease in the past 6 months  
**[RANGE for text box 0 – value provided in prior question. No decimals] [TERMINATE at end of screener IF 0-10] Error message: Please provide a number no greater than [fill in prior response], the number of type 2 diabetes patients you saw in the past 6 months**
- v. *[If question iii >0]* Approximately what percentage of your type 2 diabetes patients have **diabetic kidney disease (DKD)**?
- a. \_\_\_\_\_ % of my type 2 diabetes patients have DKD  
**[RANGE for text box 0 – 100. No decimals] [TERMINATE at end of screener IF 0] [Error message: please provide a number between 0 and 100]**
- vi. Approximately how long have you been practicing in your current specialty?
- a. \_\_\_\_\_ year(s) **[TERMINATE at end of screener IF <2] [RANGE for text box 0 – 99; no decimals]**
- vii. In what setting of care do you treat **the majority of** your patients? *Select only one response. [Randomize]*  
*[No hard quotas, but range of responses desired.]*
- a. Office-Based Private Practice *[CONTINUE]*
  - b. Community Hospital *[CONTINUE]*
  - c. Academic Medical Center *[CONTINUE]*
- viii. Approximately what percentage of your time is spent performing direct clinical care (versus administrative duties)?  
\_\_\_\_\_ % of my time is spent performing direct clinical care  
  
*[Range for text box: 0-100; no decimals.]*  
*IF clinical care ≥50%* *[CONTINUE]*  
*IF clinical care ≥0% and <50%* **TERMINATE AT END OF SCREENER**
- ix. In which state is your practice located? *[No hard quotas, but range of responses desired.]*

- a. Alabama
- b. Alaska
- c. Arizona
- d. Arkansas
- e. California
- f. Colorado
- g. Connecticut
- h. Delaware
- i. District of Columbia
- j. Florida
- k. Georgia
- l. Hawaii
- m. Idaho
- n. Illinois
- o. Indiana
- p. Iowa
- q. Kansas
- r. Kentucky
- s. Louisiana
- t. Maine *END IMMEDIATELY (because of restrictive market research rules in this state)*
- u. Maryland
- v. Massachusetts
- w. Michigan
- x. Minnesota
- y. Mississippi
- z. Missouri
- aa. Montana
- bb. Nebraska
- cc. Nevada
- dd. New Hampshire
- ee. New Jersey
- ff. New Mexico
- gg. New York
- hh. North Carolina
- ii. North Dakota
- jj. Ohio
- kk. Oklahoma
- ll. Oregon
- mm. Pennsylvania
- nn. Rhode Island
- oo. South Carolina
- pp. South Dakota
- qq. Tennessee
- rr. Texas
- ss. Utah
- tt. Vermont *END IMMEDIATELY (because of restrictive market research rules in this state)*
- uu. Virginia
- vv. Washington
- ww. West Virginia
- xx. Wisconsin
- yy. Wyoming

Target regions for programmer to create:

-Northeast (CT, ME, MA, NH, NJ, NY, PA, RI, VT)

-Midwest (IL, IN, IA, KS, MI, MN, MO, NE, ND, OH, SD, WI)

-South (AL, AR, DE, DC, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV)  
 -West (AK, AZ, CA, CO, HI, ID, MT, NV, NM, OR, UT, WA, WY)

**WELCOME**

The purpose of this survey is to obtain your insights on a test that assesses the risk of progressive decline in kidney function in patients with diabetic kidney disease (DKD).

The survey is confidential and should take about 15 minutes. We combine all answers we receive to help us understand clinicians’ overall perspectives. We recommend you finish the survey in one sitting. If you are unable to complete the survey in one sitting, you may save your work and return at any time. Once you have completed the study, please allow time for us to process your incentive. You must fully complete the survey to receive the incentive.

**Please do NOT use the arrow in your browser to return to a previous page in the survey.** (Using this arrow may prevent you from completing the survey.)

Thank you for your time and opinions!

**SURVEY**

**Diabetic Kidney Disease Care Pathway**

1. Please estimate the percentage of your type 2 diabetes patients with DKD who have the following types of health insurance. (The total must equal 100%.) *[Allowable answers 0-100; no decimals]*
  - a. \_\_\_\_\_ % Private payer/commercial plans
  - b. \_\_\_\_\_ % Medicare
  - c. \_\_\_\_\_ % Medicaid
  - d. \_\_\_\_\_ % VA/DOD/Military (e.g. Tricare)
  - e. \_\_\_\_\_ % Other insurance
  - f. \_\_\_\_\_ % Self-pay/uninsured  
=100%
  - or
  - g. I don’t know *[exclusive]*
  
2. Which test(s) do you conduct/request for your type 2 diabetes patients with DKD? Select all that apply. *[Randomize]*
  - a. eGFR
  - b. Urine albumin-to-creatinine ratio/ Albuminuria/Microalbumin
  - c. Blood urea nitrogen
  - d. HbA1c
  - e. Blood pressure
  - f. Other \_\_\_\_\_ *[Anchor, show text box]*

For your reference, the stages of DKD are outlined below:

Stages	GFR Descriptions	eGFR range (ml/min per 1.73m <sup>2</sup> )	Albuminuria
Stage 1	Normal or high	≥90	Moderately or severely increased
Stage 2	Mildly decreased	60-89	
Stage 3a	Mildly to moderately decreased	45-59	Any level

Stage 3b	Moderately to severely decreased	30-44	
Stage 4	Severely decreased	15-29	
Stage 5	Kidney failure	<15	

Please consider your type 2 diabetes patients with DKD.

What is the percent distribution by stage **at DKD diagnosis**? Note total must add to 100%.

- a. Stage 1 \_\_\_\_\_%
  - b. Stage 2 \_\_\_\_\_%
  - c. Stage 3a \_\_\_\_\_%
  - d. Stage 3b \_\_\_\_\_%
  - e. Stage 4 \_\_\_\_\_%
  - f. Stage 5 \_\_\_\_\_%
- =100%

*[Whole numbers only 0-100, no decimals] [Show running total] [% should add up to 100%.]*

3. Overall, how satisfied are you with current tests/methods for **assessing a type 2 diabetes patient’s risk for kidney function decline** on a scale of 1 to 5, where **1 is “extremely dissatisfied”** and **5 is “extremely satisfied”**?

*[Radio buttons provided]*

1	2	3	4	5
Extremely dissatisfied	Somewhat dissatisfied	Neither satisfied nor dissatisfied	Somewhat satisfied	Extremely satisfied

4. What are the diagnostic challenges pertaining to DKD in type 2 diabetes patients? Select all that apply.

*[Randomize]*

- a. No test is available to predict accurately whether the patient will develop kidney function decline before clinical symptoms appear
- b. Difficult to detect existing diabetic kidney disease in early stages (e.g., at stage 1 and 2)
- c. No test to clearly identify what stage of DKD the patient is in
- d. Other \_\_\_\_\_ *[Anchor, show text box]*
- e. None of the above *[Anchor; exclusive]*

5. At what point would you typically refer a type 2 diabetes patient to a nephrologist, if at all?

- a. At diagnosis of type 2 diabetes
- b. At diagnosis of DKD, irrespective of the stage at diagnosis
- c. When the patient is in early-stage DKD (eGFR levels >59)
- d. When the patient is in mid-stage DKD (eGFR levels 30-59)
- e. Upon progression to late-stage DKD (eGFR levels <30)
- f. I do not refer to a nephrologist
- g. Other \_\_\_\_\_ *[show text box]*

6. What would be the primary clinical benefits of accurately assessing the risk of **progressive decline in kidney function** in type 2 diabetes patients with DKD, if any? Select all that apply. *[Randomize]*
- Higher-risk patients could receive aggressive clinical action early
  - Higher-risk patients with comorbid conditions could avoid drugs that might cause further kidney damage
  - Higher-risk patients could be monitored more frequently
  - Lower-risk patients could be managed without intervention from a nephrologist
  - Other \_\_\_\_\_ *[Anchor, show text box]*

7. For the next set of questions, **please assume you have tools at your disposal that allow you to determine the risk of progressive decline in kidney function in type 2 diabetes patients with DKD.**

How would you treat most type 2 diabetes patients in early stages (1-3) of DKD who are considered to be at **low risk of progressive decline in kidney function**, specifically with respect to their diabetes medications? Select all that apply.

- Metformin
  - Meglitinides (e.g., nateglinide)
  - Thiazolidinediones (e.g., pioglitazone)
  - DPP4 inhibitors (e.g., sitagliptin)
  - Sulfonylureas (e.g., glipizide)
  - GLP1-RAs (e.g., exenatide)
  - SGLT2 inhibitors (e.g., canagliflozin)
  - Alpha-glucosidase inhibitors (e.g., acarbose)
  - Insulin
  - None of the above *[exclusive]*
8. How would you treat type 2 diabetes patients in the early stages (1-3) of DKD once they are identified as being at **increased risk of progressive decline in kidney function**, specifically with respect to their diabetes medications? *[If 9a is visible]* Select all that apply.
- [Show if prior question is not "none of the above" (8j)]* I would increase the dose of current diabetes medications to maximum tolerated
  - [Show if respondent did not select "SGLT2 inhibitors" in prior question (8g)]* I would start SGLT2 inhibitor
  - [Show if respondent did select "SGLT2 inhibitors" in prior question (8g)]* I would increase/optimize dose of SGLT2 inhibitor
  - I would not recommend the treatment option(s) described *[Anchor, exclusive]*
9. How would you treat most type 2 diabetes patients in the early stages (1-3) of DKD who are considered to be at **low risk of progressive decline in kidney function**, specifically with respect to their blood pressure medications? Select all that apply. *[Randomize]*
- ACE/ARB inhibitors
  - Thiazide diuretics
  - Mineralocorticoid Receptor Antagonists (MRAs) (e.g., eplerenone)
  - Calcium channel blockers
  - Beta blockers
  - None of the above *[Anchor, exclusive]*
10. How would you treat type 2 diabetes patients in the early stages (1-3) of DKD once they are identified as being at **increased risk of progressive decline in kidney function**, specifically with respect to their blood pressure medications? Select all that apply. *[Randomize]*

- a. *[Show if ACE/ARB selected in prior question]* Increase ACE/ARB inhibitor dose (if not already at the maximum tolerated dose)
- b. *[Show if ACE/ARB not selected in prior question]* Start ACE/ARB inhibitor
- c. *[Show if at least one of the following (thiazide diuretics, selective MRAs, calcium channel blockers, beta blockers) was selected in prior question]* Increase dose of other blood pressure medications other than ACE/ARB inhibitors
- d. *[Show if not one of the following were selected: (thiazide diuretics or selective MRAs or calcium channel blockers or beta blockers) was selected in prior question]* Start thiazide diuretics, selective MRAs, calcium channel blockers, or beta blockers
- e. None of the above *[Anchor, exclusive]*

11. About what percentage of your type 2 diabetes patients in the early-to-mid stages of DKD (eGFR  $\geq$ 30) follow the treatment protocol you recommend for managing DKD? \_\_\_\_\_% of patients *[Whole numbers only 0-100, no decimals]*

### **Adoption of Test X**

Please review the information about diabetic kidney disease and Test X.

As you continue taking the survey, you will be able to click on a link to refer back to this test description. (If you do click on the link to view the test description again, you can return to the survey questions by clicking on the “X” at the top right of the test description.) *[Show profile, including background.]*

*[Present subsequent questions about Test X through the conjoint with a link to description of Test X (test description only (pages 2 and 3), not background). Questions after the conjoint do not need this link.]*

12. *[New page]* For the remainder of the survey, please assume the following unless otherwise specified:

- Test X is commercially available and has been FDA-cleared.
- The cost of Test X is not an issue for you or your patients.

On a scale of 1-5, where **1 is “not at all likely”** and **5 is “extremely likely”**, what is your likelihood of ordering this test for predicting the risk of progressive decline in kidney function in your patients with type 2 diabetes with DKD?

*[Radio buttons provided]*

1	2	3	4	5
Not at all likely	Not very likely	Somewhat likely	Very likely	Extremely likely

13. For what percentage of your type 2 diabetes patients with DKD would you order **Test X** in a typical year? \_\_\_\_\_% *[Whole number 0-100 only, no decimals]*

14. *[If test use (q14) > 0% AND if more than 1 stage in q3 shows a value >0]* Please indicate the distribution, **by stage**, of the type 2 diabetes patients **with DKD** for whom you would use Test X. The total must equal 100%. *[Values 0-100 allowed, no decimals. Total must =100] [Show running total]*

- a. *[Show if q3a>0]* Stage 1 (**normal or high GFR and** moderately or severely increased albuminuria) \_\_\_\_\_%
- b. *[Show if q3b>0]* Stage 2 (**mildly decreased GFR and** moderately or severely increased albuminuria) \_\_\_\_\_%

- c. *[Show if q3c>0]* Stage 3a (**mildly-to-moderately decreased GFR**, regardless of albuminuria level) \_\_\_\_\_%
- d. *[Show if q3d>0]* Stage 3b (**moderately-to-severely decreased GFR**, regardless of albuminuria level) \_\_\_\_\_%  
=100% or
- e. I don't know *[Exclusive]*

### **Conjoint Analysis**

#### **Current Practice Patterns and Clinical Positioning** *[Aim: Understand the influence of specific risk factors on clinician decision-making]*

It is advisable and preferred that you finish the rest of the survey in one sitting if possible.

15. *[new page]* For the following questions you will be presented with hypothetical profiles of **type 2 diabetes patients with DKD**. You will be asked about your clinical recommendations based on descriptions of the following risk factors: eGFR, albuminuria, HbA1c, age, and blood pressure, as well as the results of Test X, where applicable.

Please assume the following:

- The cost of Test X is not an issue for you and your patients
- Test X is commercially available and has been FDA-cleared
- Your practice has adopted Test X
- Patients have not been consulting a nephrologist
- Patients have normal potassium levels

Please pay close attention and answer as you believe you would act in clinical practice. This will help ensure the test is optimized for the patients where it is needed most.

- You will see 8 screens with 1 patient per screen.

You will be able to click on the link to refer back to the test description as necessary. (If you do click on the link to view the test description again, you can return to the survey questions by clicking on the “X” at the top right of the test description.)

*[New page and keep this text here until all questions under this section have been answered]*

*[For patient 1]* You will be asked 3 clinical decision questions about the patient on this page.

For this type 2 diabetes patient with DKD and for all patients presented on subsequent pages, please assume the following:

The patients

- Have been receiving 1000 mg of metformin twice a day
- Have been receiving 50 mg of losartan per day
- Have no contraindications to or higher-than-average risk of side-effects from SGLT2 inhibitors or ACE inhibitors

*[For patients 2-8]*

You will be asked 3 clinical decision questions about the **new patient** on this page.

(For your reference, the “Recommendations by Test X Risk Result” table you have already seen is presented **again** below.) If needed, you can also click on the link below to review the patient assumptions that apply to all patients in this exercise. [*Show link to the paragraph above starting “The patients”*]

Recommendations by Test X Risk Result		
Low	Intermediate	High
<ul style="list-style-type: none"> <li>• Monitor 1x/year</li> <li>• Maintain current level of treatment with ACEi/ARBs, antihypertensives, and anti-hyperglycemic agents</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor 2x/year</li> <li>• Medication intensification:               <ul style="list-style-type: none"> <li>○ Treat with ACEi or ARB and anti-hypertensives</li> <li>○ Consider SGLT2 inhibitors (if clinically indicated)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Monitor 3x/year</li> <li>• Medication intensification:               <ul style="list-style-type: none"> <li>○ Titrate ACEi or ARBs to maximally tolerated dose</li> <li>○ Strongly consider SGLT2 inhibitors (unless contraindicated)</li> </ul> </li> <li>• Refer patient to nephrologist</li> </ul>

	Patient 1
Albuminuria	
eGFR	
Blood pressure	
Glycemic control (HbA1c)	
Age	
Test result	

[1]

Based on the clinical data provided, would you:	<input type="checkbox"/> Prescribe SGLT2s that have a DKD indication <input type="checkbox"/> Not prescribe SGLT2s that have a DKD indication
---	--

[2]

Based on the clinical data provided, would you	<input type="checkbox"/> Increase losartan dose to 100 mg per day <input type="checkbox"/> Continue losartan dose of 50 mg per day
--	---

[3]

Based on the clinical data provided, would you:	<input type="checkbox"/> Refer to a nephrologist <input type="checkbox"/> Not refer to a nephrologist
---	--

*[After patient 4 please show a new page with the following text only:]*

“You have answered questions about 4 patients and are halfway through this patient treatment exercise. We understand that these questions can be a bit tedious, but please pay close attention and answer as you believe you would act in clinical practice.”

### **Reaction to Test X**

16. What are the benefits of Test X, if any? Select all that apply. *[Randomize]*
- a. Test X's **positive predictive value (i.e., ability to avoid false positives) is 69%**
  - b. Test X's **negative predictive value (i.e., ability to avoid false negatives) is 93%**
  - c. Test X has a **fast turnaround time (7 days)**
  - d. Test X can serve as **motivation for patients to make lifestyle changes**
  - e. Test X can **increase patient compliance with treatment recommendations**
  - f. Test X **can rule out patients at low risk of progressive decline in kidney function**
  - g. Test X **can inform treatment changes** for diabetes and hypertension
  - h. Test X **can improve clinical outcomes** in DKD patients through appropriate therapeutic interventions
  - i. Test X **can save health care costs** by reducing inappropriate treatment and / or DKD progression, dialysis, and kidney transplants
  - j. Other \_\_\_\_\_ *[Anchor, show text box]*
  - k. None of the above *[anchor; exclusive]*
17. What are the limitations of Test X, if any? Select all that apply. *[Randomize]*
- a. Test X **requires a blood draw**
  - b. *[Do not show if q17=a]* Test X's **positive predictive value (i.e., ability to avoid false positives) is 69%, which is not high enough**
  - c. *[Do not show if q17=b]* Test X's **negative predictive value (i.e., ability to avoid false negatives) is 93%, which is not high enough**
  - d. *[Do not show if q17=c]* Test X has a **slow turnaround time (7 days)**
  - e. I am concerned about the potentially high **cost or lack of coverage** of Test X
  - f. Test X **might not be available in my preferred lab**
  - g. Patient data such as **UACR, eGFR, serum calcium, HbA1c, systolic blood pressure, platelets, and AST are needed** as an input for the Test X algorithm
  - h. Test X is **not included in guidelines**
  - i. Test X **might not change patient management**
  - j. I am **skeptical of artificial intelligence**
  - k. Other \_\_\_\_\_ *[Anchor, show text box]*
  - l. None of the above *[anchor; exclusive]*
18. *[If concerned about turnaround time q18d]* What is the maximum acceptable turnaround time for you to order Test X? *[Show error message "The maximum turnaround time must be less than 7 days."]*
- a. \_\_\_\_\_ Day(s) *[must be less than 7; 1 decimal allowed]*
19. *[If test use q14 > 0%]* How often do you expect you would re-test type 2 diabetes patients with DKD who have the following results with Test X (assuming the cost of Test X is not an issue for you and your patients)? *[values from >0 to 99. One decimal allowed]*
- a. **Low risk result: Every \_\_\_\_\_ month(s)** *[Show error message if low risk result number is not smaller than the intermediate and high risk result numbers]*

- b. Intermediate risk result: Every \_\_\_\_\_ month(s) *[Show error message if intermediate risk result number is not smaller than high risk result number]*
- c. High risk result: Every \_\_\_\_\_ month(s)
- d. I don't know *[Exclusive]*

***Follow-up***

20. *[Optional]* If you have any additional comments about Test X or your experience taking this survey, please let us know.

\_\_\_\_\_ *[Show text box]*

*[Show on same page as above.]* Thank you for your time and thoughtfulness in responding to our survey.

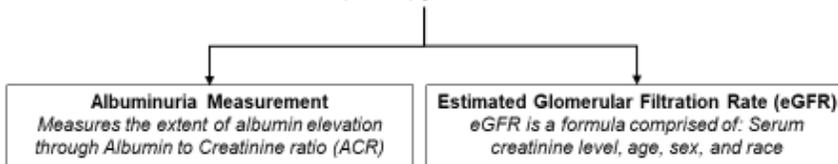
## eAppendix D. Product Profile

### Diabetic Kidney Disease (DKD) Background

#### The Problem

#### Current Methods of DKD Diagnosis and Assessment of Risk of Kidney Function Decline

DKD is currently diagnosed and monitored through two primary methods recommended in the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines:



*These tests fail to accurately identify up to 50% of patients with DKD who will experience progressive decline in kidney function in the future*

#### Outcomes

- DKD progression can lead to adverse outcomes, including cardiovascular events, and increased costs at each stage
- Unmanaged DKD can ultimately lead to end stage kidney disease (ESKD), which requires dialysis or a kidney transplant
- DKD patients in any stage can progress to dialysis if their DKD is not appropriately managed

## Test X: Artificial Intelligence (AI) In Vitro Kidney Diagnostic

<p><b>Test X Description</b></p>	<p>Test X uses the following:</p> <ul style="list-style-type: none"> <li>validated <b>blood-based protein biomarkers (sTNFR-1, sTNFR-2, and KIM-1)</b> from a <b>standard blood draw</b></li> <li><b>personalized patient data (eGFR, UACR, serum calcium, HbA1c, systolic blood pressure, platelets, and AST )</b> from the <b>electronic health record (EHR)</b></li> <li><b>an artificial intelligence-enabled algorithm</b> to stratify patients as <b>high, intermediate, or low-risk</b> for progressive decline in kidney function including <b>end stage kidney disease (ESKD)</b></li> </ul>																																														
<p><b>Target Population</b></p>	<ul style="list-style-type: none"> <li>Type 2 diabetes patients with DKD (Stages 1-3b, excluding G1&amp;A1 and G2&amp;A1)</li> </ul> <div style="border: 1px dashed black; padding: 5px; margin: 10px 0;"> <p><b>Target Population</b> Targets ambiguous areas of clinical decision making in Stages 1, 2, and 3</p> </div> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="2" rowspan="2"></th> <th colspan="3">Albuminuria stages, descriptions, and range</th> </tr> <tr> <th>A1</th> <th>A2</th> <th>A3</th> </tr> </thead> <tbody> <tr> <td colspan="2"></td> <td>Normal to mildly increased &lt;30 mg/g</td> <td>Moderately increased 30-300 mg/g</td> <td>Severely increased &gt;300 mg/g</td> </tr> <tr> <th rowspan="5">GFR stages, descriptions, and range (ml/min per 1.73m<sup>2</sup>)</th> <th>Stage 1 (G1)</th> <td>Normal or high ≥90</td> <td style="background-color: #ffff00;"></td> <td style="background-color: #ffcc00;"></td> </tr> <tr> <th>Stage 2 (G2)</th> <td>Mildly decreased 60-89</td> <td style="background-color: #ffff00;"></td> <td style="background-color: #ffcc00;"></td> </tr> <tr> <th>Stage 3 (G3a)</th> <td>Mildly to moderately decreased 45-59</td> <td style="background-color: #ffff00;"></td> <td style="background-color: #ffcc00;"></td> </tr> <tr> <th>Stage 3 (G3b)</th> <td>Moderately to severely decreased 30-44</td> <td style="background-color: #ffcc00;"></td> <td style="background-color: #ff0000;"></td> </tr> <tr> <th>Stage 4 (G4)</th> <td>Severely decreased 15-29</td> <td style="background-color: #ff0000;"></td> <td style="background-color: #ff0000;"></td> </tr> <tr> <th>Stage 5 (G5)</th> <td>Kidney failure &lt;15</td> <td style="background-color: #ff0000;"></td> <td style="background-color: #ff0000;"></td> </tr> </tbody> </table> <p style="margin-top: 10px;"><i>Legend</i></p> <table style="width: 100%; text-align: center;"> <tr> <td style="width: 25%; background-color: #008000; height: 15px;"></td> <td style="width: 25%; background-color: #ffff00; height: 15px;"></td> <td style="width: 25%; background-color: #ffcc00; height: 15px;"></td> <td style="width: 25%; background-color: #ff0000; height: 15px;"></td> </tr> <tr> <td>Low Risk</td> <td>Moderately Increased Risk</td> <td>High Risk</td> <td>Very High Risk</td> </tr> </table>			Albuminuria stages, descriptions, and range			A1	A2	A3			Normal to mildly increased <30 mg/g	Moderately increased 30-300 mg/g	Severely increased >300 mg/g	GFR stages, descriptions, and range (ml/min per 1.73m <sup>2</sup> )	Stage 1 (G1)	Normal or high ≥90			Stage 2 (G2)	Mildly decreased 60-89			Stage 3 (G3a)	Mildly to moderately decreased 45-59			Stage 3 (G3b)	Moderately to severely decreased 30-44			Stage 4 (G4)	Severely decreased 15-29			Stage 5 (G5)	Kidney failure <15							Low Risk	Moderately Increased Risk	High Risk	Very High Risk
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<p><b>Turnaround Time</b></p>	<ul style="list-style-type: none"> <li>7 days</li> </ul>																																														
<p><b>Value Proposition</b></p>	<ul style="list-style-type: none"> <li><b>Delays/prevents progression to ESKD</b> through more accurate assessment of risk of progressive decline in kidney function and earlier use of medical interventions proven to slow progression             <ul style="list-style-type: none"> <li>Identifies high-risk DKD patients who are candidates for early, more aggressive clinical action and preventive measures</li> <li>Allows low-risk DKD patients to be managed at primary care level</li> <li>Maximizes patient compliance by educating patients and clinicians</li> </ul> </li> </ul>																																														

## Test X Delivers Actionable Assessment of the Risk of Kidney Function Decline

<p><b>Test X Validation Study Results</b></p>	<ul style="list-style-type: none"> <li>• <b>93% negative predictive value (NPV)</b> for progression in patients scored as low-risk with test X versus <b>85% with Standard Risk Scoring</b> based on KDIGO <ul style="list-style-type: none"> <li>○ In other words, <b>low scoring patients have a 93% chance of not experiencing progression</b> within 5 years</li> </ul> </li> <li>• <b>69% positive predictive value (PPV)</b> for progression in patients scored as high-risk by test X versus <b>40% with Standard Risk Scoring</b> based on KDIGO <ul style="list-style-type: none"> <li>○ In other words, <b>high scoring patients have a 69% chance of experiencing progression</b> within 5 years</li> </ul> </li> <li>• <b>High scoring patients are 10 times more likely to experience progression of DKD</b> than low-risk patients</li> </ul>
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### A Holistic Approach Based on Risk-specific Recommendations

<p><b>Test X Score</b></p>	<ul style="list-style-type: none"> <li>• The test score ranges from <b>0 (lowest risk) to 100 (highest risk)</b> and correlates with the probability of progressive decline in kidney function in the tested population</li> </ul>
----------------------------	--

#### Low



#### Low score recommendations:

- Monitor 1x/year
- Maintain current level of treatment with ACEi/ARBs, antihypertensives, and anti-hyperglycemic agents

#### Intermediate



#### Intermediate score recommendations:

- Monitor 2x/year
- Medication intensification:
  - Treat with ACEi or ARB and anti-hypertensives
  - Consider SGLT2 inhibitors (if clinically indicated)

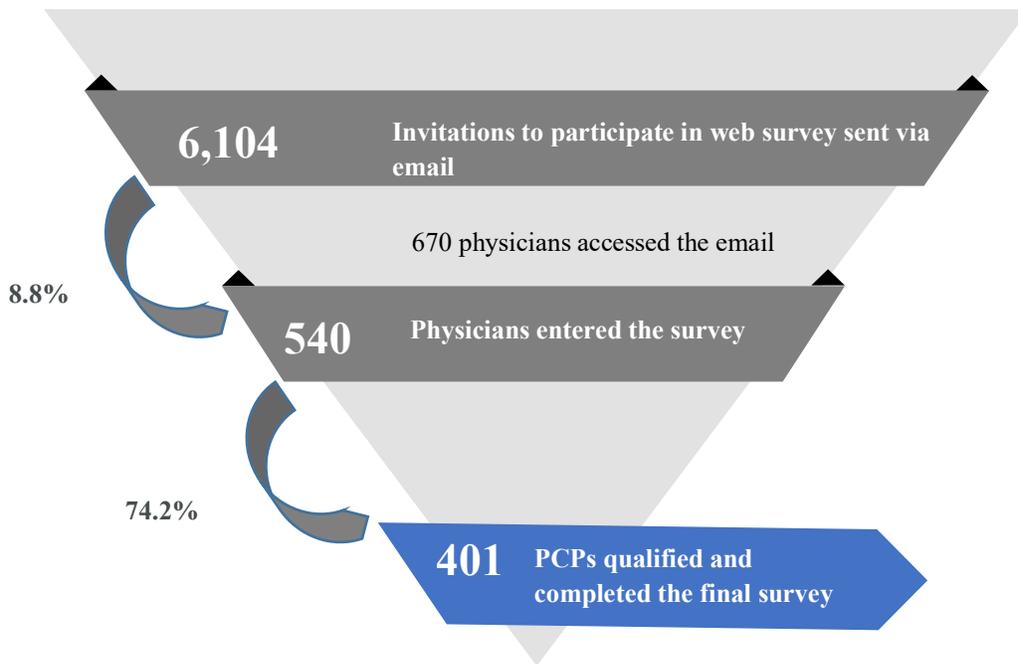
#### High



#### High score recommendations:

- Monitor 3x/year
- Medication intensification:
  - Titrate ACEi or ARBs to maximally tolerated dose
  - Strongly consider SGLT2 inhibitors (unless contraindicated)
- Refer patient to nephrologist

## eAppendix E. Sample Attrition



PCP = Primary care physicians

Attrition of respondents from outreach to final survey is presented. A total of 6,104 invitations were sent out. 8.8% of the physicians who received the invitations entered the survey, and 401 of those (74.2%) qualified and completed the survey

**eAppendix F. Table Study population characteristics (N=401)**

<b>Provider/ Practice Variables</b>	<b>Respondents</b>	<b>Percentage (%)<sup>a</sup></b>
<b>Primary Specialty</b>		
Family Medicine	146	64%
Primary Care/ Internal Medicine	255	36%
<b>Settings of Care</b>		
Office-Based Private Practice	284	71%
Community Hospital	66	16%
Academic Medical Center	51	13%
<b>Geographic Distribution</b>		
Midwest	100	25%
Northeast	85	21%
South	125	31%
West	91	23%

<sup>a</sup> Percentages may not add to 100% as a result of rounding