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.
Background and Objectives of Study
**Background and unmet needs**

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

<table>
<thead>
<tr>
<th>Topic</th>
<th>Statistics</th>
</tr>
</thead>
</table>
| **Disease Burden** | CKD prevalence in the US is 15%<sup>1</sup>  
- An estimated 40% of T2DM patients have kidney disease owing to diabetes (DKD)<sup>1</sup>  
- >$120 billion or 20% of Medicare budget spent per year for treatment of CKD and ESKD<sup>1</sup> |
| **Inefficiencies in CKD care** | Rates of laboratory testing for albuminuria or proteinuria and prescribing of ACE inhibitors or ARBs are low<sup>2</sup>  
- 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<sup>3</sup>  
  - Fewer than 20% of PCPs and Patients are Aware of CKD Stages 1-3<sup>4</sup>  
- Limited ability of the combination of eGFR and UACR to predict disease progression<sup>2</sup>  
- Suboptimal specialist referrals, including nephrologists<sup>4</sup>  
- Current guidelines in CKD classification and management (ADA, KDIGO) are complex, with nuanced interpretation of eGFR and UACR simultaneously<sup>2</sup> |

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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)

**The Solution**

**Standard blood draw**

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

**Machine Learning Algorithm**

*Harmonizes Disparate Data*

**Standard Clinical Data Elements**

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

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**Actionable Risk Assessment**

**Test Report**

**NAME**

Jane Lee

**SEX**

F

**DATE OF BIRTH**

1/1/1960

**MEDICAL RECORD #**

00998877

**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.

**95**

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

**EXAMPLE OF CLINICAL PATHWAY**

- **Frequency of Monitoring / Medication**
  - *Comprehensive Strategy to Maximize Protection for Diabetic Kidney Disease Progression and Cardiovascular Disease*?
- **Monitoring**
  - **Diabetes**
  - **Kidney** health
- **Treatments**
  - *ACE/ARB or aldosterone inhibitor, lipidator, diabetes therapy with cardiovascular events*

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Clinical Validation

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

IVKD Score

- **Low score recommendations:**
  - Monitor 1x/year
  - Maintain current level of treatment with ACEI/ARBs, antihypertensives, and anti-hyperglycemic agents

- **Intermediate score recommendations:**
  - Monitor 2x/year
  - Medication intensification:
    - Treat with ACEI or ARBs and antihypertensives
    - Consider SGLT2 inhibitors (if clinically indicated)

- **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

**A Holistic Approach Based on Risk-specific Recommendations**

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.


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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
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

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

- PCPs were asked how they would treat each hypothetical patient

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

Study Methodology

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

<table>
<thead>
<tr>
<th>Patient-related Assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>For all type 2 diabetes patients, please assume the patients</td>
</tr>
<tr>
<td>• Have been receiving 1000 mg of metformin twice a day</td>
</tr>
<tr>
<td>• Have been receiving 50 mg of losartan per day</td>
</tr>
<tr>
<td>• Have no contraindications to or higher-than-average risk of side-effects from SGLT2 inhibitors or ACE/ARB inhibitors</td>
</tr>
<tr>
<td>• Have not been consulting a nephrologist</td>
</tr>
<tr>
<td>• Have normal potassium levels</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cost and Availability Assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>For this exercise, please assume the following:</td>
</tr>
<tr>
<td>• The cost of Test X is not an issue for you and your patients</td>
</tr>
<tr>
<td>• Test X is commercially available and has been FDA-cleared</td>
</tr>
<tr>
<td>• Your practice has adopted Test X</td>
</tr>
</tbody>
</table>
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.
Results
We successfully recruited a total of 401 respondents for the final survey.

**SURVEY RESPONDENTS**

- **6,104** Invitations to web survey sent via email
- **670** physicians opened the email
- **540** Physicians entered the survey
- **401** Physicians qualified and completed the final survey

**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

Sample Attrition

- 6,104 physicians opened the email
- 540 physicians entered the survey
- 401 physicians qualified and completed the final survey

Respondents were compensated $25 to complete the 15 minute survey.
Respondent Characteristics

Survey respondents represented a range of practice settings and geographies

**Respondents, by specialty**

- Family medicine: 146 (36%)
- Primary care/internal medicine: 255 (64%)

**n=401**

**Respondents, by setting of care**

- Community Hospital: 16%
- Office-based private practice: 71%
- Academic Medical Center: 13%

**Respondents, by census region†**

- Midwest: 23%
- Northeast: 25%
- South: 31%
- West: 21%

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

- Seen for T2D in the past 6 months: 327
- Tested for DKD in the past 6 months: 249

**Average percentage of T2D patients with DKD per respondent**

- 41%

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

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

- **Percentage of PCPs**
  - No test is available to predict accurately whether the patient will develop kidney function decline before clinical symptoms appear
    - n=278
    - 69%
  - Difficult to detect existing DKD in early stages (e.g., stage 1 and 2)
    - n=265
    - 66%

*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**

- **Percentage of PCPs**
  - More than one response accepted.
  - No test is available to predict accurately whether the patient will develop kidney function decline before clinical symptoms appear
    - n=278
    - 69%
  - Difficult to detect existing DKD in early stages (e.g., stage 1 and 2)
    - n=265
    - 66%

*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**

- **Percentage of PCPs**
  - More than one response accepted.
  - Higher-risk patients could receive aggressive clinical action early
    - n=322
    - 80%
  - Higher-risk patients with comorbid conditions could avoid drugs that might cause further kidney damage
    - n=307
    - 77%
  - Higher-risk patients could be monitored more frequently
    - n=290
    - 72%
  - Lower-risk patients could be managed without intervention from a nephrologist
    - n=220
    - 55%

*Respondents were provided four response options and other

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Descriptive findings

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

<table>
<thead>
<tr>
<th>Likelihood of PCP Ordering IVKD*</th>
<th>T2D Patients In Whom Physicians Would Use IVKD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of PCPs (n=401 PCPs)</td>
<td>(n=392 PCPs who would use IVKD and did not select &quot;I don't know&quot; regarding patient staging)</td>
</tr>
<tr>
<td>5 - Extremely Likely</td>
<td>Stage 1: Normal or high GFR and moderately or severely increased albuminuria</td>
</tr>
<tr>
<td></td>
<td>Stage 2: Mildly decreased GFR and moderately or severely increased albuminuria</td>
</tr>
<tr>
<td>4 - Very Likely</td>
<td>Stage 3a: Mildly-to-moderately decreased GFR, regardless of albuminuria level</td>
</tr>
<tr>
<td>3 - Somewhat Likely</td>
<td>Stage 3b: Moderately-to-severely decreased GFR, regardless of albuminuria level</td>
</tr>
<tr>
<td>2 - Not Very Likely</td>
<td>Percentage of T2D patients for whom PCPs will order IVKD in a typical year (n=401 PCPs)</td>
</tr>
<tr>
<td>1 - Not At All Likely</td>
<td>65%</td>
</tr>
</tbody>
</table>

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

Descriptive findings

PCPs who are likely to order IVKD: 98%

- 5 - Extremely Likely: 32%
- 4 - Very Likely: 46%
- 3 - Somewhat Likely: 20%
- 2 - Not Very Likely: 1%
- 1 - Not At All Likely: 0%

*Numbers may not add to 100% as a result of rounding.
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.
High-risk IVKD results have a statistically significant impact on all decision-making outcomes compared to no IVKD

<table>
<thead>
<tr>
<th>Outcome</th>
<th>IVKD Test Result</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower Bound</td>
<td>Upper Bound</td>
</tr>
<tr>
<td><strong>Prescribe SGLT2 inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Test</td>
<td>REF</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Low Risk</td>
<td>0.80</td>
<td>0.64</td>
<td>1.01</td>
<td></td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>1.25</td>
<td>0.99</td>
<td>1.59</td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>1.64*</td>
<td>1.29</td>
<td>2.08</td>
<td></td>
</tr>
<tr>
<td><strong>Increase losartan dose to 100 mg per day</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Test</td>
<td>REF</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Low Risk</td>
<td>0.88</td>
<td>0.69</td>
<td>1.11</td>
<td></td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>1.07</td>
<td>0.85</td>
<td>1.34</td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>1.49*</td>
<td>1.17</td>
<td>1.89</td>
<td></td>
</tr>
<tr>
<td><strong>Refer to a nephrologist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Test</td>
<td>REF</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Low Risk</td>
<td>0.82</td>
<td>0.65</td>
<td>1.03</td>
<td></td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>1.12</td>
<td>0.90</td>
<td>1.39</td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>2.47*</td>
<td>1.99</td>
<td>3.08</td>
<td></td>
</tr>
</tbody>
</table>

- 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.
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