Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Chronic Kidney Disease Stages 1-3: Screening, Monitoring, and Treatment*

Draft review available for public comment from March 9, 2011 to April 6, 2011.

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Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Abbott Laboratories	Executive Summary	**Executive Summary** 1. In the final report, Abbott strongly recommends additional clarification differentiating evidence reviewed regarding benefits and harms for people with recognized risk factors versus people without recognized risk factors. 2. In addition, we strongly recommend differentiation in evidence for high risk populations regarding monitoring and treatment for Stage 3 CKD versus Stages 1 and 2 CKD. 3. Based on NHANES data, prevalence of CKD stages 1-3 is 41.1 percent in patients with diabetes, 27.8 percent in patients with hypertension, and 39.3 percent in those with cardiovascular disease. However, per the report, current data suggests that most individuals with CKD stages 1-3 are not clinically recognized to have this diagnosis. As the objective of this report is to inform patient care decisions of primary care physicians and to provide background to material to assist groups developing clinical practice recommendations, we are concerned that the Structured Abstract and the Executive Summary as written could potentially inadvertently mislead primary care physicians and other healthcare professionals to discontinue current clinical practice guidelines for CKD screening, staging, treatment and monitoring for high risk populations which could result in unintended consequences. 4. For example, we believe the Structured Abstract inadequately differentiates evidence showing that screening and monitoring people with diabetes for albuminuria and eGFR has successfully identified those who are at high risk for CKD progression and for cardiovascular complications. Diabetic nephropathy is a rapidly growing problem and its attendant association with cardiovascular and renal complications emphasizes the need to apply treatments that reduce proteinuria and slow CKD progression through attenuation of the renin-angiotensin system (RAS). These findings are based on randomized controlled trials (RENAAL, 2001, IDNT, 2001) as well as on large, well designed observational studies (Lancet, 2010). Specific and evidenced based guidelines for screening, monitoring and treatment have guided many primary care and specialist physicians in the proper management of patients with diabetic nephropathy over the last ten years. As such, we believe it is important that this report clearly highlight and recognize the accepted standard of care for this population. Such activities have aided physicians in making decisions regarding when to start	**Executive Summary** 1. In the revised report, additional emphasis was made on the effect of different patient risk factors on benefits and risks of screening, monitoring and treatment. Subgroup results were presented in the body of the report where they could be determined. The report notes the substantial limitations in available subgroup data and suggested this as an important area for future research. 2. In the revised report, we more explicitly noted the limitations in data available to differentiate the impact of monitoring and treatment by CKD stage. We also describe this as an important area of future research. 3. We appreciate these comments. It was the aim of the report to perform an evidence synthesis in which we systematically reviewed, analyzed and accurately interpreted the data regarding screening for, and monitoring and treatment of CKD stages 1-3. We sought to be transparent in our methodology, including stating that our threshold for benefit was improvement in clinical outcomes. Further, while being aware of the context for the key clinical questions to be addressed by our evidence synthesis, we were not to a priori constrain our report to be consistent with existing guidelines regardless of our findings. 4. This report acknowledges existing CKD management guidelines in its background text. We've described the general approach we took to complete this evidence synthesis in answer #3 above, so won't repeat that here. In the revised report, we sought to more clearly distinguish where the evidence addressing screening, monitoring and treatment may differ based on patient subgroup (e.g. diabetes). The report also discusses the

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		RAS inhibitors and diuretics, how to maximize RAS inhibition through dose titration, and who would be suitable candidates for inclusion into ongoing randomized clinical trials that are investigating new treatments for diabetic nephropathy. By grouping diabetes with other less well researched populations at risk for CKD, the message is lost that there is evidence showing that diabetic patients benefit from screening and monitoring according to current guidelines; e.g. ADA, KDOQI, and KDIGO. 5. Abbott also believes that the report's grouping of CKD Stages 1-3 together for discussion of screening and monitoring lacks needed guidance for monitoring and treating high risk populations. Based on a recent large observational study of patients with CKD (Lancet, 2010), those with Stage 3 CKD showed a more rapid progression to ESRD and more cardiovascular events than earlier stages, particularly if they had coincident macroalbuminuria. While these data do not represent results from a randomized controlled trial, this study was included in this review and the extremely large size of the study enabled the recognition that macroalbuminuria and Stage 3 CKD were independent risk factors for CKD progression and cardiovascular complications. 6. In summary, Abbott strongly recommends that the Structured Abstract and Executive Summary should include Results and Conclusions that more specifically reflect the totality of clinical research in diabetic nephropathy which has led to current standard of care. The studies were included in this report; however, we recommend editing to prominently differentiate the evidence regarding benefit and harms for high risk populations so that appropriate recommendations about screening and monitoring patients with diabetes is more prominently displayed. These findings not only justify screening, as a prelude to kidney-specific therapy (renin-angiotensin system blockers) and monitoring of that therapy, but form the clinical practice recommendations published by national kidney and diabetic organizations. (KDOQI). **Structured Abstract: Results Section** 1. Abbott disagrees with the statement that "There was no direct evidence regarding the benefits or harms of systematic screening for CKD. " There was evidence regarding the benefits or harms of systematic screening for CKD in high risk subgroups including diabetic patients and non-diabetic patients. Screening with creatinine-based glomerular filtration rate (GFR) and urinary albumin excretion (urine albumin-	limitations of available data for specific risk groups. 5. As stated above, in the revised report, additional effort has been made to describe the impact of CKD stage (e.g., 1 versus 2 versus 3) on the benefits and risks of CKD screening, monitoring and treatment. The revised report also discusses the limitations of available data for different CKD stages within the larger CKD stages 1-3 group. 6. As stated above, in the revised report additional effort has been made to describe the impact of patient characteristics on the benefits and risks of CKD screening, monitoring and treatment. The report also discusses the limitations of available data for specific risk groups. **Structured Abstract: Results Section** 1. We stand by our statements that there is at present no direct evidence regarding the benefits or harms of systematic screening for CKD, and that there is no direct evidence regarding the benefits and harms monitoring patients with CKD stages 1-3 for progression of their CKD. Direct evidence addressing screening would require an RCT that randomized participants to systematic CKD screening versus an alternative regimen (e.g. usual care) and reported clinical outcomes (e.g. death, ESRD, MI) by assigned group. However, there is no RCT that is able to make this direct link. Similarly, there is no RCT that is able to make such a direct link regarding monitoring. The available evidence to address the screening and monitoring questions is indirect in that multiple studies collectively must be considered to make a link between screening or monitoring and clinical outcomes. While there is very strong evidence that both eGFR and albuminuria are prognostic markers for bad outcomes,

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		creatinine ratio) tests appears sensitive for detection of kidney abnormalities that may reflect undiagnosed CKD. For example, screening for macroalbuminuria in diabetic patients and for eGFR in non-diabetic, high-risk groups (e.g. hypertension, old age) will produce a high yield, however, it may be associated with a non-negligible false positive rate in non-diabetic populations. While there was no direct evidence regarding the benefits or harms of systematic monitoring of patients with CKD stages 1 and 2 for worsening kidney function/damage, there was evidence from large observational studies showing that patients with Stage 3 CKD had a more rapid progression to ESRD and more cardiovascular events than earlier stages, particularly if there was coincident macroalbuminuria. Targeting subgroups at risk for worsening CKD severity will increase monitoring yield, though GFR testing already is common in usual care, and sensitivity and false positive rates for detection of significant decline (e.g., CKD stage change) is unknown. **Structured Abstract: Conclusions Section** 1. There was evidence regarding the benefits or harms of screening with diabetes for macroalbuminuria to determine the need for kidney specific therapy to slow CKD progression. No direct data currently exist regarding benefits and harms of screening for or monitoring of CKD in non-diabetic populations. Studies to determine the actual sensitivity and false-positive rates of CKD screening and monitoring, and updated modeling studies incorporating estimated GFR, albuminuria, and testing related harms would be informative. ACEI, ARB, and beta blockers improve important clinical outcomes in subgroups of CKD patients, with evidence suggesting treatments may be more effective in patients with more advanced CKD. Statins also lower risk of important health outcomes in CKD patients. New, well-designed RCTs of other treatments, and combination treatments should inform clinical practice. **Executive Summary: CKD Screening Section** 1. It is clear that screening diabetic patients for macroalbuminuria, at any stage of CKD, identifies patients that would benefit from kidney-specific therapy to slow CKD progression. 2. It is unclear whether screening non-diabetic populations for CKD is beneficial. In the strictest sense, for screening in non-diabetic patients to be beneficial, it must improve important clinical outcomes (while limiting harms) for individuals	there is not direct RCT evidence that intervening on patients with these markers improves clinically important outcomes. **Structured Abstract: Conclusions Section** 1. We appreciate these comments. **Executive Summary: CKD Screening Section** 1. As noted in the revised report, RCT data suggest that patients with diabetes, hypertension and proteinuria (macroalbuminuria) randomized to ACEI or ARB have reduced risk of ESRD compared to placebo. That isn't quite the same as saying that screening patients who have both diabetes and hypertension for proteinuria (macroalbuminuria) benefits patients. It doesn't mean that screening these patients for proteinuria (macroalbuminuria) is not beneficial, but there isn't a direct link that goes all the way from screening to outcomes in these patients. We have tried be clear on this point in the revised report. 2. We appreciate these comments. 3. As stated above, in the revised report, additional effort was made to highlight possible benefits and risks of CKD screening in specific risk groups. The report also discusses the limitations of available data for specific risk groups. 4. We appreciate these comments. **Executive Summary (page ES-6): Results Section** 1. As stated above, in the revised report, additional effort was made to highlight possible benefits and risks of CKD screening in specific risk groups, including diabetes. The report also discusses the limitations of available data for specific risk groups. 2. We appreciate these comments, but do not entirely agree with them. We believe that the absence of direct RCT evidence regarding screening and monitoring

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		diagnosed with CKD through screening compared to outcomes of treatment started at a later time or stage. 3. The effect of screening on treatment outcomes should be examined for specific risk groups as well as for the broader population. 4. A further intricacy is that potential CKD treatments may be indicated for conditions associated with CKD. Therefore, demonstration of benefit from CKD screening in non-diabetic patients may require further evidence: First, that treatment benefits CKD populations with no other indication for their use; and second that, among patients with another indication, those with CKD have a relatively greater benefit from treatment than those without CKD. **Executive Summary (page ES-6): Results Section** 1. Abbott strongly recommends that the Executive Summary should include Results that more specifically reflect the totality of clinical research in diabetic nephropathy which has led to current standard of care. The studies were included in this report; however, we recommend editing this section to prominently differentiate the evidence regarding benefit and harms for high risk populations so that appropriate recommendations about screening and monitoring patients with diabetes is more prominently displayed. 2. We recommend that the Results should include the following key points: <u>a. Screening Benefits and Harms</u> -There is sufficient evidence that systematic screening in diabetic patients improved clinical outcomes. -There is insufficient evidence regarding whether systematic screening of non-diabetic adults for CKD improves clinical outcomes or increases harms. -There is indirect evidence that suggests benefits from CKD screening are more likely in populations at higher risk for CKD, its progression, its complications, and/or for whom RCT evidence suggests treatment benefit. Such non-diabetic populations may include older patients and those with hypertension, cardiovascular disease, or hyperlipidemia. <u>b. Monitoring Benefits and Harms</u> -There is sufficient evidence that systematic monitoring of diabetic patients with macroalbuminuria for worsening kidney function and/or damage improves clinical outcomes. -There is insufficient evidence regarding whether systematic monitoring of non-diabetic patients with CKD stages 1-3 for worsening kidney function and/or damage improves clinical	diabetic patients for CKD and assessing clinical outcomes plus limitations in relevant indirect evidence (e.g. uncertain test accuracy, uncertain screening and monitoring harms) makes it less clear whether CKD screening and monitoring in diabetics is beneficial in the manner expressed by the reviewer.

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		outcomes or increases harms. - There is indirect evidence to suggest that monitoring of stage 3 CKD for worsening of kidney function and/or damage will improve clinical outcomes. • Indirect evidence suggests that monitoring of patients with CKD stages 1-2 for worsening of kidney function and/or damage is feasible, but it is uncertain whether such monitoring will improve clinical outcomes. -There is indirect evidence to suggest that potential harms of monitoring include adverse effects from increased medication use and additional testing.	
Aysha Hasan	Executive Summary	1. No mention of auto immune diseases such as vasculitis?	1. We did not identify trials that reported a substantial prevalence of vasculitis or other auto immune diseases in their participants or that reported results for such subgroups.
Public reviewer patient	Executive Summary	1. I believe the research omitted an essential treatment option. Based on my experience as a CKD patient. instead of relying on medications to improve and/or halt the further worsening of the condition of the CKD patient the study should have included interviews with renal nutritionists to assess how effective changing the diets of CKD patients has been based on the CKD patients who have been referred to them for treatment. 2. I am a CKD patient; an individual at the National Kidney Foundation gave me the information and materials which enabled me to change my diet to conform to a diet lower in potassium, phosphorous, sodium and protein. I followed up on her suggestion that I get from the American Assoc. of Kidney Patients the AAKP Nutrition Counter - A Reference for the Kidney Patient. I became a member of the AAKP and befitted from reading information on their website and printed materials I receive as a member. I studied the materials she sent to me and the notes I took during our extended phone conversation. I demanded from the owner of my medical center that I immediately be referred to a renal nutritionist. As a result of taking the measures described above, my GFR rose from 37 to 51 in less than six months and has remained at that level and/or risen higher. I've discussed my experience with friends who have been on insulin for many years. None of them know the significance of their GFR results; their endocrinologists have never discussed it with them. At my repeated suggestion one woman got a copy of her lab test results and found out her GFR was 36. She got a referral to a	1. The report evaluated all eligible RCTs of dietary interventions versus control in patients with CKD stages 1-3 (or approximating these stages). The majority of these trials compared low protein versus usual protein diets. Results from these trials are reported both in the executive summary and in more detail in the body of the report. 2. We appreciate these comments on your experience. 3. We agree with this suggestion that future research is needed regarding the risks and benefits of dietary and other nonpharmacological interventions in patients with CKD stage 1-3. We have modified the future research section in the revised report accordingly.

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		renal nutritionist who instructed her on how she needs to change her diet and she is showing improvement. Other members of AAKP, either transplant donors, patients on dialysis and patients recovering from a kidney transplant have told me they were never told they needed to change their diet to prevent their condition from worsening. 3. I would hope that ongoing research includes more than medications as a treatment option; it should study how effective changing the diet of CKD patients is in improving their kidney function and/or preventing further worsening of the CKD patients condition. Some medications can have serious side effects for CKD patients, especially older patients; also the drugs could have dangerous interactions with medications that CKD patients are taking for other medical conditions. A change of diet can be beneficial for the CKD patient with no unpleasant or dangerous side effects and more economical for CKD patients and their insurers	
Andrew Levey	Executive Summary	My comments are limited to the Executive Summary (ES), but apply to the other sections from which the ES is derived. Overall, the report is clearly written and accurate. 1. Major omissions: Page ES-3. Reduction in risk for complications is not mentioned as a CKD treatment goal. Reducing CVD risk is inferred from treatment of underlying conditions such as diabetes and hypertension, and is well reviewed, but it would be appropriate to refer to this as reduction in risk for CVD complications. Other possible complications are not mentioned. a. Metabolic and endocrine complications, such as hyperparathyroidism and anemia. Since these are more common in CKD stage 4. Treatment guidelines exist, and it would be acceptable to state that these problems are largely handled by nephrologists and are beyond the scope of this work. b. Side-effects from medications and procedures, such as improper drugs dosage for the level of GFR and kidney toxicity from non-steroid anti-inflammatory drugs, iodine or gadolinium contrast procedures, phosphate based enemas for bowel procedures. Substantial effort in reducing errors is related to identifying improper use of drugs in patients with decreased GFR (CKD stage 3). This has achieved greater prominence since this question was nominated for review, but should either be mentioned as outside the scope of the review, or the review should be broadened to include it. While I suspect	1. We agree with the reviewer that reduction in risk of complications is an important CKD treatment goal. This is why we used impact on clinical outcomes, such as mortality, ESRD, MI, and other vascular outcomes as the criteria for judging the impact of CKD screening, monitoring and treatment. It is possible that we did not make this sufficiently explicit. We have sought to make this more clear in the revised report. 1.a. We agree with the reviewer that hyperparathyroidism and anemia are complications of CKD more common in CKD stage 4. In the revised report, we acknowledged that CKD stages 4-5 are beyond the scope of this report and that patients with this level of CKD are largely managed by nephrologists. 1.b. We agree with the reviewer that prevention of side-effects from medications and procedures is an important goal in CKD patients. We identified one RCT that compared a structured multidisciplinary effort to prevent such side-effects versus usual care. It did not find a significant difference in outcomes between treatment groups. We suggest this as an important

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		there are no clinical trials, most medication labels for drugs that are excreted by the kidneys contain information to adjust the drug dosage according to the level of kidney function, so failing to monitor the level of kidney function in patients with CKD prior to drug administration would be a major omission. 2. Page Page ES-10. Results. Key question 5. There is some data suggesting strict blood pressure control versus standard blood pressure control for patients with proteinuria. This has been reviewed in a recent article in Annals of Internal Medicine. This should be mentioned. 3. Minor correction: Page ES-2. "Kidney Disease: Improving Global Outcomes"	area of future research. 2. We thank the reviewer for alerting us to this recently published systematic review (Upadhyay A, Annals Intern Med 2011;154:541). The Annals review limited eligibility to studies published since July 2001, included both RCTs and observational studies, and included both clinical events and rate of eGFR decline as outcomes. Our report included studies published since 1985, was restricted to RCTs while excluding observational studies, and excluded rate of eGFR decline as an outcome. Our report included all RCTs included in the Annals review plus three others. We found no significant difference between standard and tight blood pressure control for any clinical outcome, which was consistent with the overall finding from the Annals review. We didn't perform subgroup analyses based on proteinuria. The limited evidence suggesting a possible benefit to tighter blood pressure control in the proteinuria subgroup in the Annals paper is derived primarily from the observational extensions of the MDRD and AASK trials. It was not observed in the trial portion of the three studies reviewed except for in one of three composite outcomes from the AASK trial and for the rate of eGFR decline from the MDRD trial. Given these results and the substantial heterogeneity in how proteinuria was defined between studies, we believe that these intriguing results should be considered at most hypothesis generating and one that may be evaluated in future RCTs. 3. We have corrected the error noted by this reviewer
Paul Smedberg American Society of Nephrology	Executive Summary	April 6, 2011 Agency for Healthcare Research and Quality Effective Healthcare Program RE: AHRQ Draft Comparative Effectiveness Review (CER) on Screening for and Management of Chronic Kidney Disease Stages 1-3 To Whom It May Concern: On behalf of the American Society of Nephrology (ASN), a not-for-	1. In the revised report, we made an effort to more explicitly distinguish between where there was evidence for a lack of an effect and where there was insufficient or a low strength of evidence.

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		profit organization of 11,000 physicians and scientists dedicated to promoting excellence in the care of patients with kidney disease, thank you for the opportunity to provide comment on the Agency for Healthcare Research and Quality (AHRQ) Draft Comparative Effectiveness Review (CER) on Screening for and Management of Chronic Kidney Disease Stages 1-3. ASN members are committed to providing the best possible care and want to help ensure that physicians have the information necessary to make the most appropriate decisions concerning screening for, monitoring of, and treatment of, chronic kidney disease (CKD) for their patients, regardless of age, gender, or race/ethnicity. CKD is a serious and growing public health threat. Most people with CKD are unaware they have the disease until the late stages, but when identified early, its progression can be slowed or halted. ASN supports AHRQ's efforts to address this issue through a draft CER, and appreciates that AHRQ took into account comments that ASN submitted in March 2010 as the agency was initiating work on the CER. ASN respectfully submits the following comments regarding the March 2011 draft CER on Screening for and Management of Chronic Kidney Disease Stages 1-3. 1. Lack of evidence on effectiveness of screening vs. Evidence that screening is ineffective The draft CER focuses on endpoints for end-stage renal disease (ESRD), cardiovascular disease (CVD), and all-cause mortality as the primary clinically meaningful outcomes, as these are the endpoints for most of the randomized clinical trials (RCTs) where screening benefit can be examined. A central theme of the draft CER is that insufficient evidence exists showing that screening for Stage 1-3 CKD would translate into effective interventions to improve outcomes. ASN wishes to clarify, however, that a lack of evidence is not the same as evidence that screening, or subsequent intervention, are not effective. For instance, investigators have reported that CKD patients have traditionally been excluded from clinical trials of coronary artery disease (Charytan et al., Kidney Int 2006; 70: 2021-30). In particular on page 25, the draft CER suggests a rather negative viewpoint of screening benefits. ASN suggests that this be tempered to reflect the difference between a lack of available evidence and evidence that screening is not effective. ASN recommends that this subtle but important perspective should be added on page 25, and throughout the report, as AHRQ finalizes the draft CER. 2. High-risk patients: Minority populations ASN is concerned	2. As stated above, in the revised report, additional effort was made to highlight possible benefits and risks of CKD screening in specific risk groups, including, among others, racial/ethnic minorities. Most notable, however, is the limitation in available data for these specific risk groups. 3. We agree that quality of life is an important patient-centered outcome. From the start (in the analytical model framing the project), we considered quality of life an important clinical outcome, we looked for quality of life outcomes data in our search for eligible articles, and we sought to identify such data for our data extraction. However, we did not identify eligible RCTs that reported quality of life outcomes data. In the revised report, we describe evaluation of CKD screening, monitoring and treatment on quality of life as an important area of future research. 4. In the revised report we more explicitly addressed the situation raised by the reviewer, regarding whether intensification of treatment improves outcomes, and whether this could be a justification for screening to identify CKD. In this context, we considered that indirect evidence for possible benefit from identifying could exist under two circumstances: (a) if benefit is associated with treatment to a lower target in patients with CKD than in those without CKD and the patient currently is between the two targets, or (b) if the patient is receiving one of several treatments that are associated with comparable benefit for the non-CKD indication, but is not receiving the treatment that is associated with greater benefits in the subset of patients who also have CKD. 5. We agree with the reviewer that direct GFR measurement is not performed in usual care, but rather it is estimated GFR

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		that the issue of patient race/ethnicity is relatively neglected in the draft CER. It is well-recognized that non-caucasian groups, particularly African-Americans and Latinos, have an elevated risk for developing ESRD. The risk of developing CKD and ESRD in these groups is likely not explained entirely by the higher prevalence of diabetes and hypertension in these populations.African-Americans, for example, are at disproportionate risk for developing Focal Segmental Glomerulosclerosis (FSGS) and primary glomerulopathy. ASN strongly suggests that AHRQ reconsider whether non-caucasians might benefit from screening—especially among non-caucasian patients who have a family history of kidney disease. ASN recognizes that insufficient data may exist regarding the benefits of screening in these subgroups, but recommends that more research be conducted in order to ensure the highest quality of care is available to patients of all races and ethnicities. 3. Relationship between early CKD and quality of life measures. A recent and growing body of literature reports on the association between early CKD and quality of life (QOL) measures, such as cognitive and physical function. [Please refer to work by M. Kurella-Tamura, K. Yaffe, S. Jassal, and others in recent years for cognitive function, and to results from the Dynamics of Health, Aging and Body Composition study (M. Odden and M. Shlipak) and the Nurses' Health Study (J. Lin and G. Curhan) for physical function.] These QOL outcomes represent an important public health issue in the aging U.S. population who are at risk for both CKD and QOL decline. While screening and intervention for early CKD on these QOL outcomes have yet to be demonstrated because awareness of this relationship has only recently been growing, ASN suggests that AHRQ should consider incorporating QOL outcomes besides those of ESRD, CVD, and all-cause mortality. 4. Effect of Screening on Treatment With regard to whether evidence exists that systematic screening or routine care that identifies CKD states 1-3 amongst adults leads to treatment that affects clinical outcomes, the authors state that there is no evidence that treating patients with greater doses of angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ACE/ARB) or beta blockers (BB) improve clinical outcomes. They therefore conclude that evidence for screening affecting treatment would be low. ASN suggests that AHRQ consider whether patients in the trials studied	that is calculated from measurement of plasma creatinine. This inaccuracy was corrected in the revised report. Further, the reviewer's clinical observation seems consistent with Medicare data reported by USRDS and included in the draft report. This data indicated annual urinary microalbumin testing in about 30 percent of diabetics and 4 percent of hypertensives, and annual serum creatinine testing in fewer than 20 percent of patients with either diabetes or hypertension. Though we did not find data on the frequency of testing in patients without CKD and without risk factors, our assumption is that it is lower still. We have tried to correct any language in the draft report that gives an impression otherwise. 6. We appreciate the reviewer comments and agree with the suggestion that incorporation of data from KEEP and other ongoing screening programs into simulation models would be a potential area of future research. We have added this suggestion to the section of the report on potential future research. 7. We agree with the reviewer suggestion and have added to the report several specific potential harms that we believe leaders of cohort screening studies like KEEP should be aware of and consider tracking.

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		were treated to pre-specified treatment goals (such as a specific blood pressure goal range). If patients in the studies were treated to goals, then screening might be useful in some cases—such as, for instance, for patients who are already under care for a given condition (e.g. high blood pressure). 5. Plasma creatinine measurement vs. Direct glomerular filtration rate meaurement The abstract of the draft CER states that "GFR testing is already common in usual care". ASN wishes to clarify that, it is plasma creatinine measurements, which in turn yield an estimated GFR (eGFR), that are common in usual care. Importantly, the eGFR is not a direct measurement of GFR, which the sentence as currently worded might imply. Furthermore, some primary care providers are strongly encouraged to not obtain "unnecessary" tests on otherwise healthy patients. Based on anecdotal feedback from members of ASN's CKD Advisory Group, relatively few patients receive plasma creatinine measurements or, perhaps more importantly, screening for microalbumin if there are no existing risk factors. As such, ASN suggests that AHRQ may wish to modify this sentence in the abstract to clarify the difference between plasma creatinine and eGFR measurements and to consider rephrasing the prevalence of such testing amongst patients with no existing risk factors. 6. Future Research ASN concurs with the principle outlined in the "Future Research" section that more investigation is necessary to fully understand the benefits and harms of screening for CKD. The "Future Research" section appropriately notes that the "most direct [research direction] would be to conduct a large-scale RCT of CKD screening plus treatment for confirmed diagnoses versus usual care… However, such an RCT likely would require tens of thousands of participants followed for a dozen or more years to have adequate power to evaluate final clinical outcomes. Such a study is not likely to be feasible." It also appropriately reviews cost-effective alternatives, such as prospective evaluations of the impact of Kidney Early Evaluation Program (KEEP) and other existing screening programs, which could provide some useful information without requiring a trial. In the future, these data could be used with simulation models to help inform policy decisions and future patient care recommendations. 7. ASN suggests that the draft CER specify the potential harms that leaders of large cohort screening studies, such as KEEP, should be aware of. For instance, a final CER could include	

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Joseph Vassalotti National Kidney Foundation, Inc.	Executive Summary	**Executive Summary** 1. Although the comparative effectiveness review concludes that there is insufficient evidence regarding whether systematic screening of adults for CKD improves clinical outcomes, some of the report's findings (quoted below) could be the basis for a different conclusion, e.g.: —Indirect evidence suggests benefits from CKD screening are more likely in populations at higher risk for CKD…Such populations may include older patients and those with hypertension, diabetes, cardiovascular disease, or hyperlipidemia.‖ —The natural course of CKD stages 1-3 is usually of slow worsening over years, but…with faster GFR decline in certain risk groups (e.g., diabetes, proteinuria, increased blood pressure, older age, obesity).‖ Finally, —evidence suggesting treatments may be more effective in patients with more advanced CKD.‖ The discrepancy could have been avoided if the evaluation of the benefits of screening and following individuals with CKD stage 3 had been considered separately from the benefits of identification and monitoring of individuals with earlier stages of CKD.	1. We appreciate the comments. In the revised report, additional effort has been made to describe the benefits and risks of monitoring and treatment in patients with different CKD stages within the larger category of stages 1-3. Additional effort has been made to consider how screening for different levels of CKD (e.g. macroalbuminuria, microalbuminuria, impaired eGFR, or some combination) may impact the benefits and risk of CKD screening, monitoring and treatment. The revised report also discusses the limitations of available data for different CKD stages within the larger CKD stages 1-3 group.
Peer Reviewer #5	Executive Summary	1. Page ES-1: Title: should also include the word 'monitoring' as that is one of the key areas for which detailed literature review was conducted. I suppose one could argue that management includes monitoring and treatment. It may be better explicitly stated, however as there are 3 areas of focus, namely screening, monitoring and treatment of early stage CKD. 2. Page E-1, first paragraph. The 'target audience' is preferably identified under a separate header. I think its very important that this document be identified as background material to assist groups developing clinical practice recommendations. 3. Page ES-2, under definition of CKD, toward the end, where the report of the KDIGO consensus conference is alluded to, it would be important to add the fact that the group recommended identification of the possible etiology of CKD in addition to the 2 points highlighted as bullet points. 4. Page ES-2, under epidemiology of CKD, the rise in prevalence of CKD is due predominantly to rise in CKD stage 3 rather than all stages, although statistically significant rises occurred in stages 2-4. This statement could therefore be modified based on reference 6. 5. Page ES-2. Under risk factors for CKD the list is incomplete.	1. We agree with the suggestion for the reasons stated and have revised the title to the following: "Chronic Kidney Disease Stages 1-3: Screening, Monitoring and Treatment." 2. We appreciate this comment. In the revised report, we did not create a separate section for "target audience." However, we broke the Objectives text into two paragraphs, with the second paragraph focused on the target audience. We believe this will make more visible the explicit language describing the target audience that already was present in the draft report. 3. We have added this information to the revised report. 4. The reviewer is correct in that approximately three-quarters of the increase in CKD prevalence is due to a rise in CKD stage 3. We have modified the report text to reflect this.

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		Gender is not considered a risk factor at all by clinicians. There is no apriori reason for that. It may simply be a vagary of the MDRD formula and there is not data provided in support of this assertion. 6. Family History would be important to mention as a clinically relevant risk factor. Recent evidence suggests that there is a definite genetic predisposition to CKD and this could be added (The Spectrum of MYH9-Associated Nephropathy CJASN June 2010 5): (6) 1107-1113; published ahead of print March 18, 2010, doi:10.2215/CJN.08721209). 7. Other important risk factors may be considered for mention such as chronic NSAID use, other nephrotoxic drugs and environmental toxins as well as nephrolithiasis. Connective tissue disorders such as SLE are commonly seen as predisposing to CKD. Cancers and chemotherapy are other risk factors. A table providing a comprehensive list may be appropriate for this otherwise very detailed report. 8. Page ES-2. Under CKD Screening, KDIGO = Kidney Disease Improving Global Outcomes (it says 'inspiring' which is not correct	5. We agree with the reviewer that there is not consistent evidence for gender as a CKD risk factor. We found only inconsistent data reporting it as a CKD risk factor, which we tried to reflect in our wording (i.e. “perhaps”) in the draft report. However, the purpose of this background section is not to provide a complete list of all CKD risk factors, and certainly not to cause controversy about a point very peripheral from the purpose of the report. Therefore, we removed gender from the risk factors listed. In addition, we have revised this section of the report to be more complete by adding ethnicity and family history as listed CKD risk factors. 6. We agree that leaving out family history as a clinical risk factor for CKD was an oversight. It has been included in the revised report. We have chosen not to list specific genetic polymorphisms as CKD risk factors as we believe it would be highly unlikely for a doctor to know this genetic information and then be able to consider it in a decision regarding whether to screen for CKD. 7. We agree that chronic NSAID use and certain other drugs can have adverse renal effects, and that other conditions may be associated with CKD. The suggestion to insert a table in the report with a comprehensive list of CKD risk factors was one we strongly considered. However, we ultimately decided not to include such a table. It was not a priority of this report to provide a comprehensive list of CKD risk factors, and we believed doing so could dilute attention from the smaller set of risk factors that account for most cases of CKD and on which we believed a clinician considering screening, monitoring or treatment decisions in a population of patients should focus. 8. We have corrected this error in the revised

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			report.
Peer Reviewer #1	Introduction	1. Introduction adequately set the stage for the report.	1. We appreciate this comment.
Peer Reviewer #2	Introduction	1. Introduction frames question well.	1. We appreciate this comment.
Peer Reviewer #3	Introduction	1. A relatively minor comment: I have issue with the statement in the ABSTRACT that "GFR testing is already common in usual care". First of all, it is plasma creatinine measurements, which in turn yields and estimated GFR, not a direct measurement of GFR that could be implied by this sentence. Second, my impression is that primary care providers are strongly encouraged to not obtain "unnecessary" tests on otherwise healthy patients, and what I observe clinically is that a relatively few numbers receive pCr or (perhaps more importantly) screening for microalbumin if there are no existing risk factors.	1. As addressed above in the similarly worded comment from the ASN, we agree with the reviewer that direct GFR measurement is not performed in usual care, but rather it is estimated GFR that is calculated from measurement of plasma creatinine. This inaccuracy was corrected in the revised report. Further, the reviewer's clinical observation seems consistent with Medicare data reported by USRDS and included in the draft report. This data indicated annual urinary microalbumin testing in about 30 percent of diabetics and 4 percent of hypertensives, and annual serum creatinine testing in fewer than 20 percent of patients with either diabetes or hypertension. Though we did not find data on the frequency of testing in patients without CKD and without risk factors, our assumption is that it is lower still. We tried to correct any language in the draft report that gives an impression otherwise.
Peer Reviewer #4	Introduction	1. The introduction of the scope of this effort is well laid out. The introduction also includes a clear description of the pertinent questions under review.	1. We appreciate this comment.

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Peer Reviewer #5	Introduction	1. (Page 1) Scope and purpose: please indicate again who the audience is. 2. Page 2; Prevalence: It is evident that the CKD EPI equation is favored by the authors. Hence the prevalence estimates calculated by using the CKD-EPI are provided. For full disclosure, and since the potential advantages and disadvantages are still under investigation by a number of authors, prevalence estimates by MDRD should also be provided as most clinicians are currently not using the newer equation in clinical practice. Most health care systems certainly haven't yet moved to this yet and may not do so unless they see significant advantage, which is not the case thus far. More and more literature is emerging in this area, and whether it will become universally accepted is not totally clear at present. 3. Page 3 please provide reference for CKD and frailty, as references are provided for all other adverse health associations. 4. Figure 1 is not annotated well and appears suddenly. The term 'node' should be explained. The practical utility of this diagram is questionable. It also understates the potential importance of obesity and completely omits the metabolic syndrome as a risk factor for CKD. This has been the topic dealt with by a number of association studies	1. We have modified the revised report as suggested. 2. Prevalence estimates based on CKD-EPI were provided in the report because these more accurately estimate measured GFR. The estimated number of U.S. adults with CKD, overall and within each stage is not dramatically different when derived using the CKD-EPI formula versus the MDRD formula. With either formula, the basic epidemiology is the same. For this reason and for readability, we have chosen to not provide detailed prevalence estimates using both formulas. In the draft report, we discussed the test properties of the MDRD and CKD-EPI formulas. In the revised report, we also acknowledge that currently the MDRD is most commonly used in clinical practice. 3. In the revised report, the stated association between CKD and frailty has been appropriately referenced (PMID 19559169). 4. We agree with the reviewer that insufficient context was provided for Figure 1 and that it was not essential to the report. We have deleted it from the revised report. We did not list metabolic syndrome as a risk factor for several reasons, including that there are multiple proposed definitions that don't completely agree with each other, and because we already listed many of its components as risk factors.
Joseph Vassalotti National Kidney Foundation, Inc.	Introduction	1. First, the National Kidney Foundation recommends and advocates for screening of populations at risk for CKD in contrast to general or mass screening. The major CKD risk conditions are diabetes, hypertension and age 60-years and older. More than half the U.S. population has at least one of these risk conditions. In addition, the prevalence of type-2 diabetes accounts for the CKD disparity or unequal distribution among African Americans, Hispanics, Asians/Pacific Islanders and American Indians. Cardiovascular disease (CVD) is also an important risk condition that is encompassed by the detection of CKD	1. We appreciate these comments. 2. We agree with the reviewer that reduction in risk of AKI and improved patient safety are potential benefits of identifying CKD. When eligible RCTs reported AKI as an outcome, which was rare, we extracted this data. However, there was no standard definition of AKI across studies. Further, an increase in creatinine or decline in eGFR beyond a specific threshold, which was usually used to define AKI, often is

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		associated with the above three conditions, since individuals younger than 60 years without diabetes or hypertension have low prevalence of CVD. 2. Second, although many important benefits are considered in the review, the potential benefits of targeted screening include two critical areas not considered in this comparative effectiveness review, acute kidney injury (AKI) and patient safety. The CKD prognosis consortium data (1) show that even stages 1 and 2 CKD have increased risk for AKI, particularly for those with high levels of albuminuria. Acute kidney injury detection in the U.S. is increasing over time. Prevention of AKI and drug prescription that considers the level of eGFR are key elements in the promotion of patient safety. Making care safer is the first priority of the National Strategy for Quality Improvement in Health Care that the Department of Health and Human Services released last month. CKD is an under-recognized threat to patient safety. (2) Recognition of CKD makes it possible to adjust drug dosing, avoid prescribing pharmacologic agents that are contraindicated for individuals with CKD, informing selection or avoidance of contrast media for diagnostic procedures, tailoring oral preparations for bowel examinations, exercising caution in NSAID and COX-2 inhibitor use. (3) These agents can cause acute injury. Moreover, any drug or drug metabolite that is cleared by the kidney can accumulate for individuals with stage 3 CKD. For example, patients with stage 3 CKD (inferred) are recommended to not use metformin, because of the potential risk of lactic acidosis, according to the FDA package insert. Third, the CKD Prognosis Consortium analyses of 45 cohorts including over 1.5 million individuals from general, high-risk, and kidney disease populations, provide strong epidemiological evidence for the association of eGFR and albuminuria with a broad spectrum of important clinical outcomes. Stages 1 to 3 CKD conferred significant increases in the relative risk of all 5 parameters assessed; all-cause and cardiovascular mortality, kidney failure onset, acute kidney injury, and progressive CKD or loss of kidney function over time. See Figure 5 from page 7 of (1). Fourth, the trend in the annual incidence rate of kidney failure attributed to diabetic nephropathy has been improving in all regions of the U.S., according to the CDC. The period of time in which these improvements occurred is contemporaneous with promulgation of practice guidelines by the American Diabetes Association and the National Kidney	completely asymptomatic and should be considered an intermediate health outcome rather than a final health outcome (e.g., ESRD, death, MI, etc.). We identified only one RCT that compared an intervention similar to what this reviewer is describing (NSAID or contrast avoidance or drug renal dose adjustment) versus a control group (e.g., usual care). This trial did not find a significant difference between treatment groups for clinical outcomes. We did not identify an RCT that reported prevention of procedure or medication related complications (e.g., hospitalizations) as an outcome of a screening or monitoring intervention. In the revised report, we acknowledge the lack of data in this area as a limitation, and make suggestions for future research to provide more information in this area

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		Foundation calling for enhanced detection of CKD in individuals with diabetes, followed by interventions to prevent or delay diabetes complications. —During 2007, approximately 110,000 persons in the United States and Puerto Rico began treatment for end-stage renal disease (ESRD) (i.e., kidney failure requiring dialysis or transplantation). Diabetes is the leading cause of ESRD in the United States, accounting for 44% of new cases in 2007. Although the number of persons initiating treatment for kidney failure each year who have diabetes listed as a primary cause (ESRD-D) has increased since 1996 , ESRD-D incidence among persons with diagnosed diabetes has declined since 1996 . To determine whether this decline occurred in every U.S. region and in every state, CDC analyzed 1996—2007 data from the U.S. Renal Data System (USRDS) and the Behavioral Risk Factor Surveillance System (BRFSS). During the period, the age-adjusted rate of ESRD-D among persons with diagnosed diabetes declined 35% overall, from 304.5 to 199.1 per 100,000 persons with diagnosed diabetes, and declined in all U.S. regions and in most states. No state showed a significant increase in the age-adjusted ESRD-D rate. Continued awareness of risk factors for kidney failure and interventions to improve diabetes care are needed to sustain and improve these trends.‖ (4) (1) Levey AS, de Jong PE, Coresh J, Nahas ME, Astor BC, Matsushita K, Gansevoort RT, Kasiske BL, Eckardt KU. The definition, classification and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2010 Dec 8. [Epub ahead of print] PMID: 21150873 (2) J. Fink, et al. —CKD as an Underrecognized Threat to Patient Safety.‖ ***American Journal of Kidney Diseases***, Vol 53, No 4 (April) 2009; pp. 681-688. (3) K. Gooch, et al. —NSAID Use and Progression of Chronic Kidney Disease‖ ***American Journal of Medicine*** (2007) 120, 280.e1-280.e7 (4) Incidence of End-Stage Renal Disease Attributed to Diabetes Among Persons With Diagnosed Diabetes --- United States and Puerto Rico, 1996—2007. MMWR October 29, 2010/59(42);1361-1366	
Peer Reviewer #1	Methods	1. The methods used to include/exclude studies were systematic, appropriate and well-explained.	1. We appreciate this comment.

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Peer Reviewer #2	Methods	1. All methods are appropriate. Would have liked to have seen more than 10% of the abstracted articles double reviewed, especially since there was little to no evidence for most of the questions. However, I am not suggesting this be done at all at this point.	1. To clarify, 10% of abstracts were reviewed at the stage of screening abstracts for potential eligibility. We agree that it would have been optimal to have double reviewed all abstracts for potential eligibility. We believe that it is at least possible that one or more articles not considered eligible by a single reviewer met eligibility criteria and would have been identified as eligible by a second reviewer. Of note, all data that was extracted into evidence and results tables was subsequently double reviewed.
Peer Reviewer #3	Methods	1. Overall well executed, but in the Executive Summary Table 1, definitions for levels of evidence grades of "insufficient", "low", and "moderate" should be better quantified and clarified.	1. In the revised report, a footnote was added to Executive Summary Table 1 that defines the evidence grades.
Peer Reviewer #4	Methods	1. The search strategies employed were logical and appropriate. Limiting the search to just Medline and the Cochrane database may have missed relevant studies in the pipeline that may have been published as abstracts in professional meetings. 2. The statistical methods were appropriately applied. 3. The inclusion of the graphic was a great idea but the resolution is terrible at least in the pdf version of the file that I reviewed.	1. MEDLINE and Cochrane did not identify trials published only as meeting abstracts. However, we reviewed the following grey literature to search for relevant trials and other material to estimate the likelihood of publication bias: (a) regulatory documents from U.S. FDA, Health Canada, and the European Union; (b) ClinicalTrials.gov, Current Controlled Trials, Clinical Study Results, and World Health Organization's Clinical Trials clinical trial registries; and (c) conference papers and abstracts from the CSA Conference Papers Index and Scopus. 2. We appreciate this comment. 3. We are not certain whether the reviewer is referring to the Analytic Framework figure from the Executive Summary, but to improve its readability we greatly increased the font size in the revised report. Regarding a second figure, which was intended to illustrate the impact of age, diabetes, hypertension, and obesity on the prevalence of CKD, we decided to remove it after deciding that it added little to the text and also didn't have great resolution.

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Peer Reviewer #5	Methods	1. Overall the methods section is written well and the methods used are acceptable. 2. Sometimes it is not clear whether a meta analysis approach is uniformly used or only selectively. It is not clear that this is required for a systematic review of this nature. 3. Inclusion and exclusion criteria are mentioned but not explicitly stated (page 9). 4. 'Grey literature' is not a familiar term for most of us (page 9 and page 14). Please provide a reference and preferably define the term itself. It appears mostly peer reviewed and published reports were used for this review, so it might be helpful to say what proportion of references are actually grey literature citations.	1. We appreciate this comment. 2. If our judgment was that clinical heterogeneity of patient populations, interventions, and outcomes was minimal, we mathematically pooled results (meta analysis). If we judged that clinical heterogeneity was more than minimal, we did not pool. 3. In the revised report, we added language within the Inclusion/Exclusion section indicating where the specific inclusion and exclusion criteria for each pair of key questions are located. Of note, the inclusion criteria are referred to by the phrase in the report: "We restricted the review to studies that…" 4. In the revised report, we defined grey literature and provided a reference from the AHRQ Methods Guide. We identified no references from the grey literature that were included in the report. This was noted in the draft report (and remains in the final report) as follows: "The grey literature search yielded 1,899 documents or citations; 1,065 from regulatory sources, 416 from clinical trials, and 418 conference papers and abstracts. Of the treatments analyzed for this report, our literature review yielded the most references for ACEIs. We therefore looked at the grey literature for ACEI studies not identified in our literature search. In the conference abstract and papers grey literature, there were 74 references pertaining to ACEIs. Ten of the references were identified in our literature search. The remainder did not meet inclusion criteria. In the clinical trials grey literature, there were 13 citations pertaining to ACEIs. Nine did not meet inclusion criteria. The four remaining studies are in progress with no results reported, to date. We concluded that our literature search adequately identified the relevant studies."

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Joseph Vassalotti National Kidney Foundation, Inc.	Methods	1. The National Kidney Foundation maintains that scope of comparative effectiveness research relating to CKD should not be limited to analysis of randomized controlled trials (RCTs) since there are few RCTs concerning CKD or involving CKD patients. (5) (6) 2. In addition, RCT to assess screening are not feasible, since withholding assessment of kidney function and albuminuria is not possible or ethical. 3. The National Kidney Foundation recommends that the comparative effectiveness analysis be revised to differentiate the risk/benefit of identification and monitoring for individuals with Stage 3 CKD, as opposed to those who have stage 1-2 CKD. 4. The National Kidney Foundation recommends that the comparative effectiveness analysis be revised to emphasize the risk/benefit of detection and follow up for individuals in high risk groups. 5. The comparative effectiveness analysis is incomplete without a consideration of the disparity in the burden of CKD and the co-morbidities that accompany it (e.g. diabetes and hypertension) among members of racial and ethnic minority groups. This is reflected in morbidity of minority populations in all the stages of kidney disease. The risk of cardiovascular events is higher in Hispanic versus non-Hispanic white adults with CKD. (7). Minority populations with CKD have more rapid progression to end-stage renal disease (ESRD), which results in the need for chronic dialysis treatments or a kidney transplant to survive. (8) Conversely rigorous screening and follow up for CKD by the Indian Health Service has been shown to reduce the incidence rate of kidney failure in that population. (5) G. Strippoli, et al. —The Number, Quality, and Coverage of Randomized Controlled Trials in Nephrology,‖ ***J Am Soc Nephrol*** 15:411-419, 2004. (6) J. Himmelfarb, —Chronic Kidney Disease and the Public Health: Gaps in Evidence from Interventional Trials.‖ ***JAMA***, June 20, 2007--Vol 297, No. 23. (7) C. A. Peralta, et al. ***J Am Soc Nephrol***. 2006;17:2892-9 (8)Joseph A. Vassalotti, et al. —Kidney Early Evaluation Program: A Community-Based Screening Approach to Address Disparities in Chronic Kidney Disease,‖ Seminars in Nephrology, Vol 30, No 1, January 2010, pp 66-73.	1. We agree with the reviewer that limits in the quantity and quality of RCTs may be an impediment to the ability of a CER to address specific clinical questions. However, RCTs are the most rigorous design for minimizing bias in evaluating the comparative effectiveness of different intervention strategies. Non-RCTs are more prone to many types of bias and therefore we made the a priori decision to focus this review on RCTs. The limited quantity and/or quality of RCTs to address some of the questions raised in this CER points out the need for future RCTs in these areas. 2. We agree that an RCT to assess CKD screening may not be feasible, but not for the reason asserted by this reviewer. While we agree that forbidding measurement of kidney function and albuminuria may not be feasible in an RCT, we believe that it would be both feasible and ethical to randomize study participants to usual care. As documented in the draft report, in current usual care the majority of patients do not have serum creatinine or albuminuria measured each year. 3. We appreciate this comment. In the revised report, additional effort has been made to describe the benefits and risks of monitoring and treatment in patients with different CKD stages within the larger category of stages 1-3. The revised report also discusses the limitations of available data for different CKD stages within the larger CKD stages 1-3 group. 4. As stated above, in the revised report, additional effort has been made to describe the impact of different individual patient risk factors (e.g. diabetes, hypertension, etc.) on the benefits and risks of CKD screening, monitoring and treatment. The report also discusses the

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			limitations of available data for different risk groups. 5. As stated above, in the revised report, additional effort has been made to describe the impact of different individual patient risk factors (e.g. race, ethnicity, etc.) on the benefits and risks of CKD screening, monitoring and treatment. The report also discusses the limitations of available data for different race, ethnicity risk groups.
Peer Reviewer #1	Results	1. Results are well delineated and explained. Given the lack of RCTs addressing these issues, it might have been reasonable to look at the implications from smaller studies (<50 patients), which were excluded from this review, in a separate section.	1. Extension of our inclusion criteria from 100+ patients to trials that included 50-99 patients identified some additional trials, but these trials almost uniformly reported no clinical outcomes. They weren't designed to assess clinical outcomes, and so when these were reported it generally appeared to be based on ad hoc data collection and there were few or no outcomes. Further, a large proportion of these studies had substantial methodological problems and none impacted the major conclusions of our report. We expect that trials that collection, evaluation, and reporting of data from trials that included fewer than 50 patients would be even less informative. No separate discussion of the possible implications of excluding these studies has been added to the revised report.
Peer Reviewer #2	Results	1. Yes, all adequate	1. We appreciate the comment.
Peer Reviewer #3	Results	1. The authors did an excellent job summarizing the vast amount of data across many published studies.	1. We appreciate the comment.
Peer Reviewer #4	Results	1. I particularly liked the key finding sections of the results. These would be very useful. The amount of information presented in the more detailed sections of the results is sufficient for a researcher to see that careful consideration was given to all of the issues and potential sources of bias. The studies included were appropriate.	1. We appreciate the comments.

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Peer Reviewer #5	Results	1. This forms the bulk of the report, as it should and most of the evidence focuses on Key Question 5 and 6 as those are the areas with most of the evidence. In general very well organized and comprehensive; this could qualify as a reference tomb for issues discussed. 2. Appendices are very detailed and the bibliography exhaustive (over 4600!). Perhaps it would be helpful to provide a shorter bibliography which includes those that provide the highest level of evidence and create a list of these separately from the several thousand. Landmark trials and observational studies for example that are a must read for those interested in reviewing key papers in this ocean of references.	1. We appreciate the comments. 2. We agree with the reviewer comment that the bibliography is exhaustive (and probably exhausting for the reader). All RCTs that met eligibility criteria are discussed and referenced in the body of the report. Other articles that we believed were relevant for the background, discussion and other sections of the report also are referenced in the body of the report. In total, these represent about 150 references listed at the end of the report (not in an appendix). We did not consider observational studies eligible for our systematic review, so this report may not be the best source from which to identify references to "key" CKD observational studies.
Abbott Laboratories	Results	1. We strongly recommend additional clarification differentiating evidence reviewed regarding benefits and harms for people with recognized risk factors versus people without recognized risk factors. 2. In addition, we strongly recommend differentiation in evidence for high risk populations regarding monitoring and treatment for Stage 3 CKD versus Stages 1 and 2 CKD.	1. As stated above, in the revised report, additional effort has been made to describe the impact of different individual patient risk factors (e.g. diabetes, hypertension, race, etc.) on the benefits and risks of CKD screening, monitoring and treatment. The report also discusses the limitations of available data for different risk groups. 2. As stated above, in the revised report, additional effort has been made to describe the impact of CKD stage (e.g., 1 versus 2 versus 3) on the benefits and risks of CKD screening, monitoring and treatment. The report also discusses the limitations of available data for different CKD stages within the larger CKD stages 1-3 group.
Joseph Vassalotti National Kidney Foundation, Inc.	Results	1. The National Kidney Foundation recommends that the conclusion of the comparative effectiveness report be revised to reflect the value of CKD screening for individuals in high risk groups, including members of racial and ethnic minority populations, and the value of monitoring CKD for patients with more advanced CKD. 2. It is difficult to reconcile the conclusions of the draft report with the NQF-endorsed performance measures in the CMS	1. As stated above, in the revised report, additional effort has been made to describe the impact of specific risk factors (e.g. race/ethnicity, diabetes, hypertension, etc.) for CKD incidence and progression on the benefits and risks for screening, monitoring and treatment. The report also discusses the limitations of

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		Physician Quality Reporting System, or the recommendations of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. For instance, in regard to the Physician Quality Reporting System, please note: Measure # 3 concerning target level for high blood pressure control in diabetes mellitus, Measure # 119, urine screening for microalbumin or medical attention for nephropathy in diabetic patients, measure #122, blood pressure management in CKD. According to Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, the blood pressure goal for patients with diabetes and chronic kidney disease should be <130/80 mm Hg) whereas the treatment goal for individuals with hypertension and no other compelling conditions is <140/90 mm Hg. The Joint National Committee also recommends annual measurement of urinary albumin excretion or albumin/creatinine ratio (ACR) for those with diabetes or kidney disease	available data to address these questions. 2. We reviewed the documents to which the reviewer refers. **With respect to screening**, the reviewer correctly points out that JNC7 recommends annual urine albumin-creatinine ratio measurement in all patients with combined hypertension and diabetes, and recommends collection of urinalysis (which would provide dipstick proteinuria) and serum creatinine (or preferably eGFR) before initiating therapy in all patients with hypertension. Further, CMS considers it a positive measure of performance (#119) that all diabetics either are treated with an ACEI or ARB or are tested annually for urine protein or albumin. The National Quality Forum has endorsed this same performance measure. **With respect to monitoring**, JNC recommends annual quantitative measurement of urine albumin in all patients with "kidney disease." CMS performance measure 119 stated that "the role of annual microalbuminuria assessment is less clear after diagnosis of microalbuminuria and institution of ACEI or ARB therapy and blood pressure control." **With regard to treatment**, JNC7 recommends a blood pressure goal for patients with diabetes or CKD of <130/80 compared to a goal of <140/90 for other patients. CMS performance measure 122 does not appear relevant to the current report as it advocates blood pressure <130/80 in patients with CKD stages 4-5, but doesn't address patients with CKD stages 1-3. CMS performance measure 3 advocates blood pressure <140/90 in all diabetics. It further states that "all (diabetic) individuals should be evaluated during health encounters to determine whether they are at increased risk of having or of developing chronic kidney disease." However, it does not explicitly

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			refer to screening for CKD. The documents to which the reviewer refers are clinical guidelines or performance measures whose purpose is to make specific clinical recommendations or encourage specific clinical behavior. The current report is an evidence synthesis which focuses on the evidence from RCTs that reported clinical outcomes. It is not the purpose of this report to make specific clinical recommendations. In the revised report, we have tried to be careful to keep that distinction in mind. It is beyond the scope of this report to determine how the developers of these and other similar documents reached their recommendations. Parties who utilize this final report to inform their development of future clinical guidelines or performance measures will be required to exercise clinical judgment where there are gaps in the evidence and may choose to consider other sources of evidence beyond those considered in the current evidence synthesis.
Ruben Velez Renal Physicians Association		*In asymptomatic adults with or without recognized risk factors for CKD incidence, progression or complications, what direct evidence is there that systematic CKD screening improves clinical outcomes?* *1.* Screening allows for risk stratification which may benefit some patients and may also be key when dealing with co-morbid conditions that are common in CKD patients, many of which require treatment decisions that influence renal status/function. CKD staging matters mainly when associated with knowledge of the patient's degree of albuminuria. Essentially, the risk of adverse cardiovascular events increases in proportion to the level of albuminuria for each stage of CKD. The risk is significant even in Stage 1 with high level of albuminuria. In Stage 3a (eGFR 45-60) there is increased risk with mild proteinuria, while for Stage 3b (eGFR 30-45) there is increased risk even without proteinuria. This is the basis for a new proposed staging system. (Levey AS et al. Ann Intern Med 2011:154:65-67.) *2.* The decision to estimate GFR on routine determinations of	1. We agree with the reviewer that both eGFR and albuminuria are strong prognostic factors and allow risk stratification. However, that is not the question addressed by this report. In this evidence synthesis, we have attempted to answer whether screening for CKD improves clinical outcomes, for which we found no direct data. 2. We agree with the reviewer that the decision to estimate GFR on routine measurements of serum creatinine has to be "all or none." We did not intend to imply that GFR should be estimated from creatinine in some patients but not others. Given that serum creatinine may provide a misleading estimate of kidney function and that eGFR more closely estimates true GFR, we agree with the practice of

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		serum creatinine has to be 'all or none', as it cannot be determined beforehand that a particular serum creatinine will fall into a particular CKD stage. It would be very difficult to not screen patients with higher GFR while screening those with lower GFR. 3. A 2006 study showed recognition of CKD by primary care physicians (PCPs) and subsequent referral to nephrologic care resulted in more significant BP lowering and reduction in the slope of decline of renal function, with the latter being associated with a reduction in mortality (Jones C. et al. N. Dialysis Transplant, 2006). A VAH study of diabetics with Stages 3a, 3b, and 4 showed association between number of nephrology visits (up to 4 per year) with reduced mortality (Tseng, Chin-Lin et al. Arch of Intern Med 2008: 168 (1):55-62.). Stage 3 patients were included in the study. 4. The use of ACE-I medications with or without ARB medications is recommended by KDOQI and other guidelines when micro-albuminuria is present in the setting of DM or HTN. This requires screening in patients who have DM and HTN. Most authorities suggest screening only for high risk groups: DM, HTN, hyperlipidemia, CVD, smokers and HIV or Hep C viral infection. 5. A recent study by the Chronic Renal Insufficiency Cohort (CRIC) Study Group showed that treatment of secondary hyperparathyroidism (if present) provides a mortality reduction benefit but only if started by Stage 3. (Isakova T et al. Diuretics, calciuria and secondary hyperparathyroidism in the Chronic Renal Insufficiency Cohort. Nephrol Dial Transplant 2011; first published online March 7, 2011) 6. RPA is aware of the recent increase in labs across the county reporting eGFR by MDRD, and the consequent increase in persons perhaps "unintentionally" screened for CKD. We strongly believe that if the intent is to appropriately provide information for primary care physicians to use in decision making, it is incongruent to suggest that there is evidence suggesting that perhaps this isn't necessary. We therefore urge AHRQ to proceed cautiously in evaluating the appropriateness of systematic CKD screening. *What harms result from systematic CKD screening in asymptomatic adults with or without recognized risk factors for CKD incidence, progression or complications?* 7. The primary concern is the overuse of resources. While the PREVEND Study showed that 40-50% of adults with proteinuria did not fall into recognized high risk groups and	automatically estimating GFR when serum creatinine is measured as part of a patient's regular clinical care. However, we believe this issue is distinct from whether or not CKD screening should be performed. 3. While the cited studies are interesting, both are observational studies, more prone to bias than RCTs, and fall outside the types of studies included in this review. 4. Based on the methodology utilized in this evidence synthesis, such screening potentially could be demonstrated as beneficial by direct evidence if an RCT of diabetic or hypertensive patients randomized to systematic microalbuminuria screening vs. a control intervention demonstrated a reduction in clinically important outcomes in the screened group. Absent such direct evidence, benefit might be inferred from indirect evidence if: (1) diabetic or hypertensive patients weren't receiving ACEI or ARB, (2) they didn't already have an indication for ACEI or ARB, and (3) RCT data showed that ACEI or ARB treatment compared to control reduced clinically important outcomes in diabetic and hypertensive patients with microalbuminuria but not in those without microalbuminuria. 5. We agree that this is an interesting and potentially important study. However, it is an observational study and therefore falls outside the types of studies included in this review. 6. We also are aware of the increase in labs calculating and reporting eGFR when patients have serum creatinine measured as part of their regular clinical care. This is a separate issue from whether or not patients should be systematically screened for CKD, and is outside the scope of this report.

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		therefore would have been missed if only people from those groups are screened, it was rare for people in this subgroup to progress to ESRD. 8. However, there is some risk of improper diagnosis. In older individuals (at or above age 70) widespread use of eGFR suggests 38% of those without HTN or DM in the US had eGFR <60ml/min. (Coresh J, Astor BC, Greene T, et al. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 2003; 41:1.) However, concern has been raised such diagnosis in this group may not provide benefit. (Glassock RJ, Winearls C. Screening for CKD with eGFR: doubts and dangers. Clin J Am Soc Nephrol 2008; 3: 1563.). Likewise, the eGFR can give misleading information for certain ethnic groups and for either morbidly obese or malnourished patients. The key to avoiding the harm from estimating GFR from creatinine is education of primary care givers. *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?* 9. As with screening, labs for CKD are commonly drawn as part of routine care and abnormal values need to be addressed. Again, these patients are likely to be monitored whether intentionally for CKD or not. However, this does not mean this is not necessary, particularly given the preponderance of CHF patients with CKD who 'qualify' for an ACE or ARB for the former. Monitoring should make the caregiver sensitive as to whether or not more aggressive treatment is needed, potentially to the benefit of the patient. This would then relate to question #5 below. *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 and/or kidney damage?* 10. No harm will result from monitoring. *Among adults with CKD stages 1-3, whether detected by systematic screening or as part of routing care, what direct evidence is there that treatment improves clinical outcomes?* 11. If the rate of decline of GFR can be slowed, there is evidence of reduction in mortality rate. (Tseng, Chin-Lin et al. Arch of Intern Med 2008: 168 (1):55-62.) 12. For non-diabetic CKD patients, antihypertensive treatment is	7. We appreciate this comment. We agree that screening for proteinuria (as well as screening for impaired eGFR) has the potential to identify many individuals as having disease who will not experience adverse clinical consequences. In the report, we have included this as a potential harm of screening for CKD. 8. We appreciate this comment regarding the risk of improper diagnosis. 9. With respect to monitoring, the intent of this report was to evaluate the evidence for systematic monitoring of CKD patients for worsening kidney function or damage. The scenario described by this reviewer pertains to nonsystematic assessment of kidney function that occurs as a result of regular clinical care. 10. This reviewer's assurance aside, there are numerous potential harms that could result from monitoring patients with CKD stages 1-3 for progression of their CKD as detailed in the report. Although we did not identify any RCTs that reported data on monitoring associated harms, this is not the same as evidence that there are no harms associated with monitoring. 11. We appreciate this comment and this reference. However, this article is an observational study and thus outside of the type of studies we considered as evidence for the benefit of interventions for CKD in this report. 12. We appreciate this comment. However, an a priori decision was made to not consider rate of decline in eGFR as an outcome for this report, as it a laboratory measure that doesn't itself directly impact patients (in contrast to death, ESRD, MI, stroke, etc.). 13. We appreciate the comment. 14. In the report, we did not conclude that there was evidence for no benefit, but rather we concluded that there was insufficient evidence regarding whether

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		most effective when there is moderate or greater level of albuminuria. In that setting, ACE-I treatment, ARB treatment, use of spironolactone, and use of diltiazem has been shown to decrease rate of decline in GFR. In at least one study, it was shown that the earlier Ramipril was started in the course of CKD the better for renal protection. (Ruggenenti P, Perna A, et al. ACE inhibitors to prevent end-stage renal disease: when to start and why possibly never to stop; a post hoc analysis of the REIN trial results. Ramipril Efficacy in Nephropathy. J Am Soc Nephrol 2001; 12:2832.) *Among adults with CKD stages 1-3, whether detected by systematic screening or as part of routing care, what harms result from treatment?* 13. RPA acknowledges that treatment for CKD patients is not completely without potential for harm. For example, there is a potential for reduction of GFR from overly aggressive treatment with ACE-inhibitors or ARB, for hyperkalemia (especially when using ACE-I therapy and spironolactone together), and in older patients with low degree of albuminuria, there is exposure to risk with little chance of benefit. 14. However, extreme caution should be used when presenting and discussing the intricacies of glycemic control, as we strongly believe that the two clinical trials on glycemic control are not robust enough to warrant a change in current thinking about the supremacy of tight glycemic control in retarding microvascular complications of diabetes. Similarly, in regard to multidisciplinary care, RPA advises AHRQ to exercise caution if it is considering suggesting a lack of benefit based on the limited evidence presented. 15. Finally, RPA would like to note that the current estimating formulas are not good at differentiating CKD stages at GFRs above 60 though CKD-EPI is better than MDRD. Thus, one does not screen for CKD stages 1 versus 2, only if the person is stage 3 or worse. 16. Also, thinking of all stage 3 patients as one group is erroneous. Later stage 3 (eGFR 30-45) bears much more significance than earlier (eGFR 45-60). 17. Further, the decision to estimate GFR on routine determinations of serum creatinine, as noted previously, has to be all or none as one can not know beforehand that a particular serum creatinine falls into a particular CKD stage. It would be very difficult to not screen patients with higher GFR while screening those with lower GFR.	intensive diabetes control prevented mortality or clinical vascular outcomes in patients with diabetes and CKD, and a low strength of evidence that intensive diabetes control reduced risk for conversion from microalbuminuria to macroalbuminuria. This distinction between evidence for no benefit and limited evidence for benefit is important. In the revised report, we have made an effort to make this distinction more clear throughout. 15. We agree with the reviewer regarding the limitations of current formulas for estimating GFR at distinguishing between CKD stages 1 and 2. These limitations apply as well for using these formulas to distinguish between normal GFR and CKD stages 1 or 2. So, eGFR currently may only be used to screen for CKD stage 3 or worse. 16. We have been aware that patients with an eGFR of 30-45 have a much different prognosis than those with an eGFR of 45 – 60. Therefore, we have sought to collect data for these two groups separately whenever provided by eligible RCTs. However, we found that the reporting of data broken out in this manner was rare. 17. As stated above, we agree with the reviewer that the decision to estimate GFR on routine measurements of serum creatinine has to be "all or none." We did not intend to imply that GFR should be estimated from creatinine in some patients but not others. Given that serum creatinine may provide a misleading estimate of kidney function and that eGFR more closely estimates true GFR, we agree with the practice of automatically estimating GFR when serum creatinine is measured as part of a patient's regular clinical care. However, we believe this issue is distinct from whether or not CKD screening should

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			be performed.
Peer Reviewer #1	Discussion	1. Findings are clearly discussed as was the need to look at both direct and indirect evidence to come to conclusions.	1. We appreciate the comment.
Peer Reviewer #2	Discussion	1. With regard to whether screening would change treatment: The authors state that there is no evidence that treating with greater doses of ACE/ARB or BB improve clinical outcomes. They therefore conclude the evidence for screening changing treatment would be low. One of the issues to consider here is whether patients in trials were treated to goals (e.g. blood pressure goals). If they were, then screening might be useful if patients who are already under care are not being treated to these goals. For instance-- patients could already be on ACE/ARB but if not reaching goals achieved in the trials, would not necessarily receive benefit. If screening raises providers' awareness of the need to alter goals, then screening could be potentially beneficial.	1. In the revised report we more explicitly addressed the situation raised by the reviewer, regarding whether intensification of treatment improves outcomes, and whether this could be a justification for screening to identify CKD. In this context, we considered that indirect evidence for possible benefit from identifying could exist under two circumstances: (a) if benefit is associated with treatment to a lower target in patients with CKD than in those without CKD and the patient currently is between the two targets, or (b) if the patient is receiving one of several treatments that are associated with comparable benefit for the non-CKD indication, but is not receiving the treatment that is associated with greater benefits in the subset of patients who also have CKD. The reviewer seems to be suggesting that provider knowledge that a patient has CKD might lead to a change in treatment that better meets pre-existing treatment targets. One could argue that if patients are being treated for a non-CKD indication (e.g. hypertension) and are not at treatment goal for that indication, no additional information regarding CKD status should be necessary to prompt modification of treatment to get closer to the treatment goal. Still, this is a question that could merit a study to examine its impact on outcomes. We did not identify such a trial.
Peer Reviewer #2	Discussion	1. Mention of work to be done in large screened cohorts such as Keep to classify harms: the report should be explicit about what types of harms these studies should be paying attention to. For instance, the potential for over diagnosis leading to unnecessary workups, labeling could be mentioned here.	1. We agree with the reviewer and have modified the future research section of the revised report to list more specifically the potential harms we recommend would be valuable for large cohort screening studies to collect.

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Peer Reviewer #2	Discussion	1. Can the discussion consider at all what the new classification might do to considerations of the approach to screening or monitoring?	1. The revised report has attempted to address the potential impact the newly proposed CKD classification might have on the benefits and harms associated with CKD screening or monitoring, including the severe limits on evidence available to address this issue.
Peer Reviewer #3	Discussion	1. The information included is overall well executed, but there are some important omissions as detailed in General Comments above.	1. We have responded to the comments where specified above.
Public Reviewer #1	Discussion	1. Generally, this report reaches appropriate conclusions based on the evidence. However, the more important treatment question is whether treatment based solely on the presence of CKD results in benefit. Most of the subjects with CKD had comorbidities that might have driven treatment regardless of CKD status. From that perspective, a finding that tight BP control did not result in reductions in mortality or CV events is useful (ie, despite comorbidities, there was no benefit). Many of the analyses were post-hoc, which reduces the quality of the evidence even further, even if the risk of bias of the original studies was low. Nevertheless, the lack of evidence is not negative evidence, and treatment to prevent progression of renal disease may be warranted until evidence is firm. This may be controversial given the impact of the disease on patients and their desire to prevent some of the outcomes	1. We agree with the reviewer that lack of evidence is not equivalent to negative evidence. In the revised report, we have sought to be more clear in making this distinction.

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Peer Reviewer #5	Discussion	1. Screening. Remains controversial. The authors favor modeling studies over large cumbersome and potentially long drawn clinical trials. This assertion itself is controversial. 2. In general, management of CKD involves not just trying to slow progression, but also management of associated complications such as anemia, bone and mineral disorder, volume excess, etc. Even though not within the scope of the current document, there should be some text devoted to this issue. 3. Additionally evidence suggests that early referral to nephrologist is associated with better outcomes. This topic is well within the domain of primary care physicians for whom this document provides no guidance in this regard.	1. We don't "favor" modeling studies over clinical trials to clarify the benefits and harms of screening for CKD stages 1-3. We believe that an appropriately designed RCT would be the most direct way to evaluate this question. We were trying to make the point that a large RCT comparing systematic CKD screening versus usual care or an alternative regimen may be less feasible than a modeling study. We have sought to make this distinction more clear in the revised report. 2. We agree with the reviewer that management of CKD involves management of CKD complications such as those listed. However, these complications largely occur in patients with CKD stages 4-5, which is beyond the scope of the report. In the revised report, we explicitly state in the objectives of the report its limitation to addressing CKD stages 1-3. 3. The evidence the reviewer refers to are observational studies. We did not find any RCTs of early nephrology referral versus usual care in patients with CKD stages 1-3. We believe this would be a good topic for further study, ideally with an RCT. In the absence of an RCT, it might be enlightening to study this question using observational cohort or administrative data, looking at outcomes and accounting for factors that predict early referral (e.g. a propensity analysis). We address this in the recommendations for future research section of the report.

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Joseph Vassalotti National Kidney Foundation, Inc.		1. The report includes more discussion of potential harm, in the absence of evidence, than of potential benefits. One of the potential harms of systematic screening or monitoring for CKD that is cited is —[i]ncreased difficulty of obtaining/keeping health insurance coverage. However, this concern has been addressed by the Affordable Care Act. 2. Although the evidence center found that ACEI and ARB significantly reduced risk of ESRD in patients with proteinuria and doubling of baseline creatinine in CKD patients overall, this finding is not emphasized.	1. To the general point about the report emphasizing potential harms, in the revised report we tried to be more explicit about the limitations of the evidence on potential screening and monitoring harms. With respect to the insurance coverage issue, we agree that when the Affordable Care Act is fully implemented, assuming it isn't repealed in Congress or overturned by the Supreme Court, it should provide protection to patients from denial or termination of insurance coverage because of a diagnosis of CKD. Provisions of the Act implemented in 2010 provide for some protection, including access to temporary coverage. However, because of the uncertainty regarding what temporary coverage will mean, when insurance exchanges will be available in each state, the staged implementation of the Act provisions, and the political uncertainty regarding the Act's future, we believe that the statement as written is accurate. 2. In revising the draft report, we have made effort to more clearly communicate the key findings from the evidence synthesis, including both "positive" and other outcomes.
Peer Reviewer #1	Conclusion	1. The future research needs and the challenges to conducting these studies are so great that this section may not have been able to drill down to specific, realistic study suggestions.	1. In the revised report, further effort was made to suggest specific, realistic future research needs.
Peer Reviewer #2	Conclusion	1. When proposing future studies: One of the things would be to disentangle a bit more the difference between screening for eGFR versus screening for macroalbuminuria. If one were to screen for macroalbuminuria, which clearly increases risk of progression to ESRD, then screening interventions might be proven useful and could possibly be studied in a trial since the outcomes would be more proximal.	1. We agree with this suggestion, and in the revised Future Research section of the revised report, we have tried to address this issue in suggesting potentially useful future studies.
Peer Reviewer #2	Conclusion	1. I think the Future Research section can be expanded a bit to more explicitly address all the weaknesses and gaps identified in the literature	1. As suggested by the reviewer, in the revised report the future research section has been expanded in an effort to better address the weaknesses and gaps identified in the literature.

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Peer Reviewer #3	Conclusion	1. One consideration for new research that was not mentioned is the possibility of targeting suitable funded cohort studies or clinical trials (either on-going or starting) for additional resources to collect biosamples and data on renal parameters for eGFR and albuminuria. This may represent a cost-efficient yet scientifically strong approach to addressing the relevant issues raised in the document.	1. We agree with this suggestion and have added this idea to the future research section in the revised report.
Peer Reviewer #4	Conclusion	1. We enjoyed the clarity of the conclusions to the different questions. 2. We read the recommendations and suggested areas for further studies with care as we believe that some of these recommendations will have to be addressed by our agency and partners. We agree that the modeling exercise can be expanded to assess, test and generate hypotheses for some of the gaps in knowledge and we have already started working on some of these issues.	1. We appreciate this comment. 2. We are pleased to learn of this ongoing work, which we believe will be helpful in addressing some of the knowledge gaps that exist regarding screening, monitoring and treatment of CKD.
Peer Reviewer #5	Conclusion	1. Future research section is well written.	1. We appreciate this comment.

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Joseph V. Bonventre American Society of Nephrology	Conclusion	**Future Research** 1. ASN concurs with the principle outlined in the "Future Research" section that more investigation is necessary to fully understand the benefits and harms of screening for CKD. The "Future Research" section appropriately notes that the "most direct [research direction] would be to conduct a large-scale RCT of CKD screening plus treatment for confirmed diagnoses versus usual care… However, such an RCT likely would require tens of thousands of participants followed for a dozen or more years to have adequate power to evaluate final clinical outcomes. Such a study is not likely to be feasible." It also appropriately reviews cost-effective alternatives, such as prospective evaluations of the impact of Kidney Early Evaluation Program (KEEP) and other existing screening programs, which could provide some useful information without requiring a trial. In the future, these data could be used with simulation models to help inform policy decisions and future patient care recommendations. 2. ASN suggests that the draft CER specify the potential harms that leaders of large cohort screening studies, such as KEEP, should be aware of. For instance, a final CER could include explicit mention of the potential for over-diagnosis leading to unnecessary workups, as well as issues related to labeling. 3. An additional consideration for future research that was not mentioned in the draft CER is the possibility of targeting suitable funded cohort studies or clinical trials (either on-going or starting) for additional resources to collect biosamples and data on renal parameters for eGFR and albuminuria. This may represent a cost-efficient and scientifically strong approach to addressing the relevant issues raised in the document. 4. AHRQ also may wish to consider recommending that, as future studies are conducted, investigators could weigh screening for eGFR and macroalbuminuria. If one were to screen for macroalbuminuria, which clearly identifies increased risk of progression to ESRD, then screening interventions might be proven useful and could possibly be studied in a trial since the outcomes would be more proximal.	1. We appreciate these comments and appreciate the suggestion to incorporate data from large screening cohorts into modeling studies. We have addressed this in the revised Future Research section. 2. We agree with this suggestion. In the revised report, we have more specifically listed potential harms that we believe may be informative to track in large cohort screening studies. 3. As stated above, we agree with this suggestion and have added this idea to the future research section in the revised report. 4. As stated above, additional effort has been made in the revised report to consider how screening for different levels of CKD (e.g. macroalbuminuria, microalbuminuria, impaired eGFR, or some combination) may impact the benefits and risk of CKD screening, monitoring and treatment.

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Joseph Vassalotti National Kidney Foundation, Inc.	Conclusion	**Future Research** 1. A Work Group of the Kidney Disease Improving Global Outcomes (KDIGO) program is reviewing evidence for an update of the KDOQI Guidelines for the Evaluation, Classification and Stratification of Chronic Kidney Disease, including CKD screening. The projected publication date for this KDIGO analysis is August 2012. AHRQ might want to delay final publication of the —Comparative Effectiveness Review: Screening for and Management of Chronic Kidney Disease, Stages 1-3‖ until the recommendations from the KDIGO update can be compared with the comparative effectiveness findings. Longer term, the data being collected and analyzed by the CKD Prognosis Consortium should inform discussion of the kind of issues that are covered in the Comparative Effectiveness Review.	1. We anticipate publication of this AHRQ report in 2011. We understand that it will not be the last word on screening for, and monitoring and treatment of patients with CKD stages 1-3. We expect that the KDIGO analysis and ongoing and future research studies will make important contributions in addressing knowledge gaps noted in the AHRQ report.
Abbott Laboratories	Figures	1. Abbott recommends the following changes to Figure 1 on page ES-5 in the Executive Summary: We strongly recommend that the abstract, executive summary and relevant sections of the report regarding screening and monitoring should better reflect the totality of clinical research in diabetic nephropathy which has led to current standard of care. These findings not only justify screening, as a prelude to kidney-specific therapy (renin-angiotensin system blockers) and monitoring of that therapy, but form the clinical practice recommendations published by national kidney and diabetic organizations. (ref KDOQI). In this context, the analytic framework depicted in figure 1 (page ES-5) should more correctly reflect the current standard of care in a diabetic patient where a CKD treatment decision is often made following the initial screening for and detection of albuminuria and not only after long-term monitoring. 2. Duration of diabetes, control of glucose and blood pressure levels and the identification of macroalbuminuria at any stage of eGFR, are important risk factors for CKD progression.	1. As suggested by the reviewer, the figure was modified to reflect that treatment decisions may be made either prior to or following monitoring. 2. We appreciate this comment.

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Joseph Vassalotti National Kidney Foundation, Inc.	References	1. Although there is a reference to an article in ***Nephrology Times,*** reporting on a KDIGO conference that proposed changes to CKD classification (9), the evidence center apparently did not consider the summary of the conference that was published in the ***Lancet*** (10), nor any of the peer-reviewed publications originating from the CKD Prognosis Consortium that was organized as a result of that conference and that have appeared in peer-reviewed literature. (1, 11-13). (9) M. Hogan,— KDIGO Conference Proposes Changes to CKD Classification, but not to the Definition.‖ Nephrology Times 2009; 2(12):9-10. (10) Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010 Jun 12;375(9731):2073-81. (11) Astor BC, Matsushita K, Gansevoort RT, van der Velde M, Woodward M, Levey AS, Jong PE, Coresh J; The Chronic Kidney Disease Prognosis Consortium. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. Kidney Int. 2011 Feb 2. [Epub ahead of print] PMID: 21289598. (12) Gansevoort RT, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, Jong PE, Coresh J; The Chronic Kidney Disease Prognosis Consortium. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes in both general and high-risk populations. A collaborative meta-analysis of general and high-risk population cohorts. Kidney Int. 2011 Feb 2. [Epub ahead of print] PMID: 21289597. (13) van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey A, de Jong P, Gansevoort RT; the Chronic Kidney Disease Prognosis Consortium. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney Int. 2011 Feb 9. [Epub ahead of print] PMID: 21307840	1. The draft report cited and described results from the 2010 Lancet Matsushita paper. The other publications listed by the reviewer all were published after the completion of the draft report. We thank the reviewer for bringing these most recent articles to our attention. They were useful in updating the background section of the report.

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Peer Reviewer #1	Genera	1. The key questions are very explicitly stated and clinically relevant. The authors had an especially difficult task, given the relative lack of evidence in this area, to neither overstate what can be concluded nor to miss the key points that the evidence (at least indirectly) does provide--they walked this fine line well. The result is not explicitly and immediately clinically-relevant, but should inform national organizations looking to update their clinical guidelines.	1. We appreciate these comments.
Peer Reviewer #1	General	1. The main points are clearly stated. Clinicians find this type of report frustrating as they serve mostly to highlight the lack of evidence for what current guidelines already require them to do. They also clarify few of the clinical issues faced in daily practice. However, the use of this report should rather be to help future guideline writers be more cautious in their recommendations, including more explicitly stating when a recommendation is actually based on evidence or on expert opinion--something this field has often lacked.	1. We appreciate these comments.
Peer Reviewer #2	General	1. The team is to be congratulated on a very thorough review and a well thought out approach to the review. Key questions are very specific and well-stated.	1. We appreciate these comments.

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Peer Reviewer #3	General	1. This manuscript is clearly the result of many, many hours of detailed and thoughtful literature review and writing. The information included on the literature review for the topics addressed appears to be comprehensive and well summarized. There are at least a couple aspects of the current CKD literature, however, that are neglected and need to be incorporated in the next draft. 2. #1: The report focuses on ESRD, CVD, and all-cause mortality as the primary clinically meaningful outcomes as these are the endpoints for most of the RCT's where this can be examined. A theme is that there is insufficient evidence that screening for Stage 1-3 CKD would translate into effective interventions to improve outcomes. Investigators have reported, however, that CKD patients have traditionally been excluded from clinical trials of CAD (Charytan et al., Kidney Int 2006; 70: 2021-30). A lack of evidence is not the same as evidence that screening/intervention is not effective and the rather negative spin on screening benefits on page 25 should be tempered when taking this into consideration. 3. Related to #1 above, there is no mention of the recent associations reported in early CKD and quality of life measures such as cognitive function or physical function. Please see the work published by Drs. Kurella-Tamura, Yaffe, Jassal, and others in recent years for cognitive function and results from the Health ABC study (M. Odden and M. Shlipak) and Nurses' Health Study (J. Lin and G. Curhan) for physical function. These QOL outcomes represent an important public health issue in the aging U.S. population who are at risk for both CKD and QOL decline and while screening and intervention for early CKD on these QOL outcomes have yet to be demonstrated because of the recent growing awareness of the relationship, QOL outcomes should be incorporated. 4. The issue of race/ethnicity is relatively neglected in this report. It is well recognized that non-Caucasian groups such as African-Americans and Latinos have an elevated risk for ESRD; whether the CKD and ESRD risk is explained entirely by the higher prevalence of diabetes and hypertension in these populations is not clear as, for example, blacks are at disproportionate risk for developing FSGS, an primary glomerulopathy. I would consider non-Caucasians as warranting screening especially in patients who have a family history of kidney disease	1. We appreciate these comments. 2. We agree with the reviewer that a lack of evidence is not equivalent to having sufficient evidence for a lack of effect. In the revised report, we have attempted to make this distinction more clear. 3. As stated above, we agree that quality of life is an important patient-centered outcome. From the start, we considered quality of life an important clinical outcome, we looked for quality of life outcomes data in our search for eligible articles, and we sought to identify such data for our data extraction. However, we did not identify eligible RCTs that reported quality of life outcomes data. The articles cited by this reviewer are important, but are not RCTs and thus fall outside the scope of the types of studies considered in this report. They In the revised report, we describe evaluation of CKD screening, monitoring and treatment on quality of life as an important area of future research. 4. As stated above, in the revised report, additional effort has been made to describe the impact of different individual patient risk factors including race on the benefits and risks of CKD screening, monitoring and treatment. The report also discusses the limitations of available data for different race groups.
Peer Reviewer #3	General	1. Very well organized and clearly written	1. We appreciate this comment.

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Peer Reviewer #4	General	1. This is a well researched and conducted review of the current state of knowledge about CKD. This document will become a very useful one source document for CKD researchers and the public at large. We would like to take this opportunity to congratulate the workgroup for their diligence and deliberation	1. We appreciate this comment.
Peer Reviewer #4	General	1. The conclusions from this report will add to the body of evidence which suggest that screening for CKD in the general population is not supported by the current evidence and that targeted screening may be beneficial in high risk groups. 2. The report on the whole is well written and organized and we enjoyed reading it. 3. The appendices on the other hand were quite extensive and indigestible. For brevity we would suggest that the search strings be included in package but the "list of excluded studies" and "Evidence Tables and Other Supporting Tables" be provided on request or on the AHRQ website as a separate download	1. We appreciate this comment. 2. We appreciate this comment. 3. We appreciate the reviewer feedback regarding the difficulty dealing with the appendices as currently accessible on the AHRQ website. Though web page management is beyond the scope of the authors of this report, we have recommended to AHRQ that the different sections of the appendices be divided into separate files for easier use (i.e., search strings, excluded studies, tables and figures).
Peer Reviewer #5	General	1. The report will be a most valuable addition to the field of screening, monitoring and management of early CKD. 2. The target population is broad and includes the health care system as a whole (Providers-particularly PCPs and Nephrologists, health plans, purchasers, government programs, etc). This target audience is identified in the preface and in the first paragraph of the Executive Summary. 3. The key questions are explicitly stated, clearly worded and evidently had buy in by the organizers/advisors to this document. 4. In the Preview section, however, only 4 questions are stated. Questions 5 and 6 are inadvertently omitted. This should be corrected.	1. We appreciate this comment. 2. We appreciate this comment. 3. We appreciate this comment. 4. We were unable to determine which section the reviewer was describing. However, in the revised report, we tried to clarify the Structured Abstract to more clearly refer to the six key questions.
Joseph V. Bonventre American Society of Nephrology	General	1. **Lack of evidence on effectiveness of screening vs. Evidence that screening is ineffective.** The draft CER focuses on endpoints for end-stage renal disease (ESRD), cardiovascular disease (CVD), and all-cause mortality as the primary clinically meaningful outcomes, as these are the endpoints for most of the randomized clinical trials (RCTs) where screening benefit can be examined. A central theme of the draft CER is that insufficient evidence exists showing that screening for Stage 1-3 CKD would translate into effective interventions to improve outcomes. ASN wishes to clarify, however, that a lack of evidence is not the same as evidence that screening, or subsequent intervention, are not effective. For instance, investigators have reported that CKD patients	1. We agree with the reviewer that a lack of evidence is not equivalent to having sufficient evidence for a lack of effect. In the revised report, we have attempted to make this distinction more clear. 2. As stated above, in the revised report, additional effort was made to highlight possible benefits and risks of CKD screening, monitoring and treatment in specific racial/ethnic minorities (e.g., African American, Latino, American Indian) to the extent that such data were available. The revised report also discusses the

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		have traditionally been excluded from clinical trials of coronary artery disease (Charytan et al., Kidney Int 2006; 70: 2021-30). In particular on page 25, the draft CER suggests a rather negative viewpoint of screening benefits. ASN suggests that this be tempered to reflect the difference between a lack of available evidence and evidence that screening is not effective. ASN recommends that this subtle but important perspective should be added on page 25, and throughout the report, as AHRQ finalizes the draft CER. 2. **High-risk patients: Minority populations.** ASN is concerned that the issue of patient race/ethnicity is relatively neglected in the draft CER. It is well-recognized that non-caucasian groups, particularly African-Americans and Latinos, have an elevated risk for developing ESRD. The risk of developing CKD and ESRD in these groups is likely not explained entirely by the higher prevalence of diabetes and hypertension in these populations. African-Americans, for example, are at disproportionate risk for developing Focal Segmental Glomerulosclerosis (FSGS) and primary glomerulopathy. ASN strongly suggests that AHRQ reconsider whether non-caucasians might benefit from screening—especially among noncaucasian patients who have a family history of kidney disease. ASN recognizes that insufficient data may exist regarding the benefits of screening in these subgroups, but recommends that more research be conducted in order to ensure the highest quality of care is available to patients of all races and ethnicities. 3. **Relationship between early CKD and quality of life measures.** A recent and growing body of literature reports on the association between early CKD and quality of life (QOL) measures, such as cognitive and physical function. [Please refer to work by M. Kurella- Tamura, K. Yaffe, S. Jassal, and others in recent years for cognitive function, and to results from the Dynamics of Health, Aging and Body Composition study (M. Odden and M. Shlipak) and the Nurses' Health Study (J. Lin and G. Curhan) for physical function.] These QOL outcomes represent an important public health issue in the aging U.S. population who are at risk for both CKD and QOL decline. While screening and intervention for early CKD on these QOL outcomes have yet to be demonstrated because awareness of this relationship has only recently been growing, ASN suggests that AHRQ should consider incorporating QOL outcomes besides those of ESRD, CVD, and all-cause mortality.	limitations of available data for these race and ethnicity risk groups, and addresses this as a future research need. 3. As stated above, we agree that quality of life is an important patient-centered outcome. From the start, we considered quality of life an important clinical outcome, we looked for quality of life outcomes data in our search for eligible articles, and we sought to identify such data for our data extraction. However, we did not identify eligible RCTs that reported quality of life outcomes data. In the revised report, we describe evaluation of CKD screening, monitoring and treatment on quality of life as an important area of future research. 4. As stated above, if patients are being treated for a non-CKD indication (e.g. hypertension) and are not at treatment goal for that indication, no additional information regarding CKD status should be necessary to prompt modification of treatment to target the treatment goal. Identification of CKD may only be of potential benefit in this situation under two circumstances: (a) if there exists evidence that treatment benefit is associated with treatment to a lower target in patients with CKD than in those without CKD and the patient currently is between the two targets, or (b) if the patient is receiving one of several treatments that are associated with comparable benefit for the non-CKD indication, but is not the one that is associated with greater benefits in the subset of patients who also have CKD. In the revised report, we have made additional effort to better specify patient subgroups in whom identification of CKD may change treatment. 5. We agree with the reviewer that direct GFR measurement is not performed in usual care, but rather it is estimated GFR

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		4. **Effect of Screening on Treatment.** With regard to whether evidence exists that systematic screening or routine care that identifies CKD states 1-3 amongst adults leads to treatment that affects clinical outcomes, the authors state that there is no evidence that treating patients with greater doses of angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ACE/ARB) or beta blockers (BB) improve clinical outcomes. They therefore conclude that evidence for screening affecting treatment would be low. ASN suggests that AHRQ consider whether patients in the trials studied were treated to pre-specified treatment goals (such as a specific blood pressure goal range). If patients in the studies were treated to goals, then screening might be useful in some cases—such as, for instance, for patients who are already under care for a given condition (e.g. high blood pressure). 5. **Plasma creatinine measurement vs. Direct glomerular filtration rate measurement.** The abstract of the draft CER states that "GFR testing is already common in usual care". ASN wishes to clarify that, it is plasma creatinine measurements, which in turn yield an estimated GFR (eGFR), that are common in usual care. Importantly, the eGFR is not a direct measurement of GFR, which the sentence as currently worded might imply. Furthermore, some primary care providers are strongly encouraged to not obtain "unnecessary" tests on otherwise healthy patients. Based on anecdotal feedback from members of ASN's CKD Advisory Group, relatively few patients receive plasma creatinine measurements or, perhaps more importantly, screening for microalbumin if there are no existing risk factors. As such, ASN suggests that AHRQ may wish to modify this sentence in the abstract to clarify the difference between plasma creatinine and eGFR measurements and to consider rephrasing the prevalence of such testing amongst patients with no existing risk factors.	that is calculated from measurement of plasma creatinine. This inaccuracy was corrected in the revised report. Further, the reviewer's clinical observation seems consistent with Medicare data reported by USRDS and included in the draft report. This data indicated annual urinary microalbumin testing in about 30 percent of diabetics and 4 percent of hypertensives, and annual serum creatinine testing in fewer than 20 percent of patients with either diabetes or hypertension. Though we did not find data on the frequency of testing in patients without CKD and without risk factors, our assumption is that it is lower still. We have tried to correct any language in the draft report that gives an impression otherwise.

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Joseph V. Bonventre American Society of Nephrology	General	1. Finally, given the significance of the growing CKD burden and the importance of building consensus for support of the final CER within the kidney community, ASN recommends that AHRQ convene a meeting of kidney community stakeholders—including ASN, the National Kidney Foundation, and the National Institutes of Diabetic, Digestive, and Kidney Disease—to discuss the draft CER	1. In the process of refining and completing a CER, all AHRQ CERs are informed by input from a broad group of stakeholders at multiple timepoints, including during refinement to discuss proposed key questions, in response to a posting document (preliminary protocol), and in response to the draft report. Stakeholders at different timepoints may include clinical and research experts; primary care providers, specialists and other clinicians; patients; advocacy organizations; and insurers and other policymakers. Our team of investigators leading this CER benefitted from insightful public input from these parties, including from stakeholders from the kidney community (e.g., ASN, NKF) in response to our pre-protocol and later to our draft final report. While we understand the value of building consensus for support of the final CER within the kidney community, the AHRQ process protects the independence of the investigative team, which writes and retains final word on the report. We are unaware of any AHRQ protocol for a separate meeting with stakeholders as described in this reviewer comment.
Joseph Vassalotti National Kidney Foundation, Inc	General	1. **Conclusion of National Kidney Foundation Comments.** Thank you for your consideration of these comments. In summary, NKF is concerned that opportunities to attenuate progression of CKD and its complications, and reduce incidence of AKI will be set back if the Draft Comparative Effectiveness Review is finalized without a critical examination of the issues that we have raised, This will result in unnecessary human suffering and avoidable demands on the resources of the health care system.	1. We appreciate the thoughtful and detailed comments from NKF on the entire draft report. We have spent considerable time critically evaluating the many issues raised in the NKF review, both before completing the draft report and while revising the report. It is our hope that these efforts are reflected in the revised final report.

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Ruben Valez Renal Physicians Association	General	**General Discussion** 1. RPA is concerned that the report's focus on CKD Stages 1-3 as a group may mislead the primary care audience. Irrespective of the fact that many with CKD Stages 1-3 do not progress, a wide range of clinical expectations can accompany the diagnosis of each of these stages, any of which influence the timing and/or need for monitoring and of course, treatment as well as prognosis. Stage 1 CKD is not the same as Stage 3, the former associated with less likelihood of attendant complications such as CKD-related anemia/mineral metabolism abnormalities. 2. Additionally, the tenor of the report might be interpreted to suggest that most CKD occurs in isolation rather than as one of a myriad of medical conditions. 3. The overlap of co-morbid diseases is common enough that in the case of isolated CKD, there is likely to be a need to search for other co-morbid conditions typical of CKD patients. The use of screening might be appropriate in this regard. 4. The report states that there is evidence to support treatment of CHF, hypertension, diabetes and other medical problems that are present and may be causative in CKD but not CKD in isolation. This is common practice, and not only it is difficult to tease out a benefit for CKD when a patient is already on treatment for other co-morbid conditions, but given the magnitude of the overlap, the need to do so may be less of a priority than the tenor of this report suggests. 5. The report should acknowledge the potential benefits of not missing the presence of CKD and given the large numbers of patients with disease overlap who may be prescribed an ACE or ARB, knowledge of the creatinine prior to the start of such a medical exam is necessary. 6. Furthermore, while the evidence presented supports the conclusions, and the quantity of studies reviewed is admirable, the quality of some studies may not be representative. For example, the two clinical trials on glycemic control are not robust enough to warrant a change in current thinking about the supremacy of tight glycemic control in retarding microvascular complications of diabetes. 7. Finally, RPA believes a most valuable aspect of this report is that the evidence supports recent consensus statement conclusions regarding the propriety of subdividing Stage 3 into 3a and 3b and categorizing albuminuria by grade.	1. As stated above, in the revised report, additional effort has been made to describe the impact of CKD stage (e.g., 1 versus 2 versus 3) on the benefits and risks of CKD screening, monitoring and treatment. The report also discusses the limitations of available data for different CKD stages within the larger CKD stages 1-3 group. 2. We disagree with the reviewer statement that "the tenor of the report might be interpreted to suggest that most CKD occurs in isolation." The draft report clearly states that most CKD occurs in the setting of other associated conditions, including diabetes, hypertension, and cardiovascular disease. 3. Whether patients identified with CKD without co-existing medical conditions, such as diabetes, hypertension, cardiovascular disease or others, should be screened for these conditions is beyond the scope of this report. 4. We appreciate these comments. 5. The reviewer is correct in that measurement of serum creatinine before initiation of ACEI or ARB treatment will identify CKD in some patients, and that this is common as part of regular clinical care. For evidence of benefit, this evidence report sought to determine whether systematic screening for CKD led not just to identification of CKD, but resulted in improved clinical outcomes. 6. The reviewer correctly points out the variable quality of RCTs available to help evaluate the benefits and risks of CKD treatment. 7. We appreciate this comment.

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Peer Reviewer #5	Clarity and Usability	1. Giant, well written document that will evidently be useful as a comprehensive reference for groups developing clinical practice guidelines. Please see comment above re. possibly providing a shorter list of the top priority references in addition to the comprehensive list. Which of the references constitute the best available evidence? 2. The authors stop short of actually coming up with clinical practice guidelines although I suppose it was not their mandate to begin with, even though they could easily do it based on their extensive review of the literature.	1. As stated above, we would direct the reviewer to the list of approximately 150 references at the end of the report text. This list includes all eligible RCTs and additional articles considered to provide important information for the background, discussion and other text sections. 2. The reviewer is correct in that it is not the mandate of the authors or of AHRQ to formulate clinical practice guidelines.