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KidneyintelX.dkd: An Innovation in Precision Medicine for Diabetic Kidney Disease

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Title: **KidneyintelX.dkd**

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Background of the problem

The leading cause of chronic kidney disease (CKD) is type 2 diabetes and up to 40% of individuals with CKD have diabetic kidney disease (DKD).[1] The clinical course of DKD is variable amongst individuals, who may have fluctuating levels of albuminuria and may or may not lose a significant proportion of kidney function over time.[2]

Despite the availability of newer kidney protective medications, only a fraction of eligible patients receive these therapies.[3] One of the reasons for intertia may be a lack of clinical tools to identify which patients are by therapy benefits can be optimized in relation to side effects. Recent guidelines,[1] as well as world experts,[4,5] strongly advocate for risk assessment as a critical tool to inform risk–benefit ratio of interventions and to enable a personalized approach to treatment and identification of who would benefit most from multifaceted therapy to slow progression.

The solution

In 2017-2018, we sought to develop a multi-input prognostic test that combined biologic and clinical to stratify patients with type 2 diabetes and prevalent CKD for risk of progression. At the time, several blood-based biomarkers reflective of CKD/DKD pathophysiology were repeatedly shown to be independently associated with kidney function decline. Specifically, three biomarkers were chosen for futher development; specifically plasma tumor necrosis factor receptors (TNFR)-1 and TNFR-2 and kidney injury molecule (KIM)-1.[6] Since we were seeking to incorporate intra-correlated biomarkers and a various clinical variables extracted from the medical records, we intended use to machine learning models since traditional statistical models often struggle with electronic health record (EHR) data due to its size, inconsistencies in how data is collected or structured, and the complex relationships between different variables. Machine learning addresses these challenges by analyzing diverse and complex data more effectively, identifying patterns that improve predictions. In 2018, we obtained plasma samples from patients with type 2 diabetes from the Mount Sinai BioMe Biobank (MSBB), and extracted clinical data from the EMR on this patients. The three biomarkers were measured using a custom optimized multiplex electrochemilluminence assay on the Mesoscale platform, and the first pilot version of

the KidneyIntelX prognostic model was created, that had moderate discriminatory performance for a composite kidney outcome in individuals with type 2 diabetes with and without prevalent CKD at baseline.[7] With these data in hand, we applied for Breakthrough Designation for devices from the FDA which was granted (Figure 1).

In robust dialogue with the FDA, we sought to refine the assays for the 3 biomarkers, the algorithm inputs, and to better define the intended use population, clinical outcomes, follow-up period for prognostication. For the next set of clinical validation studies, we use banked plasma samples from the MSBB and the Penn Medicine Biobank (PMBB) and trained an algorithm using 10-fold cross-validation for prediction of a composite kidney of rapid decline in kidney function (eGFR > 5 ml/min/1.73 m2), a sustained 40% decline in eGFR, or kidney failure, all within 5 years of baseline. This version of the test provided a 15-fold gradient in risk for the composite outcome between high and low risk, and outperformed a comprehensive model made of clinical variables alone, or KDIGO risk strata.[8] The final model included the concentrations of the 3 biomarkers and their ratios, and 7 clinical variables (eGFR, UACR, systolic BP, HbA1c, and 3 others). The version of KidneyIntelX was approved by the New York Stage Department of Health as a Laboratory Developed Test (LDT). Both CAP and CLIA approved the laboratory for the test in NYC, and the initial LDT version of KidneyIntelX was launched in a multi-center real world evidence (RWE) program across several primary care, endocrine, and nephrology practices in the Mount Sinai Health System, and Wake Forest Health System in North Carolina in 2021.

To build the kidneyintelx.dkd model that was used in the final dossier to the FDA, we used the PMBB for derivation alone, and the MSBB for validation, with additional verification in a subgroup of participants from the Canagliflozin Cardiovascular Assessment Study (CANVAS) trial cohort, all with prevalent DKD G1-G3b at baseline and banked plasma samples. We used a comprehensive protocol and analysis plan to ensure that all data was blinded, and performance outcomes were statistically and clinically significant to satisfy stringent FDA requirements for a novel or “de novo” test. In validation, 57%, 35%, and 8% of individuals were classified as low, moderate, and high risk, respectively. The cumulative incidence of the composite kidney outcome in

the three risk groups was 6%, 21%, and 67%, respectively. After adjustment for standard demographic and clinical risk factors for DKD progression (age, sex, race, eGFR, UACR, HbA1c, systolic blood pressure), the adjusted hazard ratios (HRs) were 7.7 (95% CI 3.0-19.6) for high risk vs. low risk and 3.7 (95% CI 2.0-6.8) for moderate risk vs. low risk groups. These associations remained consistent in CANVAS and across several key subgroups.[9] The test was granted FDA breakthrough status and then after some delays due to the pandemic, was granted full marketing authorization in 2023.

Implications for FDA Approval of kidneyintelX.dkd and Potential Clinical Benefits

The FDA De-novo marketing authorization pathway applies to medical devices or diagnostic devices which are novel in nature whereby no suitable comparator, or "predicate device" exists against which the safety and performance can be assessed.[9] KidneyIntelX.dkd is the first prognostic test for kidney disease to be approved under a new classification of device established by the FDA. The rigorous collaborative process with the agency involving a number of innovations including blending of patient laboratory test data taken from patient records with biomarker measurements based on analytical validation which adhered to Clinical Laboratory Standards Institute (CLSI) standards and FDA regulations, and the use of a machine learning model for generation of the risk level.[10] The new device classification established by the FDA provides a regulatory framework and pathway for future versions of the test and research is ongoing to identify additional biomarkers that can add further valuable insights into patients' risk of progression in the evolving care landscape.

Clinical Translation and Real-World Impact

The kidneyintelX.dkd is now commercially available across the US and is in use on a daily basis. To bridge the chasm between development and implementation, several key factors have been addressed including integration of the test into clinical workflows, seamless ordering and reporting through interface with the EHR, sample logistics, and provider and patient education. In addition, the EHR provides a medium

for results to be delivered to physicians and patients, and incorporated into care pathways at population scale.

KidneyintelX.dkd is an important addition in care management since guideline-based care for DKD involves multiple medications. Clinical guidelines base their recommendations on group-level data, however, decisions in clinical practice are made on the individual level. DKD is a heterogeneous disease with great variability in disease progression and treatment responses. In clinical practice, a sizable proportion of individuals do not tolerate the guideline-advised doses because of adverse effects, resulting in suboptimal dosing and reduced efficacy. An individualized, risk-based treatment approach helps select the optimal treatments, balancing the risks and benefits for an individual. Indeed, the recently published KDIGO guidelines recommend "risk assessment to assist with delivery of personalized care for people with CKD."[1] With multiple new drug classes now available for DKD management in addition to baseline RAAS inhibition, precision medicine solutions such as kidneyintelX.dkd can change the current paradigm to a more individualized approach. Some experts advocate an "accelerated risk-based approach" in which prioritization for "quadruple therapy" is reserved for those at highest absolute risk for progression, given costs and potential adverse events.[4]

A key step in clinical adoption is securing reimbursement. To this end, the aforementioned comprehensive RWE program was established to demonstrate risk assessment utility. At the two large centers, outcomes on the initial tranche of patients tested demonstrated a 60% increase in guideline-based medication use among high risk patients from baseline, including improvements in hemoglobin A1c (HbA1c) and UACR, stabilization of kidney function, and population-level risk reduction within 12 months of testing with KidneyIntelX.[10] Finally, economic analyses demonstrate potential substantial economic benefits with testing of a broad population of patients with type 2 diabetes and CKD.[11]

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Because Dr. Girish Nadkarni is an Associate Editor of *JASN*, he was not involved in the peer-review process for this manuscript. Another editor oversaw the peer-review and decision-making process for this manuscript.

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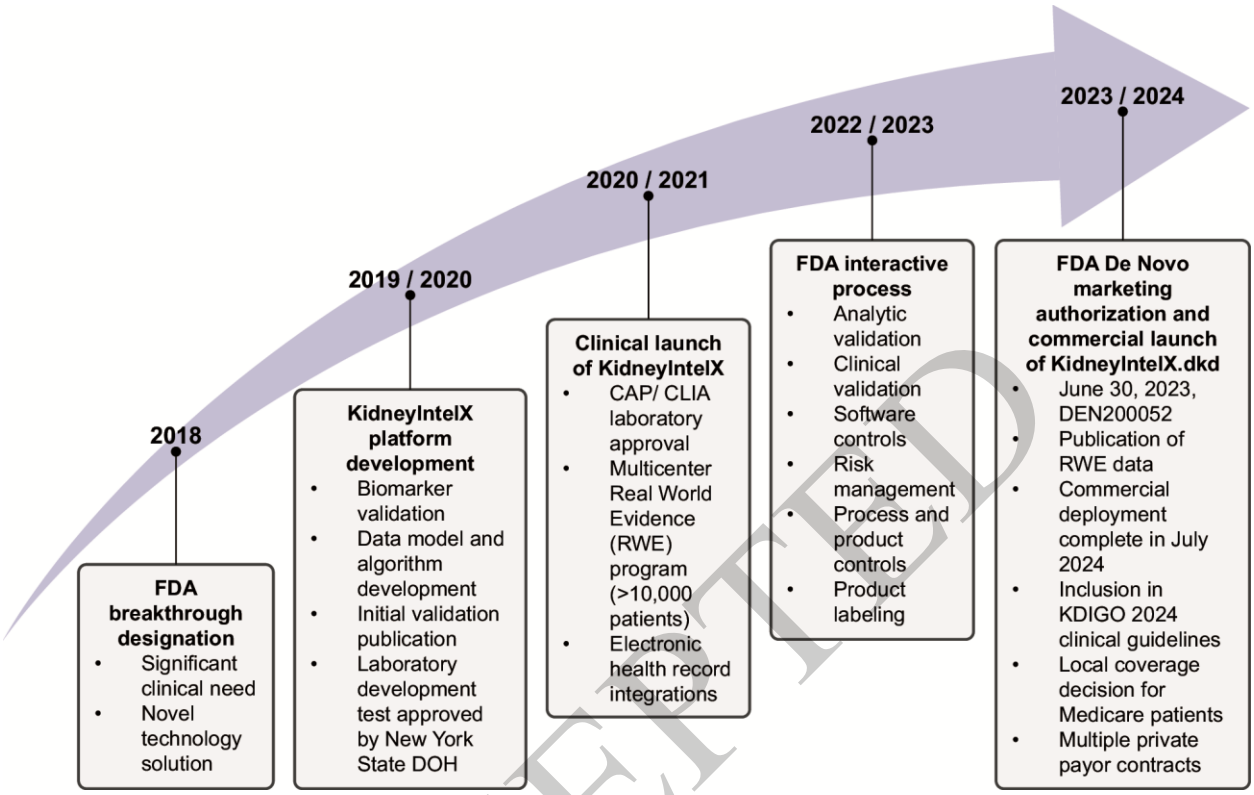
Figure 1. Timeline of Development of KidneyIntelX



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