Anthem

Medical Policy

Subject: Machine Learning Derived Probability Score for Rapid Kidney Function Decline
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Description/Scope

This document addresses the use of a machine learning derived probability score (i.e., artificial intelligence) which may combine a variety of clinical characteristics such as, biomarkers, genetics, gender or race, to generate prognostic information with the end-goal of facilitating a more personalized approach to the management of chronic kidney disease (e.g., KidneyIntelX™). This document does not address the standard use of blood-based biomarkers, estimated glomerular filtration rate (eGFR) or urinary albumin and creatinine levels in the prognostic evaluation of newly diagnosed kidney disease.

Position Statement

Investigational and Not Medically Necessary:

Use of a machine learning derived probability score (e.g., KidneyIntelX) to predict rapid kidney function decline in chronic kidney disease is considered **investigational and not medically necessary** for all indications.

Rationale

Chronic kidney disease (CKD) is defined by the Kidney Disease Improving Global Outcomes (KDIGO) organization as abnormalities of kidney structure or function, present for > 3 months. In the KDIGO Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease, factors associated with CKD progression to inform prognosis include the etiology of CKD (e.g., diabetes, hypertension, etc.), level of GFR, level of albuminuria, age, sex, race/ethnicity, elevated blood pressure, hyperglycemia, dyslipidemia, smoking, obesity, history of cardiovascular disease and ongoing exposure to nephrotoxic agents (ungraded recommendation; Stevens, 2012). A standardized system for integrating sociodemographic risk factors with clinically relevant biomarkers to accurately identify those most at risk for progression is not yet available in most practice settings, potentially hampering clinicians' timely intervention in CKD management. Recently, the use of machine learning approaches that can combine biomarkers and electronic health record data to produce prognostic risk scores have been explored. One such approach is the KidneyIntelX, a proprietary artificial intelligence-enabled algorithm which combines blood-based biomarkers, genetics and personalized data from electronic health records to generate a unique risk score which is then used to develop a prediction of progressive kidney function decline in diabetes-related CKD.

In 2020, Chan and colleagues published results of a study evaluating the clinical utility of KidneyIntelX. This retrospective cohort enrolled 1146 individuals with diabetes-related CKD age 21-81. During the follow-up period (median of 4.3 years) 241 study enrollees (21%) experienced progressive decline in kidney function. KidneyIntelX stratified 46%, 37% and 16.5% of validation cohort (n=460) into low-, intermediate- and high-risk groups, respectively, with a positive predictive value (PPV) of 62% (PPV of 37% for the clinical model and 40% for KDIGO; p<0.001) in the high-risk group and a negative predictive value (NPV) of 91% in the low-risk group. The net reclassification index for events into the high-risk group was 41% (p<0.05). In this retrospective, exploratory validation study, KidneyIntelX scores accurately classified more cases into the KidneyIntelX-defined low, intermediate and high-risk strata (p-value<0.05) relative to KDIGO risk strata. The study authors conclude, "A machine learned model combining plasma biomarkers and EHR [electronic health record] data improved prediction of progressive decline in kidney function within 5 years over KDIGO and standard clinical models in patients with early DKD [diabetes-related CKD]." Given the retrospective study design and marginal statistical significance, further investigation in the setting of a large, ideally randomized, trial is warranted to establish whether use of KidneyIntelX materially improves net health outcomes compared to established alternatives, such as the KDIGO guideline's specified sociodemographic risk factors, pertinent health history and clinically relevant biomarkers.

In 2022, Lam and colleagues published results from a retrospective study of samples collected during conduction of a prospective randomized controlled trial, CANagliflozin cardioVascular Assessment Study (CANVAS). In total, 1325 CANVAS participants with diabetic kidney disease and baseline plasma samples were enrolled into the study. KidneyIntelX risk scores were generated from the available samples at baseline and years 1, 3, and 6 of study follow-up. The study's primary aim was to assess the association of changes from baseline in KidneyIntelX scores with progression of diabetic kidney disease; composite outcomes included, (1) rapid kidney function decline, (2) a sustained 40% decline in eGFR, or (3) kidney failure. During the mean follow-up of 5.6 years, 131 study participants (9.9%) experienced a composite kidney outcome. Using risk cutoffs established from previous validation studies, KidneyIntelX stratified participants into low- (42%), intermediate- (44%), and high-risk (15%) groups with cumulative incidence for the outcomes of 3%, 11%, and 26%, respectively (risk ratio=8.4; 95% confidence interval [CI], 5.0-14.2) for the high-risk versus low-risk groups. Changes in KidneyIntelX score within the first year were significantly associated with future risk of a composite outcome (odds ratio [OR; per 10 unit decrease]=0.80; 95% CI, 0.77, 0.83; p<0.001). Study authors conclude that "KidneyIntelX risk-stratified a large multinational external cohort for progression of DKD [diabetic kidney disease]…". Given the retrospective design and unclear clinical significance of these findings, further study is warranted to determine the impact of KidenyIntelX on net health outcomes.

In 2022, Tokita and colleagues evaluated the clinical performance of KidneyIntelX in a large hospital system over a 6-month follow-up period. Study outcomes included visit frequency, medication management changes, referral to a specialist and selected lab values. A total of 1686 individuals were enrolled and tested using KidneyIntelX scoring and the hospital's pathway management for individuals with stages 1 to 3 diabetic kidney disease. Following testing with KidneyIntelX, a clinical encounter occurred in the first month in 13%, 43%, and 53% of low-risk, intermediate-risk, and high-risk individuals, respectively and in 46%, 61%, and 71% of the study participants at least 1 action was implemented within the first 6 months. Participants classified as high-risk were more likely to be placed on SGLT2 inhibitors (OR=4.56; 95% CI, 3.00-6.91 vs low-risk), and more likely to be referred to a specialist such as a nephrologist, endocrinologist, or dietician (OR=2.49; 95% CI, 1.53-4.01) compared to participants classified as low-risk. Systolic blood pressure (49% of participants were hypertensive at baseline) and eGFR remain unchanged across all 3 risk stratification levels throughout the study. The addition of the KidneyIntelX to the management of individuals with early diabetic kidney disease did not demonstrate a clinically meaningful benefit in this prospective trial.

Summary

Currently, there is no guidance from specialty medical societies addressing the use of machine learning to generate prognostic information in the treatment of CKD. The published peer-reviewed medical literature has not established KidneyIntelX, or any technology like it, as a proven method that materially improves net health outcomes nor has any benefit been established beyond currently available alternatives (e.g. KDIGO guidelines).

Background/Overview

In 2021, approximately 37 million Americans reportedly had chronic kidney disease (CKD), with over 131, 000 requiring initiation of treatment for kidney failure, also known as end stage renal disease (ESRD). There was a steady rise in the rate of ESRD from 1980 to 2011, since then, the incidence rate of ESRD has started to decline. The most prevalent causes of kidney disease are diabetes and hypertension, which account for approximately 39% and 26% of ESRD cases, respectively (CDC, 2021). On average, 50,000 individuals with diabetic kidney disease progress to kidney failure annually in the United States (Chan, 2020).

Predicting which newly diagnosed diabetic kidney disease cases may progress to ESRD has proved challenging for clinicians, potentially resulting in delayed diagnosis of individuals and the subsequent need for life-saving dialysis or kidney transplants. Typically, prognosis is achieved through integration of established sociodemographic risk factors (i.e., smoking, obesity, and race/ethnicity) along with clinically relevant biomarkers, such as glycemic levels, eGFR, and lipid levels. KidneyIntelX is described by the manufacturer (RenalytixAI) as a validated machine-learned, prognostic risk score which combines data from EHRs and circulating biomarkers to predict diabetic kidney disease progression. More specifically, KidneyIntelX combines three blood-based biomarkers (tumor necrosis factor receptor [TNFR]1, TNFR2 and kidney injury molecule 1) with seven clinical indicators (eGFR, urine albumin-creatinine ratio, serum calcium, hemoglobin A1C, systolic blood pressure, platelets, and aspartate aminotransferase [AST]) to generate a risk score purported to help clinicians determine if an individual is at low, intermediate, or high risk for rapid decline in kidney function. The end goal of incorporating KidneyIntelX into practice, is to slow the progression of kidney disease and progressive kidney function decline which may result in kidney failure and ultimately long-term dialysis or kidney transplant (Chan, 2020).

Definitions

Artificial Intelligence (AI): A science of computer simulated thinking processes and human behaviors, which involves computer science, psychology, philosophy and linguistics.

Chronic renal disease: The permanent loss of kidney function.

End stage renal disease: Persistent decline in renal function as documented by falling creatinine clearance in an individual diagnosed with a renal disease whose natural history is progression to renal impairment requiring renal replacement (dialysis or transplant).

Glomerular filtration rate (GFR): A test used to check how well the kidneys are functioning by estimating how much blood passes through the glomeruli each minute.

Glomeruli: A cluster of nerve endings, spores, or small blood vessels, in particular a cluster of capillaries around the end of a kidney tubule, where waste products are filtered from the blood.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure code, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

0105U	Nephrology (chronic kidney disease), multiplex electrochemiluminescent immunoassay (ECLIA) of tumor necrosis factor receptor 1A, receptor superfamily 2 (TNFR1, TNFR2), and kidney injury molecule-1 (KIM-1) combined with longitudinal clinical data, including APOL1 genotype if available, and plasma (isolated fresh or frozen), algorithm reported as probability score for rapid kidney function decline (RKFD) KidneyIntelX™, RenalytixAI, RenalytixAI
0407U	Nephrology (diabetic chronic kidney disease [CKD]), multiplex electrochemiluminescent immunoassay (ECLIA) of soluble tumor necrosis factor receptor 1 (sTNFR1), soluble tumor necrosis receptor 2 (sTNFR2), and kidney injury molecule 1 (KIM-1) combined with clinical data, plasma, algorithm reported as risk for progressive decline in kidney function kidneyintelX.dkd™, Renalytix Inc, Renalytix Inc, NYC, NY

ICD-10 Diagnosis

	All diagnoses

References

Peer Reviewed Publications:

1. Chan L, Nadkarni G, Fleming F, et al. Derivation and validation of a machine learning risk score using biomarker and electronic patient data to predict progression of diabetic kidney disease. Diabetologia. 2021; 64(7):1504-1515.
2. Chauhan K, Nadkarni GN, Fleming F, et al. Initial validation of a machine learning-derived prognostic test (KidneyIntelX) integrating biomarkers and electronic health record data to predict longitudinal kidney outcomes. Kidney360. 2020; 1(8):731-739.
3. Lam D, Nadkarni GN, Mosoyan G, Net al. Clinical utility of KidneyIntelX in early stages of diabetic kidney disease in the CANVAS Trial. Am J Nephrol. 2022; 53(1):21-31.
4. Tokita J, Vega A, Sinfield C, et al. Real world evidence and clinical utility of KidneyIntelX on patients with early-stage diabetic kidney disease: interim results on decision impact and outcomes. J Prim Care Community Health. 2022. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9677284/pdf/10.1177_21501319221138196.pdf. Accessed on April 20, 2023.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Centers for Disease Control and Prevention. National chronic kidney disease fact sheet. 2021. Available at: https://www.cdc.gov/kidneydisease/pdf/Chronic-Kidney-Disease-in-the-US-2021-h.pdf. Accessed on March 31, 2023.
2. Stevens PE, Levin A; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes (KDGO) 2012 clinical practice guideline. Ann Intern Med. 2013; 158(11):825-830.
3. U.S. Food and Drug Administration (FDA) Denovo Notification Database. KidneyIntelX Summary of Safety and Effectiveness. DEN200052. Rockville, MD: FDA. June 29, 2023. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm. Accessed on November 05, 2023.

Websites for Additional Information

1. American Diabetes Association. Type 2 diabetes. Available at: http://www.diabetes.org/diabetes-basics/type-2/?loc=db-slabnav/. Accessed on March 31, 2023.
2. American Society of Nephrology. Available at: https://www.asn-online.org/. Accessed on March 31, 2023.
3. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). What is Kidney Failure? Updated January 2018. Available at https://www.niddk.nih.gov/health-information/kidney-disease/kidney-failure/what-is-kidney-failure. Accessed on March 31, 2023.

Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
	04/01/2024	Updated Coding section with 04/01/2024 CPT changes; revised descriptor for 0407U.
	12/06/2023	Revised References section.
	09/27/2023	Updated Coding section with 10/01/2023 CPT changes; added 0407U.
Reviewed	05/11/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Rationale, Background/Overview, References and Websites sections.
Reviewed	05/12/2022	MPTAC review. Updated Rationale, References and Websites sections.
New	05/13/2021	MPTAC review. Initial document development.
