renalytix™ Right here, until kidney disease isn't.

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Olatokunbo Awodele, M.O.
Stephen Boren, M.O., MBA
Medicare Contractor Medical Director
National Government Services, Inc.
Medical Policy Unit
Attention: New LCD Request
P.O. Box 7108
Indianapolis, IN 46207-7108

RE: Formal Local Coverage Determination Request for KidneyIntelX (010SU)

Dear Ors. Awodele and Boren:

We are writing on behalf of Renalytix to formally request coverage through a Local Coverage Determination (LCD) for our KidneyIntelX test to assist in the clinical management of patients with type 2 diabetes anp early-stage chronic kidney disease (stages 1-3b) based on scientific evidence and published clinical literature. KidneyIntelX stratifies patients who are at low, int rmediate, or high risk for near-term rapid progressive decline in kidney function. We have enclosed a clinical dossier that summarizes and attaches the peer-reviewed evidence demonstrating the analytical validity, clinical validity, and clinical utility of the KidneyIntelX test. Based on this published clinical evidence, we respectfully request that National Government Services, Inc. (NGS) establish coverage criteria for KidneyIntelX for patients with type 2 diabetes (T2D) and early-stage chronic kidney disease (stages 1-3b).

I. Clinical Background on Type 2 Diabetes with Early-State Chronic Kidney Disease and KidneyIntelX

A. Type 2 Diabetes with Early-Stage Chronic Kidney Disease

Kidney disease is a public health epidemic affecting over 850 million people globally, and is one of the most common causes of premature death worldwide.[1] The Centers for Disease Control and Prevention estimates that 15% of U.S. adults, or over 37 million people in 2018, suffered from chronic kidney disease (CKO).[2] Nearly 95% of people with CKD suffer from early-stage CKD *(i.e.,* CKD stages 1-3).[3] Early-stage CKD is underdiagnosed and undertreated, largely because it is asymptomatic at this time in the disease's progression.

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[1] International Society ofNephrology, More than 850 Million Worldwide have some form of Kidney Disease: Help Raise Awareness. *Available at* https://www.theisn.org/blog/2020/11/27/more-than-850-million-worldwide-have-some-form-of-kidney-disease-help-raise-awareness/.

[2] Centers for Disease Control and Prevention, CKD in US. *Available at* https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html.

[3] United States Renal Data System, 2021 Annual Report. *Available at* https://adr.usrds.org/2021/chronic-kidney-disease/1-ckd-in-the-general-population.

Indeed, CKD in general is underdiagnosed and undertreated. As many as nine in ten adults with CKD, and two in fiv adults with severe CKD do not know they have the condition.[4] Almost half of adults with diabetes may have kidney disease.[5] Undiagnosed and undertreated kidney disease can complicate the effective management of diabetes and high blood pressure and lead to cardiovascular complications, increased hospitalizations, and kidney failure. When kidney disease is not identified early, its risk factors cannot be proactively controlled, and patients can lose up to 90% of their kidney function as the condition silently worsens, resulting in significant morbidity and mortality.[6]

The disease burden of kidney disease disproportionately impacts minority populations. African-Americans experience kidney failure at three times the rate of Caucasians. Although they make up only 13.5% of the US population, African Americans make up more than 35% of dialysis patients.[7]

Kidney disease is also a significant financial burden for the US health system. As an example, published data shows ttie Medicare program spends more than $130 billion:_more than 24 percent of its total spending - on patients with kidney disease. End-stage kidney disease, which affects only 1% of Medicare beneficiaries, accounts for 7% of Medicare spending.[8]

Better tools for risk stratification are needed to identify those at the highest risk of rapid kidney disease progression, including T2.D patients with early-stage CKD. Current methods of risk stratification based on UACR and eGFR used for staging CKD can vary for several factors unrelated to kidney disease, limiting their clinical utility and accuracy in identifying patients who will experience a rapid near-term progressive decline in kidney function, especially in earlier stages of CKD.[9]

B. KidneyIntelX

The KidneyIntelX test applies a machine learning algorithm that incorporates plasma biomarkers and clinical variables to produce a composite risk score to predict a rapid near-term progressive decline in kidney function in patients with T2D and early-stage CKD. KidneyIntelX, was developed to accurately predict the risk of early-stage kidney disease progression to reduce the substantial clinical and economic burden of CKD. This assay supports clinical decision-making and the implementation of guideline-recommended care in patients with kidney disease. KidneyIntelX provides insights that promote optimal pharmacy management, timely intervention, and appropriate consultation with and referrals to specialists early in the management of patients with CKD. Patient-specific risk assessment also allows clinicians to increase the intensity of management in patients wit and CKD with T2D who are classified

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[4] Centers for Disease Control and Prevention, *supra* note 2.
[5] *Id*
[6] World Kidney Day, Chronic Kidney Disease. *Available at* https://www.worldkidneyday.org/facts/chronic-kidney-disease/.
[7] ational Kidney Foundation, Social Determinants of Kidney Disease. *Available at* https://www.kidney.o rg/atoz/content/kidneydiscauses.
[8] ational Kidney Foundation, Federal Investment. https://www.kidney.org/advocacy/legislative-priorities/federal-investment.
[9] Dunkler, D., Gao, P., Lee, S. F., Heinze, G., Clase, C. M., Tobe, S., ... Oberbauer, R. (2015). Risk prediction for early CKD in type 2 diabetes. Clinical Journal of the American Society ofNephrology, 10(8), 1371-1379.

as higher-risk, while also avoiding costly pharmacotherapy and unnecessary interventions in low-risk patients.

Renalytix is a CUA-certified laboratory with a location in New York where we perform the KidneyIntelX test. KidneyIntelX is a diagnostic tool that assesses a patient's risk level for rapid near-term progressive kidney function decline with 90% accuracy. KidneyIntelX includes a laboratory-developed test combined with an artificial intelligence (AI) enabled clinical diagnostic solution that accurately predicts the risk of developing rapid near-term progressive decline in kidney function over the ensuing 5 years in patients with DKD stages 1-3. An in vitro diagnostic, KidneyIntelX assesses the risk of adverse kidney outcomes in patients with type 2 diabetes and early-stage CKD.

Specifically, the KidneyIntelX solution is intended for the risk stratification of patients through the combination of a blood test to measure circulating plasma biomarkers including the sTNFRI, sTNFR2, and KIM-1 biomarkers with clinical variables including, but not limited to, sex, age, race, comorbidities, standard laboratory variables, procedures, and medications, in a machine-learning algorithm to create a composite risk score for rapid near-term progressive decline in kidney function categorized as low, intermediate, or high-risk. The test report includes the risk of rapid near-term progressive decline in kidney function along with treatment protocols based on test results from the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline recommendations. By providing a personalized risk score, KidneyIntelX empowers physicians and patients to work together to design a care plan that meets their individual needs. The test is performed on a blood specimen and a test report is returned to the ordering clinician in about 5 days.

KidneyIntelX was assigned CPT code 0105U effective October 1, 2019. The full descriptor for the code is ***"Nephrology (chronic kidney disease), multiplex electrochemi/uminescent immunoassay (ECLIA} of tumor necrosis factor receptor 1A, receptor superfami/y 2 (TNFR1., TNFR2), and kidney injury molecu/e-1 {KIM-1) combined with longitudinal clinical data, including APOLI genotype if available, and plasma (isolated fresh or frozen), algorithm reported as probability score for rapid kidney function decline (RKFD)."*** CPT 0105U is priced on the Clinical Laboratory Fee Schedule (CLFS) at a payment rate of $950.

II. Medicare Coverage for KidneyIntelX

This is a formal LCD request that meets the requirements to request a new LCD as set forth in chapter 13, section 13.2.2.3 of the Medicare Program Integrity Manual and Article A56198. First, the request is in writing and is being sent to NGS by email. Second, the benefit categories for KidneyIntelX are diagnostic services (Section 1861(s)(2)(C) of the Social Security Act) and diagnostic laboratory tests and other diagnostic tests (Section 1861(s)(3) of the Social Security Act). Third, the requested language for the LCD is identified in section IV of this letter. Fourth, there is an extensive body of peer-reviewed evidence in support of KidneyIntelX that is discussed in section III. Fifth, the letter demonstrates the impact on patient management for clinicians the using KidneyIntelX. Finally, this letter demonstrates how the KidneyIntelX test may be used in clinical practice.

Under section 1862(a)(l)(A) of the Social Security Act, an item or service may be covered by Medicare if it is "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." Pursuant to chapter 13, section 13.5.4 of the Medicare Program Integrity Manual, "reasonable and necessary" is defined to mean the item or service is (i) safe

and effective, (ii) not experimental or investigational, and (iii) appr.opriate, including the duration and frequency that is considered appropriate for the item or service.

With respect to the third requirement in section 13.5.4, appropriateness is based on whether the item or service is (i) furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function ofa malformed body member, (ii) furnished in a setting appropriate to the patient's medical needs and condition; (iii) ordered and furnished by qualified personnel, (iv) one that meets, but does not exceed, the patient's medical need, and (v) at least as beneficial as an existing and available medically appropriate alternative.

Evidence of analytical validity, clinical validity, and clinical utility is used to demonstrate that a test is reasonable and necessary. Based on the enclosed materials, KidneyIntelX has been extensively validated in several clinical trials. Validation studies demonstrate the test accurately predicts the risk of early-stage kidney disease progression and consequently reduces the substantial clinical and economic burden of CKD_.Clinical utility studies with leading academic health systems demonstrate the test's ability to modify physician management of patients based on the risk stratification information provided. The enclosed validity and utility evidence, as well as published literature, establishes that the KidneyIntelX test is reasonable and necessary for Medicare beneficiaries.

111. PubHshed Evidence of Analytical Validity, Clinical Validity, and Clinical Utility to Support Medicare Coverage

A. Analytical Validity

As an initial matter, analytic validity refers to the accuracy with which a particular characteristic is identified in a given laboratory test. Renalytix used standard prot9cols and procedures to demonstrate the analytical.validity of KidneyIntelX. Two analytical validation publications support the test. The first study demonstrated robust analytical performance across all three biomarkers contributing to the KidneyIntelX risk score, meeting or exceeding specifications established during characterization studies.[10] In this first study, the reproducibility of the composite risk score was examined and proven across twenty experiments across multiple days, operators, and reagent lots.

Similarly, the second study demonstrated that KidneyIntelX accurately determined individual patient risk based on changes in glucose, blood pressure, and albuminuria.[11] Further, this study found that KidneyIntelX is not only accurate, but more efficient in assessing the integrated impact of changes in key risk factors compared to historical measurements commonly used today.

B. Clinical Validity

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[10] °Connolly P, Stapleton S, Mosoyan G, et al. Analytical validation of am.ulti-biomarker algorithmic test for prediction of progressive kidney function decline in patients with early-stage kidney disease. Clin Proteomics. 202I; I 8(1):26. Published 2021Nov 17. 001:10.1186/s12014-021-09332-y.

[11] adkarni G., Chauhan K., Fleming F., Coca S. Data presented at IS | WS (International Society of ephrology | World Congress of ephrology). *Kidney International Reports*. (2022).

Clinical validity refers to a test's ability to detect or predict the cliriical disorder or phenotype associated with the genotype. Three published clinical validation studies demonstrate tha theKidneyIntelX test improves the prediction of rapid kidney disease progression. This enhanced clinical insight will improve clinical management, allowing for closer monitoring, appropriate pharmacy management, appropriate specialist referral, and enrollment into disease management programs for at-risk patients who have T2D and early-stage CKD.

KidneyIntelX was first validated in a study using biobank samples and clinical data from a racially diverse, Medicare-eligible population divided into two cohorts with high CKD burden. One cohort was comprised of individuals with T2D (n=871), and the second was comprised of persons with African ancestry with the APOLI-HR genotype (n=498).[12] The study resulted in positive predictive values for KidneyIntelX of 62%, versus 46% for the clinical models (P< 0.01) in the high-risk (top 15%) stratum for T2D. The negative predictive value for KidneyIntelX was 92% in T2D, versus 85% for the clinical model {P = 0.76) in the low-risk stratum (bottom 50%). This validation study showed that KidneyIntelX can predict the risk of CK.D progression and distinguish high from low-risk patients in two populations that are considered high risk for CKD in the absence of additional clinical data.

A second publication using biobank samples and longitudinal health record data from 1,146 patients from two different academic health systems - Mount Sinai and the University of Pennsylvania - confirmed clinical validation of a machine learning-based risk score.[13],[14] The publication found that the algorithmic assay has a model accuracy of 0.7. These results demonstrated that, among a population at a high baseline risk of having progression of CKD with T2D, KidneyIntelX can accurately refine the risk of CKD progression, and therefore improve the prediction of kidney disease progression and outcomes.

A third study, consisting of a multinational cohort of 1,325 participants with early-stage CKD and T2D, demonstrated that the KidneyIntelX test accurately predicted the progression of DKD.[15] Results showed comparable risk-stratification with prior validation studies, in which participants identified by . KidneyIntelX as high risk (15% of the study population, from 667 centers in 30 countries) had more than an 8-fold higher rate of disease progression of DKD compared with those that scored low risk (42% of the population).

C. Clinical Utility

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[12] Chauhan K, adkarni 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. DOI:10.34067/kid.0002252020.

[13] Chan L, adkarni 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. DOI:I 0.1007/sOOI 25-021-05444-0.

[14] Chan L, adkarni GN, 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. DOI:I0.1007/sOOI 25-021-05444-0.

[15] Lam D, adkarni G, eal B, et al. Pos-223 clinical utility of KidneyIntelX in patients·with early stages of diabetic kidney disease in CA VASparticipants. American Journal of ephrology. Jan 2022, 11:1-11.DOI: I0.1159/000519920.

Finally, clinical utility of a test is a measure of its usefulness in the clinical setting and resulting changes in clinical endpoints. There is an extensive body of clinical utility evidence demonstrating that KidneyIntelX is useful for physicians seeking to address significant unmet clinical needs in early-stage kidney disease patients. This is because the test provides clinicians with an easy-to-understand, actionable risk score that contributes to a care path that enables early action before health declines and significant kidney damage can occur.

We completed a real-world evidence study at Mount Sinai Health System and it involved 1,112 high-risk CKD patients. The study results demonstrate the clinical utility of KidneyIntelX in driving guideline-appropriate use of therapies, including SGLT-2 and RAAS inhibitor use, and timely consultation with specialists.[16] In the study, there was a significant increase in SGLT2i prescriptions with increased level of risk score across all clinicians. Additionally, more than half of KidneyIntelX prognostic tests were ordered by primary care physicians, followed by endocrinologists. Referrals to specialists were made for 20%, 12%, and 6% of high-risk, intermediate-risk, and low-risk patients, respectively. These results show application of guideline-based care, including therapeutics and appropriate specialist consultation, increased in proportion to the test's reported risk for rapid near-term progressive decline in kidney function.

Another study, published in the *American Journal of Managed Care,* demonstrates the adoption and clinical utility of KidneyIntelX with PCPs. This study included 401 PCPs from across geographic regions and different practice and payer models in the United States. The results confirmed that PCPs understand the value of KidneyIntelX risk assessment in making guideline-informed treatment decisions. Results demonstrate growing awareness among PCPs in terms of the recognized value of KidneyIntelX in clinical decision-making. First, the study found that the KidneyIntelX test had greater relative importance than the standard of care (eGFR and UACR) for PCPs in prescribing guideline-recommended therapies and deciding when to consult with a specialist. Second, 98% of PCPs responded they were somewhat, very, or extremely likely to use KidneyIntelX to predict which of their patients will experience rapid near-term progressive kidney function decline. Third, the study indicated a behavioral shift among PCPs after the introduction of KidneyIntelX. Approximately 80 percent of PCPs in the study noted risk assessment would support the decision to take more aggressive, guideline-recommended clinical actions in high-risk, early-stage (stage 1 through 3b) patients to prevent the development of CKD.

A separate, qualitative study focused on identifying gaps in primary care and the unmet needs in the diagnosis and monitoring of patients among PCPs.[17] The study results confirmed the importance of risk assessment testing for addressing treatment ambiguity in the early stages of DKD and for improving patient engagement and adherence. Testing and engagement represent two major barriers to slowing or preventing early-stage DKD progression and preserving kidney health. In this qualitative study involving 16 primary care physicians (PCP), 100% of clinician study participants confirmed that early-stage kidney risk assessment, like that provided by KidneyIntelX, will help them to address suboptimal

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[16] Tokita J, Donovan M, Fields R. Clinical Utility of KidneyIntelX on Patients with Early-Stage Diabetic Kidney Disease: A Real-World Evidence Study. Diabetes. 71(Supplement_1):14-LB. https://doi.org/10.2337/db22-14-LB.

[17] Datar M, Ramakrishnan S, Montgomery E, Coca S, Vassalotti J, Goss T. A qualitative study documenting unmet needs in the management of diabetic kidney disease (DKD) in the primary care setting. BMC Public Health. 2021;21(1):930. Published 2021 May 17. DOI:10.1186/s12889-021-10959-7.

therapy, which can lead to rapid progression, increased hospital admissions, emergency room visits, potential kidney failure, need for dialysis, decreased quality of life, and increased costs.

IV. Recommended LCD Coverage Criteria for KidneyIntelX

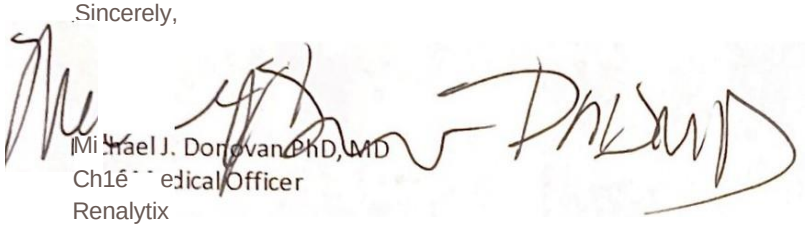
KidneyIntelX can efficiently and accurately identify and stratify patients with T2D and early-stage CKD into low, inte_rmediate, and high risk for near-term rapid progressive decline in kidney function. This can serve to improve the quality of care and deploy resources more efficiently in terms of costly medications and referrals to specialists. 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. More proactive care leads to better health outcomes and improved quality of life for patients, including avoidance or delay of kidney failure and hemodialysis. This also often results in substantial savings for patients and the Medicare program based on slowed disease progression, delayed or prevented dialysis and transplants, and fewer dialysis crashes.

Below, we recommend specific coverage criteria for patients eligible without previous biomarker testing for patients with type 2 diabetes and early-stage chronic kidney disease:

- Each KidneyIntelX test is intended to be used in conjunction with clinical evaluation as an aid in the risk assessment of kidney function decline within a period up to 5 years and each test result is generated by using an algorithm to analyze a combination of biomarker results and selected patient health record features.
- The KidneyIntelX test is covered once and intended for use as an aid to further access the risk of progressive decline in kidney function within a period of up to 5 years in patients over the age of 21 years of age or older, with:
    - Type 2 diabetes (T2D) and existing early-stage chronic kidney disease (CKD) CKD) (stages 1-3b)
        - eGFR of 30- 59 ml/min/1.73 m2 (Stages 3a and 3b) or
        - eGFR of> 60 ml/min/1.73 m^2 and albuminuria [UACR] ><!: 30 mg/g (Stages G1A2, GlA3, G2A2, G2A3)
- KidneyIntelX will be considered reasonable and necessary when the test is performed in a CUA certified laboratory qualified to perform high complexity testing and ordered by a treating physician.
- KidneyIntelX is not intended as a screening or standalone diagnostic test.
- KindeyIntelX is not reasonable and necessary for:
    - Patients with eGFR <30
    - Patients with eGFR <!: 60 ml/min/l.73m 2 without albuminuria
    - Patients with ESRD or on renal recovery treatments
    - Patients who are pregnant
    - Patients who are currently hospitalized
    - Patients taking Enbrel
- Kidney function decline is defined as:
    - a decline in eGFR slope of<!: 5 ml/min/l.73m 2 /year; or
    - . a sustained decrease in eGFR <!: 40% confirmed at least 3 months apart; or
    - kidney failure, defined by sustained eGFR < 15 ml/min/l.73m.

For the foregoing reasons, Renalytix respectfully requests that NGS consider coverage of OlOSU for the KidneyIntelX test through an LCD. We ask that a Proposed LCD be issued in advance of the LCD Open Meeting in February 2023. Thank you for your consideration of this request. Following your review of the evidence, we are available to meet to discuss any questions.

Sincerely,



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