BOSTON HEALTHCARE ASSOCIATES

April 7, 2021

Clinical utility of a new prognostic test to predict the risk of kidney function decline in diabetic kidney disease patients

National Kidney Foundation® 2021 Spring Clinical Meeting

Agenda and Disclosures

- **Agenda**
  - Background and Aim of our Study
  - Methods
  - Key Results
  - Conclusions

- **Acknowledgement of my coauthors on this research: Saranya Ramakrishnan, Jennifer Chong, Thomas F. Goss, Elizabeth Montgomery, Steven G. Coca, Joseph A. Vassalotti**

- **Disclosure statement: This study was funded by a research grant from RenalytixAI, Inc.**

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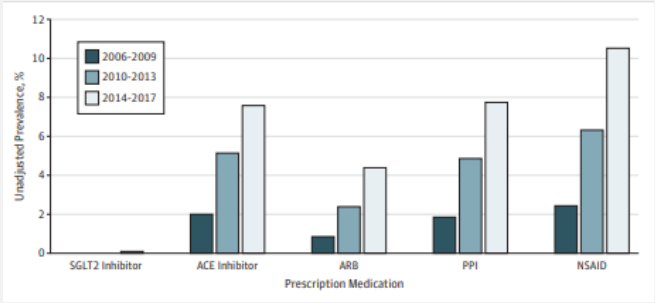
Background and Objectives of Study

Diabetic kidney disease is a major health challenge with unmet needs pertaining to accurate risk stratification

Topic	Statistics
Disease Burden	 More than 1 in 7 US adults are estimated to have CKD • CKD prevalence in the US is 15%[1] • An estimated 40% of T2DM patients have kidney disease owing to diabetes (DKD)[1] • >$120 billion or 20% of Medicare budget spent per year for treatment of CKD and ESKD[1]
Inefficiencies in CKD care	 • Rates of laboratory testing for albuminuria or proteinuria and prescribing of ACE inhibitors or ARBs are low[2] • Appropriate use of known cardio- and reno-protective medications including SGLT2 inhibitors, ACE inhibitors, and ARBs is low

Unmet needs	• Insufficient Recognition of CKD by Clinicians & Patients:
	  • About 1 in 2 people with very low kidney function (not on dialysis) don't know they have CKD[3]
	  • Fewer than 20% of PCPs and Patients are Aware of CKD Stages 1-3[4]
	• Limited ability of the combination of eGFR and UACR to predict disease progression[2]
	• Suboptimal specialist referrals, including nephrologists[4]
	• Current guidelines in CKD classification and management (ADA, KDIGO) are complex, with nuanced interpretation of eGFR and UACR simultaneously[2]

1. United States Renal Data System. 2020 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2020.
2. Clinical Characteristics of and Risk Factors for Chronic Kidney Disease Among Adults and Children: An Analysis of the CURE-CKD Registry. JAMA Netw open. 2019;2(12):e1918169.
3. National Kidney Foundation. Kidney Disease: The basics. Accessed on December 27, 2020 https://www.kidney.org/news/newsroom/factsheets/KidneyDiseaseBasics
4. Szczech LA, Stewart RC, Su HL, et al. Primary care detection of chronic kidney disease in adults with Type-2 diabetes: The ADD-CKD study (awareness, detection and drug therapy in type 2 diabetes and chronic kidney disease). PLoS One. 2014;9(11):1-16. doi:10.1371/journal.pone.01105352. Wheeler DC, James J, Patel D, et al. SGLT2 Inhibitors: Slowing of Chronic Kidney Disease Progression in Type 2 Diabetes. *Diabetes Ther*. 2020;11(12):2757-2774.

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The comprehensive *in vitro* kidney diagnostic (IVKD) can identify the risk of progression in early-stage DKD

- Indicated for DKD Stages 1-3b (excluding G1&A1 and G2&A1)
- NY state-approved for clinical use
- Granted Breakthrough Device designation by the US Food and Drug Administration (FDA)

Standard blood draw

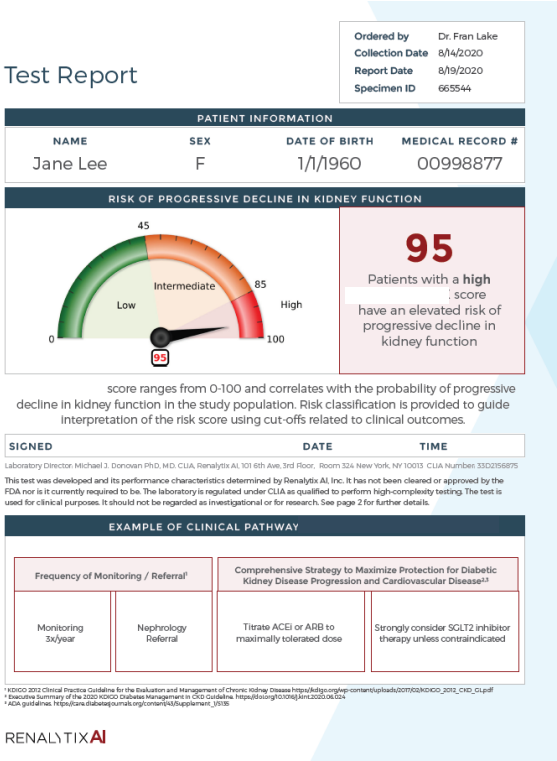
Biomarkers sTNFR-1, sTNFR-2, and KIM-1

Standard Clinical Data Elements

eGFR, UACR, serum calcium, HbA1c, systolic BP, platelets, AST

Machine Learning Algorithm Harmonizes Disparate Data

Actionable Risk Assessment



Test Report

Ordered by	Dr. Fran Lake
Collection Date	8/14/2020
Report Date	8/19/2020
Specimen ID	665544

PATIENT INFORMATION

NAME	SEX	DATE OF BIRTH	MEDICAL RECORD #
Jane Lee	F	1/1/1960	00998877

RISK OF PROGRESSIVE DECLINE IN KIDNEY FUNCTION

95

Patients with a **high** score have an elevated risk of progressive decline in kidney function

score ranges from 0-100 and correlates with the probability of progressive decline in kidney function in the study population. Risk classification is provided to guide interpretation of the risk score using cut-offs related to clinical outcomes.

SIGNED DATE TIME

Laboratory Director: Michael J. Donovan PhD, MD, CLIA, Renalytix AI, 101 6th Ave, 3rd Floor, Room 324 New York, NY 10013 CLIA Number: 33D2156875

This test was developed and its performance characteristics determined by Renalytix AI, Inc. It has not been cleared or approved by the FDA nor is it currently required to be. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. The test is used for clinical purposes. It should not be regarded as investigational or for research. See page 2 for further details.

EXAMPLE OF CLINICAL PATHWAY

Frequency of Monitoring / Referral[1]		Comprehensive Strategy to Maximize Protection for Diabetic Kidney Disease Progression and Cardiovascular Disease[2,3]	
Monitoring 3x/year	Nephrology Referral	Titrate ACEi or ARB to maximally tolerated dose	Strongly consider SGLT2 inhibitor therapy unless contraindicated

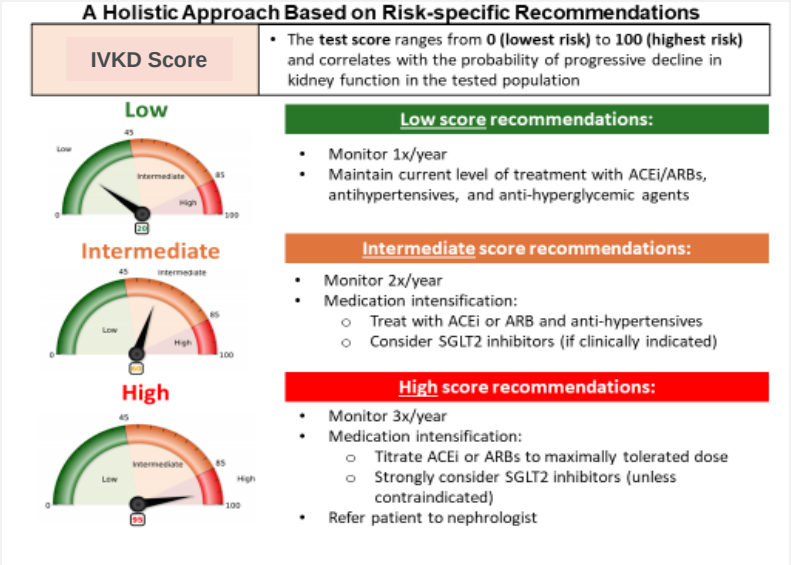
[1] KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_CG.pdf
[2] Executive Summary of the 2020 KDIGO Diabetes Management in CKD Guideline. https://doi.org/10.1016/j.kint.2020.06.024
[3] ADA guidelines. https://care.diabetesjournals.org/content/43/Supplement_1/S135

RENALYTIX AI

IVKD Clinical Validation Study Results and Test Result Interpretation

IVKD validation study results

- **93% negative predictive value (NPV) for progression in patients scored as low-risk with IVKD versus 85% with Standard Risk Scoring based on KDIGO risk classification**
  - **In other words, low-risk patients have a 93% chance of not experiencing progression within 5 years**
- **69% positive predictive value (PPV) for progression in patients scored as high-risk by IVKD versus 40% with Standard Risk Scoring based on KDIGO risk classification**
  - **In other words, high-risk patients have a 69% chance of experiencing progression within 5 years**
- **High-risk patients are 10 times more likely to experience progression of DKD than low-risk patients**



The validated IVKD delivers an accurate and actionable assessment of the risk of kidney function decline

It offers a holistic approach based on risk-specific recommendations

Chan, L., Nadkarni, G.N., Fleming, F. *et al*. Derivation and validation of a machine learning risk score using biomarker and electronic patient data to predict progression of diabetic kidney disease. *Diabetologia* (2021). https://doi.org/10.1007/s00125-021-05444-0

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Study Objectives

- **The overall goal of this study was to assess the clinical utility of IVKD when used by primary care physicians who routinely manage T2D patients**
- **Specific objectives were as follows:**
  - **Recruit primary care physicians (PCPs) involved in the management of T2D patients**
  - **Assess care pathways and standard of care solutions used by PCPs for risk assessment in these patients**
  - **Evaluate the decision impact of IVKD results in T2D patient management**

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Methodology

A conjoint analysis experiment through a web-based survey was used to determine the impact of IVKD on physician decision-making

- Hypothetical patient profiles were created using one level from each attribute
- Attributes and levels were based on a literature review, previous primary research with PCPs, and discussion with clinical experts

Attribute	Level 1	Level 2	Level 3	Level 4
IVKD result*	No test	Low-risk	Moderate-risk	High-risk
Albuminuria (mg/g)[1]	15 (mildly increased)	175 (moderately increased)	850 (severely increased)	NA
eGFR (ml/min/1.73m^2)[1]	80 (mildly decreased)	52 (mild-to-moderately decreased)	37 (moderate-to-severely decreased)	NA
Age (years)[2]	31 (younger)	55 (middle aged)	73 (older)	NA
Blood pressure (mmHg)[3]	125/78 (normal)	135/85 (moderately elevated)	145/90 (high)	NA
Glycemic control (HbA1c) (%)[4]	6.1 (normal)	7.3 (moderately elevated)	8.2 (severely elevated)	NA

- PCPs were asked how they would treat each hypothetical patient

How would you treat?	Operationalization (single select)
Would you prescribe an SGLT2 inhibitor that has a DKD indication for this patient?	Yes or no
Would you increase losartan dose from 50mg to 100mg per day for this patient?	Yes or no
Would you refer this patient to a nephrologist?	Yes or no

1. BHA Primary Research, April 2020; Baumgarten, M., & Gehr, T. (2011). Chronic kidney disease: detection and evaluation. *American family physician*, *84*(10), 1138–1148.; Lin, Y., Chang, Y, et. al. (2018). Update of pathophysiology and management of diabetic kidney disease, *ScienceDirect*, 117(8). https://www.niddk.nih.gov/health-information/kidney-disease/chronic-kidney-disease-ckd/tests-diagnosis.
2. Chronic Kidney Disease in the United States, 2019 https://www.cdc.gov/kidneydisease/publications-resources/2019-national-facts.html?utm_source=miragenews&utm_medium=miragenews&utm_campaign=news. Last Updated March 11, 2019.
3. BHA Primary Research, April 2020; https://www.cdc.gov/kidneydisease/publications-resources/2019-national-facts.html?utm_source=miragenews&utm_medium=miragenews&utm_campaign=news; https://www.mayoclinic.org/diseases-conditions/high-blood-pressure/in-depth/blood-pressure/art-20050982.
4. BHA Primary Research, April 2020; Lin, Y., Chang, Y, et. al. (2018). Update of pathophysiology and management of diabetic kidney disease, *ScienceDirect*, 117(8).; Nakanishi, S., Hirukawa, H., et. al. (2019). Comparison of HbA1c levels and body mass index for prevention of diabetic kidney disease: A retrospective longitudinal study using outpatient clinical data in Japanese patients with type 2 diabetes mellitus. *Diabetes research and clinical practice*, 155, 107807.

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To control for patient-related variables, the survey directed respondents to make assumptions about patient management/characteristics and IVKD cost and availability

Patient-related Assumptions

For all type 2 diabetes patients, please assume 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/ARB inhibitors
- Have not been consulting a nephrologist
- Have normal potassium levels

Cost and Availability Assumptions

For this exercise, 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

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Given the large number of possible patient profiles, an orthogonal design was generated

Orthogonal design generated

Sawtooth Software's CVA module was used to generate an orthogonal design[1] of 42 unique patient profiles that maximized D-efficiency as close to 1.00 as possible (0.97)[2,3] while minimizing respondent burden

Minimum number of profiles determined

Minimum of 8 profiles per respondent were necessary to reduce the standard errors (<0.1)[4]

- Survey software randomly selected 8 patient profiles for each respondent based on a least fill methodology, so a subset of respondents viewed each patient type

Survey pilot

Two PCPs took the survey and commented on content and design while the BHA team observed and recorded notes

- Feedback from the pilot interviews was used to refine the survey

Survey full launch

Following survey refinement, survey was full-launched through an external recruiting agency.

- The research was deemed to be exempt from IRB review by an independent IRB.

1. Orthogonality indicates each pair of levels (across different attributes) appears equally within the design
2. D-efficiency, a relative measure comparing a design against a benchmark, ranges from 0 to 1; designs closer to the benchmark show a D-efficiency closer to 1.
3. Kuhfeld WF. *Experimental Design: Efficiency, Coding, and Choice Designs*. Accessed November 4, 2020. http://support.sas.com/techsup/technote/mr2010c.sas.
4. Orme B. *MBC v1.1: Software for Menu-based choice analysis*. 2016. https://sawtoothsoftware.com/uploads/sawtoothsoftware/originals/mbcmanual.pdf.

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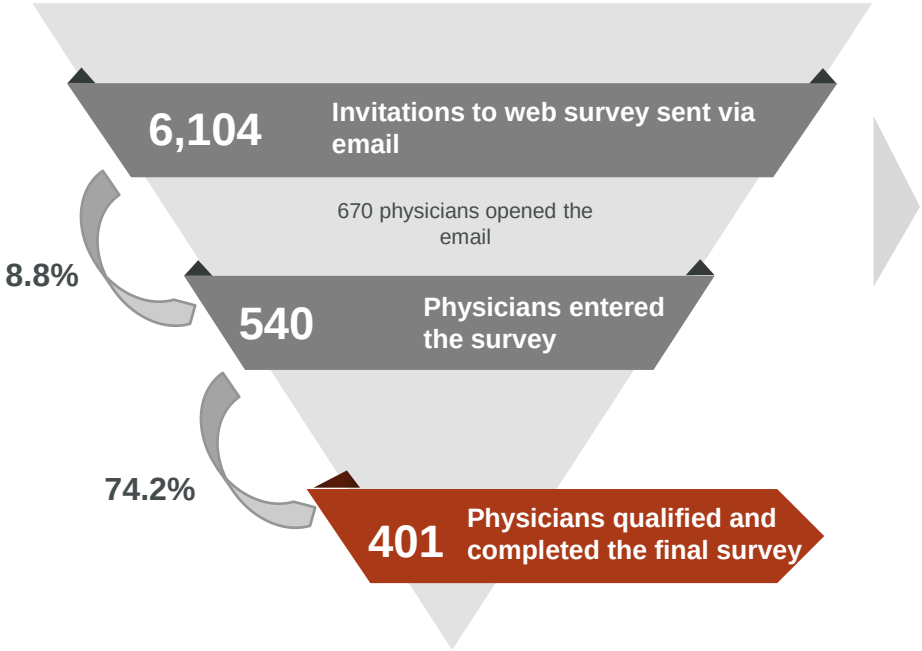
Results

We successfully recruited a total of 401 respondents for the final survey

SURVEY RESPONDENTS



SCREENING CRITERIA

- ✓ Board-certified
- ✓ ≥2 years of managing patients
- ✓ >20 T2D patients seen in the last 6 months
- ✓ >10 T2D patients tested for DKD in the last 6 months
- ✓ >0 T2D patients with DKD
- ✓ ≥50% of time spent in direct clinical care
- ✓ Physicians practicing in Maine and Vermont excluded due to restrictive market research laws

- Respondents were compensated $25 to complete the15 minute survey

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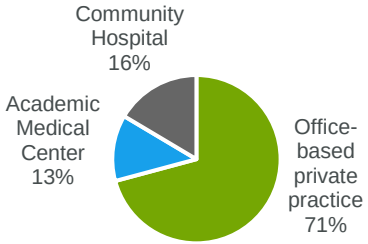
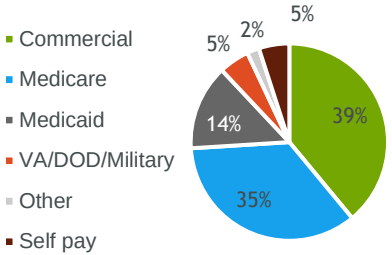
Survey respondents represented a range of practice settings and geographies

Respondents, by specialty

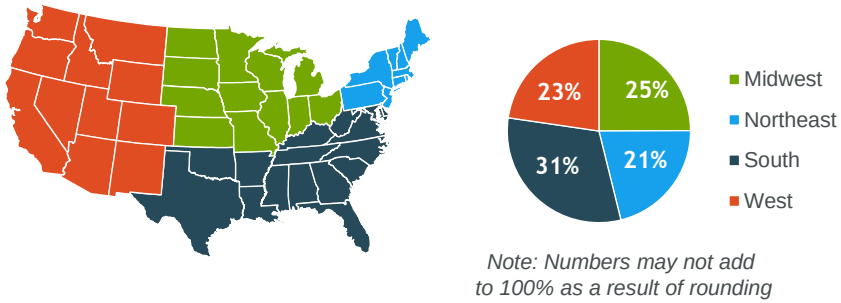
Respondents, by setting of care



Types of health insurance of T2D patients

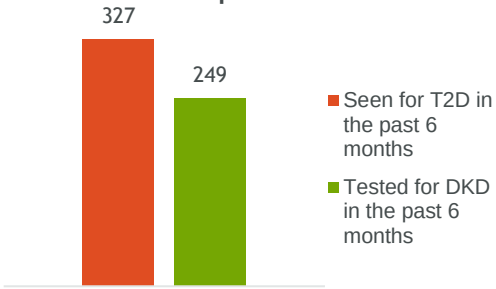


Respondents, by census region†

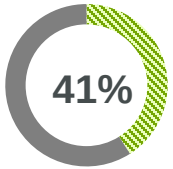


Note: Numbers may not add to 100% as a result of rounding

Average number T2D patients seen in the past 6 months vs tested for indications of kidney disease in the past 6 months per respondent



Average percentage of T2D patients with DKD per respondent

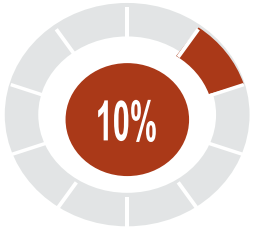


† Geographic distribution of survey respondents is representative of the geographic distribution in the US: https://www.fsmb.org/siteassets/advocacy/publications/2016census.pdf

Satisfaction with current tests informing DKD progression is low. Highest unmet need perceived by PCPs is predicting kidney function decline before symptoms appear

Satisfaction with Current Tests Informing DKD Progression*

(n=401 PCPs)

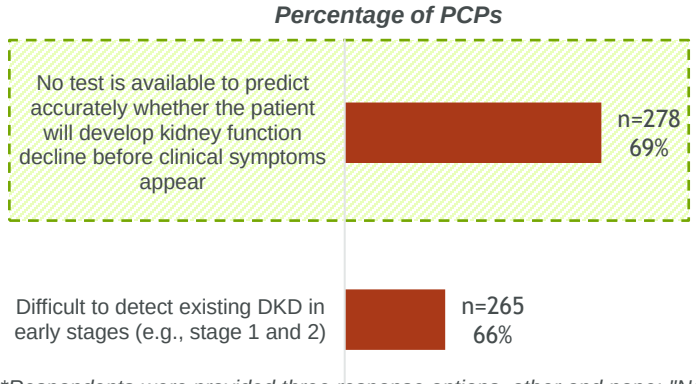


*10% are extremely satisfied with current methods for assessing risk of kidney function decline and provided a rating of 5 on a scale of 1-5 where 1 is “extremely dissatisfied” and 5 is “extremely satisfied”

Top Two Diagnostic Challenges Pertaining to DKD in T2D Patients*

(n=401 PCPs)

More than one response accepted.

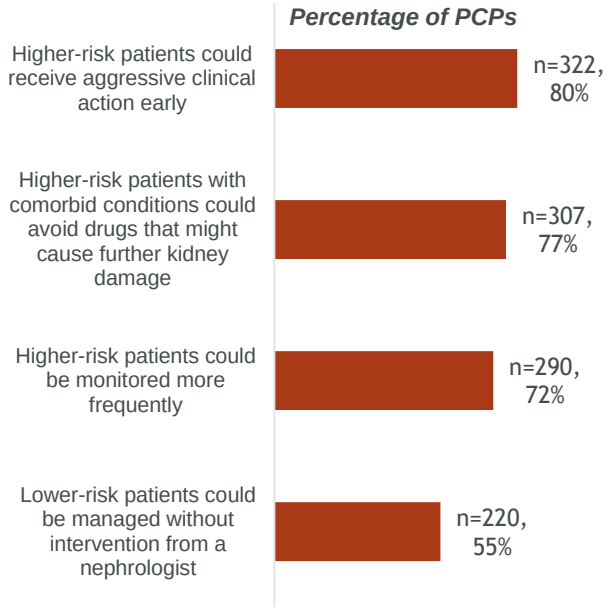


**Respondents were provided three response options, other and none; "No test to clearly identify what stage of DKD the patient is in" was the third option provided to respondents*

Clinical Benefits of Assessing the Risk of Progressive Decline in Kidney Function in T2D Patients*

(n=401 PCPs)

More than one response accepted.



**Respondents were provided four response options and other*

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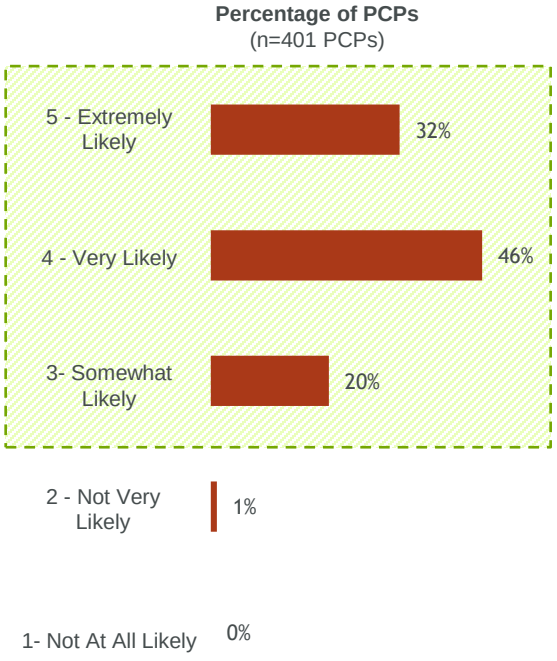
PCPs rated IVKD positively and expect to order the test in 65% of their T2DM patients, on average

Likelihood of PCP Ordering IVKD*



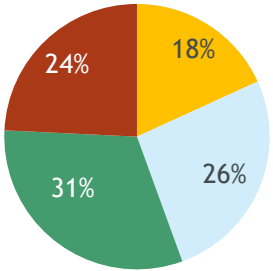
PCPs who are likely to order

98%

*Numbers may not add to 100% as a result of rounding

T2D Patients In Whom Physicians Would Use IVKD*

(n=392 PCPs who would use IVKD and did not select "I don't know" regarding patient staging)

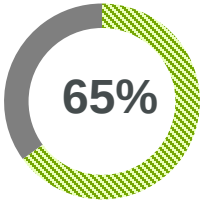


Stage 1	Normal or high GFR and moderately or severely increased albuminuria
Stage 2	Mildly decreased GFR and moderately or severely increased albuminuria
Stage 3a	Mildly-to-moderately decreased GFR, regardless of albuminuria level
Stage 3b	Moderately-to-severely decreased GFR, regardless of albuminuria level

*Numbers may not add to 100% as a result of rounding

Percentage of T2D patients for whom PCPs will order IVKD in a typical year

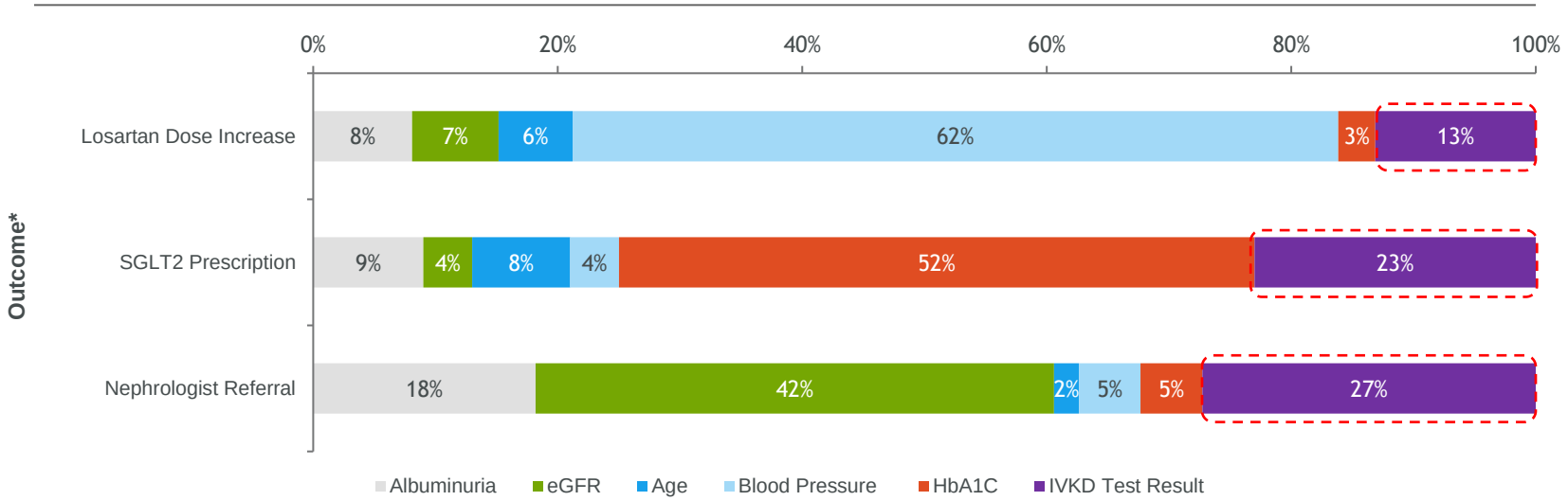
(n=401 PCPs)



IVKD result consistently ranks as a very important attribute in PCP decision-making

Relative Importance of IVKD Results and Other Attributes

(n= 401 PCPs)



*To determine the relative importance of each attribute, "Prescribe SGLT2 with DKD indication" is compared with "Not prescribe SGLT2 with DKD indication." "Increase losartan dose to 100 mg per day" is compared with "Continue losartan dose of 50 mg per day." "Refer to a nephrologist" is compared with "Not refer to a nephrologist."

Numbers may not add to 100% as a result of rounding.

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High-risk IVKD results have a statistically significant impact on all decision-making outcomes compared to no IVKD

Impact of IVKD Results on Physician Decision-Making					
Outcome	IVKD Test Result	Odds Ratio	95% Confidence Interval		Interpretation
			Lower Bound	Upper Bound	
Prescribe SGLT2 inhibitors	No Test	REF	-	-	A **high-risk IVKD test result** is associated with significantly **higher odds of PCPs prescribing SGLT2 inhibitors with a DKD indication compared with no IVKD test**
	Low Risk	0.80	0.64	1.01	
	Moderate Risk	1.25	0.99	1.59	
	High Risk	1.64*	1.29	2.08	
Increase losartan dose to 100 mg per day	No Test	REF	-	-	A **high-risk IVKD test result** is associated with significantly **higher odds of PCPs increasing the dose of losartan compared with no IVKD test**
	Low Risk	0.88	0.69	1.11	
	Moderate Risk	1.07	0.85	1.34	
	High Risk	1.49*	1.17	1.89	
Refer to a nephrologist	No Test	REF	-	-	A **high-risk IVKD test result** is associated with significantly **higher odds of PCPs referring to a nephrologist compared with no IVKD test**
	Low Risk	0.82	0.65	1.03	
	Moderate Risk	1.12	0.90	1.39	
	High Risk	2.47*	1.99	3.08	

- Significant at α=0.05 (i.e., the confidence interval does not include 1)
- REF = Reference category

Values are from an aggregate logit model assessing the impact of IVKD test results and other independent variables (attributes) on physician decision-making

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Key Conclusions

Ability to Address Unmet Needs	• IVKD can address existing unmet needs by helping PCPs accurately risk stratify and appropriately treat patients with early-stage DKD, including optimizing referrals to specialists
Acceptability	• 98% of PCPs are willing to adopt IVKD to identify T2D patients at risk of kidney function decline
Clinical Utility	• PCPs would use the risk score generated by the IVKD more than albuminuria and eGFR when making decisions in their T2D patients including increased use of cardio- and reno-protective therapies such as ACE inhibitors, ARBs, and SGLT2 inhibitors and nephrologist referrals

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