Payer budget impact of an artificial intelligence *in vitro* diagnostic to modify diabetic kidney disease progression

Manasi Datar\(^a\), William Burchenala\(^a\), Michael J. Donovan\(^{b,c}\), Steven G. Coca\(^c\), Elaine Wang\(^a\) and Thomas F. Goss\(^a\)

\(^a\)Boston Healthcare Associates Inc., Boston, MA, USA; \(^b\)Renalytix Inc., New York, NY, USA; \(^c\)Department of Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

**ABSTRACT**

**Aim:** To evaluate the U.S. payer budget-impact of KidneyIntelX, an artificial intelligence-enabled *in vitro* diagnostic to predict kidney function decline in Type 2 Diabetic Kidney Disease (T2DKD) patients, stages 1–3b.

**Materials and methods:** We developed an Excel-based model according to International Society of Pharmacoeconomics and Outcomes Research (ISPOR) good practices to assess U.S. payer budget impact associated with the use of the KidneyIntelX test to optimize therapy T2DKD patients compared to standard of care (SOC) (without KidneyIntelX). A hypothetical cohort of 100,000 stages 1–3b T2DKD patients was followed for 5 years. Peer-reviewed publications were used to identify model parameter estimates. KidneyIntelX costs incremental to SOC (without KidneyIntelX) included test cost, additional prescription medication use, specialist referrals and PCP office visits. Patients managed with KidneyIntelX experienced a 20% slowed progression rate compared to SOC (without KidneyIntelX) attributed to slowed DKD progression, delayed or prevented dialysis and transplants, and reduced dialysis crashes. Associated costs were compared to SOC (without KidneyIntelX). Sensitivity analyses were conducted by varying the definition of progression and the DKD progression rate associated with KidneyIntelX testing and related interventions.

**Results:** Projected undiscounted base case 5-year savings for 100,000 patients tested with KidneyIntelX were $1.052 billion, attributed mostly to slowed progression through DKD stages. The break-even point for the health plan adopting KidneyIntelX is expected to occur prior to year 2 after adoption. Sensitivity analysis based on the assessment of the most conservative definition of progression and a 5% reduction in progression rate attributed to KidneyIntelX, resulted in a projected 5-year savings of $145 million associated with KidneyIntelX.

**Limitations and conclusions:** Limitations included reliance on literature-based parameter estimates, including effect size of delayed progression supported by the literature. Incorporating KidneyIntelX in contemporary care of early-stage T2DKD patients is projected to result in substantial savings to payers.

**Introduction**

Chronic Kidney Disease (CKD) is a critical public health challenge that currently affects more than 37 million adults in the United States (U.S.)\(^1\). CKD is the ninth leading cause of death in the U.S.\(^2\). A Recent U.S. Center for Disease Control and Prevention (CDC) report suggests that one out of two people with very low kidney function who are not on dialysis are not aware that they have CKD\(^1\). Currently, 44% of new CKD cases are associated with diabetes, more than any other cause\(^3\). Approximately 12 million individuals in the U.S. have diabetic kidney disease (DKD)\(^4,5\). Diabetes is the leading cause of the end-stage renal disease (ESRD), presenting as the primary cause of kidney failure in approximately 45% of patients who develop ESRD every year\(^6\). The prevalence of DKD in type two diabetes (T2DM) is as high as 40% and has a significant impact on the well-being of these patients\(^4\). DKD patients have a 31.1% mortality rate at 10 years, which is nearly three times greater than the mortality rate for diabetic patients without kidney disease (11.5%) over the same time period\(^7\). Despite this, a recent qualitative study with PCPs documents that only 56% of PCPs are routinely performing guideline-recommended kidney function testing in their T2DM patients\(^8\).

A proportion of patients with DKD experience progression of kidney disease which can lead to ESRD, dialysis, kidney transplants or death\(^9\). Even though there are only ~125,000...
new cases of ESRD reported each year, the high prevalence of DKD and high costs associated with ESRD have led to an enormous financial burden on the U.S. healthcare system. DKD costs are estimated to be approximately 14% (~$40 billion) of all Medicare spending in 2017. Prior studies have reported annual treatment costs of $17,969 (2012 US$) for stage 1 DKD and Stage 5 DKD costs of $76,969 (2013 US$) per year. Patients with progressing DKD are also at a high risk of having an emergent need to start dialysis (a “crash”) directly from their current stage without necessarily progressing all the way to ESRD. Up to 63% of patients with existing kidney disease initiate dialysis due to a crash. Crashes increase costs per patient by approximately $53,000 during the first year of dialysis. These patients ultimately require long-term dialysis or a kidney transplant, which has an average cost of $262,000 with additional 1-year post-transplant costs of $29,920. This puts an increased financial strain on payers that incur the increased costs of treating DKD.

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend an annual assessment of albuminuria and an estimated glomerular filtration rate (eGFR) to identify DKD progression. Although KDIGO guidelines recommend an annual assessment of albuminuria and eGFR, our previous research suggests that PCPs are most frequently using eGFR alone to assess DKD. Despite the lack of guideline adherence, these standard of care (SOC) tests fail to accurately identify approximately 70–80% of patients with DKD who will experience progression of kidney disease in a 5-year period. As a result, many at-risk patients are not referred to a nephrologist and/or do not receive effective treatments and optimal disease management in the earlier stages of the disease which have been proven to delay progression to ESRD. Moreover, guidelines of the American Diabetes Association (ADA) do not provide specific treatment recommendations for patients with earlier stage DKD (Stages 1 through 3), which represent ~93% of the total U.S. DKD population. The ADA guidelines only suggest that a treating clinician refer the patient to a nephrologist for “uncertainty about etiology of CKD, difficult management issues, or Stage 4 CKD”. Most experts agree that Stage 4 of DKD is too late to intervene, and that effective preventative and treatment options that are currently available need to be implemented in patients with earlier stages of DKD (Stages 1 through 3).

The present study sought to evaluate the payer budget impact of artificial intelligence (AI) – enabled predictive diagnostic solution, KidneyIntelX, which assesses the risk of progressive decline in kidney function (PDKF) in patients with DKD. The KidneyIntelX test combines a blood test to measure circulating plasma biomarkers including sTNFR1, sTNFR2 and KIM-1 with clinical variables from electronic health records (EHRs) to create a test score from 5 to 100. This score is then used to stratify patients into low, intermediate, or high risk of experiencing kidney disease progression over 5 years. This diagnostic tool, validated elsewhere, improves the ability to accurately identify patients at high risk for adverse kidney events (61% classified as high risk with KidneyIntelX compared to 40% classified as high risk with the standard of care KDIGO criteria (p < .001), allows physicians to optimize the treatment pathway with preventative measures at an earlier stage, which can slow progression to ESRD and improve patient outcomes.

The KidneyIntelX test can be integrated with EHR systems and supporting Care Navigation teams and software of health systems to track treatment changes, referrals, and other physician actions in response to test results. For example, the KidneyIntelX test was introduced into the Mount Sinai Health Care System in New York, NY in the fall of 2020 as part of a Real World Evidence (RWE) study. Treating physicians are educated on the implementation and use of the test including a Mount Sinai Population Health-recommended Care Path which is incorporated into the test report as a way to guide management based on each patient’s KidneyIntelX risk profile. KidneyIntelX is a recommended strategy for risk stratification for patients with T2DM and CKD in both, the Mount Sinai guidelines for practitioners facing Diabetes and CKD patients.

Participants and methods

Model overview

The model was developed in accordance with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) standards for model development and modeling, including the recommendations for model structure and validation. The model was developed using TreeAge Pro software and incorporated into the Mount Sinai EHR system. The model was calibrated using real-world data from Mount Sinai Health Care System, which includes demographic, clinical, and cost data for patients with diabetes and kidney disease. The model was validated using data from a real-world study of patients with T2DM and CKD, which was conducted at Mount Sinai Health Care System. The model was further validated using data from a large national cohort of patients with diabetes and kidney disease, which was collected through the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI) registry.

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Research (ISPOR) good practices for budget impact analysis. It is an MS-Excel-based model that estimates the payer budget impact of the use of KidneyIntelX in the management of DKD stage 1–3b patients. The model uses cohort data from the validation study of KidneyIntelX to estimate the rate of disease progression in the SOC (without KidneyIntelX) and the KidneyIntelX arm. In addition, two practicing clinicians provided clinical expert opinions on the DKD treatment pathways and model assumptions.

Patients evaluated with the KidneyIntelX test have three possibilities for test results to predict a composite kidney endpoint of PDKF, which is defined as eGFR decline of at least 5 ml/min/1.73m²/year, (2) sustained 40% decline in eGFR and (3) one of the following: (a) kidney failure, defined as a sustained eGFR < 15 ml/min/1.73m², (b) long-term dialysis or (c) kidney transplant:

1. **High-risk result:** Score >85, translating into a positive predictive value (PPV) of 61% for the composite kidney outcome over 5 years. Patients should be considered for more intensive therapy and/or referral to a nephrologist and aggressive medical management.

2. **Intermediate-risk result:** Score 50–85, which represents the population-level risk in the validation study. Patients should be frequently monitored (e.g. at least twice annually) by PCPs or endocrinologists.

3. **Low-risk result:** Score <50, translating into a negative predictive value (NPV) of 90% for the composite kidney outcome. Patients should remain on their current treatment regimen and should be considered for monitoring by their PCP or endocrinologist on at least an annual basis.

The model calculates potential undiscounted costs of savings from a US managed care perspective over a 5-year time horizon based on the following outcomes when results of KidneyIntelX described above are acted upon to implement guideline-based treatment plans:

- Slowed progression through DKD stages,
- Delayed or prevented dialysis and transplants, and
- Reduction in dialysis crashes

**Key data sources**

A focused literature review was used to identify relevant studies from which to derive key parameter estimates pertaining to the prevalence and cost of CKD by stage. A total of 19 articles were identified that had relevant epidemiologic and cost data. Articles were evaluated by the research team to assess validity and generalizability of findings to inform parameter estimation for use in the model, and when possible, suitability to be used in combination with other studies to compute weighted average parameter estimates across multiple studies. The focused literature review for cost data was supplemented by other sources including the validation study by Chan et al. to identify other parameter estimates relevant to the model.

The validation study aimed to prove that predicting progression in DKD is critical to improving outcomes. Chan et al. developed a machine-learned, prognostic risk score combined with EHRs and biomarkers (KidneyIntelX) and compared the performance (AUC, positive and negative predictive values, and net reclassification index) to that of a clinical model and KDIGO categories for predicting a composite outcome of eGFR decline of ≥5 ml/min per year, ≥40% sustained decline, or kidney failure within 5 years. The study concluded that KidneyIntelX improved prediction of kidney outcomes over KDIGO and clinical models in individuals with early stages of DKD, thus enabling targeted interventions in patients at all levels of risk.

**Population estimates**

The model was built using a hypothetical health plan with 100,000 DKD patients within stages G1 or G2 with A2 or A3, or G3a-G3b with A1-A3 (using the KDIGO classification), the target population for KidneyIntelX. Stage 1 patients with G1&A1 and G2&A1 were not included in the test population, as these are not classified as having chronic kidney disease by KDIGO. At the start of the model, the 100,000 patients were stratified into stages 1–3b of DKD based on recently published prevalence estimates. The payer mix for the health plan was assumed to be 60% Medicare and 40% Commercial for the base case analysis, although this proportion can readily be varied according to an individual plan demographic (Table 1).

**Progression rates**

This was a model tracking the movement of a cohort of patients through various stages of DKD each year, for 5 years. A proportion of the patients starting in DKD stages 1–3 progressed to the next stage each year. Progression rates for the SOC (without KidneyIntelX) were obtained from patient-level biomarker and EHR clinical data of a study by Chan et al. conducted among 1,146 patients with T2DM and early stage DKD (Table 2). Patient progression data from this study in the form of Kaplan–Meier curves used to derive these progression rates are provided in Appendix 1. Three different definitions of progression to the next stage of DKD were used in the validation study:

- “Least Stringent”: ≥1 eGFR value(s) in the next stage of DKD (e.g. G1 to G2 or G3, or G2 to G3a or G3a to G3b).
- “Stringent”: ≥2 eGFR values 3 months apart in the next stage.
- “Most Stringent”: ≥2 eGFR values 3 months apart in the next stage but only in the 21% of patients that ultimately experienced PDKF or kidney failure in the validation study.

Thus, in the “Least Stringent” definition of progression, more patients progressed to the next DKD stage. The “Stringent” definition of progression was used in the base case analysis and a sensitivity analysis was conducted using
the three different definitions of progression to assess its impact on the observed results.

The impact of using the KidneyIntelX test on long-term patient outcomes is not yet known based on an observed long-term outcome study. Patients tested using KidneyIntelX in the model had a 20% decrease in the rate of progression through DKD stages compared to SOC (without KidneyIntelX) due to the earlier implementation of effective interventions that were prompted by the results of the test (Table 2). This effect size was based on individual studies demonstrating the impact of treatments on DKD progression and was validated by clinical experts. This effect size was calculated from the following studies:

- A randomized, double-blind study with 1,513 patients comparing losartan (50–100 mg once daily) with placebo...
reported that losartan reduced the risk of doubling serum creatinine concentration by 25% \( (p = .006) \), end-stage renal disease by 28% \( (p = .002) \), and the composite outcome of doubling serum creatinine concentration, end-stage renal disease, or death by 16% \( (p = .02) \) \cite{25}. The average effect size from this study for the impact of losartan on the worsening of kidney disease was 23%.

Another prospective, randomized, double-blind clinical trial conducted in 1,715 patients reported that treatment with irbesartan was associated with a 20% lower risk of the primary composite endpoint (development of end-stage renal disease, doubling of the baseline serum creatinine concentration, or death) compared with the placebo group \( (p = .02) \). The irbesartan group had a 33% lower risk of doubling of the serum creatinine concentration compared to the placebo group \( (p = .003) \) and 23% lower risk of end-stage renal disease compared to the placebo group \( (p = .07) \) \cite{26}. The average effect size from this study for the impact of losartan on the worsening of kidney disease was 26%.

- A systematic review and trial-level meta-analysis of Glucagon-like peptide-1 receptor antagonists (GLP1-RA) and SGLT2 inhibitors cardiovascular outcomes trials, consisting of 77,242 patients with T2DM of whom 34,233 patients were in SGLT2 inhibitor trials, reported that SGLT2 inhibitors reduced the relative risk of the broad composite kidney outcome (new-onset macroalbuminuria sustained doubling of serum creatinine or a 40% decline in eGFR, end-stage kidney disease, or death of renal cause) by 38% compared to placebo \( (p < .001) \) \cite{27}.

- A systematic review and meta-analysis of randomized, controlled trials of the impact SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin), which included 38,723 patients with T2DM, reported that SGLT2 inhibitor treatment reduced the risk of dialysis, undergoing kidney transplant or death due to kidney disease by 33% risk of end-stage kidney disease by 35% and the risk of substantial loss of kidney function, end-stage kidney disease or death due to kidney disease by 42%. The overall effect of SGLT2 inhibitors on the substantial loss of kidney function, end-stage kidney disease, death due to cardiovascular or kidney disease across studies was 29%. All these estimates had \( p \) heterogeneity > .05, indicating that these estimates could be pooled on account of a lack of heterogeneity across the original studies \cite{28}. The average effect size from this study for the impact of SGLT2 inhibitors on the worsening of kidney disease was 38.5%.

When combined, these studies support an effect size of 20% reduction in the rate of progression by use of KidneyIntelX in our study, which was lower than the average effect size from all the studies described above. This was intended to provide an unbiased estimate of the anticipated effect size in the base case, which we further evaluated through sensitivity analyses on the effect size ranging from 5% to 35% reduction in the rate of DKD progression.

We also performed multiple multivariate sensitivity analyses simultaneously varying the definition of progression ("Least Stringent", "Stringent", "Most Stringent") and the difference in progression rates (5%, 20%, 35%) between KidneyIntelX and SOC (without KidneyIntelX). These are defined as follows:

- **Base Case Estimate:** "Stringent" definition of progression and 20% slowed progression rate with KidneyIntelX
- **Least Conservative Estimate:** "Least Stringent" definition of progression and 35% slowed progression rate with KidneyIntelX
- **Most Conservative Estimate:** "Most Stringent" definition of progression and 5% slowed progression rate with KidneyIntelX

Compliance with preventative measures recommended based on the results of the test was assumed to be 80% in the base case analysis. Patient adherence to oral hypoglycemics has been documented in the literature to be approximately 70%. A systematic literature review of studies published from 1966 to 2003 reported adherence rates of 67–85% for prospective electronic monitoring studies \cite{29}. Retrospective analyses showed that adherence to oral hypoglycemic agents ranged from 52% to 93% in generalizable populations (excluding studies with non-generalizable populations like Medicaid). Estimates for adherence to antihypertensive medications fall in a similar range. A study projecting national weighted estimates of nonadherence among 23.8 million hypertensive adults reported an adherence rate of 69% to antihypertensive medications \cite{30}. KidneyIntelX’s ability to be integrated into a health system EHR with standard order sets (including automatic generation of guideline-based treatment recommendations based on test results supported by post-test follow-up by the Care Navigation team), is expected to enhance adherence with guideline-based treatment recommendations. Our input of 80% adherence in the model is further supported by a study assessing the impact of KidneyIntelX results on clearly stated actionable treatment recommendations included in the test report. In a separate study conducted among PCPs, we found that 80% of the PCPs saw value in high-risk patients identified by the KidneyIntelX being able to avoid drugs that might cause further kidney damage and 77% PCPs believed that KidneyIntelX had value in identifying high-risk patients who need to be monitored more frequently. 98% of the PCPs in this study said they were likely to order KidneyIntelX in their patients to inform treatment decisions. Using a real-world conjoint analysis experiment, the authors found that KidneyIntelX test result was significantly more important and used more by PCPs than albuminuria and eGFR results when deciding whether to prescribe SGLT2 inhibitors (% Importance: 23% KidneyIntelX, 9% albuminuria, 4% eGFR) and increase the dose of losartan (% Importance: 13% KidneyIntelX, 8% albuminuria, 7% eGFR) among DKD patients. This provides evidence that the results from the KidneyIntelX test will be used by physicians to aid treatment decision-making in their DKD patients \cite{31}. An additional sensitivity analysis was performed by varying the level of compliance to preventative measures between 50% and 100%.
This sensitivity analysis was performed in the base case estimate using the “Stringent” definition of progression and a 20% decrease in the rate of progression using KidneyIntelX.

**Other outcomes**

Using progression rates obtained from KidneyIntelX validation studies, patients in the model progressed through stages 1–5 of DKD, followed by ESRD requiring dialysis. According to Molnar et al., up to 63% of patients initiate dialysis in an unplanned fashion. Based on this work, we assigned a probability of initiating dialysis due to crash to each stage of DKD resulting in a weighted average probability of 62.2%. The probability was assumed to decrease with increasing DKD stage, as patients are more likely to be prepared for dialysis (e.g. creation of vascular access) as they advance through the stages of DKD, an assumption validated by clinical experts.

It was assumed that 35% of patients on dialysis would ultimately have a kidney transplant after an average of 4 years, another assumption that was validated by clinical experts.

As a result of the slowed progression rate associated with KidneyIntelX testing, the rate of dialysis, dialysis crashes, and kidney transplants was reduced, in turn, delaying or preventing dialysis and transplants and reducing dialysis crashes.

**Costs**

The model includes the following costs derived from published literature (Table 1):

- Cost of each stage of DKD incurred by KidneyIntelX and SOC (without KidneyIntelX) patients (Table 1).
- The publications utilized reported Medicare and/or Commercial stage-specific annual costs of CKD, which were adjusted to reflect 2019 costs. Estimated stage-specific annual CKD costs in the model were weighted according to the payer mix (60% Medicare/40% Commercial) (Table 1). These costs did not include costs for dialysis, kidney transplants, and crashes, which were sourced from other publications.
- Cost of dialysis, kidney transplants (including post-transplant care), and dialysis crashes incurred by KidneyIntelX and SOC (without KidneyIntelX) patients (Table 1).
- Cost of the KidneyIntelX test only incurred by KidneyIntelX patients
  - The total cost of KidneyIntelX was $1,050 per patient. ($950 based on the payment assigned in the Medicare fee schedule + administration cost of $100). This test was assumed to have been administered once to the entire cohort at the start of the 5-year period.
- Incremental costs of additional preventative measures incurred by KidneyIntelX patients with a high-risk result included medications (antihypertensive and antidiabetic drugs) and office visits to nephrologists, dieticians, social workers as well as CKD education services. Based on data from the KidneyIntelX validation study, 16% of the total cohort (16,000 patients) was considered to be high-risk.

All costs were inflation-adjusted to 2019 US dollars based on the U.S. Consumer Price Index for Healthcare as recommended by ISPOR guidelines.

Distribution of the KidneyIntelX target population by stage, the annual cost per patient in each CKD stage, incremental costs of preventative measures, inputs specific to KidneyIntelX, and other cross-sectional model parameters are reported in Table 1.

The model tracked patients starting out in each stage of CKD in year 1 and followed them until year 5. Net movement into and out of each stage was calculated based on the probability of progression into the next stage for SOC (without KidneyIntelX) and KidneyIntelX. Progression rates are presented in Table 2 (base-case using “Stringent” definition of progression and 20% slowed progression rate with KidneyIntelX).

**Analysis**

The budget impact was calculated as the difference between KidneyIntelX and SOC (without KidneyIntelX) for all budget components and total costs. Potential savings upon using KidneyIntelX in the cohort of 100,000 DKD stages 1–3b patients was calculated over 5 years, in addition to annual cost savings. A break-even analysis was conducted to estimate the time after which benefits will surpass the costs of adopting KidneyIntelX.

**Results**

The total budget impact of KidneyIntelX was calculated as savings associated with KidneyIntelX from slowed progression, reduced dialysis crashes, and reduced transplants and dialysis due to ESRD minus cost of KidneyIntelX administration and increased use of preventative measures.

**Base case budget impact analysis**

In the base-case scenario, one-time KidneyIntelX testing resulted in estimated net undiscounted savings of $1.052 billion per 100,000 DKD patients tested in the health plan over the next 5 years (Figure 1) or $10,522 per patient tested. The net savings for the health plan is expected to increase to $1.249 billion, with 100% compliance to preventative measures, and $757 million, with 50% compliance to preventative measures (not shown in figure). The increase and decrease in savings can be attributed to slower or faster rates of progression resulting from lower levels of compliance with preventative measures within the KidneyIntelX population.

With base-case parameters, the breakeven point for the health plan is expected to occur just prior to year 2 after the adoption of KidneyIntelX (Figure 2). After the breakeven point, savings are expected to increase substantially in each consecutive year, with savings reaching $513 million in year 5 alone.
The greatest proportion of savings (~52%) are expected to be realized due to slowed progression through DKD stages ($551 million) (Figure 3). Savings from delayed or prevented dialysis and kidney transplants are projected to be ~$386 million; a result of ~5,000 patients having delayed or prevented dialysis treatment and ~150 patients having delayed or prevented a kidney transplant. Finally, savings from a reduction in dialysis crashes are projected to be ~$115 million; a result of ~2,800 crashes prevented in the KidneyIntelX tested cohort (Figure 3).

**Sensitivity analysis**

Results from the sensitivity analyses indicate that even with the most conservative effect size, the health plan can expect savings of $145 million over 5 years (Figure 1). With a 5% slowed progression rate with KidneyIntelX and the most stringent definition of progression, the breakeven point is expected to occur between years 3 and 4, which is still within the 5-year budget-impact period (Figure 2).

With the least conservative estimate (“Least Stringent” definition of progression and 35% slowed progression rate with KidneyIntelX), savings from KidneyIntelX are projected to be as high as $2.107 billion (Figure 1). The breakeven point with a 35% slowed progression rate with KidneyIntelX and the stringent definition of progression could be as early as 1 year after adoption (Figure 2).

The impact of uncertainty in key parameters was explored by one-way sensitivity analyses on each model parameter (Figure 4). Results of the one-way sensitivity analysis were expressed as tornado charts. The model is most susceptible to varying the effect size of a 20% reduction in progression by KidneyIntelX, given the high variability in the cost-savings.
Discussion

Our study focused on quantifying the economic value associated with KidneyIntelX owing to earlier identification and intervention in early-stage DKD patients over a 5-year timeframe. The KidneyIntelX validation study demonstrated that the current SOC (without KidneyIntelX) for staging DKD and guiding interventions associated with the KDIGO classification and treatment guidelines fail to identify 70–80% of patients who will reach the composite kidney outcome\textsuperscript{17,18}. Our study suggests that accurately identifying these patients with the KidneyIntelX test is associated with substantial cost savings for health plans (cost savings for 5 years per 100,000 DKD patients tested: $1.052 billion).

Numerous studies demonstrate that the annual treatment costs associated with CKD and DKD increase as the disease progresses\textsuperscript{11,41–43}. Previous cross-sectional studies have examined the cost of CKD in diabetes. Laliberté et al. reported that the total direct all-cause healthcare mean [median] cost difference between CKD group and the no-CKD group was $11,814 [$6,835] for the diabetes only cohort and $10,625 [$32,308] for diabetes and hypertension cohort in the U.S.\textsuperscript{43}. More recent data reported by USRDS indicate a total of 3.4 million Medicare beneficiaries reportedly had CKD in 2017\textsuperscript{10}. CKD is considered a cost multiplier in Medicare beneficiaries; among fee-for-service Medicare beneficiaries, CKD is reported in 4% of the point prevalent aged Medicare population but accounts for ~25% of total expenditures\textsuperscript{10}. In this population, per-person per-year (PPPY) costs were 87% higher for patients with CKD only, versus those with no CKD, diabetes, or heart failure ($16,112 vs $8,620)\textsuperscript{10}. In 2017, costs for patients with CKD and diabetes were 51% higher than for those without CKD\textsuperscript{10}. The relationship between diabetes, CKD, and the increased risk of progressive and more costly treatment has been long established. One of the key remaining challenges has been to have better tools to identify patients at risk of PDKF earlier in their
disease, providing clinicians the opportunity to treat more aggressively at earlier stages so as to successfully slow disease progression and reduce costs associated with DKD progression.

The KidneyIntelX in vitro Kidney Diagnostic Solution includes a laboratory-developed test (LDT) combined with an AI-enabled clinical diagnostic solution that accurately predicts the risk of developing PDKF in patients with DKD. Artificial intelligence (AI) and related technologies are becoming tools routinely used in our digital society, with direct applications to healthcare. They demonstrate the potential to transform patient care (e.g. virtual visits, use of health and wellness apps), as well as administrative processes within provider, payer, and pharmaceutical organizations. A number of studies suggest that AI can perform as well as or better than humans at key healthcare tasks, such as diagnosing disease (i.e. digital pathology, digital radiology) and that AI-enabled algorithms can improve risk prediction. In May 2019 the U.S. FDA recognized this potential when it granted breakthrough device designation for the KidneyIntelX test, identifying it as a breakthrough technology for which no approved or cleared alternative exists and meeting the criteria of providing a more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease. In the validation study, the test compares favorably to the performance observed with the standard KDIGO classification, with a 61% PPV in high-risk KidneyIntelX patients compared to the 40% PPV documented for the KDIGO algorithm and an NPV of 90% in low-risk patients compared to an NPV of 85% documented for the KDIGO algorithm (p < .001). Our study documents the potential cost savings associated with delayed progression, delayed or reduced dialysis and kidney transplants, and reduced dialysis crashes with the KidneyIntelX test’s improved ability to identify and intervene early in patients at high risk for PDKF. The ability of KidneyIntelX to be integrated with EHR and care navigation software of health plans maximizes compliance with the recommended diagnostic and prescriptive kidney care protocols, which contributes to cost savings as evidenced by the sensitivity analysis performed in our study.

There are several limitations to our study. First, we did not have a direct measure of the impact of early testing and intervention on the rate of DKD progression. In our model, we calculated a 20% reduction in the rate of progression (base case analysis) for KidneyIntelX based on individual studies demonstrating the impact of treatments on DKD progression. As noted earlier, we also performed a rigorous sensitivity analysis by varying this rate of slowed progression between 5% and 35% to ensure that the model is robust over a reasonable range of effect sizes associated with the clinical impact of the test, and even at a rate of 5% progression decline, the test was still associated with meaningful savings.

Due to the observational nature of studies that examine the association between DKD progression and increased medical costs, we cannot confirm a causal association between use of the KidneyIntelX and reduction of DKD progression and costs, but strongly believe that earlier intervention prompted by the test will delay progression and reduce overall treatment costs.

As our study seeks to estimate costs from a payer perspective, we assumed a distribution of 60% Medicare and 40% commercial beneficiaries in estimating the financial impact associated with the use of KidneyIntelX. While these results may not be generalizable to all healthcare settings (in particular, a highly managed integrated delivery network, where perhaps better risk stratification and intervention may be possible), we believe our modeling approach provides a robust, structured method for simulating the impact of the test, and it could be readily adapted to reflect a more structured care environment.

Our model followed a static cohort of patients tested with the KidneyIntelX over 5 years. It did not account for new DKD patients being eligible for the test each year, and a proportion of patients who would leave the cohort due to changing health plans or death. However, we do not have any reason to believe that the proportion of patients qualifying for the cohort each year is vastly different than the proportion of patients exiting the cohort.

Another potential limitation is that the budget impact model does not directly account for false positive or false negative test results when assessing the impact of the test on cost savings; however, we did vary the definition of progression based on three different definitions of “progression” based on biomarker data to identify patients who had progressed to the next stage of DKD severity, and the use of the test was associated with savings in all scenarios tested. In addition, in the baseline modeling analysis, we accounted for increased use of medications and other interventions that would be based on a KidneyIntelX test result indicating that a patient is at high risk of progression (which the interventions would delay). The number of false positives with KidneyIntelX is approximately 33% lower (39% for KidneyIntelX, 60% for KDIGO) compared to the use of the KDIGO risk assessment algorithm, which suggests that even with the added medication treatment costs, the base case analysis conservatively estimates the savings even accounting for false positive test results.

Lastly, our model did not include direct non-medical costs (e.g. transportation and caregiving), indirect costs (e.g. productivity losses) and intangible costs (e.g. diabetes-associated psychological distress and discomfort). Given that these costs have a significant impact on society, our estimates of savings incurred by payers are conservative relative to the overall health savings that may be obtained with better risk stratification and earlier intervention with DKD patients.

Conclusions

The progression of chronic kidney disease in T2DM is associated with high direct medical costs to health insurers. The cost of progression of DKD increases by stage of severity of DKD, signaling the clear need for early patient risk assessment and stratification, earlier intervention with guideline-based interventions to delay progression and deterioration of renal function, and improvement in patient outcomes, in an
ultimate effort to reduce the economic burden of DKD. This will be essential in the successful containment of costs associated with the increasing prevalence of DKD. KidneyIntelX shows considerable promise in not only identifying patients’ risk of PDKF, but also resulting in economic savings for the health plan in the long run. Our 5-year budget impact model showed that the test cost and cost for preventative measures adopted based on the results of KidneyIntelX can be offset by cost savings from a reduction in DKD progression, delay or prevention of dialysis and transplants, and reduction in dialysis crashes, within 2 years after test adoption by health plans.

Note
i. KidneyIntelX is a trademark of Renalytix, Inc., New York, NY, USA.

Transparency

Declaration of funding

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Declaration of financial/other relationships

SGC reports grants, personal fees and other from Renalytix Inc., during the conduct of the study; personal fees from CHF Solutions, personal fees from Boehringer-Ingelheim, personal fees from Takeda, personal fees and other from pulseData, personal fees from Relypsa, personal fees from Bayer, personal fees from inRegen, personal fees from Quark, outside the submitted work; In addition, SGC has a patent, “Derivation and Validation of a Machine Learning Risk Score Using Biomarker and Electronic Patient Data to Predict Rapid Progression of Diabetic Kidney Disease”, licensed to Renalytix Inc.

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Author contributions

MD: Conceptualization of study, model development and programming, analysis and manuscript preparation. WB: Model development and programming, analysis and manuscript preparation. MJD: Analysis and manuscript preparation. SGC: Conceptualization of study, model development, analysis and manuscript preparation. EW: Model development and programming, analysis and manuscript preparation. TFG: Conceptualization of study, model development and programming, analysis and manuscript preparation.

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Data availability statement

The datasets generated during and/or analyzed during the current study may be available from the corresponding author on reasonable request.

Previous presentations

Preliminary results of this analysis have previously been presented at the 2020 National Kidney Foundation, Spring Clinical Meeting with the detailed methods and results presented here22.

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ORCID

Thomas F. Goss http://orcid.org/0000-0003-3693-3657
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