Policy Number	**MED207.163**
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KidneyIntelX and KidneyIntelX.dkd Testing

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Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

KidneyIntelX or KidneyIntelX.dkd testing **may be considered necessary** when **ALL** the following criteria are met:

- Performed once per lifetime; AND
- Results are used to facilitate therapeutic prognostic decision-making in the medical management of a selected patient population; AND
- Results are used to assess the risk of progressive decline (See Policy Guidelines) in kidney function in patients >21 years of age with:
  - Type 2 diabetes (T2D) and existing early-stage chronic kidney disease (CKD) (stages 1-3b); and
  - Test is ordered by the treating physician or qualified non-physician practitioner; and
  - Test is performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory qualified to perform high complexity testing; and
  - Specific reason for test must be documented by the treating practitioner in the medical documentation and demonstrate that the test is medically reasonable and necessary.

KidneyIntelX or KidneyIntelX.dkd testing **is considered not medically necessary** for:

- Patients with estimated glomerular filtration rate (eGFR) <30;
- Patients with eGFR ≥60 ml/min/1.73 m^2 without albuminuria;
- Patients with end-stage renal disease (ESRD) or on renal recovery treatments;
- Patients who are pregnant;
- Patients who are currently hospitalized;
- Patients taking etanercept;
- When performed as a screening or standalone diagnostic.

Policy Guidelines

Kidney function decline is defined as:

- A decline in estimated glomerular filtration rate (eGFR) slope of ≥: 5 ml/min/1.73 m^2/year; or
- A sustained decrease in eGFR ≥40% confirmed at least 3 months apart; or
- Kidney failure, defined by sustained eGFR <15.

Description

Kidney disease affects over 850 million people globally. In the United States (U.S.) alone, over 40 million people are identified as having chronic kidney disease (CKD). Approximately 50 percent of individuals with advanced (Stage IV) kidney disease are unaware of the severity of their reduced kidney function. Therefore, many individuals progress to kidney failure in an unplanned manner requiring dialysis without previously seeing a nephrologist. (2) The most common causes of CKD in adults are diabetes and high blood pressure. Other risk factors include heart disease, obesity, a family history of CKD, inherited kidney disorders, past damage to the kidneys, and older age. (3)

CKD is defined by the Kidney Disease Improving Global Outcomes (KDIGO) organization as abnormalities of kidney structure or function, present for > 3 months. (4) 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 glomerular filtration rate (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). 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 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.

Health disparities in patients with CKD and diabetes are significant and multifaceted. Studies consistently reveal disproportionate prevalence among minority populations, emphasizing the intersectionality of factors like race, socioeconomic status, and access to healthcare. (5) These disparities manifest in higher rates of CKD and diabetes, delayed diagnosis, and increased complications. Studies have found that kidney disease disproportionately affects communities of color. Black or African Americans are almost four times more likely, and Hispanics or Latinos are 1.3 times more likely to have kidney failure compared to White Americans. Although they make up only 13.5% of the population, Black or African Americans make up more than 35% of dialysis patients.

Regulatory Status

In June 2023, the United States (U.S.) Food and Drug Administration (FDA) approved KidneyIntelX™ (RenalytixAI) as a class II device under the DeNovo classification for in-vitro diagnostic use. (6) This prognostic test uses an algorithm to combine clinical variables (blood urea nitrogen [BUN], hemoglobin A1c [HbA1c] and urine albumin creatinine ratio [uACR]) and the quantitative measurements of tumor necrosis factor receptor-1 (TNFR-1), tumor necrosis factor receptor-2 (TNFR-2) and kidney injury molecule-1 (KIM-1) in human plasma employing a Meso Sector S 600 electrochemiluminescence immunoassay. It is indicated for use to aid in assessment of the risk of progressive decline in kidney function (sustained decrease in estimated glomerular filtration rate (eGFR) greater than or equal to 40% lasting more than 3 months) within a period of up to 5 years following KidneyIntelX level measurement in adult patients with type 2 diabetes and existing CKD (defined for the purposes of this device as patients with an eGFR rate of 30-59 ml/min/1.73m² or eGFR ≥ 60 ml/min/1.73m² with uACR ≥ 30 mg/g). KidneyIntelX is not intended for screening or as a stand-alone diagnostic test.

Product Code: QWZ

Rationale

This policy is based on a review of coverage guidance from the Centers for Medicare and Medicaid Services (CMS) specific to KidneyIntelX or KidneyIntelX.dkd testing. (1)

Review of Evidence

Tokita et al. conducted a prospective data collection study which enrolled 1686 patients in a large metro health system over 16 months to assess the impact of the KidneyIntelX test result on clinical decision-making and outcomes. (7) The median age was 68 years, 52% were female, 26% self-identified as Black, and 94% had hypertension. Determination of a new referral to a specialty consult service (i.e., nephrology, endocrinology, nutrition), any new prescriptions, or modification to any existing prescription medication for angiotensin-converting enzyme inhibitor (ACEi)/angiotensin II receptor blocker (ARB), sodium-glucose cotransporter-2 inhibitor (SLGT2i), or glucagon-like peptide-1 (GLP-1) agonists was based on a 6-month pre-baseline to 6-month post-test assessment. Limitations included patient compliance with filling prescriptions were not available. Fifty-three percent of all KidneyIntelX high risk patients had a follow-up

within a month while standard of care for follow-up is every 12 months. The authors found that 53% of all KidneyIntelX high-risk patients had a follow-up visit within 1 month and 57% had action taken (medication change or referral) within 3 months compared to 13% and 35%, respectively, for low-risk individuals. Traditionally, the standard-of-care for follow-up visit frequency is every 12 months. Thus, these results reflect a needed change in management for high-risk patients regarding visit frequency and any action taken. When evaluating new or modified prescriptions for antihypertensive at 6-months, both ACEi and ARBs achieved a greater than 20% change in the high-risk group (ACEi, odds ratio [OR] = 1.36; 95% confidence interval [CI]: 0.77-2.30; ARBs, OR = 1.65; 95% CI: 1.01-2.63). Early evidence suggests that the introduction of the SGLT2i lowered hemoglobin A1c (HbA1c) levels most notably in the high-risk category (median 8.2% HbA1c at 6 months pre KidneyIntelX vs 7.45% post-test. In conclusion, the authors found that patients with early-stage diabetic kidney disease (DKD) who were identified as high-risk via the KidneyIntelX score received earlier follow-up visits, necessary change in medications or specialist referral compared to those who were identified as low- or intermediate-risk patients. Specifically, high-risk patients were more likely to be referred to a nephrologist and by 6 months, these patients had a significant increase in anti-hypertension medications compared to those of intermediate- and low-risk who were more likely to receive standard of care.

Nadkarni et al. conducted a post hoc analysis, assessing the association of KidneyIntelX at baseline with the time-to-event composite end point of 57% decline in eGFR or adjudicated end-stage kidney disease (ESKD), hospitalization for heart failure (HHF), or death. (8) The authors studied 1278 participants in the CANagliflozin Cardiovascular Assessment Study (CANVAS) trial as they hypothesized that KidneyIntelX would also risk stratify patients with prevalent DKD for a clinically relevant kidney outcome, HHF, and all-cause mortality. KidneyIntelX was evaluated in the subgroup of the CANVAS population that met the criteria for prevalent DKD (eGFR ≥30–59.9 ml/min per 1.73 m^2 [G3a and G3b] or those with an eGFR ≥60 ml/min per 1.73 m^2 with a urine albumin-creatinine ratio [uACR] ≥30 mg/g) at the time of enrollment with existing bio banked blood samples. Measurements were obtained of soluble tumor necrosis factor receptors (sTNFR) 1 and 2, and kidney injury molecule-1 (KIM-1) via proprietary assays, and calculated KidneyIntelX scores using the existing validated algorithm. Among the 1278 CANVAS participants in this post hoc analysis, the mean age was 64 years, 32% were women, the mean baseline eGFR was 65 ml/min per 1.73 m^2, the median uACR was 56 mg/g, 498 (40%) had an eGFR< 60 ml/min per 1.73 m^2, and 209 (16%) had heart failure at baseline. During a mean of 5.6 years follow-up, 282 (22%) experienced the composite outcome, 41 (3%) developed a 57% decline in eGFR or ESKD, 78 (6%) were hospitalized for heart failure, and 209 (16%) died. The risk for the composite event was reduced by 22%–24% across all risk strata in participants randomized to canagliflozin versus placebo, with absolute risk reductions of 11% in the high-risk stratum, 6% in the intermediate-risk stratum, and 4% in the low-risk stratum (P<0.01 for high versus low risk). Although KidneyIntelX has been validated for an outcome of DKD progression, the results from this subsequent post hoc analysis from CANVAS demonstrated that KidneyIntelX robustly stratified patients for a composite end point consisting of clinically relevant outcomes. In conclusion, the authors found that KidneyIntelX, a composite risk score trained and validated for a kidney-specific outcome, provided risk

stratification for a triple composite end point that included not only the kidney-specific outcome of progression, but also clinically relevant outcomes of hospitalizations for heart failure and all-cause mortality, even after adjusting for several other risk factors for these outcomes.

Lam et al. measured soluble TNFR-1, soluble TNFR-2, and kidney injury molecule 1 on banked samples from 1325 CANagliflozin cardioVascular Assessment Study (CANVAS) trial participants with baseline DKD (eGFR 30–59 mL/min/1.73 m^2 or UACR ≥30 mg/g) and generated KidneyIntelX risk scores at baseline and years 1, 3, and 6. (9) The mean age of the full study population was 64 years, where 32% were female, the mean eGFR was 65 mL/min/1.73 m^2, and the median UACR was 56 mg/g. Overall, stratified by the baseline KidneyIntelX score and adjusted for the treatment arm, each 10% reduction in KidneyIntelX risk was associated with a 20% lower risk of experiencing the composite kidney outcome (adjusted OR per 10% reduction of 0.80 [95% CI: 0.77, 0.83]; $p < 0.001$). In conclusion, the authors found KidneyIntelX successfully risk-stratified a large multinational external cohort for risk of progression of DKD, with larger differences in the eGFR slope for canagliflozin versus placebo in those with higher versus lower baseline KidneyIntelX scores. The authors found the effects of the SGLT2i canagliflozin on the chronic eGFR slope were numerically greater in magnitude in participants who scored as high risk by KidneyIntelX at enrollment. Second, canagliflozin decreased KidneyIntelX risk scores over time compared to an increase in the placebo, and this improvement prognosis was maintained over the follow-up period.

Chauhan et al. studied 1369 patients that were selected from a biobank at an institutional review board-approved biorepository that includes consented access to the patients' electronic health record (EHR). (10) The authors selected two cohorts from the biobank: 1) Type 2 diabetes (T2D), enrollment eGFR 45-90 ml/min, and ≥3 years of follow-up data (n=871); and 2) APOL1-HR with African ancestry, enrollment eGFR >30 ml/min and ≥3 years of follow-up data (n=498). The authors measured plasma TNFR 1 and 2 and KIM-1 and used random forest algorithms to integrate biomarker and EHR data to generate a risk score for a composite outcome: rapid kidney function decline (RKFD) (eGFR decline of ≥5 ml/min per year), or 40% sustained eGFR decline, or kidney failure. Performance was compared to a validated clinical model and thresholds applied to assess the utility of the prognostic test (KidneyIntelX) to accurately stratify patients into risk categories. The positive predictive values for KidneyIntelX were 62% and 62% versus 46% and 39% for the clinical models ($P<0.01$) in high-risk (top 15%) stratum for T2D and APOL1-HR, respectively. The negative predictive values for KidneyIntelX were 92% in T2D and 96% for APOL1-HR versus 85% and 93% for the clinical model, respectively ($P=0.76$ and 0.93, respectively), in low-risk stratum (bottom 50%).

Liu et al. completed a database literature search to capture studies evaluating the associations between single or multiple kidney biomarkers and any of the following chronic kidney disease (CKD) outcomes: incident CKD, CKD progression, or incident ESKD (e.g., initiation of chronic hemodialysis, peritoneal dialysis requirement, or transplant). (11) One hundred twenty-nine studies were included in the meta-analysis for the most frequently studied plasma biomarkers (TNFR-1, fibroblast growth factor 23 [FGF23], TNFR-2, KIM-1, soluble urokinase plasminogen

activator receptor [suPAR], and others) and urine biomarkers (KIM-1, neutrophil gelatinase-associated lipocalin [NGAL], and others). The authors found that studies of preclinical biomarkers for CKD outcomes have considerable heterogeneity across study cohorts and designs, limiting comparisons of prognostic performance across studies. Plasma TNFR-1, FGF23, TNFR-2, KIM-1, and suPAR were among the most frequently investigated in the setting of CKD outcomes.

In a study from Connolly et al. based on Clinical Laboratory Standards Institute (CLSI) guidelines, analytical performance studies of sensitivity, precision, and linearity were performed on three biomarkers assayed in multiplexed format: KIM-1, sTNFR-1 and sTNFR-2. (12) Analytical variability across twenty experiments across multiple days, operators, and reagent lots was assessed to examine the impact on the reproducibility of the composite risk score. The sensitivity, reproducibility, and linearity of the assay for the simultaneous measurements of KIM-1, sTNFR-1 and sTNFR-2 in human plasma are integral to assuring robust and consistent results for each analyte. Additionally, demonstrating reproducibility of the risk score and disease risk categorization is key to confirming that inherent variation does not impact reported clinical results of the test. The authors found that the assays for KIM-1, sTNFR-1 and sTNFR-2 demonstrated acceptable sensitivity. The authors found that the set of analytical validation studies demonstrated robust analytical performance across all three biomarkers contributing to the KidneyIntelX risk score, meeting or exceeding specifications established during characterization studies.

Chan et al. sought to develop/validate a machine-learned, prognostic risk score (KidneyIntelX™) combining EHR and biomarkers. (13) The authors performed an observational cohort study of patients with prevalent DKD/banked plasma from two EHR-linked biobanks. The study has 1146 patients, the median age was 63 years, 51% were female, the baseline eGFR was 54 ml min^{-1} $[1.73\ m]^{-2}$, the uACR was 6.9 mg/mmol. The authors found KidneyIntelX scores correctly classified more cases into the appropriate risk strata (NRI_{event} = 55% in the derivation set and 41% in the validation set, $p < 0.05$) than the KDIGO risk strata did. $NRI_{non\text{-}event}$ was −8.2% in the derivation set and −7.9% in the validation set.

Datar et al. was a qualitative analysis based on 30–45-minute interviews with 16 primary care physicians (PCP) treating T2D patients. (14) The interviews found testing for kidney disease was not consistently top of mind, with 56% reportedly performing kidney function testing in their T2D patients. PCPs most frequently reported using eGFR alone to monitor and stage DKD; only 25% PCPs reported testing for albuminuria. The authors felt this study showcased the important unmet needs in T2D DKD testing, staging, and stratification in the PCP setting that limit effective patient care.

Datar et al. was a prospective web-based survey administered among 401 PCPs in the United States to assess the decision-making impact of an artificial intelligence-enabled prognostic test, KidneyIntelX, in the management of DKD by PCPs. (15) The survey included hypothetical patient profiles with 6 attributes: albuminuria, eGFR, age, blood pressure (BP), HbA1c, and KidneyIntelX result. For each patient, PCPs were asked to indicate whether they would

prescribe a SGLT2 inhibitor, increase ARB dose, and/or refer to a nephrologist. The authors found the relative importance of the top 2 attributes for each decision were HbA1c (52%) and KidneyIntelX result (23%) for prescribing SGLT2 inhibitors, BP (62%) and KidneyIntelX result (13%) for increasing ARB dose, and eGFR (42%) and KidneyIntelX result (27%) for nephrologist referral. The authors concluded KidneyIntelX test had greater relative importance than albuminuria and eGFR to PCPs in making treatment decisions and was second only to eGFR for nephrologist referrals.

Analysis of Evidence

The current evidence concerning KidneyIntelX or KidneyIntelX.dkd as a test to identify and stratify patients with T2D and early-stage CKD into low, intermediate, and high risk for near-term rapid progressive decline in kidney function, suggests that the early identification of high-risk patients by the test allows for more intensive patient management, selection of appropriate medications, and appropriate specialty referral or consultation. Also, the clinical principles, that more proactive care leads to better health outcomes and improved quality of life for patients, including slowed disease progression, avoidance or delay of kidney failure and need for hemodialysis, were supported by subject matter experts.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	0105U, 0407U
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

Local Coverage Determination:

1. Centers for Medicare and Medicaid Services. Local Coverage Determination for KidneyIntelX and KidneyIntelX.dkd Testing (L39726) (August 1, 2024). Available at: <https://www.cms.gov> (accessed September 8, 2025).

Other:

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
10/15/2025	Document updated. Coverage criteria revised to be consistent with coverage guidance from the Centers from Medicare and Medicaid Services. Added references 1, 5, 8, 10-12, and 14-15. Title changed from: “Machine Learning Derived Probability Score for Rapid Kidney Function Decline”.
10/01/2024	New medical document. Use of a machine learning derived probability score (e.g., KidneyIntelX) to predict rapid kidney function decline is considered experimental, investigational and/or unproven for all indications, including but not limited to individuals with chronic kidney disease (CKD).