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Re: Proposed edits to the USPSTF CKD Research Plan

Dear Drs., Mangione, Barry, and Nicholson,

The Coalition for Kidney Health (C4KH), a multistakeholder group of organizations working to transform the landscape of chronic kidney disease (CKD), writes today to respond to the United States Preventive Services Task Force (USPSTF) Chronic Kidney Disease Final Research Plan that was published on July 13, 2023.

We appreciate that this plan represents a significant step towards addressing the monumental burden of CKD, but we write to respond to several of the comments in USPSTF's "Response to the Public Comments" and to share additional information that has been published since the initial comment period closed. While the following letter documents many of our concerns, we request a meeting with USPSTF staff to enhance our shared understanding the following issues:

- 1) **USPSTF's authority and charge**
- 2) **Current practice guidelines and their limitations**
- 3) **Additional evidence related to early CKD screening**
- 4) **Implications for underserved and marginalized communities**
- 5) **Emerging Opportunities for Rare-Disease Drivers of CKD**



## 1) USPSTF's Authority and Charge

The C4KH would like to better understand USPSTF's reluctance to issue a narrower screening recommendation for CKD. In its response to Public Comments, USPSTF explained that a CKD recommendation specific to patients with type 2 diabetes or hypertension would be "deemed out of scope for the USPSTF because evaluation of kidney disease is part of disease management of these conditions."

First, we note that the USPSTF is directed by statute to develop "additional topic areas for new recommendations and interventions related to those topic areas, *including those related to specific sub-populations.*" 42 U.S.C. § 299b-4(a)(2)(A) (emphasis added). Accordingly, it is well within the USPSTF's scope to consider a narrower screening recommendation for CKD.

Consistent with this authority, there are numerous occasions where USPSTF recommends screenings to limited populations based on clinical risk factors. For example, screening recommendations for the following conditions are consistent with the approach we would recommend for CKD:

- **[Osteoporosis](#)**: USPSTF's screening recommendations around osteoporosis distinguish between the general population and at-risk populations and provide additional context and guidance to support clinicians to help them more accurately assess risk.
- **[Pre-Diabetes](#)**: USPSTF's recommends clinicians screen for pre-diabetes and type 2 diabetes in adults with overweight and obesity.
- **[Breast Cancer](#)**: USPSTF recommends biennial mammography for women aged 50 to 74 years and a more individualized, targeted approach for younger women with a family history of breast cancer.
- **[HIV](#)**: USPSTF recommends regular screening for those aged 15 to 65 years and younger adolescents or older adults who are at an increased risk for HIV and provides clinical considerations to advise clinicians in assessment of risk, screening intervals, and rescreening in pregnancy.

Additionally, USPSTF has a track record of supporting screenings and interventions that would be considered disease management, including recommendations for:

- **[Aspirin Use to Prevent Preeclampsia](#)**: USPSTF's recommendation around the use of aspirin to prevent preeclampsia in pregnant persons mirrors clinical practice guidelines of the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal–Fetal Medicine
- **[Breast Cancer](#)**: USPSTF recommends prescribing risk-reducing medications in women who are at increased risk for breast cancer and at low risk for adverse medication effects.
- **[Statin Use](#)**: USPSTF recommends the use of statins for the primary prevention of CVD for adults aged 40 to 75 years *who have 1 or more CVD risk factors* (such as dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year risk of a cardiovascular event of 10% or greater.



These examples serve as a precedent and potential template upon which the task force might approach a CKD screening recommendation. A tiered strategy ensures that those at higher risk are identified and treated promptly based on the best scientific evidence available, potentially changing the trajectory of their health outcomes. Further, by emphasizing stratified screening in each of these examples, the USPSTF ensured that preventive measures target those at the highest risk, optimizing the balance between benefits and potential harms. Targeted approaches showcase the importance of individualized care and intervention in public health. A similarly designed approach could yield parallel awareness, diagnosis, and management of people with CKD.

We also recognize that the USPSTF is tasked with developing recommendations for the primary care community in particular, *see* 42 U.S.C. § 299b-4(a)(1). Notably, consistent with the other conditions the USPSTF has used to stratify its screening recommendations, it is often primary care providers, not specialist physicians, who diagnose patients with diabetes and hypertension. Primary care providers routinely establish care plans for these patients based on such diagnoses, which can and should include potential screening for kidney disease. The CKD screening methodologies under consideration are well within the capabilities of primary care providers to administer, evaluate, and address.

## **2) Current Clinical Practice Guidelines and their Limitations**

The C4KH would also like to respond to USPSTF’s statement that “Guidelines on evaluation of kidney disease in persons with diabetes mellitus and hypertension already exist.” Unfortunately, guidelines and practice are highly inconsistent as it relates to CKD screening. Despite longstanding and strong guideline recommendations, testing for CKD with UACR and eGFR in US adults with diabetes and/ or hypertension is low (<20%) in routine clinical care.<sup>1</sup>

Both the American Diabetes Association (ADA's) Standards of Medical Care in Diabetes and the Kidney Disease: Improving Global Outcomes (KDIGO) recommend an annual assessment of urine albumin excretion as a primary tool for detecting early signs of kidney damage in persons with diabetes. Despite the strong evidence to support this approach, research shows that only 40 percent of diabetic patients undergo CKD screening annually with uACR<sup>2</sup>.

As it relates to screening in patients with hypertension, the 2017 American College of Cardiology/American Heart Association (AHA) guideline recognizes the link between hypertension and CKD and highlights the importance of kidney health in cardiovascular disease.<sup>3</sup> However, current guidelines list albuminuria testing as optional, despite the fact that 20 percent of patients with hypertension have CKD, according to the National Health and Nutrition Examination Survey.

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<sup>1</sup> Alfego, D., et al. (2021). Title of the article. *Diabetes Care*, 44(9), 2025-2032.

<sup>2</sup> <https://www.ncqa.org/hedis/measures/kidney-health-evaluation-for-patients-with-diabetes/>

<sup>3</sup> Whelton, P. K., & Carey, R. M. (2018). 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*, 71, e127–e248.

In contrast to the AHA, KDIGO has emphasized the urgency of CKD screening for high-risk populations. KDIGO's 2021 consensus statement and 2023 draft CKD guideline underscore that individuals with CKD risk factors – diabetes, hypertension, or a history of cardiovascular disease – should be screened for CKD with both eGFR and albuminuria measurements, given their critical roles in detecting and stratifying CKD. On the same lines, the Kidney Disease Outcomes Quality Initiative (KDOQI) has further updated its guidelines, stressing the diagnosis, staging, and treatment of CKD. It particularly underscores regular monitoring of kidney function in at-risk groups.

These misaligned guidelines have led to confusion in the primary care community and inconsistent real-world application in primary care settings<sup>4</sup>. A significant disconnect exists between the comprehensive guidelines set forth by expert committees and their implementation in primary care settings. The implications of this disconnect are profound, with an alarming under-screening of at-risk populations for CKD. Less than 50% of patients with diabetes receive recommended annual CKD screening, and only 10% of patients with hypertension receive annual CKD screening.

Low screening has significant implications for patient access to appropriate interventions. ACC/AHA recommend using angiotensin-converting enzyme inhibitor therapy for hypertension with level IIA evidence for those with > 300 mg/g. Albuminuria is an indication for SGLT2 inhibitor therapy for those with hypertension and also informs clinical interventions for cardiovascular risk. But these therapies are of little value if an individual is not screened.

### **3) Additional evidence related to early CKD screening.**

A recent study published in the *Annals of Internal Medicine* underscores the profound benefits and necessity of proactive measures in CKD management. This study heralds a proactive paradigm, championing the merits of early-stage screening for asymptomatic CKD stages 1-3. Its findings are enlightening:

- Systematic CKD screening can drastically diminish kidney failures requiring Kidney Replacement Therapy (KRT), benefiting up to 658,000 individuals across their lifespan.
- Early diagnosis, paired with novel therapeutics demonstrates promise to extend and enrich life, with potential gains of 0.07 life-years for individuals aged 35-75.
- SGLT2 inhibitors underscore the evolving landscape of CKD management, providing an evidence-based intervention to improve outcomes.

The study went on to find a significant improvement in patient quality of life and a subsequent decline in kidney failure episodes necessitating dialysis or transplantation. And while issues of cost are not under the purview of USPSTF, findings that early diagnosis significantly curtail the exorbitant costs associated

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<sup>4</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>



with late-stage care for kidney disease are highly relevant to persons with kidney disease who pay a significant percentage of those costs out-of-pocket.

Another aspect highlighted in the study was the role of age in CKD screenings. Age-specific screening recommendations ensure that we are not casting too wide or too narrow a net. By tailoring our screening frequencies based on age and associated risks, we can ensure that resources are optimally utilized, and those at most risk are identified and managed efficiently. For individuals aged between 35 and 75, early-stage screenings promise a significant increment of at least 0.07 life-years, emphasizing a life led with better health and fewer complications<sup>5</sup>.

While the focus of USPSTF is the evidence-based balance between clinical efficacy and risk, the therapeutic benefits of SGLT2 inhibitors and ns-MRAs in CKD's early stages to reduce CKD progression, limit cardiovascular hospitalization and reduce mortality must not be overlooked. Their inclusion promises not just slowing of CKD progression, but a potential prevention of the lifetime need for dialysis, a prospect that was unimaginable until recently. Central to this study's findings is the strong indication that CKD screening strategies that encompass SGLT2 inhibitors and ns-MRAs in DKD can dramatically improve patient outcomes. Not only does this approach extend life expectancy, but it notably amplifies the quality of the additional years. Lastly, benefits to reduce cardiovascular hospitalization were not considered in the analysis, underestimating the overall impact of screening.

Our continued commitment to healthcare compels us to constantly seek the best for our patients. The findings from the *Annals of Internal Medicine* reiterate the importance of early-stage CKD screening, promising improved quality of life, reduced complications, and a forward-thinking approach to CKD management. Given the downstream implications of this evidence, we sincerely urge the USPSTF to consider this in their final research plan, ensuring its methodologies are aligned with the most recent and impactful evidence-based medicine.

#### **4) Implications for underserved and marginalized communities**

The current landscape of CKD underdiagnosis, especially among marginalized communities, is alarming. The asymptomatic nature of CKD in its early stages compounds the issue. Essential tools like albuminuria testing, crucial for CKD diagnosis and prognosis, remain significantly underutilized, emphasizing the need for heightened awareness and adherence to clinical guidelines. Both nephrologists and primary care physicians must shoulder the responsibility of proactive CKD screening, diagnosis, and treatment.

The stark inequities related to CKD among racially and ethnically diverse populations have been well-documented, with Black/African Americans bearing the highest burden. Progression to ESRD is substantially higher among Black individuals. The systemic challenges, including racial concordance barriers in organ transplantation and lesser financial commitments at the national level, further compound these disparities. Ground-breaking research highlighting conditions like APOL1-mediated kidney disease in those of west African genetic ancestry and IgA Nephropathy's high prevalence in people of Asian genetic ancestry underscores the importance of tailored approaches to screening and

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<sup>5</sup> Marika M.Cusick, MS "Population-Wide Screening for Chronic Kidney Disease" *ACP Journals, Annals of Internal Medicine*, June 2023. <https://www.acpjournals.org/doi/full/10.7326/M22-3228>



intervention<sup>6</sup>. Yet, current evidence may not holistically represent these communities. With underrepresentation in clinical trials and race-based differences in treatments and care delivery measures, there's an undeniable need for rectification<sup>7</sup>.

## 5) Emerging Opportunities for Rare-Disease Drivers of CKD

In the same way there is clinical value for screening for CKD within a population at risk for CKD due to underlying diabetes and hypertension, there is an increasing opportunity for clinical practice and patient outcomes to benefit from identification of rare diseases as drivers of CKD, most of which are classified as glomerular diseases. For instance, the USRDS shows that, of patients for which a treatment modality is identified, approximately 100,000 patients with ESRD out of approximately 750,000 ESRD patients represented have glomerulonephritis identified as their primary cause of ESRD.<sup>8</sup> Such patients especially represent an opportunity for earlier and cost-effective diagnosis and treatment, in line with the goals of USPSTF recommendations, because these patients are disproportionately young and also disproportionately likely to receive transplants as a treatment.<sup>9</sup>

Identifying these conditions has also become both higher-value and more feasible in recent years, with the emergence of two FDA-approved treatments for glomerular diseases,<sup>10</sup> dozens of trials in progress, and a feasible path identified for screening for these diseases through proteinuria testing. Without a plan for diagnosing patients with such diseases, a significant driver of CKD and ESRD will not be addressed by USPSTF's research work.

As noted above regarding other drivers of CKD, racial minorities are disproportionately impacted by glomerular-disease drivers of CKD, such as rare diseases, and failure to diagnose these conditions. Ground-breaking research highlighting conditions like APOL1-mediated kidney disease in African Americans and IgA Nephropathy's high prevalence in Asians has underscored the importance of tailored approaches to screening and intervention.<sup>11</sup> The current evidence and research plan as proposed by USPSTF may not adequately represent the challenges facing these communities.

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<sup>6</sup>Kdigo 2022 Clinical Practice Guideline for Diabetes Management In Chronic Kidney Disease: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://kdigo.org/wp-content/uploads/2022/03/KDIGO-2022-Diabetes-Management-GL\_Public-Review-draft\_1Mar2022.pdf

<sup>7</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>8</sup> National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), U.S. Renal Disease System (USRDS) Annual Report, Figure 1.10 Distribution of modality in prevalent ESRD, 2020. Available at: <https://usrds-adr.niddk.nih.gov/2022/end-stage-renal-disease/1-incidence-prevalence-patient-characteristics-and-treatment-modalities>. See also Kazi AM, Hashmi MF. Glomerulonephritis. [Updated 2023 Jun 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK560644/> ("Glomerulonephritis (GN) is a prominent cause of renal impairment[,leading] to 10% to 15% of end-stage renal disease cases in the United States").

<sup>9</sup> USRDS Annual Report, Figure 14.12.

<sup>10</sup> U.S. Food & Drug Administration, FDA approves first drug to decrease urine protein in IgA nephropathy, a rare kidney disease (Dec. 17, 2021), available at: <https://www.fda.gov/drugs/fda-approves-first-drug-decrease-urine-protein-iga-nephropathy-rare-kidney-disease>; U.S. Food & Drug Administration, Accelerated Approval for Filspari (Feb. 17, 2023), available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2023/216403Orig1s000ltr.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2023/216403Orig1s000ltr.pdf).

<sup>11</sup>Kdigo 2022 Clinical Practice Guideline for Diabetes Management In Chronic Kidney Disease: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://kdigo.org/wp-content/uploads/2022/03/KDIGO-2022-Diabetes-Management-GL\_Public-Review-draft\_1Mar2022.pdf



In closing, we urgently appeal to the USPSTF to reconsider its approach to assessing the evidence in support of CKD screening. A focused approach that recognizes documented variations in CKD risk, advancements in clinical treatment in the past 20 years, and the profound effect that CKD has on communities of color will yield a strategy that appropriately targets limited healthcare resources where they are likely to have the greatest effect. We welcome the opportunity to speak with you directly about these important issues. To arrange a meeting with the Coalition, please contact Ignacio Alvarez at [Ignacio.Alvarez@kidney.org](mailto:Ignacio.Alvarez@kidney.org).

Sincerely,

C4KH