Evidence-based Practice Center Systematic Review Protocol

Project Title: Screening for and Management of Chronic Kidney Disease Stages 1-3

I. Background and Objectives for the Systematic Review

Topic Nomination

The nominator of the topic, initially titled "Management of Mild Renal Impairment," proposed questions related to clinical typology, frequency of monitoring, calculation of creatinine clearance, management, and secondary prevention of mild renal impairment. Concurrently, a second nominator presented questions related to screening for and treatment of screen-detected chronic kidney disease (CKD). It was determined to be feasible to combine the two sets of questions. Subsequently, to clarify the purpose of this project, its title and the language used throughout were changed to be consistent with the currently accepted terminology for referring to impairments in kidney function and kidney damage as established by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI),[1] and later modified by the Kidney Disease Improving Global Outcomes (KDIGO).[2]

Definition of Chronic Kidney Disease (CKD)

There has been substantial debate regarding how best to define early stages of kidney disease. The definition of CKD developed by K/DOQI was[1]:

1. Kidney damage for ≥ 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR), manifest by either pathological abnormalities; or markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests. Most frequently, evidence for kidney damage has been based on identification of elevated levels of albuminuria (e.g., urinary albumin-creatinine ratio [ACR] ≥30 mg/g) or proteinuria.

OR

2. GFR <60 mL/min/1.73 m^2 for ≥3 months, with or without kidney damage.

Within this framework, K/DOQI then classified CKD into five stages as follows:

- Stage 1: Kidney damage with GFR ≥90 mL/min/1.73 m^2

- Stage 2: Kidney damage with GFR 60-89 mL/min/1.73 m^2
- Stage 3: GFR 30-59 mL/min/1.73 m^2
- Stage 4: GFR 15-29 mL/min/1.73 m^2
- Stage 5: GFR <15 mL/min/1.73 m^2 or kidney failure treated by dialysis or transplantation

A limitation of the K/DOQI definition and staging was that they were based on cross sectional data, and that there were limited data associating adverse clinical outcomes with specific levels of GFR, albuminuria, or proteinuria. However, based on a meta-analysis examining the longitudinal association of reduced estimated GFR and albuminuria or proteinuria with total and cardiovascular mortality in 1.5 million individuals, a recent consensus conference led by KDIGO, on Chronic Kidney Disease: Definition, Classification and Prognosis, advocated that the current CKD definition be preserved, but that staging should be altered as follows[2]:
(1) Stage 3 CKD should be subdivided into 3a (GFR 45-59 mL/min/1.73 m^2) and 3b (GFR 30-44 mL/min/1.73 m^2).
(2) Albuminuria stages should be added within each GFR stage (urinary ACR <30 mg/g, 30-299 mg/g, or ≥300 mg/g).
In addition, it was suggested that a cause of CKD should be assigned when possible.

Epidemiology of CKD

Based on the K/DOQI CKD definition and stage classification, and utilizing a urinary ACR ≥30 mg/g (adjusted to estimate persistence) as the marker for kidney damage and the Modification of Diet in Renal Disease (MDRD) formula to estimate GFR, the prevalence of stages 1-4 CKD in U.S. adults aged 20 and older was estimated from 1999-2004 National Health and Nutrition Examination Survey (NHANES) data at 13.1% (26.3 million), with 11.1% in men and 15.0% in women. Of the population,1.8% (3.6 million) individuals were classified in stage 1 CKD, 3.2% (6.5 million) in stage 2 CKD, 7.7% (15.5 million) in stage 3 CKD, and 0.4% (0.7 million) in stage 4 CKD.[3] U.S. prevalence was estimated to be lower, at 11.5% (23.2 million), when applying the more accurate Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula to estimate GFR to1999-2006 NHANES data, primarily due to a lower prevalence of CKD stage 3 in women, whites, and people younger than age 70 years.[4] Approximately half of individuals classified with CKD had albuminuria only (nearly all with microalbuminuria [ACR 30-299 mg/g]), 1/3 had reduced estimated GFR only, and 1/6 had both albuminuria and reduced estimated GFR.[3]

Analyses of NHANES data also suggest that the prevalence of CKD is rising, with more individuals being classified into every stage of CKD in 1999-2004 than in 1988-1994, with differences statistically significant for CKD stages 2 through 4 and overall.[3] The number of patients with stage 5 CKD requiring dialysis also has increased. In 2006, 101,306 patients began hemodialysis and 327,754 individuals were receiving hemodialysis, increases of 71.4% and 84.2%, respectively, compared with 1995.[5] It has

been estimated that more than 700,000 individuals will have end-stage renal disease (ESRD) by 2015.[6]

Association of CKD with Adverse Clinical Outcomes

Numerous adverse health outcomes have been associated with the presence of CKD. The majority of evidence associating CKD with adverse outcomes is derived from cohort or observational studies. The vast majority of studies have suggested that a GFR 30-59 mL/min/1.73 m^2 is associated with an increased risk of mortality,[7,8] cardiovascular disease,[9] fractures,[10] bone density loss,[11] infections,[12] cognitive impairment,[13] and frailty. Further, there appears to be a graded relationship between the severity of proteinuria or albuminuria and adverse health outcomes, including mortality,[8,14] ESRD,[15] and cardiovascular disease.[16] Finally, the risk for adverse outcomes conferred by reduced GFR and increased albuminuria (or proteinuria) appears to be independent and multiplicative.[8,15]

How Does CKD Influence Adverse Outcomes?

There are a number of possible explanations for the observed association of CKD with adverse health outcomes. First, CKD shares many of the same risk factors as other vascular diseases, such as older age, hypertension, and diabetes, so CKD may be a marker for undiagnosed vascular disease or for a worsened prognosis among individuals with known vascular disease. Second, CKD may be associated with a number of nontraditional risk factors for vascular disease and mortality such as increased inflammation or bone mineral disorders. Third, CKD may be a marker for individuals less likely to receive proven medical therapies. For example, among individuals with a myocardial infarction, those with CKD are less likely to receive proven effective therapies such as coronary artery bypass, ace-inhibitors (ACEI), beta-blockers, or HMG CoA-reductase inhibitors (i.e., statins) medications.[17] Therefore, systematic undertreatment may in part underlie the association between CKD and adverse health outcomes. Finally, these associations may be related to a combination of the above mechanisms.

Screening for CKD

The general rationale for screening for a medical condition is that the condition is sufficiently prevalent and/or associated with adverse impacts (e.g., health outcomes and/or costs) as to be of public health importance, the condition is detectable while asymptomatic or in an early clinical stage, and that treatment at this asymptomatic or early stage improves important health outcomes more than treatment once symptomatic, while limiting harms. The USPSTF makes recommendations based on the balance of benefits and harms; therefore, it requires evidence on both the benefits and harms of screening and early treatment. The USPSTF, in its Procedure Manual, Appendix X, further incorporates the following factors: (1) Whether attributable risk and

potential burden of the targeted condition is limited to or increased significantly in subgroups of people who are easily identified by one or more of the following factors: age, gender, ethnicity, particular behaviors, and/or co-morbid or biological risk factors; (2) Whether the accuracy of available screening tests differs or is uncertain in particular subgroups of people; (3) Whether the feasibility, efficacy, and/or harms of treatment for the risk factor or target condition differ in particular subgroups of people; and (4) Whether the potential to avert risk and burden is decreased by competing risks such as short life expectancy.

As described above, the public health burden of CKD is high. Causes of CKD can be broken down into primary kidney diseases (predominantly glomerular diseases, tubulointerstitial diseases, obstruction, and polycystic kidney disease) versus those in which the kidney damage is secondary to other medical conditions such as diabetes and hypertension. The vast majority of CKD is related to secondary causes of kidney damage. NHANES data on CKD prevalence in U.S. adults aged 20 and older illustrates the importance of diabetes,[18] hypertension,[19] age, and obesity as predictors of CKD (see **Figure 1**) and indicates that screening targeted to these groups should identify a higher percentage of individuals with previously undiagnosed CKD. However, a high screening yield in itself is not sufficient evidence to support the benefit of screening; screening for CKD may be beneficial if it enables earlier CKD diagnosis and intervention(s) that improve clinical outcomes compared to outcomes in individuals diagnosed with CKD at a later time or more advanced stage.

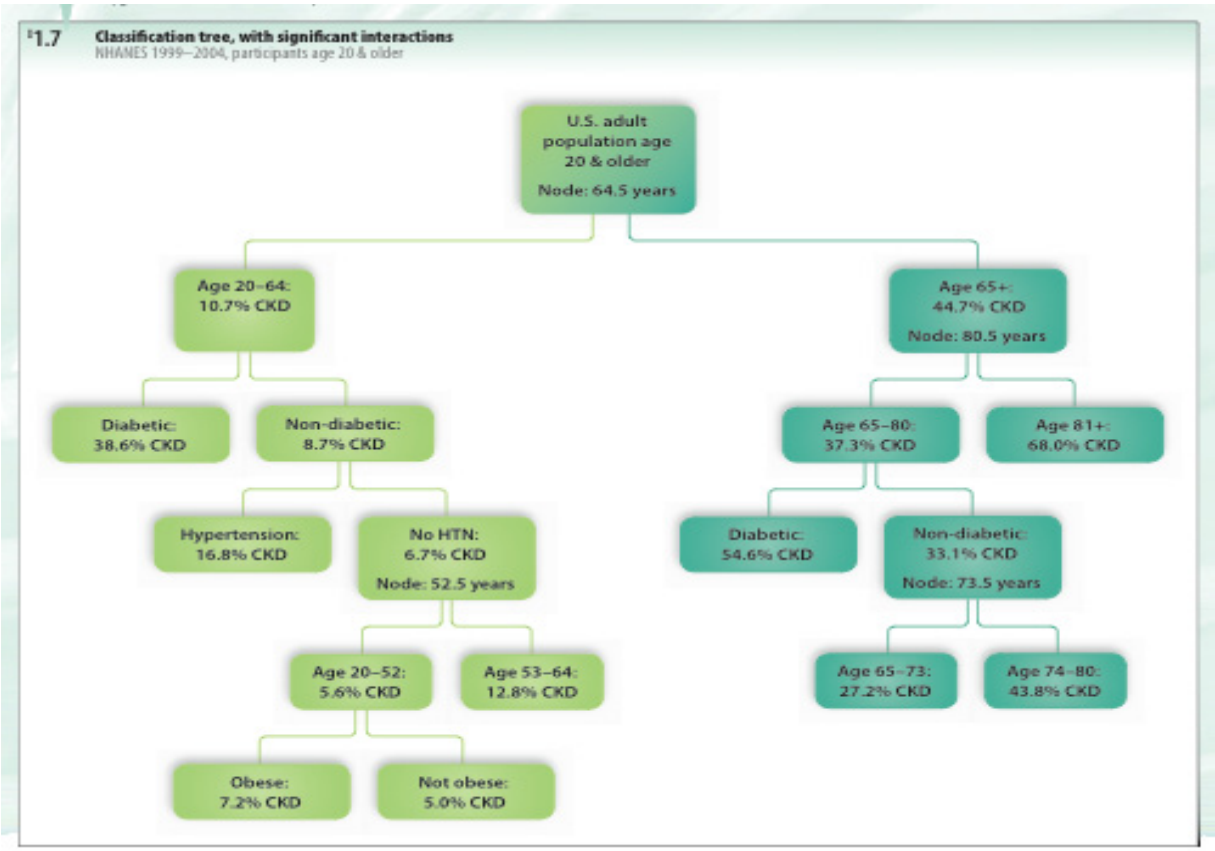


Figure 1. Prevalence of CKD in U.S. adults age 20 and older as a function of age, diabetes, hypertension, and obesity (USRDS Annual Data Report, 2008)[5]

Monitoring CKD

Because CKD in stages 1-3 is usually asymptomatic, monitoring these CKD patients for worsening function or damage is only possible with laboratory testing (i.e., measures to estimate GFR, albuminuria). Yet, there is little evidence regarding the benefits, harms, and optimal frequency of monitoring kidney function or damage in these individuals. Conceptually, monitoring of CKD may be beneficial only if it prompts intervention that improves clinical outcomes compared to less frequent monitoring or no monitoring. We currently are unaware of any recommendations for how frequently estimated GFR or albuminuria should be measured in those with CKD. The U.K. National Health Service (NHS) National Institute for Health and Clinical Excellence (NICE) guidelines suggest "more frequent monitoring" in CKD patients with worsening kidney function and a "relaxed frequency" of estimated GFR measurements in patients with stable kidney function.[20]

Treatment of CKD

In the majority of patients treated for non-primary kidney disease, treatment is not directed specifically at the CKD, but at the associated underlying conditions or cardiovascular risk factors, such as hypertension or diabetes,[21] with therapeutic goals for these conditions sometimes set lower for CKD patients than for non-CKD patients.[22] It has been suggested that medications such as angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) may be directed specifically towards treatment of CKD. However, whether their impact on CKD (e.g. on incident stage 4 CKD or ESRD, or as estimated by improvement in albuminuria[23]), is independent of their blood pressure lowering effect is not clear.[24] Other nonspecific therapies for CKD may include drug dosage adjustment, avoidance of potential nephrotoxins, and, in later stages of CKD, treatment of complications associated with CKD, such as anemia and bone and mineral disorders.

Multiple treatment strategies will be considered for their impact on clinical outcomes within CKD patients in the context of the current review, including treatments targeted at albuminuria reduction, blood pressure control, glycemic control, cholesterol control, smoking cessation, and/or obesity treatment. When possible it will be noted whether CKD was identified through screening or usual care. In addition, this review will consider the impact on clinical outcomes in CKD patients of treatment with individual medications or medication classes, including the following:

- Angiotensin converting enzyme inhibitors (ACEI)
- Angiotensin receptor blockers (ARB)
- Calcium Channel Blockers (CCB)
- Aldosterone antagonists
- Alpha Blockers
- Beta Blockers
- Loop Diuretics
- Thiazide and Related Diuretics
- Insulin
- Sulfonylureas
- Thiazolidinediones
- Biguanides (Metformin)
- HMG CoA-reductase inhibitors (Statins)
- Bile Acid Sequestrants
- Cholsterol Absorption Inhibitors (Ezetimibe)
- Anorexiants
- Lipase Inhibitors

Note that due to space constraints, U.S. Food & Drug Administration (FDA) status, indications, and warnings for these medications are included in a separate document.

II. The Key Questions

Public comments received on the posted key questions and additional feedback received during and after the first Technical Expert Panel (TEP) conference call were used to revise the key questions as follows:

- We clarified the CKD definition, both to be consistent with that established by K/DOQI and to include incorporation of just updated recommendations from KDIGO on staging, substaging CKD stage 3, and incorporation of albuminuria level at every GFR level.
- We clarified what we meant in referring to the "increased (or average) risk screening populations.
- We clarified that we meant clinically diagnosed CKD to refer to CKD diagnosed as part of routine care, which often occurs incidentally.
- We eliminated our attempt to categorize all CKD treatments into those which were renal-specific and those which were for vascular disease or vascular risk factors.
- We added evaluation of screening test properties to the project scope, specifically regarding their accuracy and reliability.
- We more precisely defined potential renal outcomes, while maintaining that there remains a distinction between renal outcomes that may be considered "clinical outcomes" and those considered "intermediate outcomes." We did not subdivide intermediate renal outcomes into surrogate outcomes and intermediate outcomes of greater importance as suggested by one reviewer.
- We expanded and made the list of potential harms possibly associated with screening, monitoring, and/or treatment more specific.

KEY QUESTION 1:
In asymptomatic adults with or without recognized risk factors for chronic kidney disease (CKD) incidence, progression or complications, what direct evidence is there that systematic CKD screening improves clinical outcomes?

- In asymptomatic adults with or without risk factors for CKD incidence, progression or complications, what is the accuracy and reliability of CKD screening and the prevalence of CKD identifiable by screening?
- Does initiating treatment for CKD as a result of systematic screening improve clinical outcomes compared to treatment initiated after incidental CKD diagnosis during routine clinical practice?
- How do patient factors and CKD screening thresholds modify the yield of CKD screening and its association with clinical benefits?

KEY QUESTION 2:
What harms result from systematic CKD screening in asymptomatic adults with or without recognized risk factors for CKD incidence, progression or complications?

- How do patient factors and CKD screening thresholds modify the association of CKD screening with harms?

- **Population(s):**
  - Asymptomatic adults (≥18 years) not known to have CKD:
    - Unknown GFR or last measured or estimated GFR ≥ 60 ml/min/1.73 m^2 (e.g. based on creatinine or creatinine-based formulas or cystatin-C or cystatin-C based formulas), AND
    - Unknown urine albumin or last known urinary ACR < 30 mg/g or last known 24 hr urine albumin < 30 mg.
  - Patient factors that may increase risk for CKD incidence, worsening or complications, and that may impact likelihood of benefits and/or harms from screening, include existing vascular disease (e.g., coronary artery disease [CAD], peripheral arterial disease [PAD], cerebrovascular disease [CVD]), vascular risk factors (e.g., hypertension, diabetes, obesity, hyperlipidemia, smoking, male gender, older age), race/ethnicity, and history of acute kidney injury (AKI).
- **Interventions:**
  - Systematic screening (universal, targeted, or opportunistic, but not haphazard) using estimated GFR (e.g., creatinine or creatinine-based formulas, cystatin C or cystatin C-based formulas), albuminuria (e.g., urinary ACR or proteinuria). The focus will be on screening methods that are feasible within a primary care setting.
- **Comparators:**
  - Usual care without systematic screening, or an alternative screening regimen. Comparisons of screening vs. no screening, different screening intervals (e.g., "frequent" vs. "infrequent"), or different screening parameters will be eligible.
- **Outcomes for each question**
  Benefits
  - Clinical outcomes:
    - Reduced mortality
    - Reduced/delayed incidence of end-stage kidney disease (i.e., dialysis or transplantation, stage 5 CKD without dialysis or transplantation)
    - Reduced hospitalization for acute kidney injury (AKI)
    - Cardiovascular morbidity(e.g., myocardial infarction, congestive heart failure, stroke, other)
    - Physical functioning/well-being/activities of daily living (ADLs)
    - Measures of quality of life (QOL)

  - Will consider studies both in which these outcomes were primary or secondary outcomes
- Intermediate outcomes:
  - Delayed progression of CKD (e.g., incidence of stage 4 CKD, doubling of creatinine or halving of estimated GFR, incident macroalbuminuria)
  - Prevention of CKD complications (e.g., hypertension, anemia, hyperparathyroidism, hyperphosphatemia, vitamin D deficiency, hyperkalemia)

Possible Harms

- Misclassification/false positive diagnosis
- Unnecessary tests and associated effects, e.g., phlebotomy-associated bruising; possible discomfort, bleeding with need for transfusion, and infection associated with renal biopsy
- Increased visits to primary provider, increased referrals to specialists
- Anxiety associated with diagnostic label and evaluations, increased difficulty obtaining/keeping health insurance coverage
- Adverse effects associated with increased treatment, possibly including worsened estimated GFR, hyperkalemia, hypotension, cough, hospitalization for AKI, cardiovascular morbidity, other
- While increased costs to patient and health system also may be harms associated with CKD screening, these are considered beyond the scope of this report

- **Timing:**
  Clinical outcomes: ≥6 months
  - Harms: ≥ 6 months

- **Settings:**
  - Randomized controlled trials (RCTs) conducted in community-dwelling patients, e.g., primary care setting. In the absence of appropriate RCTs, large population-representative cohort studies may be used to provide evidence on the yield of screening and contribute partial, indirect evidence on the benefit and harms of screening.

KEY QUESTION 3:
Among adults with CKD stages 1-3, whether detected by systematic screening or as part of routine care, what direct evidence is there that monitoring for worsening kidney function and/or kidney damage improves clinical outcomes?

- How do patient factors, CKD severity/stage, and CKD monitoring intervals modify the association of CKD monitoring with clinical benefits?

KEY QUESTION 4:
Among adults with CKD stages 1-3, whether detected by systematic screening or as part of routine care, what harms result from monitoring for worsening kidney function/kidney damage?

- How do patient factors, CKD severity/stage, and CKD monitoring intervals modify the association of CKD monitoring with harms?
- **Population(s):**
  - Adults (≥ 18 years) with CKD stages 1-3. In addition to overall evaluation of this population, we will consider separate evaluations by CKD stage, including further subdivision of stage 3 CKD into substages 3a (GFR 45-59 mL/min/1.73 m^2) and 3b (GFR 30-44 mL/min/1.73 m^2).
  - Patient factors that may increase risk for CKD incidence, worsening or complications, and that may impact likelihood of benefits and/or harms from monitoring, include existing vascular disease (e.g., CAD, PAD, CVD), vascular risk factors (e.g., hypertension, diabetes, obesity, hyperlipidemia, smoking, male gender, older age), race/ethnicity, and history of acute kidney injury (AKI).
- **Interventions:**
  - Monitoring with measures of estimated GFR (creatinine or creatinine-based formulas, cystatin C or cystatin C-based formulas), albuminuria (e.g., urinary ACR) and/or proteinuria. The focus will be on monitoring methods that are feasible within a primary care setting.
- **Comparators:**
  - Usual care without monitoring, an alternative monitoring regimen. Comparisons of monitoring vs. no monitoring, different monitoring intervals (e.g., "frequent" vs. "infrequent"), or different monitoring parameters will be eligible.
- **Outcomes for each question**
  Benefits
  - Clinical outcomes:
    - Reduced mortality
    - Reduced/delayed incidence of end-stage kidney disease (i.e., dialysis or transplantation, stage 5 CKD without dialysis or transplantation)
    - Reduced hospitalization for acute kidney injury (AKI)
    - Cardiovascular morbidity (e.g., myocardial infarction, congestive heart failure, stroke, other)
    - Physical functioning/well-being/activities of daily living (ADLs)
    - Measures of quality of life (QOL)
    - Will consider studies both in which these outcomes were primary or secondary outcomes
  - Intermediate outcomes:

  - Delayed progression of CKD (e.g., incidence of stage 4 CKD, doubling of creatinine or halving of estimated GFR, incident macroalbuminuria)
  - Prevention of CKD complications (e.g., hypertension, anemia, hyperparathyroidism, hyperphosphatemia, vitamin D deficiency, hyperkalemia)

Possible Harms

- Misclassification of CKD severity
- Unnecessary tests and associated effects, e.g., phlebotomy-associated bruising; possible discomfort, bleeding with need for transfusion, and infection associated with renal biopsy
- Increased visits to primary provider, increased referrals to specialists
- Anxiety or other important psychological harms associated with diagnostic label and evaluations, increased difficulty obtaining/keeping health insurance coverage
- Adverse effects associated with increased treatment, possibly including worsened estimated GFR, hyperkalemia, hypotension, cough, hospitalization for AKI, cardiovascular morbidity, other
- While increased costs to patient and health system also may be harms associated with CKD monitoring, these are considered beyond the scope of this report

- **Timing:**
  - Clinical outcomes: ≥6 months
  - Harms: ≥ 6 months
- **Settings:**
  - Randomized controlled trials conducted in community-dwelling patients, e.g., primary care setting.

KEY QUESTION 5:
Among adults with CKD stages 1-3, whether detected by systematic screening or as part of routine care, what direct evidence is there that treatment improves clinical outcomes?

- Does the presence of CKD modify the likelihood of improvement in clinical outcomes associated with treatment of vascular disease or vascular risk factors?
- Among adults with CKD, what patient factors modify the association of specific treatments with improved clinical outcomes?

KEY QUESTION 6:
Among adults with CKD stages 1-3, whether detected by systematic screening or as part of routine care, what harms result from treatment?

- Does the presence of CKD modify the likelihood of harms associated with treatment of vascular disease or of vascular risk factors?
- How do patient factors and CKD severity/stage modify the association of CKD treatment with harms?

- **Population(s):**
  - Adults (≥ 18 years) with CKD stages 1-3. In addition to overall evaluation of this population, we will consider separate evaluations by CKD stage, including further subdivision of stage 3 CKD into substages 3a (GFR 45-59 mL/min/1.73 m^2) and 3b (GFR 30-44 mL/min/1.73 m^2).
  - Patient factors that may increase risk for CKD incidence, worsening or complications, and that may impact likelihood of benefits and/or harms from treatment, include existing vascular disease (e.g., CAD, PAD, CVD), vascular risk factors (e.g., hypertension, diabetes, obesity, hyperlipidemia, smoking, male gender, older age), and race/ethnicity, and history of acute kidney injury (AKI).

- **Interventions:**
  - Blood pressure control
  - Angiotensin converting enzyme inhibitors (ACEI)
  - Angiotensin receptor blockers (ARB)
  - ACEI/ARB combination
  - Aldosterone antagonists
  - Other classes of antihypertensive medications (e.g,. calcium channel blockers, beta blockers, loop diuretics, thiazide diuretics, alpha blockers)
  - Glycemic control
  - Individual classes of diabetes medications (e.g., insulin, sulfonylureas, thiazolidinediones, biguanides)
  - Lipid control
  - Individual classes of lipid control medications (e.g., statins, bile acid sequestrants)
  - Low protein diets
  - Nephrology specialist referral
  - Gadolidum avoidance
  - NSAID avoidance
  - Imaging contrast agent avoidance
  - Obesity treatment, including anorexiants and/or behavioral interventions
  - Smoking cessation
  - Comparison of individual active treatments (whether high or low dose, or tight control vs. less tight control) vs. placebo, vs. each other, and vs. combinations

will be eligible.

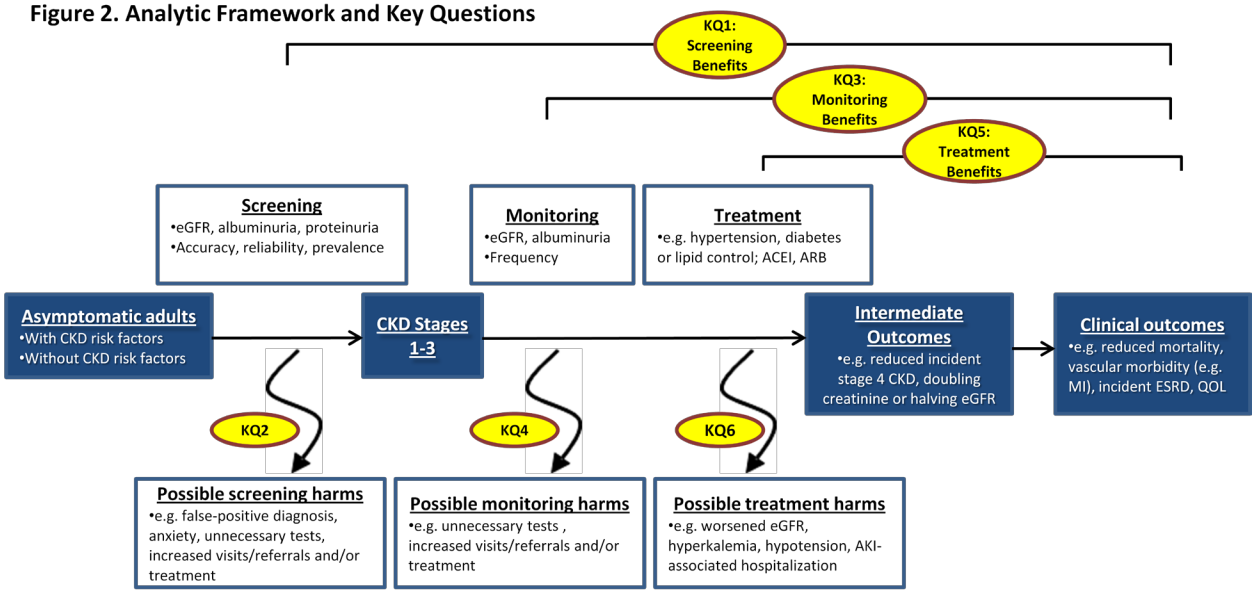
- **Comparators:**
  - Placebo, usual care, or active control
- **Outcomes for each question**

  Benefits
  - Clinical outcomes:
    - Reduced mortality
    - Reduced/delayed incidence of end-stage kidney disease (i.e., dialysis or transplantation, stage 5 CKD without dialysis or transplantation)
    - Reduced hospitalization for acute kidney injury (AKI)
    - Cardiovascular morbidity(e.g., myocardial infarction, congestive heart failure, stroke, other)
    - Physical functioning/well-being/activities of daily living (ADLs)
    - Measures of quality of life (QOL)
    - Will consider studies both in which these outcomes were primary or secondary outcomes, acknowledging this difference
  - Intermediate outcomes:
    - Delayed progression of CKD (e.g., incidence of stage 4 CKD, doubling of creatinine or halving of eGFR, incident macroalbuminuria)
    - Prevention of CKD complications (e.g., hypertension, anemia, hyperparathyroidism, hyperphosphatemia, vitamin D deficiency, hyperkalemia)

  Possible Harms
  - Unnecessary tests and associated effects, e.g., phlebotomy-associated bruising; possible discomfort, bleeding with need for transfusion, and infection associated with renal biopsy
  - Increased visits to primary provider, increased referrals to specialists
  - Side effects associated with increased treatment, possibly including worsened eGFR, hyperkalemia, hypotension, cough, hospitalization for AKI, cardiovascular morbidity, other
  - While increased costs to patient and health system also may be harms associated with CKD treatment, these are considered beyond the scope of this report
- **Timing:**
  - Clinical outcomes: ≥ 6 months
  - Harms: ≥ 6 months
- **Settings:**
  - Randomized controlled trials conducted in community-dwelling patients, e.g., primary care setting.

III. Analytic Framework

Figure 2. Analytic Framework and Key Questions



KQ1: In asymptomatic adults with or without recognized risk factors for chronic kidney disease (CKD) incidence, progression or complications, what direct evidence is there that systematic CKD screening improves clinical outcomes?
KQ2: What harms result from systematic CKD screening in asymptomatic adults with or without recognized risk factors for CKD incidence, progression or complications?
KQ3: Among adults with CKD stages 1-3, whether detected by systematic screening or as part of routine care, what direct evidence is there that monitoring for worsening kidney function and/or kidney damage improves clinical outcomes?
KQ4: Among adults with CKD stages 1-3, whether detected by systematic screening or as part of routine care, what harms result from monitoring for worsening kidney function/kidney damage?
KQ5: Among adults with CKD stages 1-3, whether detected by systematic screening or as part of routine care, what direct evidence is there that treatment improves clinical outcomes?
KQ6: Among adults with CKD stages 1-3, whether detected by systematic screening or as part of routine care, what harms result from treatment?

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

Overall: We will include studies that enrolled an adult population (18 years of age and older) and were published since 1985 and in the English language. As justification for the proposed language restriction, evidence suggests that for systematic reviews of conventional medicine, as are being evaluated in the present review, including only English language trials should not bias estimates of the effectiveness of the interventions.[25] Only full articles or dissertations will be included. Systematic reviews will be included if the research question is considered relevant as outlined in the chapter titled "Finding Evidence" in the Methods Guide.[26] Relevant grey literature, e.g. as identified from scientific information packets submitted to pharmaceutical companies,

also may be included. We may contact authors to obtain more information about unreported outcomes or ambiguous data.

Screening Questions: For the screening questions (Key Questions 1 and 2), we will include studies that enroll adults with or without recognized risk factors for CKD, without known CKD, who were systematically screened for CKD. We will include randomized (RCT) or controlled (CCT) clinical trials designed to assess the direct impact of screening on clinical outcomes and harms. If no or few RCTs or CCTs are identified, we will consider including large observational studies. We will exclude RCT or CCT with a sample size of less than 100 participants (total enrollment) and those with a follow-up duration measured from initial screening of less than 6 months. We believe that studies with smaller sample sizes and/or shorter follow-up duration would have extremely low power to identify clinically relevant outcome measures, and thus almost certainly would have been designed to assess only intermediate/surrogate outcomes.

Monitoring Questions: For the monitoring questions (Key Questions 3 and 4), we will include studies that enroll adults with CKD stages 1-3 who were systematically monitored following diagnosis for the purpose of following CKD disease progression and/or directing later CKD-related management decisions. We will include RCTs or CCTs that assess the direct impact of monitoring on clinical outcomes and harms. If no RCTs or CCTs are identified, we will consider including large observational studies. Studies that compare monitoring with no monitoring, different monitoring intervals, or different monitoring parameters will be included. We will exclude studies with a sample size of less than 50 participants (total enrollment) and those with a follow-up duration measured from time of study enrollment of less than 6 months.

Treatment Questions: For the treatment questions (Key Questions 5 and 6), we will include studies that enroll adults with CKD stages 1-3. Treatments may be CKD-specific or non-specific. We will include RCTs or CCTs that compare active treatments with placebo, with usual care, or with each other (including different dose levels, tight control vs. less tight control, and combinations of medications) and report clinical outcomes or harms. We will exclude studies with a sample size less than 50 participants (total enrollment across groups) and follow-up of less than 6 months.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions.

We will search the MEDLINE database as well as the Cochrane Database of Systematic Reviews. We developed separate literature search strategies for the three areas of interest: screening, monitoring, and treatment. We will use search strings we developed and tested to identify RCTs or CCTs. If we do not find sufficient evidence from RCTs and CCTs, we will modify the screening and monitoring searches to identify relevant, large observational studies.

For the screening search, we will search for studies pertaining to mass screening or early diagnosis and kidney disease. For the monitoring search, we will search for studies pertaining to monitoring or disease progression and kidney disease. For the treatment search, we will search for studies pertaining to both CKD specific and non-specific treatments and kidney disease.

Abstracts from studies identified in the electronic literature searches, during the public comment phase, or from TEP members, will be triaged for potential eligibility according to pre-established inclusion/exclusion criteria. If no abstract is available electronically, the full text of the article will be obtained for this review. To ensure consistency, all abstract reviewers will attend a training session where the inclusion and exclusion criteria will be presented and discussed. All abstracts that appear eligible will be pulled for full article review, while if the initial reviewer is uncertain about eligibility, one of the physician project leads will review the abstract (or article) and make a final decision about inclusion or exclusion. All abstracts for which eligibility remains uncertain after this additional review will be pulled for full article review. We will randomly select a 10% sample of all abstracts for repeat review by one of the physician project leads. If it appears that errors are being made in the initial abstraction, either in inclusion or exclusion, additional training will be provided for the abstractors, and potentially 100% of abstracts will be reviewed twice. In the abstract review process, we will err on the side of inclusion rather than exclusion. Reasons for exclusion will be tallied and documented in the final report.

The initial literature searches will be repeated in November 2010. We will apply the original inclusion/exclusion criteria to studies identified in the updated search as well as to articles suggested for inclusion during the public and peer review phases. A detailed search strategy appears in Appendix A.

C. Data Abstraction and Data Management

Separate data extraction forms will be developed for screening, monitoring, and treatment studies. The forms will be designed to capture relevant information from each study about the patients, interventions, comparators, outcomes, timing, and settings as well as the quality of the study.

Each study will be extracted by a trained clinician or research assistant. A second clinician or research assistant will confirm the abstracted information by comparing the abstracted information with the original article. Similar to the abstract review process, reasons for exclusion of articles at the extraction phase will be documented in the full report.

The study search coordinator and the project manager will track the status of each article identified in the search process. A spreadsheet will be created and updated to include, for each article retrieved, the names of the study team members responsible for

initial abstraction and verification along with the completion dates for each step. Reviewers will be monitored weekly for progress in completing the article reviews.

Data entry will be on-going during the abstraction process. The project manager and project director will verify data entry. In addition, the project staff will meet periodically to discuss progress to date (abstraction and data entry), results, studies that have been difficult to interpret or abstract, and any other questions. All project staff will be asked to communicate via e-mail any questions or concerns that arise during the article abstracting and data entry process.

Evidence tables will be organized by key question. Draft summary tables and figures to be included in the results section of the report will be discussed at project staff meetings and with TEP members.

D. Assessment of Methodological Quality of Individual Studies

The quality of treatment studies included in the review will be assessed according to recommendations presented in Chapter 6 the Methods Guide chapter "Assessing the Quality and Applicability of Included Studies."[26] As suggested in the guide, we will examine (as applicable based on the study design) subject recruitment, randomization, allocation concealment, sample size, similarity of groups at baseline, the extent to which valid outcomes were described and assessed, blinding, the use of intention-to-treat analyses, loss to follow-up, and conflict of interest. Studies will be rated as Good (low risk of bias), Fair, or Poor (high risk of bias) as described in the Methods Guide. The quality of studies of diagnostic tests included in the review will be assessed using the QUADAS (quality assessment of diagnostic accuracy studies) tool.[27,28]

E. Data Synthesis

We will present results in evidence and summary tables organized by key question. Results will be analyzed qualitatively and quantitatively, as appropriate. Summary calculations may include weighted averages, odds ratios with 95% confidence intervals, risk differences, and numbers needed to treat. Results for the key questions will be examined overall and, where possible, stratified by patient CKD risk factors, baseline CKD severity, and other factors.

F. Grading the Evidence for Each Key Question

The strength of the evidence for each key question will be graded according to the approach outlined by Owens et al.[29] This system involves consideration of four major, required domains: risk of bias, consistency, directness, and precision. Additional domains may be considered, when appropriate. The strength of the evidence is graded as high, moderate, low, or insufficient.

V. References

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VI. Definition of Terms

All relevant terms have been defined above in the text.

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

NOTE: The following protocol elements are standard procedures for all protocols.

VIII. Review of Key Questions

For Comparative Effectiveness reviews (CERs) the key questions were posted for public comment and finalized after review of the comments. For other systematic reviews, key questions submitted by partners are reviewed and refined as needed by the EPC and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed.

IX. Technical Expert Panel (TEP)

A TEP panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. The TEP provides information to the EPC to identify literature search strategies, review the draft report and recommend approaches to specific issues as requested by the EPC. The TEP does not do analysis of any kind nor contribute to the writing of the report.

X. Peer Review

Approximately five experts in the field will be asked to peer review the draft report and provide comments. The peer reviewer may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. On some specific reports such as reports requested by the Office of Medical Applications of Research, National Institutes of Health there may be other rules that apply regarding participation in the peer review process. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

It is our policy not to release the names of the Peer reviewers or TEP panel members until the report is published so that they can maintain their objectivity during the review process.