Diabetes mellitus is the most common cause of ESKD in the United States, and cardiorenal disease is markedly increased in those patients. Recently, there has been a dramatic increase in clinical trials in diabetic nephropathy utilizing new nonsteroidal mineralocorticoid receptor antagonists, glucagon-like peptide-1 receptor agonists, and sodium-glucose transporter type II inhibitors (SGLT2i), which have demonstrated efficacy in slowing progression of chronic diabetic kidney disease. In addition, in clinical trials, glucagon-like peptide-1 receptor agonists and SGLT2i have been shown to reduce cardiovascular risk in patients with diabetes mellitus. However, how these agents can best be utilized in patients with different stages of CKD with and without cardiorenal disease has not yet been elucidated. This conundrum has led to numerous reviews and studies evaluating both the utility of outcomes predictors of both cardiorenal disease and progressive CKD from diabetic nephropathy.

Early studies in diabetic nephropathy used proteinuria as an outcome measure in diabetic CKD. These studies showed increasing levels of proteinuria predicted a more rapid decline in GFR and that the use of angiotensin receptor blockers to diminish proteinuria improved these outcomes (1,2). The kidney failure risk equation was created in 2011 from a large population of stages 3–5 CKD from numerous causes, including diabetic nephropathy. These studies utilized clinical and laboratory data to predict progression to ESKD (3). A subgroup analysis of this data for diabetic nephropathy was never performed. Thereafter, three additional studies utilizing primarily clinical data including eGFR and the degree of albuminuria showed only modest correlations to the progression of CKD in general or in diabetic mellitus. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines only showed modest effects, but greater urinary proteinuria did predict a more rapid decline in GFR in patients with glomerulonephritis or diabetic nephropathy (4). Dunkler and colleagues analyzed the ON TARGET and ORIGIN data from two trials in diabetics utilizing clinical and demographic data. They found that eGFR and the degree of proteinuria were modestly predictive in early CKD from type 2 diabetes mellitus and that the addition of the demographic, clinical, and laboratory data did little to improve the predictive performance (5). Finally, a multinational study of 34 cohorts of patients from the CKD Progression Consortium, totaling 5,222,711 individuals, applied clinical and demographic data and found a C statistic for reduced eGFR of 0.845. Another cohort without diabetes had a C statistic of 0.801 for the 5-year risk of declining GFR in the diabetic cohort (6). However, none of these predictive studies reached wide acceptance for clinical use in CKD patients, and none studied diabetes specifically. A recent article showed that the risk prediction for CKD progression using eGFR and albuminuria have powerful predictive value but are underutilized (7).

In an attempt to find other factors involved in the progression of CKD, the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases initiated the CKD Biomarker Consortium in order to find blood or urinary biomarkers that could predict progression of CKD, especially in diabetes mellitus. The Joslin Clinic investigation of TNF-1 and TNF-2 showed that circulating inflammatory cytokines predicted progression to ESKD in patients with type 2 diabetes nephropathy with stage III CKD and in patients with type 1 diabetes mellitus (8,9). Further work by the CKD Biomarker Consortium extended these observations and found that higher KIM-1, TNF-1, TNFR-2, MCP-1, suPAR, and YKL-40 levels were associated with a greater risk of progression of diabetic kidney disease after adjustment for clinical factors (10). These serum biomarkers have also been shown to be useful predictors of CKD progression in other populations, including the AASK and VA NEPHRON-D studies and the Boston Kidney Biopsy Cohort and Chronic Renal Insufficiency Cohort (CRIC) Studies (11,12).

Despite the robust promise of serum biomarkers, newer studies of urinary biomarkers have led to more complicated results. The CKD Biomarker Consortium in the CRIC Study found that only urinary KIM-1 was associated with cardiovascular outcomes and death, and none of the urinary biomarkers after adjustment...
for eGFR and albuminuria were associated with diabetic kidney disease progression (13,14). However, recent studies in diabetes showed that urine MCP-1 was associated with renal decline, and urinary markers of proximal tubular origin, inflammation, and fibrosis were associated with progression of diabetic CKD (15,16).

To fill the void and current predictive models of diabetic CKD, investigators for the CKD Biomarker Consortium and others have developed a machine learning-derived prognostic test, KidneyIntelX, which has integrated known biomarkers consisting of levels TNF-1, TNF-2, and KIM-1 with electronic health record (EHR) data to predict longitudinal outcomes in two populations: a Mount Sinai biobank of patients with type 2 diabetes mellitus and an African American registry database of patients with APO L-1 risk alleles (17). Their study utilized random forest models with two inputs: biomarker concentrations and EHR factors, including laboratory data, diagnostic codes, demographics, medication, and health care history. Further iterations were modeled by the three hyperparameters (17). The composite renal outcome was rapid decline in kidney function, defined as a decline in GFR of ≥5 ml/min per 1.73 m² per year, or a 40% sustained GFR decline, or ESKD within 5 years. The AUC for KidneyIntelX was 0.77 in type 2 diabetes mellitus and 0.8 in patients with APOL-1 risk alleles. The negative predictive value was 92% for type II diabetic and 96% for APOL-1 homozygous patients. Patients were stratified into three groups: low risk, intermediate risk, and high risk for CKD progression. Patients in the low-risk group were recommended to follow up with their primary care provider with annual KidneyIntelX values. Patients in the high-risk group were recommended to be referred to a nephrologist to minimize their risk for CKD progression (17). The investigators confirmed the accuracy and usefulness of KidneyIntelX again for the BioMe Biobank and PMBB from PENN in diabetics with a mean baseline eGFR of 54 ml/min per 1.73 m² and albumin/creatinine ratio of 6.9 mg/mg (18). They used the same primary end points as previously described. Patients were stratified as 46% low risk, 51% intermediate risk, and 17% high risk. The positive predictive value for progressive decline in GFR in the high-risk group was 61% by KidneyIntelX but only 40% utilizing the KDIGO categorizations.

The beneficial effect of canagliflozin was confirmed by KidneyIntelX in the CANTAS Trial (18). The CANTAS Trial had two treatment arms involving nearly 10,142 patients with type 2 diabetes mellitus and high cardiovascular risk. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, and cerebrovascular accident, which was significantly improved by canagliflozin (19). The secondary outcome was the composite of a sustained 40% reduction in eGFR, the need for RRT, or death from renal-related causes. Both outcomes favored canagliflozin over placebo but were not quite statistically significant. However, when KidneyIntelX was utilized for the patients who had diabetic kidney disease (eGFR 30–50 ml/min per 1.73 m² or urinary albumin/creatinine ratio >30 mg/g), the program stratified patients into low risk (42%), intermediate risk (44%), and high risk (15%) of the composite renal outcome of >5 ml/min per 1.73 m² per year eGFR decline, >40% decline in eGFR, or ESKD.

In addition, SGLT2i have been shown to improve outcomes not only in the CANVAS Trial but also in the EMPA-RE, DECLARE-TIMI, and CRESCENDO trials (20,21). However, to date, no SGLT2i study in diabetes stratified the cardiovascular outcomes in these patients. In the May issue of Kidney360, Nadkarni and colleagues assessed the ability of KidneyIntelX to stratify patients within the CANVAS Trial for a combined cardiorenal outcome defined as a composite end point of 57% decline in eGFR, development of ESRD, heart failure hospitalization, or death (22). They also added a sensitivity analysis evaluation as a 40% decline in eGFR rather than a doubling of the serum creatinine (57% decline of GFR). Both analyses easily stratified the patients into low, intermediate, or high risk for cardiorenal outcomes. This is the first study of its kind to combine serum biomarkers with additional machine learning and artificial intelligence of EHR data to provide risk stratification for cardiorenal outcomes in patients with diabetes treated with SGLT2i. Patients at high risk were recommended to be referred to a nephrologist and cardiologist (in an attempt to diminish the likelihood for progressive CKD or worsening cardiac outcomes). Prospective studies using KidneyIntelX to guide best therapies for intermediate- and high-risk diabetic patients, and cardiorenal outcomes will be needed to confirm benefits from this risk-based care approach.

Finally, other biomarkers besides those utilized in KidneyIntelX have been shown to correlate with type I diabetic kidney disease, including calbindin, osteoactivin, Trefoil-3, VEGF, β2 microglobulin, cystatin C, osteopontin, and neutrophil gelatinous-associated lipocalin (23). In addition, novel microRNAs (miRNAs) that regulate fibrosis, inflammation, hypertrophy, autophagy, podocyte injury, and oxidative stress have been implicated in diabetic kidney disease (24). Indeed, Satake and colleagues have recently shown circulating miRNAs are strongly associated with a 1-year risk of ESKD, and diabetic miRNAs target proteins in the axon guidance pathway also correlated with 10-year risk of ESKD in diabetics (25).

Taken together, the history of biomarker research looking at CKD outcomes has now evolved into the arena of cardiac trends in the outcomes of diabetic nephropathy. Using artificial intelligence of the EHR data in these patients will hopefully lead to better models to predict progression of CKD and cardiorenal outcomes and will hopefully lead to new targeted precision therapies to slow progression of his CKD and diabetes (26).

Disclosures
G.L. Braden reports being an employee of Kidney Care and Transplant Services of New England, and an advisory or leadership role for Dascena. D.L. Landry reports being an employee of Kidney Care and Transplant Services of New England, and an advisory or leadership role for the Medical Advisory Council at the National Forum of ESRD Networks (chair) and the Medical Review Board for ESRD Network 1 (chair) but receives no financial compensation for either position.

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Author Contributions

G.L. Braden was responsible for conceptualization; D.L. Landry reviewed and edited the manuscript; and both authors were responsible for visualization and wrote the original draft of the manuscript.

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