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Dear Drs., Mangione, Barry, and Nicholson,

The Coalition for Kidney Health (CKH), a multi-stakeholder group of partners with an interest in earlier detection and management of chronic kidney disease (CKD), applauds the United States Preventive Services (USPSTF) for developing a draft research plan to assess screening, interventions, outcomes, and disparities in chronic kidney disease (CKD). Given the significant burden of CKD on patients – and current underdiagnosis of CKD even among patients with advanced illness -- it is imperative that we improve early identification and treatment of CKD.

While our comments broadly follow the outline of questions asked by the Task Force, the Coalition begins by voicing our serious concerns that, as currently drafted, the research plan emphasizes screening of asymptomatic patients with CKD 1 -3, while excluding “studies in which patients were selected on the basis of having conditions associated with CKD (e.g., hypertension, diabetes)”. **This approach is fundamentally flawed**, as those are the populations most in need of screening and where evidence demonstrates the greatest benefit but where significant gaps in care exist. As currently designed, the research plan will likely yield a similar result as the 2012 review and will be inconclusive.

We strongly recommend that the research plan be amended to review current clinical practice guidelines and the existing evidence base around CKD screening in at risk populations. Further, we recommend a systematic review that allows for stratification of screening recommendations – as USPSTF does in mammography, diabetes screening, and other areas – to **proactively recommend screening where evidence is strongest: for people with diabetes and/or hypertension**. A stratified approach will assure that there is no ambiguity around screening for at risk populations while allowing for secondary recommendations in other risk categories where the evidence is evolving.

## I. Comments on the Proposed Contextual Questions

We agree that it is appropriate to explore racial and ethnic disparities in CKD screening and management, the effectiveness of existing interventions aimed at reducing disparities, and potential harms associated with CKD diagnosis. However, the current approach does not explore other important topics in CKD screening that are necessary for this exercise. We recommend that the contextual framework be amended and expanded to explore the following:

- 1) The *benefits* and harms of CKD screening and diagnosis.
- 2) CKD's disproportionate impact on communities of color.
- 3) CKD underdiagnosis even among at risk populations.
- 4) The effectiveness of CKD interventions.

### *Benefits and Harms of CKD Screening and Diagnosis*

As currently drafted, the contextual questions focus on the harms of CKD screening without exploring the harms of failure to screen, or the benefits of early diagnosis. For the patients affected by CKD, the harms of screening are few, but the benefits myriad. Failure to screen, however, which is currently all too common, can result in catastrophic – and avoidable – harm.

CKD must become a public health priority due to its significant national and worldwide prevalence, the burden it takes on patients, and its cost to our healthcare system. CKD is the tenth leading cause of death in the United States with a five-year survival rate for the average dialysis patient of only 35 percent. Medicare spends an estimated \$136.2 billion annually, nearly 25 percent of Medicare expenditures, on the care of people with a kidney disease diagnosis. Individuals with ESKD represent 1 percent of Medicare beneficiaries but comprise 6 percent of Medicare fee-for-service expenditures.

Delayed screening and diagnosis of CKD can cause significant harm. Patients may sustain substantial kidney damage before they exhibit any symptoms related to CKD.<sup>1</sup> The American Diabetes Association's (ADA) guidelines recommend patients be screened one to three times annually based on their albuminuria.<sup>2</sup> Patients with diabetes and hypertension have an increased risk of developing CKD. Forty percent of people diagnosed with diabetes develop CKD,<sup>3</sup> and nearly 50 percent of adults in the US have hypertension,<sup>4</sup> which is both a cause and complication of CKD.<sup>5</sup>

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<sup>1</sup> Ng, J.K.-C. and Li, P.K.-T. (2018), Chronic kidney disease epidemic: How do we deal with it?. *Nephrology*, 23: 116-120. <https://doi.org/10.1111/nep.13464>

<sup>2</sup> American Diabetes Association. "16. Diabetes Advocacy: *Standards of Medical Care in Diabetes-2019*." *Diabetes care* vol. 43, Suppl 1 (2020): S203-S204. doi:10.2337/dc20-S016

<sup>3</sup> Skolnik, Neil S, and Alyssa J Style. "Importance of Early Screening and Diagnosis of Chronic Kidney Disease in Patients with Type 2 Diabetes." *Diabetes therapy: research, treatment, and education of diabetes and related disorders* vol. 12,6 (2021): 1613-1630. doi:10.1007/s13300-021-01050-w

<sup>4</sup> Centers for Disease Control and Prevention. [Hypertension Cascade: Hypertension Prevalence, Treatment and Control Estimates Among U.S. Adults Aged 18 Years and Older Applying the Criteria from the American College of Cardiology and American Heart Association's 2017 Hypertension Guideline—NHANES 2015–2018](#). Atlanta, GA: U.S. Department of Health and Human Services; 2021. Accessed March 12, 2021.

<sup>5</sup> Pugh, D., Gallacher, P.J. & Dhaun, N. Management of Hypertension in Chronic Kidney Disease. *Drugs* 79, 365–379 (2019). <https://doi.org/10.1007/s40265-019-1064-1>

When detected early, however, implementing targeted therapies can significantly improve patient outcomes by attenuating the progression of CKD to kidney failure, CVD, and death,<sup>6</sup> especially for at-risk communities.

Pharmacological interventions that are proven to reduce the effects of CKD, hypertension, cardiovascular disease (CVD), and diabetes include angiotensin-converting-enzymes inhibitors (ACEi), angiotensin-receptor blockers (ARB), and sodium-glucose cotransporter 2 (SGLT-2) inhibitors.<sup>7,8</sup> These treatments are appropriate not only to people with late-stage illness. As noted in the following “heat map”, patients can have increased risk for CKD and related complications even with a relatively normal estimated Glomerular Filtration Rate (eGFR). Early identification and intervention can have impact at every stage of illness.

**Kidney Numbers and the CKD HEAT MAP**

**Prognosis of CKD by GFR and Albuminuria Categories**

				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (ml/min/1.73 m <sup>2</sup> ) Description and range	G1	Normal or high	≥90	Green	Yellow	Orange
	G2	Mildly decreased	60-90	Green	Yellow	Orange
	G3a	Mildly to moderately decreased	45-59	Yellow	Orange	Red
	G3b	Moderately to severely decreased	30-44	Yellow	Red	Red
	G4	Severely decreased	15-29	Red	Red	Red
	G5	Kidney failure	<15	Red	Red	Red

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.  
KDIGO 2012

Behavioral interventions, such as nutritional therapy and exercise, can have a considerable impact on the reducing the progression of CKD, while also mitigating the effects of diabetes and hypertension.<sup>9</sup> Educational intervention can also profoundly affect the self-management of CKD when patients and their caregivers are empowered and supported with education and awareness.<sup>10</sup> These interventions must happen proactively before CKD advances to late stages when kidney function becomes too severely compromised.

CKD screening can easily be integrated into primary care practice. Physicians can use non-invasive, cost-effective testing to assess kidney function via eGFR and albumin-to-creatinine ratio (uACR), a crucial step towards improving American population health.<sup>11</sup> The eGFR and serum creatinine measures are currently included in the basic metabolic panel and would not require additional testing for the patient.

<sup>6</sup> Levin, A., Stevens, P. Early detection of CKD: the benefits, limitations and effects on prognosis. *Nat Rev Nephrol* 7, 446–457 (2011). <https://doi.org/10.1038/nrneph.2011.86>

<sup>7</sup> Turner, J.M., Kodali, R. Should Angiotensin-Converting Enzyme Inhibitors ever Be Used for the Management of Hypertension?. *Curr Cardiol Rep* 22, 95 (2020). <https://doi.org/10.1007/s11886-020-01352-8>

<sup>8</sup> Cowie, M.R., Fisher, M. SGLT-2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. *Nat Rev Cardiol* 17, 761–772 (2020). <https://doi.org/10.1038/s41569-020-0406-8>

<sup>9</sup> Cupisti A, D’Alessandro C, Fumagalli G, Vigo V, Meola M, Cianchi C, Egidi M, F: Nutrition and Physical Activity in CKD patients. *Kidney Blood Press Res* 2014;39:107-113. doi: 10.1159/000355784

<sup>10</sup> Donald, Maoliosa, et al. “Identifying Needs for Self-Management Interventions for Adults with CKD and Their Caregivers: A Qualitative Study.” *American Journal of Kidney Diseases*, vol. 74, no. 4, 2019, pp. 474–482., <https://doi.org/10.1053/j.ajkd.2019.02.006>.

<sup>11</sup> Nikita Stempniewicz, Joseph A. Vassalotti, John K. Cuddeback, Elizabeth Ciemins, Amy Storfer-Isser, Yingying Sang, Kunihiko Matsushita, Shoshana H. Ballew, Alex R. Chang, Andrew S. Levey, Robert A. Bailey, Jesse Fishman, Josef Coresh; Chronic Kidney Disease Testing Among Primary Care Patients With Type 2 Diabetes Across 24 U.S. Health Care Organizations. *Diabetes Care* 1 September 2021; 44 (9): 2000–2009. <https://doi.org/10.2337/dc20-2715>

The uACR is necessary for identifying and staging kidney damage and is a simple, non-invasive urine test. The screening itself exposes the patient to almost no harm.

We caution against exploring the harms of being “*labeled* (emphasis added) with a diagnosis of CKD 1 – 3.” There is no evidence to suggest that a CKD diagnosis might cause psychological “harm”. On the contrary, most patients want to be equal partners in their healthcare. They value shared decision-making and the ability to make collaborative choices with an interdisciplinary healthcare team based on their lifestyle and personal goals. Patients are more likely to be psychologically harmed by a late diagnosis (and the concomitant late-stage illness) than any potential harms associated with screening for early CKD. The National Kidney Foundation surveyed several patients with CKD on this topic and each one of them stated unequivocally that they would have wanted to know about their CKD diagnosis as early as possible. In addition, nephrotic uACR results or greater than 2,200 mg/g should generally result in referral to nephrology to consider kidney biopsy that can detect glomerular diseases that may be treated with immunosuppression.”<sup>12</sup>

Other harms are certainly relevant, and we acknowledge the burden of multiple screening recommendations on primary care providers. To minimize that burden, we recommend screening primarily for at-risk populations, rather than the general population.

#### *CKD’s Disproportionate Impact on Communities of Color*

The stark inequities associated with CKD across racial, ethnic, and culturally diverse populations have been observed worldwide for decades.<sup>13</sup> According to 2021 estimates examining population-level data from the 2000 U.S. Census, CKD is more common in non-Hispanic Blacks/African Americans (16 percent) than in non-Hispanic Whites (13 percent) or non-Hispanic Asian adults (13 percent).<sup>14</sup> As worsening CKD progresses into ESRD, Black individuals are affected at a rate “nearly double that of Hispanic individuals, nearly triple that of Asian individuals, and more than quadruple that of White individuals”.<sup>15</sup> In a study of urban poor in San Francisco examining non-genetic factors contributing to CKD progression, younger males of color with “public health insurance coverage (Medicare and Medicaid), diabetes, lower eGFR, higher proteinuria, lower hemoglobin level, and lower serum albumin concentration were significantly associated with a higher adjusted risk of progression to ESRD”.<sup>16</sup> When optimal treatments for ESRD are available for communities of color (i.e., organ transplantation via living donation), racial concordance is another barrier to overcome, with approximately 75 percent of living donors being White.<sup>17</sup>

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<sup>12</sup> Nephcure, We Deserve Better: Revolutionizing Rare Kidney Disease (2021). <https://nephcure.wpenginepowered.com/wp-content/uploads/2021/07/We-Deserve-Better-CTA.pdf>.

<sup>13</sup> Crews D, Liu Y, Boulware E. Disparities in the Burden, Outcomes and Care of Chronic Kidney Disease. *Curr Opin Nephrol Hypertens*. 2014; 23(3):298–305. <https://doi:10.1097/01.mnh.0000444822.25991.f6>

<sup>14</sup> Centers for Disease Control and Prevention. Chronic Kidney Disease in the United States (2021). <https://www.cdc.gov/kidneydisease/publications-resources/CKD-national-facts.html>

<sup>15</sup> United States Renal Data System. 2022 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2022. <https://usrds-adr.niddk.nih.gov/2022>

<sup>16</sup> Crews D, Liu Y, Boulware E. Disparities in the Burden, Outcomes and Care of Chronic Kidney Disease. *Curr Opin Nephrol Hypertens*. 2014; 23(3):298–305. <https://doi:10.1097/01.mnh.0000444822.25991.f6>

<sup>17</sup> Godwin, M. Advocating for Health Equity in Kidney Care: An Urgent Need. *Kidney Medicine*. 2021; 3(6):1082–1085. <https://doi.org/10.1016/j.xkme.2021.05.012>

Race, inadequate access to quality healthcare, and health-related social needs are prime factors that directly contribute to exacerbated disparities in the screening and diagnosis of worsening CKD.<sup>18</sup> In a 2021 evaluation of glomerular filtration rate (GFR) estimation equations, it was found that the CKD-EPI eGFR<sub>cr</sub> equation without a race modifier would eliminate health disparities in kidney disease for communities of color by allowing for earlier diagnosis of CKD, referral to a nephrologist, and access to the kidney transplant waitlist.<sup>19</sup> Younger African Americans at high risk for CKD or with CKD are more likely to engage in inadequate access to quality and routine medical care; a decision influenced by comorbidities, psychosocial factors and socio-demographics that leads to missed opportunities for disease management and shared-decision making more frequently experienced by White patients.<sup>20</sup> At present, there is no commitment at the national level to increase financial investments in health-related social needs specifically against the progression of CKD.

In addition, research has advanced to help target diseases that disproportionately affect communities of color and demonstrate the relationship between APOL1 gene and APOL1-mediated kidney disease, including a severe rare kidney disease called focal segmental glomerular sclerosis (FSGS). APOL1 kidney risk alleles (G1 and G2) are common throughout sub-Saharan Africa and in individuals with African admixture. APOL1 risk alleles protect against trypanosome infection and increase risk for CKD. Approximately 14 percent of African Americans carry 2 APOL1 risk alleles.<sup>21</sup>

Similarly, studies have shown that IgA Nephropathy, the most common cause of glomerulonephritis worldwide, accounts for a higher proportion of ESKD in Asians. A study published in 2013 analyzed a cohort of Asians and non-Asians living with biopsy proven IgA Nephropathy to track time from biopsy to ESRD.<sup>22</sup> Results showed that Asians have a higher risk of disease progression as compared to their non-Asian counterparts. With an increasing number of Asian Americans residing in the U.S., these data sets inform renal outcomes in IgAN patients of Asian or Pacific Islander descent living in the U.S.<sup>23</sup>

The Mapping Medicare Disparities Tool developed by Centers for Medicare & Medicaid Services (CMS) shows CKD was highest among Black/African American (36 percent), followed by American Indian/Alaska Native (32 percent), Hispanic (29 percent), and Asian/Pacific Islander (26 percent).<sup>24</sup>

It is also important to note that the current evidence base may not accurately represent the experience of patients of color, who often experience differences in clinical trial recruitment and attrition,

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<sup>18</sup> Centers for Disease Control and Prevention. Chronic Kidney Disease in the United States (2021),

<https://www.cdc.gov/kidneydisease/publications-resources/CKD-national-facts.html>

<sup>19</sup> Kramer H, Jaar B, Choi M, et al. An Endorsement of the Removal of Race From GFR Estimation Equations: A Position Statement From the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. *Am J Kidney Dis.* 2022; 80(6):691–696.

<https://doi.org/10.1053/j.ajkd.2022.08.004>

<sup>20</sup> Diamantidis C, Davenport C, Lunyera J, et al. Low use of routine medical care among African Americans with high CKD risk: the Jackson Heart Study. *BMC Nephrol.* 2019; 20(11) <https://doi.org/10.1186/s12882-018-1190-0>

<sup>21</sup> Limou S, Nelson GW, Kopp JB, Winkler CA. Kidney Risk Alleles: Population Genetics and Disease Associations. *Adv Chronic Kidney Dis.* September. 2014 Sep;21(5):426-33. doi: 10.1053/j.ackd.2014.06.005. PMID: 25168832; PMCID: PMC4157456, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4157456/>.

<sup>22</sup> Sean J. Barbour, Daniel C. Cattran, S. Joseph Kim, Adeera Levin, Ron Wald, Michelle A. Hladunewich, and Heather N. Reich: International Society of Nephrology, Individuals of Pacific Asian Origin with IgA Nephropathy Have an Increased Risk of Progression to End-Stage Renal Disease, 2013.

<sup>23</sup> *Id.*

<sup>24</sup> Centers for Medicare & Medicaid Services. Data Snapshot: Chronic Kidney Disease Disparities in Medicare Fee-for-Service Beneficiaries. March 2022. <https://www.cms.gov/files/document/data-snapshot-ckd-march-2022.pdf>.

guideline-recommended care delivery and outcome measure performance for CKD. The U.S. Food and Drug Administration (FDA) 2020 Drug Trial Snapshot reports that among 32,000 patients enrolled in clinical trials, 8 percent were Black or African American, 6 percent were Asian, 11 percent were Hispanic, and 75 percent were White.<sup>25</sup> To achieve health equity in the diversity of clinical trial recruitment and outcomes for Black patients with CKD in particular, enrollment numbers should match their disproportionate representation within the disease prevalence ( $\geq 35$  percent), as opposed to their representation within the U.S. population ( $< 14$  percent).<sup>26</sup>

Evidence shows race-based differences in treatments utilized within communities of color and performance across several care delivery measures. Per the 2022 United States Renal Data System (USRDS) Racial and Ethnic Disparities Supplement, older Black Medicare fee-for-service (FFS) beneficiaries with CKD were less likely to receive SGLT-2 inhibitors, a novel diabetes therapy with cardiovascular and kidney-protective benefits.<sup>27</sup> Achievement of lower blood pressure and glycemic targets in harmony with KDIGO clinical practice guidelines for the evaluation and management of CKD, blood pressure, and lipid management of CKD were more poorly controlled in Black Medicaid Advantage adults with CKD from 2012 to 2019.<sup>28</sup> Due to better performance on process type care delivery measures by patients within this cohort, researchers suggest an amalgamation of both regimented healthcare (“testing, prescribing, and referring to match guideline recommendations”) and implementation of health-related social needs interventions to narrow health disparities among communities of color.<sup>29</sup>

Given the role that social determinants of health, low health literacy, poor access to health care, and racism play in poor CKD outcomes, it is imperative that screening recommendations favor proactive screening of this uniquely vulnerable community.

#### *CKD Underdiagnosis Among at Risk Populations.*

The framework and questions crafted by USPSTF for this exercise implies an assumption that CKD screening in at-risk populations is adequate, but this is not the case. Only 10 percent of the 37 million adults with CKD in America are aware and have access to the care, education, and monitoring needed to manage the condition. The absence of policies to standardize early CKD screening, detection, and intervention is harmful, especially to historically marginalized communities facing health disparities because of racial, social, economic, and environmental inequities.<sup>30</sup>

At its onset, CKD is asymptomatic, and only routine screening can identify it in its earliest stages. Even among at-risk populations, such as those with diabetes and hypertension, CKD often goes undetected

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<sup>25</sup> U.S. Food & Drug Administration. 2020 Drug Trials Snapshots Summary Report. Silver Spring (MD): U.S. Food & Drug Administration; 2021 February. <https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots>

<sup>26</sup> Nicholas S, Cervantes L; American Society of Nephrology Health Care Justice Committee. Health Care Equity and Justice Scorecard to Increase Diversity in Clinical Trial Recruitment and Retention. *JASN*. 2022; 33(9):1652-1655. <https://doi:10.1681/ASN.2022040427>

<sup>27</sup> United States Renal Data System. 2022 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2022. <https://usrds-adr.niddk.nih.gov/2022>

<sup>28</sup> Chu C, Powe N, McCulloch C, et al. Trends in Chronic Kidney Disease Care in the US by Race and Ethnicity, 2012-2019. *JAMA Network Open*. 2021; 4(9):e2127014. <https://doi:10.1001/jamanetworkopen.2021.27014>

<sup>29</sup> Chu C, Powe N, McCulloch C, et al. Trends in Chronic Kidney Disease Care in the US by Race and Ethnicity, 2012-2019. *JAMA Network Open*. 2021; 4(9):e2127014. <https://doi:10.1001/jamanetworkopen.2021.27014>

<sup>30</sup> Clark-Cutaia, Maya N.a; Rivera, Eleanororb; Iroegbu, Christinc; Squires, Allisond. Disparities in chronic kidney disease—the state of the evidence. *Current Opinion in Nephrology and Hypertension* 30(2):p 208-214, March 2021. | DOI: 10.1097/MNH.0000000000000688

until its later stages.<sup>31</sup> *Approximately half of CKD stage 3 patients are undiagnosed* and, as a result, are less likely to access guideline-concordant care for delaying and managing CKD.<sup>32</sup> More troubling, as many as *thirty-eight percent of patients with end-stage kidney disease* learn of their diagnosis only after their kidneys have failed, requiring them to initiate dialysis in the emergency room in what is known as a “crash” start. As much as sixty-three percent of patients begin unplanned, emergent dialysis.<sup>33</sup> Crashing into dialysis is traumatic for patients, increases mortality, and creates an economic burden.

Even among people with diabetes and hypertension – the two leading causes of kidney disease -- CKD screening is inadequate. Albuminuria is an essential component of chronic kidney disease diagnosis, staging, and prognosis but it is significantly underutilized, with annual testing rates of approximately 40 percent for diabetes and less than 10 percent for hypertension according to national data. Elevated urine albumin can detect CKD in people with diabetes and monitor its progression, but obstacles preventing early detection persist, including lack of awareness of CKD in the general population, poor adherence to clinical guidelines, and county-level variations in screening and treatment incentives.<sup>34</sup>

Decreased CKD awareness among patients is closely linked to low CKD testing and recognition by providers.<sup>35</sup> While CKD testing and management has commonly been the task of nephrologists, primary care physicians must also be responsible for proactively screening, diagnosing, and treating CKD.

### *The Effectiveness of CKD Interventions*

In 2012, treatment for CKD was generally targeted to comorbid medical conditions, such as diabetes, hypertension, and CVD (CVD). The 2012 USPSTF CKD screening recommendation (or lack thereof) was built on the assumption that a CKD diagnosis would not necessarily change the treatment plan.

In recent years, however, CKD has become increasingly modifiable and screening high risk individuals for CKD has become even more important. As noted earlier, simple interventions can improve kidney and CVD outcomes, like blood pressure control, diabetes control, and renin-angiotensin-aldosterone blockade that are underutilized despite strong evidence of efficacy in specific CKD populations. The class of SGLT-2 inhibitors have shown efficacy at attenuating risk of dialysis and CVD, particularly heart failure in patients with diabetes and CKD, as well as in patients with CKD without diabetes. In addition, there are several interventions that have no effect on CKD progression, but reduce risk of CVD, including statin-based therapies and the glucagon-like peptide receptor agonists (GLP-1 RA) drug class for Type 2 Diabetes (T2D). Observational studies have shown multidisciplinary care that may include a dietitian,

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<sup>31</sup> Dharmarajan, Sai H et al. “State-Level Awareness of Chronic Kidney Disease in the U.S.” *American journal of preventive medicine* vol. 53,3 (2017): 300-307. doi: 10.1016/j.amepre.2017.02.015

<sup>32</sup> Maciejewski, M, Onstad, K, and Tamayo, L. Chronic Kidney Disease Often Undiagnosed in Medicare Beneficiaries. CMS OMH Data Highlight No.20. Baltimore, MD: CMS Office of Minority Health 2020.

<sup>33</sup> Molnar, A.O., Hiremath, S., Brown, P.A. et al. Risk factors for unplanned and crash dialysis starts: a protocol for a systematic review and meta-analysis. *Syst Rev* 5, 117 (2016). <https://doi.org/10.1186/s13643-016-0297-2>

<sup>34</sup> De Boer, Ian H. et al “Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and kidney disease: Improving Global Outcomes (KDIGO)” *Diabetes Care* 2022;45(12):3075–3090 <https://doi.org/10.2337/dci22-0027>

<sup>35</sup> Tuot, Delphine S et al. “chronic kidney disease awareness among individuals with clinical markers of kidney dysfunction.” *Clinical journal of the American Society of Nephrology: CJASN* vol. 6,8 (2011): 1838-44. doi:10.2215/CJN.00730111

pharmacist and nephrologist is also associated with improved outcomes for the T2D with CKD population.<sup>36</sup>

The evolution has been so rapid that the *KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease* followed only two years after the original *2020 Clinical Practice Guideline on management in Chronic Kidney Disease*. The short interval between guidelines reflects the rapid pace of advances in the management of diabetes and CKD. It is also a call from the community to help guide application of these new data.

### *Lifestyle Changes*

The *KDIGO 2022 guideline for Diabetes Management in Chronic Kidney Disease* advocates a layered approach to care, starting with a foundation of lifestyle interventions and first-line pharmacotherapy that has been demonstrated to improve clinical outcomes. Added to this are therapies to reduce the risk of adverse outcomes and control known risk factors for CKD progression and cardiovascular events, such as blood pressure, glycemia, and lipids. To maximize the chances that combination treatments can be tolerated, it recommends starting patients on medications that affect intrarenal hemodynamics serially (e.g., ACEi, ARB, SGLT-2i, and other antihypertensive medications).<sup>37</sup>

### *Novel Therapies*

As noted earlier, SGLT-2 inhibitors have emerged as a first-line therapy in diabetes due to their cardiovascular and kidney-protective benefits. A growing body of evidence has demonstrated that the clinical benefits of SGLT-2 inhibitors extend to nondiabetic CKD. SGLT-2 inhibitors have proven to be clinically and cost effective for treatment of both diabetic and nondiabetic CKD.

For example, in one study, researchers conducted a systematic review and meta-analysis of 13 large, double-blind, placebo-controlled, SGLT-2 inhibitor trials lasting at least six months in duration and encompassing a total of 90,409 patients.<sup>38</sup> The study evaluated whether the SGLT-2inhibitors, empagliflozin, reduced the risk of kidney disease progression or cardiovascular (CV) death of patients with CKD, including various underlying etiologies, with or without T2D, and across the spectrum of both eGFR (20-90ml/min/1.73m<sup>2</sup>) and albuminuria levels (including those within the normal range). Similarly, in July 2021, the FDA approved finerenone to reduce the risk of sustained eGFR decline, end-stage kidney disease, CV death, non-fatal myocardial infarction (MI), and hospitalization for heart failure

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<sup>36</sup>Kdigo 2022 Clinical Practice Guideline for Diabetes Management In Chronic Kidney Disease: chrome-extension://efaidnbmnnnibpcjpcglclefindmkaj/https://kdigo.org/wp-content/uploads/2022/03/KDIGO-2022-Diabetes-Management-GL\_Public-Review-draft\_1Mar2022.pdf

<sup>37</sup> KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease: chrome-extension://efaidnbmnnnibpcjpcglclefindmkaj/https://kdigo.org/wp-content/uploads/2022/03/KDIGO-2022-Diabetes-Management-GL\_Public-Review-draft\_1Mar2022.pdf.

<sup>38</sup> Nuffield Department of Population Health Renal Studies Group, the SGLT2 Meta-Analysis Cardio-Renal Trialists' Consortium. *Lancet* 2022; published online Nov 6. [https://doi.org/10.1016/S0140-6736\(22\)02074-8](https://doi.org/10.1016/S0140-6736(22)02074-8)

(HF) in individuals with CKD associated diabetes, based on results from the FIDELIO-DKD study.<sup>39</sup> In the FIGARO-DKD study, the findings showed that finerenone significantly reduced the risk of the primary composite endpoint of time to first occurrence of CV death, non-fatal MI, and hospitalization for HF by 13 percent. This was found over a median duration of 3.4 years when added to a maximum tolerated dose of an ACEi or ARB in adults with CKD associated with T2D.<sup>40</sup>

### *Medical Nutrition Therapy*

Retrospective studies have shown that medical nutrition therapy (MNT) can slow progression of CKD and improve biochemical markers, however therapy continues to be underutilized. Nutrition management can slow CKD progression but few individuals with CKD receive medical nutrition therapy with a registered dietitian nutritionist before initiating dialysis.<sup>41</sup> The impact of MNT for patients in any stage of CKD is associated with higher risk for morbidity, mortality, and length of hospital stay.

A preliminary analysis of data was presented at the Vermont Academy of Nutrition and Dietetics and concluded that people with CKD who received MNT were less likely to start dialysis and had improved nutritional biomarkers than participants who did not receive MNT. In the study, the MNT/CKD group had less of a decline in eGFR and the non-MNT group was 3.15 more likely to initiate dialysis. When stratified by Stages 3 and 4 that hazard ratio increased (3.47 and 3.45, respectively).<sup>42</sup>

The guideline points towards the provision of nutrition assessment and interventions to delay kidney disease progression in addition to comorbid conditions such as diabetes mellitus, dyslipidemia, gout, nephrolithiasis and crucially CVDCVD.

### *Cost Benefits*

In November 2022, *Kidney Medicine* published a study where 269,187 patients (mean age 65.6 years) with diabetes and CKD of moderate or high baseline risk were monitored leveraging Optum's electronic health records from January 2007 to December 2019. Among high-risk patients, 63.9 percent of stage G3b/G3a and 56.0 percent of stage G2 patients progressed to very high risk. The study showed that within the same eGFR stage, a higher uACR stage was associated with a 4-to7-times higher risk of progressing to very high risk and faster eGFR decline.<sup>43</sup>

The results attest to the high sensitivity of uACR test for CKD diagnosis and for CKD progression. Crucially, the study point towards the lower cost burden attributed to patients that reported none or lower progression of CKD; reportedly having lower annual medical costs (\$16,924) than patients who

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<sup>39</sup> FDA Approves Drug to Reduce Risk of Serious Kidney and Heart Complications in Adults with Chronic Kidney Disease Associated with Type 2 Diabetes: <https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-drug-reduce-risk-serious-kidney-and-heart-complications-adults-chronic-kidney-disease>.

<sup>40</sup> De Boer, Ian H. et al "Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and kidney disease: Improving Global Outcomes (KDIGO)" *Diabetes Care* 2022;45(12):3075–3090 <https://doi.org/10.2337/dci22-0027>

<sup>41</sup> Pace, Rory C. et al "Academy of Nutrition and Dietetics and National Kidney Foundation: Revised 2020 Standards of Practice and Standards of Professional Performance for Registered Dietitian Nutritionists (Competent, Proficient, and Expert) in Nephrology Nutrition" *Journal of the Academy of Nutrition and Dietetics*; <https://doi.org/10.1016/j.jand.2020.10.012>

<sup>42</sup> De Waal, Desiree et al "Medical Nutrition Therapy for Chronic Kidney Disease Improves Biomarkers and Slows Time to Dialysis" *Science Direct*; <https://www.sciencedirect.com/science/article/abs/pii/S105122761500148X>

<sup>43</sup> Mullins, Daniel C. et al "CKD Progression and Economic Burden in Individuals With CKD Associated With Type 2 Diabetes" *National Library of Medicine*; DOI: 10.1016/j.xkme.2022.100532

progressed from moderate risk to high risk (\$22,117), from high risk to very high risk (\$32,204), and from moderate risk to very high risk (\$35,092).<sup>44</sup>

## II. Comments on Questions for Systematic Review

The following section offers comments on the questions for systematic review. We reiterate our primary concern that the current design excludes “studies in which patients were selected on the basis of having conditions associated with CKD (e.g., hypertension, diabetes)”. We recommend that questions 1 through 3, specifically, be amended as articulated below.

### 1. In asymptomatic adults without known chronic kidney disease (CKD), what are the effects of screening for CKD vs. no screening on clinical outcomes?

As noted earlier, even among at-risk populations, such as those with diabetes and hypertension, CKD often goes undetected until its later stages.<sup>45</sup> A thoughtful and selective approach to CKD screening seems to be cost-effective and clinically valuable. Given that asymptomatic patients could potentially capture the entire population, we recommend a study design that separates symptomatic adults in the general population with asymptomatic adults with risk-factors for CKD. This question should be amended to read:

*1.a. In asymptomatic adults with known risk factors for CKD (e.g., diabetes or hypertension), what are the effects of screening for CKD vs. no screening on clinical outcomes?*

*1.b. In asymptomatic adults without known chronic kidney disease (CKD), what are the effects of screening for CKD vs. no screening on clinical outcomes?*

### 2. What are the harms of screening for CKD vs. no screening?

Similar to the comments above, this question would be more instructive if broken up to assess the harms of screening v. no screening based on risk factors for CKD.

*2.a. What are the harms of screening for CKD vs. no screening in asymptomatic adults with known risk factors for CKD?*

*2.b. What are the harms of screening for CKD v. no screening in asymptomatic adults?*

### 3. What is the diagnostic accuracy of screening to identify adults with CKD stages 1–3?

A current barrier to timely CKD diagnosis is failure to measure uACR in at risk populations. In addition to reviewing the accuracy of current screening tools, the research review should assess performance on whether comprehensive CKD screening using both eGFR and uACR is occurring.

*3.a. What is the diagnostic accuracy of screening to identify adults with CKD stages 1 – 3?*

*3.b. Is use of the UACR screening being maximized?*

*3.c. How does diagnostic accuracy vary in populations defined by race, ethnicity, age, and sex?*

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<sup>44</sup> Mullins, Daniel C. et al “CKD Progression and Economic Burden in Individuals with CKD Associated With Type 2 Diabetes” National Library of Medicine; DOI: 10.1016/j.xkme.2022.100532

<sup>45</sup> Dharmarajan, Sai H et al. “State-Level Awareness of Chronic Kidney Disease in the U.S.” *American journal of preventive medicine* vol. 53,3 (2017): 300-307. doi: 10.1016/j.amepre.2017.02.015

**4. Among adults with CKD stages 1–3<sup>‡</sup>, what are the effects of monitoring for worsening kidney function, kidney damage, or both vs. no monitoring on clinical outcomes?**

As noted earlier, individuals may sustain substantial kidney damage before they exhibit any symptoms related to CKD. Further, incidence and prevalence of cardiovascular events is already significantly higher in patients with early CKD stages (CKD stages 1–3) compared with the general population<sup>46</sup>. Earlier detection at every stage is critically important for purposes of delaying progression of kidney disease and related complications.

Implementing targeted therapies early can significantly improve patient outcomes by attenuating the progression of CKD to kidney failure, cardiovascular disease, and death, especially for at-risk communities. These interventions can slow progression at every stage – preserving kidney health in early stages, and prolonging kidney function to allow more optimal dialysis starts and preemptive transplantation in later stages. As such, we recommend that this question be amended to include adults with CKD stages 1 – 4.

**5. Among adults with CKD stages 1–3<sup>‡</sup>, what are the harms of monitoring for worsening kidney function, kidney damage, or both vs. no monitoring?**

NKF appreciates USPSTF’s objectives for examining the benefits and harms of CKD screening. Differences in harm versus benefit in diagnosis CKD may vary by stage in early CKD, and patient preferences regarding screening and early indication of CKD should also be considered. The burden to the healthcare system of screening at-risk populations must be balanced against the significant burden of managing people with late-stage kidney disease and kidney failure. Given those factors, and consistent with recommendations from the American Society of Nephrology, we recommend that this question be amended to include adults with CKD Stages 1 - 4.

**6. Among adults with CKD stages 1–3<sup>‡</sup>, what are the effects of treatment on likelihood of developing stage 4 or 5 CKD?**

NKF recommends USPSTF add CKD stage 4 to its draft plan to evaluate the impact only for CKD stages 1-3. We also believe that there could be significant differences in the impact of screening to detect CKD stages 1 or 2 versus stage 3. We acknowledge that there is likely much less precision and reliability in screening for CKD 1-2 versus CKD 3. Differences in harm versus benefit in diagnosing CKD may vary by stage in early CKD, and patient preferences regarding screening and early indication of CKD should also be considered. CKD stage 1-3 is largely managed by a primary care provider (PCP).

Currently, PCPs act as a critical role in CKD prevention, diagnosis, and early treatment. It is far too common that by the time patients are referred to nephrologists (stage 3 and above), opportunities for early intervention in slowing CKD progression and CV events have passed. Given that a sizeable number

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<sup>46</sup> Joachim Jankowski, Jürgen Floege, Danilo Fliser, Michael Böhm and Nikolaus Marx, “Cardiovascular Disease in Chronic Kidney Disease Pathophysiological Insights and Therapeutic Options” 15 Mar 2021 <https://doi.org/10.1161/CIRCULATIONAHA.120.050686> Circulation. 2021;143:1157–1172

of patients discover their late stage or fast progressing CKD status after screening, the assessment of diagnostic accuracy of CKD screening and as a result effective and timely treatment should not be limited to diagnosing CKD stage 1-3 but the full spectrum of CKD.

**7. Among adults with CKD stages 1–3,<sup>‡</sup> what are the effects of treatment on clinical outcomes?**

Similarly, given that a sizeable number of patients discover their late stage or fast progressing CKD status after screening, the assessment of effective and timely treatment should not be limited to diagnosing CKD stage 1-3 but the full spectrum of CKD.

**8. Among adults with CKD stages 1–3,<sup>‡</sup> what are the effects of treatment on harms?**

Interventions must happen proactively before CKD advances to late stages when kidney function becomes irreversible and severely compromised.

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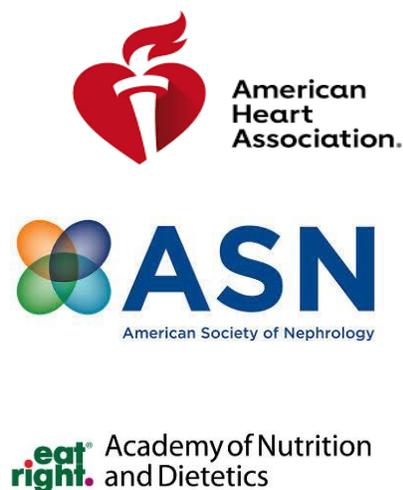
In closing, we are confident that a well-designed study will reinforce the value of CKD screening in at-risk populations. We further reiterate our strong support for a USPSTF screening recommendation for at-risk populations to empower patients to manage and mitigate their risk for CKD. We welcome the opportunity to discuss our recommendations with your team and offer additional guidance and feedback for your review. If you have questions or comments about this submission, please contact Ignacio Alvarez, Health Policy Director, at [Ignacio.Alvarez@kidney.org](mailto:Ignacio.Alvarez@kidney.org).

Thank you for your consideration of these comments.

Sincerely,

The Coalition for Kidney Health (C4KH)

List of Members for C4KH:





*The Voice of the Patient, Inc.*