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Dear Drs. Mangione, Barry, and Nicholson:

On behalf of the more than 37,000,000 Americans living with kidney diseases and the 21,000 nephrologists, scientists, and other kidney health care professionals who comprise the American Society of Nephrology (ASN), thank you for the opportunity to comment on the Draft Research Plan: Screening for Chronic Kidney Disease. ASN applauds U.S. Preventive Services Task Force (USPSTF) undertaking this important review that impacts the lives of 37,000,000 Americans.

An estimated 90 percent of people with kidney diseases are unaware that they are affected, even though kidney diseases are the tenth leading cause of death in the United States and kidney patients are at a significantly higher risk of cardiovascular disease, kidney failure (also known as end-stage renal disease [ESRD]), and death. Although guidance from Kidney Disease Improving Global Outcomes (KDIGO) and the National Kidney Foundation (NKF) recommends CKD screening among patients with hypertension, only approximately 10 percent of individuals with hypertension receive yearly screening[i]. Furthermore, American Diabetes Association's (ADA) guidelines recommend yearly CKD screening in patients with diabetes, but only 40-50% of patients receive this.

People who progress to kidney failure often require dialysis, which has a five-year survival rate of less than 50 percent—worse than nearly all forms of cancer. On average, 360 people begin dialysis treatment every 24 hours. Meanwhile, the Medicare ESRD Program spends more than $50 billion annually on the care and treatment of people with kidney failure. Overall, Medicare spends $125 billion annually on kidney diseases which does not include other payers such as private insurers, the Veterans Administration, or Indian Health Services. There is strong evidence that delays in primary care and nephrology care for patients with chronic kidney disease (CKD) are associated with worse clinical outcomes, including cardiovascular events, progression to kidney failure (ESRD) and death.

Health inequities and disparities challenge every aspect of the US health care system, but kidney diseases are particularly prone to impact the nation's most vulnerable populations. Kidney diseases and kidney failure are more common among people who are Black/African American, Hispanic/Latinx, Native/Indigenous American, Native Alaskan, Asian, and Native Hawaiian or other Pacific Islander; older adults; and people with lower socioeconomic status. All these communities have also been disproportionately affected by the COVID-19 pandemic. Additionally, the burgeoning rates of hypertension and diabetes in the United States foreshadow a growing burden on individuals predisposed to kidney diseases.

ASN's comments address both the individual elements and questions of the research plan, and those comments are grouped into 9 areas of top concerns for ASN:

1. Scope of evidence review
2. Which tests will be used for screening
3. CKD stages
4. Harm and disparities
5. Education and other non-pharmacologic interventions
6. Access to care
7. Social determinants of health
8. COVID-19
9. Study time frame

Scope of evidence review

The outsized health care and financial burden of kidney diseases argues for the development of a robust research plan able to assess the risks, harms, and disparities in kidney diseases. However, the very first question of the research plan carries the following caveat: *For screening, studies in which patients were selected on the basis of having conditions associated with CKD (e.g., hypertension, diabetes) are not eligible for inclusion. However, studies are not required to exclude patients with these conditions.*[ii] ASN expresses very strong concern regarding the exclusion of studies in which patients were selected due to preexisting conditions such as hypertension and diabetes from the research plan. Excluding these studies will markedly restrict the evidence review due to

the fact that a large bulk of the evidence selects patients on the basis of having conditions associated with CKD (e.g. hypertension, diabetes).

ASN strongly recommends that the research plan be amended to review 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 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.

The most robust evidence for CKD screening comes from targeting those with CKD risk factors. Excluding these studies from the evidence review would provide an incomplete and misleading assessment of CKD screening leading to a potential repeat of the inconclusive results of USPSTF's review in 2012. Due to the underlying causes of many cases of kidney diseases, ASN supports a different approach to a research plan that includes those studies.

For example, the NKF Kidney Early Evaluation Program (KEEP) was a targeted community-based health-screening program enrolling individuals 18 years and older with diabetes; hypertension; or a family history of kidney disease. Of the 61,675 KEEP participants, 16,689 or 27 percent had CKD[iii].

A more recent randomized clinical trial of CKD screening in persons with hypertension without diabetes published in 2020 in the Clinical Journal of the American Society of Nephrology (CJASN) found that 21% of patients had newly diagnosed CKD[iv]. Likewise, the See Kidney Disease (SeeKD) Targeted Screening Program in Canada screened patients with CKD risk factors and found that 19% of patients had unrecognized CKD[v].

In a cross-sectional survey by way of a voluntary screening of relatives of patients with kidney failure in 10 communities in one southeastern state. Among 769 screened adults, CKD (CrCl < 90 mL/min) was present in 49.3%, 13.9% had a CrCl less than 60 mL/min, and 9.9% had proteinuria of 1+ or greater[vi].

In addition, other guidelines and consensus documents focus on patients with risk factors. For instance, The National Institute for Health and Care Excellence (NICE) Clinical Guidelines in the United Kingdom published in 2021 recommend offering CKD testing to patients with risk factors[vii]. Those risk factors include diabetes, hypertension, previous episode of acute kidney injury (AKI), cardiovascular disease, and family history of ESRD or hereditary kidney disease.

Also, the Kidney Disease Improving Global Outcomes (KDIGO) conference on early identification and intervention in CKD concluded that persons with diabetes, hypertension, and/or cardiovascular disease should be screened for CKD[viii]. Specifically, "a consensus emerged that CKD screening coupled with risk stratification

and treatment should be implemented immediately for high-risk persons and that this should ideally occur in primary or community care settings with tailoring to the local context."[ix]

Which tests will be used for screening

ASN asks for clarification regarding what clinical tests will be used to determine the presence of CKD in an individual. ASN stresses that CKD is not merely a number. We recommend that studies in the evidence review be included that evaluate CKD screening using both GFR estimation and proteinuria/albuminuria measurement. Also, we request you examine methods to estimate GFR including the 2021 CKD-EPI creatinine equation (that does not include race) and cystatin C measurements – as well as methods to measure proteinuria/albuminuria including urinary albumin-to-creatinine ratio (UACR) testing, urine protein-to-creatinine ratio (UPCR) testing, and urine dipstick. ASN urges USPSTF to include an evaluation of these tests as they have the potential to significantly alter the robust and relevant findings especially with the expanded patient studies ASN has recommended.

CKD stages

ASN 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.

Harm and disparities

ASN applauds USPSTF for examining the benefits and harms of CKD screening specifically in socially disadvantaged and marginalized populations. ASN encourages the use of well-defined terminology in both the proposed key and contextual questions. We suggest clearly defining the social and demographic variables along which disparities will be assessed. These variables should be measured using the same rigorous detail as the other definitions presented in the study. Because the usage of race and ethnicity has evolved in the medical literature over time, this may lead to biased and potentially inaccurate results that could limit the clinical and policy uses of the recommendations. For example, many studies reporting CKD screening results stratified by race do not use self-reported race or conflate race (a social construct) with biology.

In accessing the potential benefits of early detection, potential harm from such actions must also be considered. First and foremost, laborious detail must be pursued regarding the definition of harm that results from screening or not screening – particularly in the context of other factors that increase the likelihood of the development of kidney

diseases in an individual. Screening findings may be individually perceived as negative (or not) and there are times when the choice to not screen is appropriate for reasons other than a potential negative outcome. For example, when the information to be gleaned may not be helpful, needed, or desired.

Special attention should also be given when considering the potential harm and benefits of screening older adults for CKD. ASN has concerns over the potential harm caused by over diagnosing older adults. The question of age-related harm from diagnoses has been addressed by USPSTF in previous studies through the implementation of age-related cut-offs. ASN urges USPSTF to consider an age-related cutoff in the CKD study as well, i.e. Age 75 and older.

Education, pharmacologic and non-pharmacologic interventions

Simply identifying a disease is futile unless it is linked to actions that improve clinical outcomes. The past several years have seen a revolution in novel therapeutics for CKD to slow disease progression, including 1) sodium-glucose co-transporter 2 (SGLT2) inhibitors, 2) nonsteroidal mineralocorticoid antagonists, and 3) glucagon-like peptide-1 receptor agonists (GLP-1 RA). Existing studies quantifying the benefits and potential harms of CKD screening are unlikely to incorporate these novel therapies. This may lead the evidence review to underestimate the benefits of CKD screening.

Since 2012, CKD has become increasingly modifiable and screening high risk individuals for CKD has become even more important. Several 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. SGLT-2 inhibitors show extraordinary 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[xxi]. In addition, there are several interventions that have no effect on CKD progression but reduce risk of CVD (the leading cause of death for people with CKD) including statin-based therapies and the GLP-1 RA drug class for T2DM. 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 (HF) in individuals with diabetic kidney disease, based on results from the FIDELIO-DKD study[xii].

There are many other non-pharmacologic steps providers and patients can take to slow the progression of CKD, especially when these steps are implemented in the earlier stages of the disease. Some of the most effective treatments to slow the progression of CKD in the earlier stages are non-pharmacologic. ASN strongly urges the evidence review to address these non-pharmacologic interventions, including patient education and counseling, dietary modifications, weight loss, smoking cessation, and the avoidance of nephrotoxic medications. Cardiovascular risk increases with the progression to CKD so many of these could also prevent heart attacks and strokes in

addition to the progression of CKD and should be evaluated as potentially powerful factors to offset potential harms from screening.

Access to care

ASN believes the proposed research study should explore the intersection of screening with access to care. This includes examining the accessibility of the early detection methods to at-risk populations and the availability, affordability, and accessibility of the treatments that follow for those diagnosed with CKD. Increased screening will inevitably increase the number of patients diagnosed with CKD. Therefore, the ability of the health system to cope with this influx of new cases and manage the appropriate follow-ups must also be assessed. In light of this potential increase in diagnoses of early-stage CKD, additional exploration is needed on how to prioritize high-risk patients in need of nephrology referral. This is especially relevant in relation to disparities in access to care.

USPSTF and the broader kidney care community need to explore the intersection of screening with access to care. Estimation of likely expansion of the population of patients diagnosed with CKD stage 1-2, 3a, 3b, 4, and 5 would have impacts on already limited access. Specifically, what needs to be addressed is how to prioritize high risk stage 3, stage 4 and 5 patients if there is an increase in diagnoses of early stage CKD, particularly in light of known disparities in access to care.

Social determinants of health

ASN recommends the USPSTF research study explore adverse social determinants of health (SDOH) as indicators for CKD screening. People with low household incomes (e.g. living in poverty) in the US have greater risk for albuminuria[xiii] as well as progression to kidney failure[xiv]. Food insecurity and housing insecurity are also risk factors for CKD and food insecurity is a risk factor for progression to kidney failure among people with CKD[xv]. Health systems are increasingly recognizing the importance of screening for adverse SDOH[xvi], thus, their consideration as indicators for CKD screening would be timely. Because of the maldistribution of SDOH in the US, their exploration also has important implications for the examination of racial and ethnic disparities in CKD and CKD screening.

COVID-19

ASN recommends USPSTF incorporate a review of the potential benefits of the prevention of severe COVID-19 (and other serious infections) in its research plan.

The research plan should incorporate a review of the evidence regarding the connection between certain conditions and serious COVID-19 illness.

- COVID-19 has caused more than 1.1 million deaths in the US and has contributed to a reduction in population life expectancy
- CKD has been identified as an independent risk factor for severe COVID-19 (e.g., hospitalization, ICU admission, death)

- Interventions such as Paxlovid and preventive measures such as COVID-19 vaccination are effective at reducing risk of severe COVID-19
- Paxlovid is only authorized for use in individuals with SARS-CoV-2 infection who have risk factor(s) for serious COVID-19 illness.
- COVID-19 vaccination coverage tends to be low in individuals who perceive themselves to not be at risk for serious complications.

Therefore, ASN is concerned that individuals with no other risk factor who have undiagnosed CKD are at risk for serious illness but would not be eligible for treatment of COVID-19 to prevent complications and might not recognize the importance of vaccination.

Study time frame

ASN believes that an extended time frame for this undertaking is crucial to its ability to properly evaluate benefits and harms.

Conclusion

ASN believes that kidney care is at an inflection point. There are now far more novel therapeutics to slow the progression of CKD, evidence to support the impact of non-pharmacologic interventions on CKD, an increased commitment in public health to confront disparities and their causes, a growing burden on public health and resources, and a far more stark vision of what happens when individuals with underlying health conditions incur serious infections like COVID-19. Plainly stated, much has changed since 2012. The pursuit of health care justice compels us to examine the most robust collection of evidence possible to address the burdens that are kidney diseases.

ASN wholeheartedly thanks USPSTF for undertaking this important initiative and stands ready to provide assistance in any way possible. We would welcome the opportunity to discuss the contents of this letter. For questions, please contact ASN Regulatory and Quality Officer David L. White dwhite@asn-online.org .

Thank you for your consideration and the opportunity to provide comments.

Sincerely,

Michelle A. Josephson, MD, FASN
President

[i] https://usrds-adr.niddk.nih.gov/2022
[ii] https://uspreventiveservicestaskforce.org/uspstf/document/draft-research-plan/chronic-kidney-disease-screening
[iii] Whaley-Connell AT, Sowers JR, Stevens LA, McFarlane SI, Shlipak MG, Norris KC, Chen SC, Qiu Y, Wang C, Li S, Vassalotti JA. CKD in the United States: kidney early evaluation program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999-2004. American journal of kidney diseases. 2008 Apr 1;51(4):S13-20.

[iv] Peralta CA, Frigaard M, Rolon L, Seal K, Tuot D, Senyak J, Lo L, Powe N, Scherzer R, Chao S, Chiao P. Screening for CKD to improve processes of care among nondiabetic veterans with hypertension: a pragmatic cluster-randomized trial. Clinical Journal of the American Society of Nephrology. 2020 Feb 7;15(2):174-81.

[v] The See Kidney Disease Targeted Screening Program for CKD - PubMed (nih.gov)
[vi] Jurkovitz C, Franch H, Shoham D, Bellenger J, McClellan W. Family members of patients treated for ESRD have high rates of undetected kidney disease. Am J Kidney Dis 2002;40(6):1173-8. (In eng). DOI: 10.1053/ajkd.2002.36866.

[vii] https://www.nice.org.uk/guidance/ng203/chapter/Recommendations
[viii] Shlipak MG, Tummalapalli SL, Boulware LE, Grams ME, Ix JH, Jha V, Kengne AP, Madero M, Mihaylova B, Tangri N, Cheung M. The case for early identification and intervention of chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney international. 2021 Jan 1;99(1):34-47.
[ix] *Ibid*
[x] https://www.nejm.org/doi/full/10.1056/NEJMoa1811744
[xi] https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2021/07/09/15/27/sglt2-inhibitors-and-glp1
[xii] 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
[xiii] https://pubmed.ncbi.nlm.nih.gov/22694949/
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[xv] https://pubmed.ncbi.nlm.nih.gov/28215947/
[xvi] https://pubmed.ncbi.nlm.nih.gov/29144894/