CKD and Type 2 Diabetes: Early Risk Assessment

Allison Trucillo, MD
Vice President, Medical Affairs
The Need for Risk Stratification in CKD
Burden of Early-stage Chronic Kidney Disease

37M
15% of adult population

~36.4M (96%
early-stage CKD (stages)

~1.5M (4%)
late-stage CKD (stages 4-5)
Chronic Kidney Disease (CKD) is the Silent Epidemic

15% (~38 M) of adult population in the U.S. have CKD

Leading Causes of CKD in the US

- Diabetes: 3/4 new CKD cases
- High blood pressure
- Glomerulonephritis
- Other causes
- Unknown

15% (~38 M) of adult population in the U.S. have CKD

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Chronic Kidney Disease in the United States, 2021 (cdc.gov)
Chronic Kidney Disease (CKD) is a Costly and Growing Epidemic in the U.S.

1 in 3
U.S. adults with diabetes have CKD

37M
U.S. adults have CKD

~95%
Of patients with CKD are in stages 1-3

References:
Know Patient Risk Early to Prevent Irreversible Kidney Disease Damage

$87B
Medicare spend 2019\(^1\)

Stage 1
Normal function but evidence of kidney damage

Stage 2
Mild loss of kidney function

Stage 3
Moderate to severe loss of kidney function

Stage 4
Severe loss of kidney function

Stage 5
Kidney failure requires treatment to live

~95% of patients with CKD\(^1\)
Improved outcomes at significant savings

~5% of patients with CKD\(^1\)

$37B
Medicare spend 2019\(^1\)

There is **Time to Intervene Prior to Disease Progression**

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
<th>Stage 5/ESKD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>≥ 90%</strong></td>
<td><strong>60-89%</strong></td>
<td><strong>30-59%</strong></td>
<td><strong>15-29%</strong></td>
<td><strong>0-14%</strong></td>
</tr>
<tr>
<td>Normal function</td>
<td>Mild loss of</td>
<td>Moderate to severe loss</td>
<td>Severe loss of</td>
<td>Kidney failure now</td>
</tr>
<tr>
<td>but evidence of kidney</td>
<td>kidney function</td>
<td>of kidney function</td>
<td>of kidney function</td>
<td>requires treatment to</td>
</tr>
<tr>
<td>damage</td>
<td></td>
<td>eGFR 60-89 mL/min/1.73m²</td>
<td>eGFR 15-29 mL/min/1.73m²</td>
<td>live eGFR &lt;15 mL/min/1.73m²</td>
</tr>
<tr>
<td>eGFR ≥ 90 mL/min/1.73m²</td>
<td>eGFR 45-59 and 30-44 mL/min/1.73m²</td>
<td>eGFR 15-29 mL/min/1.73m²</td>
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</tbody>
</table>

**OPPORTUNITY TO SHIFT DKD CARE UPSTREAM**

**FUTURE: Earlier Intervention = Better Outcomes**

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Therapies to Slow CKD Progression and Reduce Heart Failure Risk

<table>
<thead>
<tr>
<th>Effects on CKD progression</th>
<th>ACE inhibitors and ARBs</th>
<th>SGLT2 inhibitors</th>
<th>Non-steroidal MRAs*</th>
<th>Endothelin receptor antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>RENAAAL</td>
<td>CREDENCE</td>
<td>FIDELIO/FIGARO</td>
<td>SONAR†</td>
<td></td>
</tr>
<tr>
<td>21%</td>
<td>30%</td>
<td>23%</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>IDNT</td>
<td>DAPA-CKD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td>39%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RENAAAL &amp; IDNT</td>
<td>CREDENCE &amp; DAPA-CKD</td>
<td>FIDELIO/FIGARO</td>
<td>SONAR</td>
<td></td>
</tr>
<tr>
<td>RR: 0.79 (95% CI: 0.66-0.95)</td>
<td>RR: 0.70 (95% CI: 0.59-0.82)</td>
<td>RR: 0.77 (95% CI: 0.67-0.88)</td>
<td>RR: 0.72 (95% CI: 0.58-0.89)</td>
<td></td>
</tr>
<tr>
<td>RR: 0.80, P=0.02</td>
<td>HR: 0.61 (95% CI: 0.51-0.72)</td>
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<table>
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<td></td>
</tr>
<tr>
<td>23%</td>
<td>49%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RENAAAL</td>
<td>CREDENCE &amp; DAPA-CKD</td>
<td>FIDELIO/FIGARO</td>
<td>SONAR</td>
<td></td>
</tr>
<tr>
<td>RR: 0.68, P=0.005</td>
<td>RR: 0.61 (95% CI: 0.47-0.80)</td>
<td>RR: 0.78 (95% CI: 0.66-0.92)</td>
<td>RR: 1.39 (95% CI: 0.97-1.99)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR: 0.61 (95% CI: 0.34-0.76)</td>
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</tbody>
</table>

* In diabetes and CKD. † Responders and non-responders
INERTIA in Early CKD:
CKD is Missed in Stages 1-3 by PCPs; CKD is Undertreated

Inadequate Detection of CKD by Physicians
Lack of Awareness of CKD by Patients

Inadequate Treatment of CKD by Physicians

CKD Stage

Patient Awareness Data: NHANES 2018 Data

Tummalapalli, et al. CJASN 2019
Eberly et al. JAMA Open, 2021
Current Guideline Recommendations for CKD in T2D

2020 KDIGO

- **Recommendation 4.2.1**: We recommend treating patients with T2D, CKD, and an eGFR 30 ml/min/1.73 m² with an SGLT2i (1A).

- **Recommendation 4.3.1**: In patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i treatment, or who are unable to use those medications, we recommend a long-acting GLP-1 RA (1B).

2022 ADA Standards of Care

- **Recommendation 9.4b**: Other medications (glucagon-like peptide 1 [GLP-1] receptor agonists, sodium–glucose cotransporter 2 [SGLT2] inhibitors), with or without metformin based on glycemic needs, are appropriate initial therapy for individuals with type 2 diabetes with or at high risk for atherosclerotic cardiovascular disease (ASCVD), HF, and/or chronic kidney disease (CKD) (Figure 9.3). A

- **Recommendation 11.3c**: In patients with chronic kidney disease who are at increased risk for cardiovascular events or chronic kidney disease progression or are unable to use a sodium–glucose cotransporter 2 inhibitor, a nonsteroidal mineralocorticoid receptor antagonist (finerenone) is recommended to reduce chronic kidney disease progression and cardiovascular events (Table 9.2). A
Use of Cardioprotective and Anti-Diabetic Agents in Patients with T2D and ASCVD – 120 US Centers

- Statin (any): 87.6%
- High intensity statin*: 45.4%
- Ezetimibe: 9.7%
- Fish oil: 19.8%
- Fibrate: 11.8%
- PCSK9 inhibitor: 8.6%
- Antiplatelet or anticoagulant*: 8.6%
- ACE inhibitor or ARB*: 72.0%
- Metformin: 54.8%
- Insulin: 35.9%
- Sulphonylurea: 21.5%
- DPP4 inhibitor: 12.5%
- SGLT2 inhibitor*: 9.0%
- GLP-1 receptor agonist: 7.9%
- Thiazolidinediones: 4.6%
- Optimal medical therapy*: 6.0%

Lipid-Lowering Medications
CV Medications
Glucose-Lowering Medications

Courtesy Dr Mikhail Kosiborod

SV Arnold et al. Circulation. 2019;140:e618-e620
Late and Inadequate Referrals in US: Only 32% of Patients Starting Long-term Dialysis Were Under the Care of Nephrologist for > 1 Year

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2/3rds of Patient Have Late Engagement with Kidney Specialist or “Crash Start” Dialysis in the Hospital

Only 1/3rd Have Long-term Nephrology Care Prior to Dialysis

Current Standard of Care for Diagnosing CKD
Standard of Care Metrics (UACR, eGFR) are Not Accurate for Predicting Future Kidney Outcomes

High biological variability of UACR and eGFR

Intra-individual variability on repeat testing:¹
UACR: -55 to +125%
eGFR: -16 to +20%

**eGFR Poorly Reflects Underlying Kidney Damage**

Patients with normal eGFR can have 0-100% kidney fibrosis or glomerulosclerosis on biopsy²

**Hyperfiltration often precedes DKD progression**

Hyperfiltration sustains kidney function at higher levels in diabetes masking DKD³

**Age-related Decline in Kidney Function Results in False Diagnosis of CKD**

Unnecessary anxiety, workup, Treatment, and resource utilization for low risk condition⁴

**Most kidney protective Drugs decrease kidney function over first 1-2 years of Rx**

RAAS inhibitors and SGLT2i both result in decreases in eGFR due to drop in intraglomerular pressures⁵

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Significant Intra-Individual Variability in eGFR within Short Time Period

Given a median CVw in SCr of 5.4%, an increase in eGFR from baseline of 20% or a decrease of 16% can be expected by chance.

CVw = 5.4%

20% increase

16% decrease

Serum Creatinine X 2 taken < 4 weeks apart

Abbreviations: CVw = Within person coefficient of variation

High Intra-individual Variability of UACR within 4 weeks in Stable CKD Variability of eGFR and UACR in Other Studies
Movement of patients across KDIGO risk strata within < 6 months of repeat testing

<table>
<thead>
<tr>
<th>Persistent albuminuria categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description and range</td>
</tr>
<tr>
<td>A1</td>
</tr>
<tr>
<td>Normal to mildly increased</td>
</tr>
<tr>
<td>&lt;30 mg/g &lt;3 mg/mmol</td>
</tr>
<tr>
<td>A2</td>
</tr>
<tr>
<td>Moderately increased</td>
</tr>
<tr>
<td>30 – 300 mg/g 3 – 30 mg/mmol</td>
</tr>
<tr>
<td>A3</td>
</tr>
<tr>
<td>Severely increased</td>
</tr>
<tr>
<td>&gt;300 mg/g &gt;30 mg/mmol</td>
</tr>
</tbody>
</table>

- G1: Normal or high
  - GFR categories (ml/min per 1.73 m²): 
    - 90
- G2: Mildly decreased
  - GFR categories (ml/min per 1.73 m²): 
    - 60 – 89
- G3a: Mildly to moderately decreased
  - GFR categories (ml/min per 1.73 m²): 
    - 45 – 59
- G3b: Moderately to severely decreased
  - GFR categories (ml/min per 1.73 m²): 
    - 30 – 44
- G4: Severely decreased
  - GFR categories (ml/min per 1.73 m²): 
    - 15 – 29
- G5: Kidney failure
  - GFR categories (ml/min per 1.73 m²): 
    - <15

Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red, very high risk.
Early Risk Assessment: The Evidence
Knowing Risk Early Starts with a Shift: From Diagnosis to Bioprognosis™

KidneyIntelX provides you with a more complete picture of kidney disease progression

<table>
<thead>
<tr>
<th></th>
<th>Diagnosis (Assesses level of kidney function and damage)</th>
<th>Bioprognosis KidneyIntelX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STANDARD BLOOD DRAW FOR 3 PROPRIETARY MARKERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sTNFR-1</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>sTNFR-2</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>KIM-1</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td><strong>EHR CLINICAL FEATURES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>UACR</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Serum calcium</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>✓</td>
<td></td>
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<tr>
<td>Systolic BP</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

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KidneyIntelX Bioprognostic™ Integrates IVD and Key Clinical Factors to Produce Patient-specific Risk Score for Progression of DKD

Kidney Tubule Injury
Injury/Inflammation ratio
Kidney function
Kidney damage
Systemic inflammation
Mineral metabolism
Systemic inflammation
Glucose control
Hypertension control
Hematologic function
Liver function
Inflammatory balance

Composite Risk Score

Progressive Decline in Kidney Function Within 5 Years

Bioprognosis™ definition: the use of proven, highly prognostic biomarkers, select clinical features, and machine learning to best predict outcomes and to promote and preserve patient health.
New Biomarkers of Subclinical Inflammation and Kidney Injury – Allow for Early Prediction of DKD Progression

**Tumor Necrosis Factor Receptor 1:**
- Present in the glomerular and tubular endothelial cells
- Activation causes cell death
- Strongly associated with the progression of CKD

**Tumor Necrosis Factor Receptor 2:**
- Not usually present in the kidneys of healthy subjects
- Activation triggers pro-inflammatory and pro-fibrotic pathways
- Significant correlation with TNFR1
- Strongly associated with the development and progression of CKD

**Kidney Injury Molecule – 1:**
- Present in kidney tubular cells
- Detected in the urine and serum with new or ongoing kidney injury
- Elevations are **prognostic** for CKD progression

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**TNFR1, TNFR2, KIM1**

The Three Strongest and Most Studied Plasma Biomarkers for Predicting CKD Progression Compared to All Others to Date

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KIM-1, TNFR1, TNFR2 are the Three Most Often Studied Biomarkers with the Highest Strength for Prognosis

Adjusted Relative Risk per Doubling in Plasma Biomarker Concentration for CKD Incidence or Progression in Various Cohorts

CKD: Chronic Kidney Disease

Liu et al (submitted for publication)
KidneyIntelX Delivers Clinically Validated Results

Derivation and validation of a machine learning risk score using biomarker and electronic patient data to predict progression of diabetic kidney disease: *Diabetologia*. April 2021

1146 Patients
Adults 21+
Type 2 Diabetes
Chronic Kidney Disease (stages 1-3b)

eGFR of 30-59 ml/min/1.73²
or
eGFR ≥ 60 ml/min/1.73² with uACR ≥ 30mg/g

Composite Endpoint: Progressive Decline in Kidney Function over 5 Years
• Rapid kidney function decline (decline > 5/ml/min/1.73m²/year)
• Sustained decrease in eGFR (decline ≥ 40% from baseline)
• Kidney failure (eGFR < 15ml/min/1.73m², dialysis, or transplant)
KidneyIntelX Integrates the Three Strongest Biomarkers with Seven Clinical Data Features to Predict Risk of Progression of DKD

Composite Risk Score Derived from >100 Potential Features in Optimized Machine Learning Models

**Order of Importance**

**Features Considered for Inclusion**

- Patient demographics (5)
- Lab values (27)
- Medications (30)
- ICD 9/10 codes (20)
- Vital signs (3)
- Others (~23)
KidneyIntelX Outperforms the Standard of Care

40%
More patients accurately identified across all risk strata than standard of care alone (eGFR and UACR)¹

72%
Improvement vs. standard of care (eGFR and UACR) in predicting which patients are at high risk for progressive decline in kidney function¹

eGFR and UACR missed half the patients KidneyIntelX identified as high risk who progressed to end stage kidney disease (ESKD) in 5 years

**KidneyIntelX Delivers Clinically Validated Results**

<table>
<thead>
<tr>
<th>CLINICAL VALIDATION STUDY RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>The KidneyIntelX test was validated in analyses including patients with type 2 diabetes (T2D) and stage 1-3b chronic kidney disease (CKD)</td>
</tr>
</tbody>
</table>

KidneyIntelX identified 40% more patients experiencing events than the KDIGO risk strata¹

Outperformed clinical models that use standard variables alone, including the KDIGO risk categories¹

<table>
<thead>
<tr>
<th>PPV Composite Endpoint (HIGH RISK GROUP)</th>
<th>KidneyIntelX</th>
<th>KDIGO &amp; Comprehensive Clinical Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>40%</td>
<td>69%</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>NPV Composite Endpoint (LOW RISK GROUP)</th>
<th>KidneyIntelX</th>
<th>KDIGO &amp; Comprehensive Clinical Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>85%</td>
<td>93%</td>
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</table>

Low risk patients (46%) are not likely to progress to ESKD and should continue to be monitored annually\(^1\)

Intermediate risk patients (37%) require more primary care follow up (2-3 x annually) and may need pharmacy management and specialist consultation\(^1\)

High risk patients (17%) are significantly more likely to progress to ESKD and require more aggressive lifestyle changes, medication regimens, and specialist consultation\(^1\)

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Outcomes

High risk patients were 15x more likely to experience kidney function decline or kidney failure vs low risk patients¹

KidneyIntelX Risk Score by KDIGO Color Mapping

KDIGO Yellow
51% of DKD 1-3
Population
18% with events

Proportion Scored by
KidneyIntelX

Event rate
54%
9%
2x lower

Proportion Scored by
KidneyIntelX

KDIGO Orange
32% of DKD 1-3
Population
22% with events

Event rate
42%
9%
2.5x lower

Proportion Scored by
KidneyIntelX

KDIGO Red
16% of DKD 1-3
Population
40% with events

Event rate
15%
5%
8x lower

Introduction

- KidneyIntelX is a multiplex immunoassay of 3 plasma biomarkers with 7 clinical variables combined using machine-learning to generate a risk score for progressive decline in kidney function over 5 years in individuals with early-stage diabetic kidney disease (DKD)
- The test was approved by New York State Department of Health in 2020
- There are approximately 71,000 patients with type 2 diabetes and CKD in the Mount Sinai Health System across several different practices across the 5 boroughs of NYC
- Care pathways for both Type 2 Diabetes and for chronic kidney disease were developed by Mount Sinai Population Health and distributed throughout the system via the Condition Management Hub
- Both of these pathways incorporated KidneyIntelX as the method to risk-stratify patients for future progression of kidney disease

Methods

- A Population Health defined Mount Sinai approved care pathway for DKD patients informed by the KidneyIntelX test was introduced into the Mount Sinai Health System in New York, NY as part of a Real World Evidence (RWE) study (NCT04802395) (Figure 1)
- sTNFR-1, sTNFR-2, and KIM-1 were measured via proprietary assays, and KidneyIntelX scores were calculated using the existing algorithm
- Decision impact of medication management (anti-hypertensives, SGLT2 inhibitors/GLP1 agonists) and specialist referral was tracked. An interim analysis was performed for 1) Assessing comparability between RWE and a published clinical validation cohort based on KidneyIntelX risk score distribution; 2) Determining if necessary EHR clinical fields were captured using the existing algorithm

Results

- Between Mar-Nov 2021, 1,112 patients had KidneyIntelX test results, with post-test follow-up to 36 weeks
- The risk breakdown of RWE population was similar to the clinical validation cohort: High risk 13% vs. 17%, intermediate 40% vs. 37%, and low risk 46% vs 46% (Figure 2A)
- More than half of the tests were ordered during patient with their PCPs (53%) or endocrinologists (28%; Figure 2B)
- Reclassification of risk from KDIGO risk classification is shown in Figure 3A. A total of 1%, 5%, 16%, and 39% were scored as high-risk from KDIGO eGFR*UACR classification, respectively.
- Reclassification from CKD stages by eGFR strata are shown in Figure 3B. A total of 7%, 9%, 10%, and 25% were scored as high-risk on KidneyIntelX from eGFR strata ≥ 90, 60-89, 45-59, and 30-44 ml/min/1.73 m², respectively

Conclusions

- KidneyIntelX was successfully deployed in a health care system in a comparable population to the validation cohort with high data capture fidelity
- Application of guideline-based therapies and specialist referral increased in the proportion to reported risk level by 3-6 and >2-fold, respectively
KidneyIntelX is Both Adopted and Implemented in the Care Pathway

Real-world clinical utility data:\n
1,112 adult diabetic kidney disease (DKD) patients at Mount Sinai Health System*

KidneyIntelX was ordered by a high rate of PCPs\(^1\)

Primary Care 53%
Endocrinologist 28%
Nephrologist 17%

Physicians were:

- more likely to prescribe guideline-recommended therapies\(^1\)
- more likely to make a change in blood pressure medications\(^1\)
- more likely to refer high-risk patients for appropriate specialist consultation\(^1\)

---

1. Late Breaking ePoster: Clinical Utility of KidneyIntel\textsuperscript{TM} on Patients with Early-stage Diabetic Kidney Disease: A Real-World Evidence Study. Joji Tokita, MD, Michael J. Donovan PhD, MD, Robert Fields, MD, MHA. Mount Sinai Health System, New York City, NY (June 2022). *Data is being prepared for publication.*
Thank You