The case for early identification and intervention of chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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Chronic kidney disease (CKD) causes substantial global morbidity and increases cardiovascular and all-cause mortality. Unlike other chronic diseases with established strategies for screening, there has been no consensus on whether health systems and governments should prioritize early identification and intervention for CKD. Guidelines on evaluating and managing early CKD are available but have not been universally adopted in the absence of incentives or quality measures for prioritizing CKD care. The burden of CKD falls disproportionately upon persons with lower socioeconomic status, who have a higher prevalence of CKD, limited access to treatment, and poorer outcomes. Therefore, identifying and treating CKD at the earliest stages is an equity imperative. In 2019, Kidney Disease: Improving Global Outcomes (KDIGO) held a controversies conference entitled "Early Identification and Intervention in CKD." Participants identified strategies for screening, risk stratification, and treatment for early CKD and the key health system and economic factors for implementing these processes. A consensus emerged that CKD screening coupled with risk stratification and treatment should be implemented immediately for high-risk persons and that this should ideally occur in primary or community care settings with tailoring to the local context.

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Nearly 700 million persons worldwide have chronic kidney disease (CKD), and the burden falls disproportionately upon socially disadvantaged and other vulnerable groups.[1] In many regions, persons with lower socioeconomic status have a higher prevalence of CKD, limited access to treatment, and poorer outcomes.[2–5] Early

Table 1 | Key conclusions from the Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference on Early Identification and Intervention

Populations for CKD screening, risk stratification, and treatment
Conclusion 1. Persons with hypertension, diabetes, or cardiovascular disease should be screened for CKD.
Conclusion 2. CKD screening and treatment programs should also be implemented in other high-risk individuals and populations based on comorbidities, environmental exposures, or genetic risk factors.
Conclusion 3. The initiation, frequency, and cessation of CKD screening should be individualized based on kidney and cardiovascular risk profiles and individual preferences.
Measurements for early CKD
Conclusion 4. CKD screening and risk stratification must consist of a dual assessment of estimated glomerular filtration rate (eGFR) and albuminuria (UACR).
Conclusion 5. Accurate GFR estimation includes both creatinine and cystatin C measurements for initial diagnosis and staging.
Conclusion 6. The combination of creatinine, cystatin C, and UACR for CKD screening is affordable in high-income settings.
Interventions for CKD
Conclusion 7. A key rationale for CKD screening is the availability of many effective interventions to delay CKD progression and reduce cardiovascular risk.
Conclusion 8. Accurate diagnosis and staging of CKD are necessary to utilize treatments effectively.
Conclusion 9. Patient engagement is a critical component of efforts to screen for and treat CKD.
Health system and economic factors
Conclusion 10. CKD screening and treatment efforts require multi-stakeholder implementation strategies to overcome barriers to high-quality CKD care.
Conclusion 11. Financial and nonfinancial incentives need to be aligned toward CKD screening, risk stratification, and treatment.
Conclusion 12. CKD screening in high-risk groups is likely to be cost-effective.
Conclusion 13. CKD screening approaches may differ in LMIC countries.

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; LMICs, low- and middle-income countries; UACR, urine albumin-to-creatinine ratio.

identification of CKD by screening for kidney disease, followed by risk stratification and treatment, offers the potential to substantially reduce the morbidity and mortality from CKD and its related complications, such as cardiovascular disease.[6,7] However, at present, there is no accepted systematic strategy for CKD screening and treatment.

Despite effective methods to diagnose and treat CKD at its earliest stages, there is a lack of consensus on whether health systems and governments should implement CKD screening programs. Professional societies have been discordant on whether or not to screen for CKD.[8–10] To address this ongoing controversy, in October 2019, the Kidney Disease Improving Global Outcomes (KDIGO) held a Controversies Conference entitled "Early Identification and Intervention in CKD." Meeting participants represented a global multidisciplinary panel of clinicians and scientists. The rationale for CKD screening strategies was evaluated within the context of the World Health Organization (WHO) principles of screening for disease.[11,12] Four major topics were then addressed: (i) the selection of populations for CKD screening, (ii) the relative diagnostic and predictive characteristics of tests for kidney disease, (iii) the evidence base for treatments that reduce the risk of CKD progression and cardiovascular disease, and (iv) implementation strategies for CKD screening, risk stratification, and treatment programs and the key factors determining resource allocation and cost-effectiveness. The conference agenda, discussion questions, and plenary session presentations are available on the KDIGO website: https://kdigo.org/conferences/early-identification/.

After a comprehensive review of the conference topics by 4 breakout groups and by all attendees in collective discussion, consensus was reached to endorse a broad and proactive plan for CKD screening, risk stratification, and treatment with the goal of reducing the global burden of kidney disease (Table 1; Figure 1). The conference participants agreed that CKD met the WHO principles of screening for disease, as early CKD is asymptomatic, there are accurate and low-cost diagnostic tests, and effective treatments can be initiated in the early stages (Table 2[1,10,13–33]). Furthermore, the development of a CKD screening program was considered to be an equity imperative, particularly because socially disadvantaged and other vulnerable populations experience a disproportionate burden of CKD and are the least likely to receive effective treatments to reduce the risk of complications and improve outcomes.[34–36]

Two additional themes to emerge from the conference serve as important underlying principles for CKD screening strategies. First, as highlighted by patient representatives and advocates, there was a strong belief that patients overwhelmingly prefer earlier CKD screening and diagnosis and that patient education has the potential to improve self-management and disease prognosis. Second, a significant economic rationale was evident for early CKD screening, risk stratification, and treatment, particularly given the costs of kidney failure to individuals, health care systems, and society. For example, in the United States alone, Medicare spending for those with CKD or kidney failure is estimated to be more than 114 billion dollars annually.[37] The economic burden is

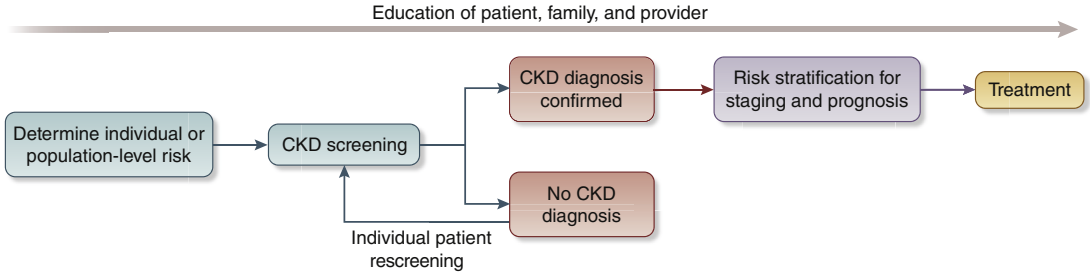

Figure 1 | Conceptual framework of a chronic kidney disease (CKD) screening, risk stratification, and treatment program.

particularly acute in low and middle income countries (LMICs); an estimated 188 million people experience catastrophic health expenditure annually as a result of kidney diseases across LMICs, the greatest of any disease group.[38] Specific components of an optimal CKD screening, risk stratification, and treatment strategy are described in the sections that follow.

Populations for CKD screening, risk stratification, and treatment

Conference participants reviewed different potential objectives for CKD screening and treatment initiatives: the identification of all persons with CKD, the identification of individuals within high-risk populations to maximize testing yield, or the identification of individuals with CKD who are most likely to progress to kidney failure or experience cardiovascular or other CKD complications. Additional topics of discussion included the definitions of high-risk populations and the optimal frequency of rescreening. The conference participants concluded that individual and population-level risk of having CKD and experiencing its complications should inform whether persons should be screened for CKD. Decisions concerning the age to initiate testing, the frequency of repeat testing, and the time to forgo or end testing should all be individualized based upon risk factors, preferences, and life expectancy.

Conclusion 1. Persons with hypertension, diabetes, or cardiovascular disease should be screened for CKD. The conference participants concluded that efforts for early CKD detection should first be implemented in individuals with established CKD risk factors, given the higher expected prevalence of CKD among those individuals. Conference participants recognized that identifying and treating all CKD cases would be the most complete approach to improving kidney health and reducing the burden of kidney disease. However, population-wide CKD screening programs were noted to have potential drawbacks, including higher costs and greater barriers to implementation than targeted high-risk CKD screening. A strategy of CKD screening in populations with common and important CKD risk factors will prioritize the identification of cases at high risk for CKD progression and cardiovascular events and with established treatment strategies. This approach would detect individuals with CKD at a lower cost per case identified but could miss CKD cases that are attributable to less common or unrecognized risk factors.

After reviewing data on worldwide CKD prevalence in high-risk populations, the conference participants concluded that CKD screening should be implemented for groups with these well-accepted CKD risk factors: hypertension, diabetes, and/or cardiovascular disease.[39] For example, in the United States, over 20% of individuals with hypertension have increased albuminuria (urine albumin-to-creatinine ratio [UACR] $\geq$ 30 mg/g), yet only 7% of those with hypertension are tested for albuminuria, representing potentially millions of patients with undiagnosed CKD.[40] Similarly, participants with self-reported cardiovascular disease in the National Health and Nutrition Examination Survey in the United States had a high CKD prevalence of over 40%.[37] The conference participants recognized that a CKD screening strategy based upon the presence of specific risk factors could miss a large population of patients who have not yet been diagnosed with those CKD risk factors or who are not followed in primary care.

Conclusion 2. CKD screening and treatment programs should also be implemented in other high-risk individuals and populations based upon comorbidities, environmental exposures, or genetic factors. Several other characteristics that may elevate an individual's likelihood of having CKD, including older age, race/ethnicity, other systemic diseases that impact kidneys (e.g. systemic lupus erythematosus, HIV infection), family history of kidney disease, genetic risk factors, poor access to health care or low socioeconomic status, high-risk occupations and environmental exposures, prior acute kidney injury,[33] preeclampsia, exposure to nephrotoxins, and obesity, were identified.[25] CKD screening for persons with these risk factors should be guided by an individualized clinical assessment and joint decision making, rather than with a uniform approach.

Conclusion 3. The initiation, frequency, and cessation of CKD screening should be individualized based on kidney and cardiovascular risk profiles and individual preferences. The time in the life course when screening for CKD should begin should be based upon the estimated likelihood of having CKD for that individual, rather than chronologic age alone. Thus, conference participants favored initiating CKD screening based on comorbidities and individualized risk assessment rather than at a specific chronologic age.

The frequency of testing is a critical aspect of CKD screening programs and has substantial impact on costs. The conference

Table 2 | CKD screening meets the WHO's principles of screening for disease

WHO criteria	CKD screening
1. The condition sought should be an important public health problem.	• CKD is highly prevalent, costly, and its worldwide disease burden is increasing.[1]
2. There should be an accepted treatment for patients with recognized disease.	• Treatments for recognized CKD can be initiated during early stages, are accepted, and are highly effective. Use of ACEi/ARBs in CKD patients substantially reduces risk of kidney failure. A meta-analysis of randomized trials showed that ACEi/ARB therapy lowered the odds of kidney failure by 30%–39% and of CVD events by 18%–24%.[13] • Statin use has been shown to significantly decrease risk of cardiovascular events and mortality in patients with CKD.[14] • In randomized trials, intensified blood pressure control in CKD patients reduced rates of fatal and nonfatal CVD events and all-cause mortality.[15] • In type 1 diabetes, long-term glycemic control reduces incidence of CKD.[16] In type 2 diabetes, glycemic control may be particularly beneficial in earlier CKD stages.[17] • SGLT2 inhibitors in patients with CKD with proteinuria and diabetes reduce the risk of kidney failure by 30%–40%.[18,19]
3. Facilities for diagnosis and treatment should be available.	• CKD screening and treatment in earlier stages could occur in primary-care practices or community-based settings.
4. There should be a recognizable latent or early symptomatic stage.	• CKD is asymptomatic until late stages. The asymptomatic stage contributes to low awareness of CKD in patients with the diagnosis.[20] Therefore, a screening program could shift recognition of CKD into much earlier stages relative to current practice.
5. There should be a suitable test or examination.	• There are low-cost and accurate tests for CKD. Serum creatinine and cystatin C are accurate tests to estimate GFR. Quantitative UACR is a sensitive measurement of kidney damage, whereas urine dipstick proteinuria is lower-cost but has lower sensitivity.[21]
6. The test should be acceptable to the population.	• Testing for CKD is accepted by the population. CKD is tested through standard venipuncture and non-invasive urine testing, and individuals with CKD express a preference for early communication about a CKD diagnosis.[22]
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.	• The natural history of CKD, including consequences of inadequate treatment, are well-understood. A large body of evidence has shown that CKD increases the risk of cardiovascular events and mortality. If not adequately treated, CKD may progress to kidney failure, and this risk can be predicted using risk equations.[23,24]
8. There should be an agreed policy on whom to treat as patients.	• There are clear guidelines for CKD treatment upon CKD detection. KDIGO guidelines recommend ACEi/ARB therapy in diabetic and nondiabetic adults with CKD and urine albumin excretion >300 mg/24 hours (or equivalent), and suggest ACEi/ARB use in diabetic adults with CKD and urine albumin excretion 30–300 mg/24 hours (or equivalent).[25] • Statin use is recommended for all patients with CKD above the age of 50 or with intermediate or high atherosclerotic cardiovascular disease risk, and CKD is a risk enhancer for patients with borderline atherosclerotic cardiovascular disease.[26,27] • Current guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) recommend that adults with hypertension and CKD should be placed in a high-risk category and be treated to a BP goal of less than 130/80 mm Hg, without delaying treatment for a trial of nonpharmacologic interventions.[28] Forthcoming KDIGO BP guideline update will advocate targeting systolic BP < 120 mm Hg. • SGLT2 inhibitors are recommended in persons with diabetes and CKD.[10]
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.	• CKD screening in high-risk groups is likely to be cost-effective. Several cost-effectiveness analyses of urine dipsticks and other methods of CKD screening have found that screening persons with hypertension or diabetes was cost-effective in simulation models.[29,30] Given the low cost of testing, strategies can be tailored to the resources of the specific health care system, as with other screening targets.[31]
10. Case-finding should be a continuing process and not a "once and for all" project.	• If a screening program is implemented, repeated screening is necessary to detect incident CKD in individuals with an initial negative screen. One-time screening does not capture high lifetime risk of CKD.[32] • An efficient detection strategy could tailor the timing of the next testing to the probability of new CKD based upon risk factors and current test results.[33]

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; SGLT2, sodium-glucose cotransporter-2; UACR, UACR, urine albumin-to-creatinine ratio; WHO, World Health Organization.

participants agreed that the frequency of repeat testing should not be uniform for all persons, but rather should be guided by each individual's risk of developing CKD, based in part upon the results of previous testing. Risk equations that estimate 5-year CKD probabilities could be used to guide the timing of subsequent testing.[33] For example, individuals with a high probability of incident CKD at 5 years could be rescreened at 1- or 2-year intervals, whereas those at low risk of incident CKD could be rescreened after several years.

The diagnosis of CKD is currently a controversial topic among older adults, who experience the greatest burden of CKD and are at the highest risk for certain complications, such as cardiovascular disease and heart failure.[41–43] Some nephrologists are concerned that CKD is overdiagnosed among older adults and have called for an age-adapted definition.[44] However, underdiagnosis of CKD in older adults also carries consequences, as older adults have the highest prevalence of CKD and CKD impacts their physical and cognitive function, medication safety, and cardiovascular prognosis. Conference participants acknowledged that there are potential harms associated with CKD overdiagnosis in older adults; in response, members emphasized that in older adults CKD should be appropriately diagnosed and risk stratified using all available measurements. For example, among those with an estimated glomerular filtration rate based on serum creatinine ($eGFR_{Cr}$) 45–59 ml/min per 1.73 m^2 and UACR $<$ 30 mg/g, the diagnosis of CKD should require confirmation by cystatin C testing, as recommended by the KDIGO 2012 guidelines (recommendation 1.4.3.5).[25] Second, in the setting of limited life expectancy, CKD treatment strategies should carefully weigh the risks and benefits of treatment. Older adults should not be excluded from CKD screening programs, and whether or not to screen for CKD in an older individual should be determined with a holistic approach to patient treatment goals as with other population-based screening programs, like cancer detection.

Measurements for early CKD

The ideal measurements for CKD testing would accurately screen, confirm, and stage CKD; risk stratify for important outcomes; and guide treatments relevant to prevention of kidney and cardiovascular complications. The conference participants reviewed the breadth of evidence related to testing methods for CKD and concluded that the ideal initial screening approach must consist of both eGFR (by creatinine, cystatin C, or both) and albuminuria measurement. Similarly, conference attendees agreed that at the stage of confirmation, the ideal CKD diagnosis would consist of the "triple marker" panel of serum creatinine, serum cystatin C, and UACR.

Conclusion 4. CKD screening and risk stratification must consist of a dual assessment of estimated glomerular filtration rate (eGFR) and albuminuria (UACR). Assessing both kidney function by eGFR and kidney damage by measuring albuminuria are critical both to detect and to risk stratify CKD.[45] Lower eGFR and higher albuminuria are both strongly associated with risks of cardiovascular events, kidney failure, and mortality, so their measurement is crucial for effective risk stratification of persons with CKD. The presence and severity of albuminuria also guides the use and dosage of treatments such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ACEi/ARBs). Despite guideline recommendations, many clinicians currently fail to assess albuminuria in patients with reduced eGFR[46–48] or diabetes.[49]

The preferred method for initial screening for CKD, in addition to eGFR measurement, is the UACR. UACR is preferred over urine protein-to-creatinine ratio because UACR specifically detects albumin, which has stronger associations with clinical outcomes and is required to appropriately stage CKD according to the KDIGO 2012 CKD guidelines.[25] Uurine protein-to-creatinine ratio also measures non-albumin proteins and may be less sensitive for albumin at the lower ranges of detection. Urine dipstick assays are inexpensive but less sensitive for detecting clinically important albuminuria, especially in the 30–300 mg/g range.[21]

Conclusion 5. Accurate GFR estimation includes both creatinine and cystatin C measurements for initial diagnosis and staging. There was strong agreement by the conference attendees that GFR should be estimated using creatinine and cystatin C in parallel, which would more accurately diagnose and stage CKD, with less misclassification, than a strategy based upon creatinine alone.[50,51] There is a low number needed to test with cystatin C to avoid CKD misclassification. For example, in a meta-analysis of 90,750 participants across 16 cohort studies, 23% of persons with eGFR 60–74 ml/min per 1.73 m^2 based on creatinine had eGFR $<$60 ml/min per 1.73 m^2 based on cystatin C.[50] Conversely, among persons with eGFR 45–59 ml/min per 1.73 m^2 by creatinine, 42% had eGFR $\geq$60 ml/min per 1.73 m^2 by cystatin C. Similarly, in the UK Biobank study of 440,526 participants, 14.5% of persons with an eGFR 60–75 ml/min per 1.73 m^2 by creatinine had eGFR $<$60 ml/min per 1.73 m^2 by cystatin C, and a total of 53.7% of persons with eGFR 45–59 ml/min per 1.73 m^2 by creatinine were reclassified to eGFR $\geq$60 ml/min per 1.73 m^2 by cystatin C.

The inclusion of cystatin C in CKD diagnosis and treatment initiatives is consistent with the KDIGO 2012 Guidelines[25] and is a critical component of accurate risk stratification, as cystatin C markedly strengthens the association between eGFR and cardiovascular events, kidney failure, and death.[50,51] Accurate eGFR staging has implications for treatment, as certain medications have indications that are determined in part by the GFR stage. Cystatin C has the additional advantage of offering GFR estimates that do not require the incorporation of a race coefficient, as is required for creatinine.[52] Although cystatin C is an integral test for the initial diagnosis and staging of CKD, conference participants agreed that it may not be required for routine monitoring after the diagnosis of CKD is made.

Conclusion 6. The combination of creatinine, cystatin C, and UACR for CKD screening is affordable in high-income settings. The cost of the tests used to screen for CKD has a major influence on the affordability and the cost-

effectiveness of a CKD screening and treatment program. Because these are all automated tests, the cost of each measure will decrease proportionately to the volume of tests that are conducted.[53] The actual costs to perform diagnostic tests often differ substantially from the reimbursement rate negotiated or set by payors for the tests, and costs are typically much lower than what a health system or laboratory might charge a private customer in the absence of health insurance or a national health plan. To assess international CKD testing availability and costs, KDIGO collaborated with the International Society of Nephrology (ISN) to conduct a global survey. Of 24 respondents (73% response rate), there was high availability of CKD laboratory tests globally and a low cost of serum creatinine and UACR testing. Reimbursement rates for the "triple marker" panel of serum creatinine, serum cystatin C, and UACR are likely affordable in high-income settings.

Interventions for CKD

A fundamental justification for the early detection of CKD is the availability of evidence-based interventions to slow the progression of CKD and reduce its complications. Accurate diagnosis and staging of CKD impact the choice of treatments. Conference participants reviewed the evidence for effective interventions in CKD.

Conclusion 7. A key rationale for CKD screening is the availability of many effective interventions to delay CKD progression and reduce cardiovascular risk. Because the utility of CKD screening and risk stratification depend upon the potential for effective treatments, the conference summarized available evidence for interventions that delay CKD progression and reduce cardiovascular risk (Figure 2[54,55]). A cornerstone of managing CKD is lifestyle modification, and although the benefits are largely inferred from observational studies,[56–60] implementing lifestyle recommendations poses no or low risk for patients. For all persons with CKD, recommendations include smoking cessation, regular exercise, and a healthy diet (fruit, vegetables, legumes, and whole grains) (Figure 3).

Intensive blood pressure lowering has been shown to reduce cardiovascular events and all-cause mortality in nondiabetic CKD, and is likely to be cost-effective.[15,61] Use of statins and ezetimibe lower the risk of major adverse cardiovascular events,[14,62,63] and low-cost statins are cost-effective in CKD.[64] Evidence is emerging on the role of intensive glucose control in reducing the risk of kidney events; however the renal benefits of intensive glucose control should be weighed with risks when using agents that cause hypoglycemia.[65] More recently, SGLT2 inhibitors show a strong benefit in slowing the progression of diabetic kidney disease, with the greatest absolute benefits in those with higher albuminuria; evidence for SGLT2 inhibitors in nondiabetic CKD is emerging.[18,19,66–68] Another class of glucose-lowering agents, glucagon-like peptide-1 (GLP-1) receptor agonists, significantly reduce cardiovascular outcomes among persons with CKD[69] and may slow diabetic kidney disease progression.[70,71] Treatment of metabolic acidosis in CKD G3 with fruits and vegetables or oral bicarbonate may preserve GFR and additional studies are ongoing.[72] In summary, contrary to the previous nihilism about the utility of CKD screening programs, there are numerous effective treatments now available for management of CKD.

Conclusion 8. Accurate diagnosis and staging of CKD are necessary to utilize treatments effectively. Accurate diagnosis and staging of CKD are critical in choosing effective treatments, dosing medications appropriately, and minimizing nephrotoxic burden. Early identification of CKD is important in the consideration of blood pressure management and targets. Identification of albuminuria impacts the choice of antihypertensive agent, as ACEi/ARBs are first-line agents in those with albuminuria, even in the absence of hypertension.

Accurate GFR estimates are crucial for safe and effective medication dosing in persons with CKD. For example, gabapentinoid use is prevalent among patients with CKD,[73] and drug accumulation increases risks of side-effects such as sedation. Similarly, the association of baclofen with risk of encephalopathy increases with higher CKD stage.[74] Diagnosis and staging of CKD also influences the need for nephrotoxin avoidance, including minimization of nonsteroidal anti-inflammatory drug exposure and i.v. contrast.

Conclusion 9. Patient engagement is a critical component of efforts to screen for and treat CKD. Patient and family education and engagement are critical to the success of early CKD care. When implemented appropriately, education can have a number of potential benefits, including improved patient activation, improved access to health care, improved access and adherence to medications, timely nephrology referral, dietician referral, and diabetes education. There is evidence suggesting that well designed, interactive, frequent, and multifaceted educational interventions that include both individual and group participation can improve knowledge and self-management for secondary prevention of CKD.[75,76] Although there is limited reimbursement for patient education on CKD in its earliest stages,[77] education programs are accessible across multiple languages and cultures and vital to providing patients information about kidney health. Barriers to educating patients about early CKD include the use of literature that is not at an appropriate level or in a familiar language,[78] poor access to multidisciplinary teams,[79] or lack of health system preparedness. Nephrology societies in individual countries can work to ensure that information is culturally appropriate.[80,81] Public education, shared decision making, culturally appropriate messaging, use of mobile technology, support groups, community outreach, community resources (food banks, housing), indigenous navigators/health coaches, and social marketing all have potential benefits for generating and maintaining engagement.

Several online tools and mobile applications are now available to engage people in the detection and management of early CKD.[82] The National Kidney Disease Education Program (NKDEP) sponsors an initiative to promote kidney

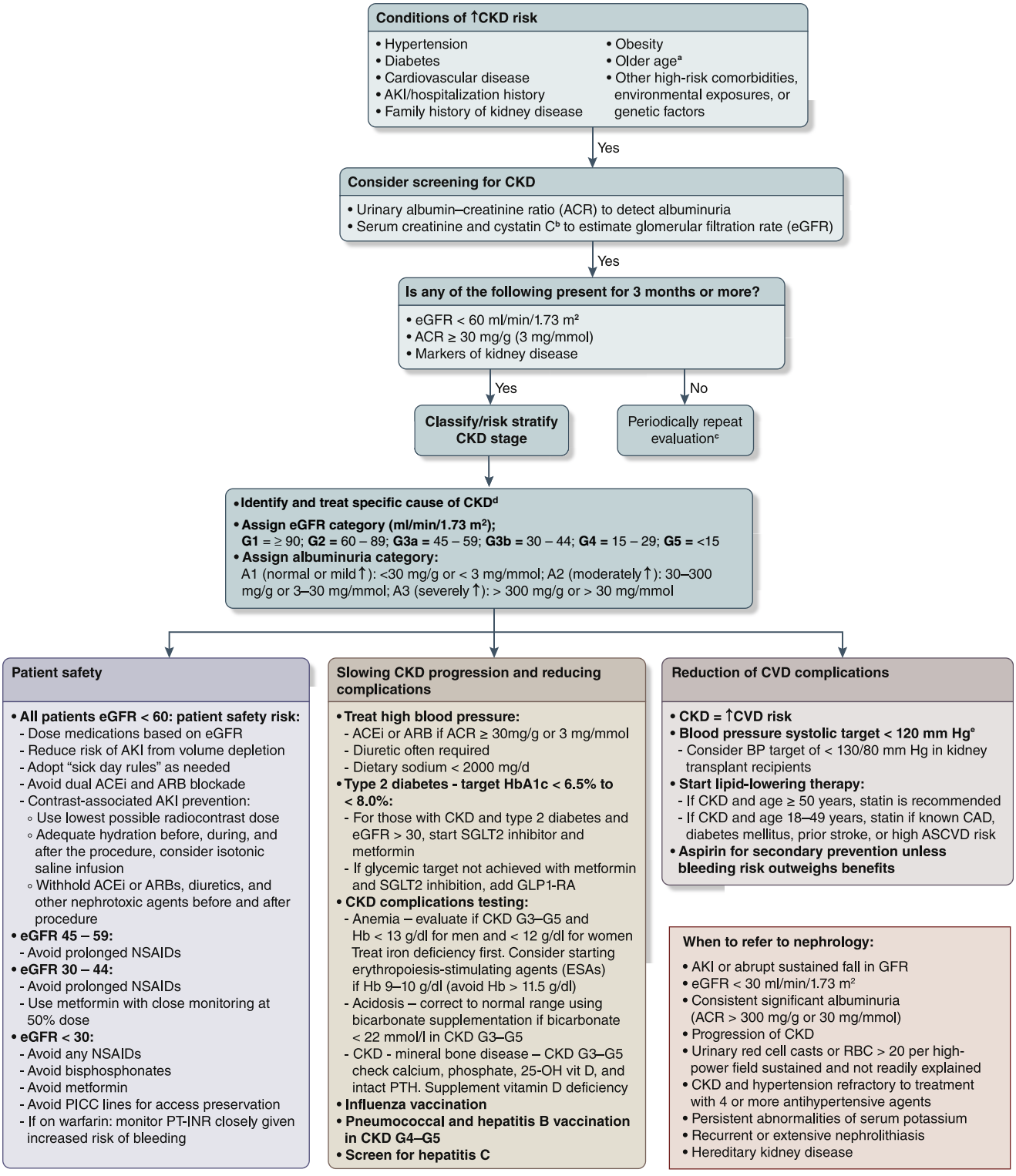

Figure 2 | Algorithm to screen, risk stratify, and treat chronic kidney disease (CKD). Based on Kidney Disease: Improving Global Outcomes (KDIGO) guidelines and adapted from Vassalotti *et al.*[54,55] [a]Care for older adults or those with limited life expectancy, including necessity of screening for CKD and treatment recommendations, should be individualized based on clinical status and patient preference. [b]If estimated glomerular filtration rate (eGFR)cr 45–59 ml/min per 1.73 m^2 or in individuals with low muscle mass, chronic illness, malnutrition, or other circumstances, order cystatin C to estimate glomeular filtration rate (GFR). [c]There are no current evidence-based recommendations regarding frequency of screening. Consider using risk equations (e.g., from CKD Prognosis Consortium) to estimate interval risk of developing CKD. [d]Cause of CKD is classified based on clinical evaluation. [e]Based on level 2 recommendation, which means a majority of people would adopt systolic blood pressure target $<$ 120 mm Hg while many others may opt for a less-intensive approach. As there is likely to be marked variability in how individual patients weigh and value the potential benefits and harms of intensive blood pressure (BP) control (continued)

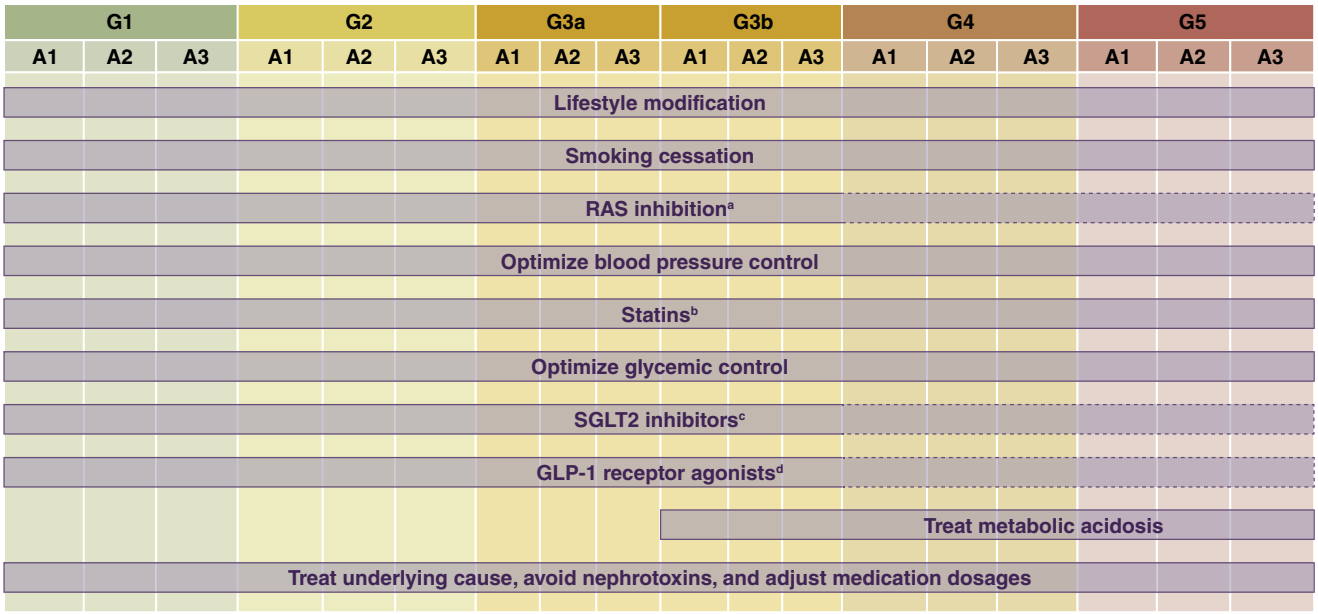

Figure 3 | Interventions to slow chronic kidney disease (CKD) progression and/or reduce cardiovascular risk. [a]Unclear if and when to discontinue renin-angiotensin system (RAS) inhibition in advanced CKD. [b]Statins should not be initiated for those beginning dialysis therapy. However, patients already receiving statins at the time of dialysis initiation can continue their statin treatment. [c]Applies to CKD patients with type 2 diabetes only. SGLT2 inhibitor is recommended as first-line treatment with metformin and may also have benefits in persons with CKD and no diabetes.[67,68] Sodium-glucose cotransporter-2 (SGLT2) inhibitors should be initiated if estimated glomerular filtration rate (eGFR) 30 ml/min per 1.73 m^2 and can be continued through G4–G5 until dialysis initiation, at which point SGLT2 inhibitor should be discontinued. There is no evidence for initiation of SGLT2 inhibitors if eGFR $<$ 30 ml/min per 1.73 m^2. [d]Applies to CKD patients with type 2 diabetes only. Glucagon-like peptide-1 (GLP-1) receptor agonist can be considered when SGLT2 inhibitor and/or metformin is not tolerated or glycemic target is not reached. Dulaglutide can be used if eGFR $>$ 15 ml/min per 1.73 m^2; exenatide can be used if creatinine clearance $>$ 30 ml/min; there are limited data for use of liraglutide, lixisenatide, or semaglutide in severe CKD. Consult dosing recommendations for use of these agents in CKD G4 and G5.

disease education via digital media and curates educational topics targeted to patients rather than providers.[83] Patient portals allowing direct access to providers and medical information can facilitate patient self-management and communication with providers.[84] As mobile technologies emerge to support health care delivery, a large portion of the CKD population may have difficulty accessing them because individuals with CKD are frequently older, may have lower socioeconomic status and health literacy,[82,84–86] and may have privacy concerns about disease labeling and health information.[85–89] Moving forward, the co-design of interventions with patients embedded in local communities will be important for ensuring utility and acceptability.

Health system and economic factors

The KDIGO 2012 guideline for the evaluation and management of CKD[25] was a major step toward defining high-quality CKD care. However, uptake in clinical practice has been suboptimal, with clinicians typically failing both to assess albuminuria for CKD diagnosis and staging[90] and to confirm the diagnosis of CKD in persons with $eGFR_{Cr}$ of 45–59 ml/min per 1.73 m^2 with measurements of cystatin C, where available.[91–94] Recognizing these large implementation gaps, the KDIGO conference participants devoted substantial effort towards considering effective implementation strategies and summarizing the barriers and facilitators for effective CKD care in the context of health system and economic factors.

Conclusion 10. CKD screening and treatment efforts require multi-stakeholder implementation strategies to overcome barriers to high-quality CKD care. The conference participants identified key strategies for CKD screening program development and success. Success of any CKD screening program will depend upon the engagement of health professionals in the local context, particularly primary care clinicians and allied health professionals, including front-line health workers. Patient-related barriers in CKD care include low patient knowledge of CKD and its associated risks and social risk factors, such as limited financial resources and low health

Figure 2 | (continued) and since this may vary with age, culture, number of drugs (both BP-lowering and other) and other factors, shared decision-making between individual patients and clinicians should be emphasized. ACEi, angiotensin converting enzyme inhibitor; ACR, albumin-creatinine ratio; AKI, acute kidney injury; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; Hb, hemoglobin; NSAID, nonsteroidal anti-inflammatory drugs; PICC, peripherally inserted central catheter line; PT-INR, prothrombin time-international normalized ratio; PTH, parathyroid hormone; RBC, red blood cell; SGLT2, sodium-glucose cotransporter-2.

Table 3 | Health system–level approaches for improving early CKD identification and management

Framework for developing initiatives
Conceptual
• Understand patient flow through the health system and identify possible tactics for engagement
• Develop risk-based approaches to identifying and treating CKD
• Integrate novel program processes with existing health services and processes
○ Augment/strengthen in view of early CKD identification and intervention
• Actively engage with:
○ Patients
○ Health care clinicians
○ Health system administrators and policy makers
• Develop monitoring and improvement strategies
Practical
• Determine population for screening based on local risk factors
• Identify existing screening programs for other diseases, such as cardiovascular
• Assess whether there is necessary political commitment
• Specify available resources (workforce/material/funding)
• Develop a technical package, strategies using the best available evidence, for CKD screening and management
• Provide specific, actionable recommendations with level of evidence
• Develop targeted versions of the guideline summary aimed at patients and primary-care providers[103,104]
• Develop visually appealing infographics and apps to aid in knowledge translation
• Integrate guideline recommendations in laboratory information systems and electronic health records with clinical decision support
• Engage medical educators to teach guideline-based CKD care in medical schools
• Engage all stakeholders—professional societies (such as ISN), patients, payers, health systems, and disease-specific foundations—in dissemination strategies
• Establish governance for monitoring, evaluation, and improvement
Framework for continued advocacy and expansion of efforts
• Identify the full health and economic burdens of kidney diseases
• Establish kidney disease registries and use collected data to drive surveillance, feedback, and integration
• Collaborate with other guideline bodies and professional societies to maximize consistency in recommendations (e.g., primary care, cardiology, endocrinology, geriatrics)
• Develop evidence-based quality measures for CKD care
• Document real-world health and economic consequences of successful interventions and models of care
• Identify methods for sustainable financing of optimal services
• Generate and promote evidence linking health promotion to improved health and economic outcomes regarding kidney diseases
• Continue advocacy from researchers, clinicians, and policy makers for healthy environments and lives
• Focus investments and reforms to develop effective primary-care systems, including pharmaceuticals and behavioral interventions
• Invest in research to identify novel risk factors for kidney diseases
• Implement cost-effective strategies to target care to individuals at increased risk of kidney disease

CKD, chronic kidney disease; ISN, International Society of Nephrology.

literacy. Health system–related barriers include perceived lack of urgency for detecting early CKD among primary care clinicians, lack of knowledge of CKD guidelines, lack of incentives for CKD interventions, lack of CKD-specific clinical quality measures, and suboptimal communication between specialties.[79,95,96]

Several efforts can improve CKD management in the primary care setting. Identifying high-risk individuals for CKD screening will require that clinicians are educated about CKD risk factors. Effective CKD risk stratification will require education about CKD staging, particularly the importance of albuminuria.[48,49,96,97] To bridge the education gap, existing guidelines could be simplified with quick reference guides for primary care clinicians. Approaches for CKD screening, risk stratification, and treatment should be integrated with existing health services and processes.[98] For example, automated laboratory reporting[55,99] and the use of risk equations and clinical decision support tools could be embedded in existing electronic health records to guide the selection of individuals for testing and the frequency of repeat testing. Subsequently, the extensively validated Kidney Failure Risk Equation[24,100] could risk-stratify patients for appropriate referral to specialty care and frequency of follow-up, thereby improving efficiency.[101] Selection of high-risk individuals and populations should be tailored to local populations, who may face distinct biological, environmental, and social risk factors.

Several models of care could be used to optimize care for newly diagnosed patients with CKD. These include co-management of care between primary care and nephrology, nephrology specialist consultation for high-risk CKD patients, and team-based multidisciplinary care.[102] Interventions for CKD early identification and intervention should be integrated into existing workflows using quality-improvement principles or as effectiveness-implementation hybrid studies. Overarching principles for development include efficiency, equity, ethics, education, sustainability, scalability, cultural appropriateness, access, and quality (Table 3[103,104]). Interventions based upon detection and management of other chronic diseases could be applied or extended to include CKD screening, risk stratification, and treatment.[105]

Table 4 | Defining success for CKD screening, risk stratification, and treatment programs

Outcomes	Indicators
Process (pertaining to health systems, providers, or patients)	
	• Screening with the correct tests (eGFR and UACR) • Timely and appropriate follow-up testing • Dietary, exercise, and smoking cessation counseling • Clinician CKD awareness as measured by documentation • Patient adherence to treatment plan • Appropriate nephrology/kidney transplant referrals • Availability of essential medicines and testing
Patient-centered	
	• Patient awareness of and attitudes toward CKD diagnosis • Patient experience and satisfaction • CKD-specific knowledge • Trust in physician • Quality of life • Shared decision-making for modality choice, including kidney replacement therapy and conservative management
Intermediate clinical	
	• Blood pressure control • Glycemic control • Statin use • ACEi/ARB use • SGLT2 inhibitor use • Vaccinations • Management of CKD-specific complications • Drug dosing/adverse drug events
Clinical	
	• CKD progression—eGFR slope, 40% decline in eGFR, doubling of serum creatinine, kidney failure • Hospitalization or emergency department visits • Cardiovascular events • Acute kidney injury events • Emergency dialysis starts • Pre-emptive transplant rates • All-cause mortality

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SGLT2, sodium-glucose cotransporter-2; UACR, urine albumin-to-creatinine ratio.

After implementation, CKD screening programs should be rigorously evaluated. There are a large variety of potential outcomes that can be studied for determining program success (Table 4). Categories of relevant endpoints include process measures (persons diagnosed with CKD, new treatments initiated), patient-centered measures (knowledge, awareness), intermediate clinical measures (blood pressure control, glycemic control), and clinical outcomes (cardiovascular events, kidney failure, and death). In addition, the resource impact and costs to the health system should be evaluated. Process, patient-centered, and intermediate clinical outcomes may be more feasible short- and medium-term targets than clinical endpoints to quantify the efficacy of CKD screening programs as they occur on shorter time horizons. In order to demonstrate an effect on clinical outcomes, studies would need to have large sample sizes and long durations of follow-up.

Conclusion 11. Financial and nonfinancial incentives need to be aligned toward CKD screening, risk stratification, and treatment. For health systems to be incentivized toward CKD early identification, payors would need to adopt a lifetime risk perspective, as the benefits of CKD screening and early intervention accrue slowly. Currently in many countries, physicians receive greater reimbursement for time spent treating patients with kidney failure than for an equal amount of time treating CKD at earlier stages.[106] To achieve success in CKD screening programs, resources need to be allocated toward prevention of kidney-related and cardiovascular adverse outcomes. CKD screening and treatment programs may benefit from utilizing financial incentives and/or penalties through pay-for-performance programs or alternative payment models. Tactics for reducing program costs include high-throughput testing, leveraging generic treatments including fixed-dose combinations, price negotiations, and strategic purchasing.

Conclusion 12. CKD screening in high-risk groups is likely to be cost-effective. The conference included experts in health economics who reviewed existing simulation models that evaluated the cost-effectiveness of CKD screening strategies and their impact on downstream health outcomes. Existing CKD detection and treatment simulation models indicate that screening high-risk individuals for CKD, including those with hypertension or diabetes, is likely to be cost-effective in high-income countries based upon thresholds of approximately $50,000-$150,000 USD per quality-adjusted life year.[30,107] However, it was emphasized that cost-effectiveness is not a binary assessment but rather represents a likelihood of cost-effectiveness at each $/quality-adjusted life year threshold, sensitive to the assumptions of the model. Important drivers of cost-effectiveness for CKD screening are the frequency of

testing, expected prevalence and incidence (testing yield) of CKD, and costs of confirmatory tests and treatment, among others.[30,108,109]

Several limitations of existing cost-effectiveness studies were identified and their correction suggested as future research directions.[109] First was the predominant focus on proteinuria, primarily dipstick proteinuria, which is insensitive for low levels of albuminuria. Second, there was very limited inclusion of cardiovascular outcomes, which are key complications of CKD that drive hospitalizations and mortality; most CKD patients are at much higher risk for cardiovascular events than progression to kidney failure. Third, few cost-effectiveness studies included LMICs. Fourth, models did not incorporate patient perspectives and patient-reported outcomes. Last, many models had outdated or incomplete evidence and potentially inaccurate assumptions.

The conference participants concluded that the appropriate time frame for simulating the effect of a CKD screening program is at minimum a decade and preferably a lifetime horizon. In addition, the health system perspective may undervalue the cost-effectiveness of CKD screening programs due to benefits in reducing disability and unemployment, so the societal perspective should also be considered. Projecting and monitoring cost-effectiveness may be done using high-quality natural history observational studies, clinical trial data on intervention effects, and local health system data on outcomes and costs.

Conclusion 13. CKD screening approaches may differ in LMIC countries. The conference members concluded that CKD screening approaches depend on the screening setting and available resources.[110] Managing the cost of early CKD screening programs is important for their successful implementation, especially in LMICs.[111,112] The conference participants recognized that the cost of measuring creatinine, cystatin C, and UACR in LMICs may be prohibitive.[113] In such settings, creatinine testing and dipstick screening for albuminuria were deemed to be an acceptable first step if followed by appropriate confirmatory testing. The conference participants called for universal availability of eGFR and albuminuria testing in primary care globally. The commitment and resources to treat persons who have newly detected CKD are critical components for any CKD screening program, as screening must be linked directly with risk-stratification and treatment capabilities.

In some countries, widespread testing for low eGFR by creatinine or cystatin C is already in place. In such settings, addition of a screening program designed to identify individuals with albuminuria but normal eGFR could identify additional high-risk individuals among whom treatments such as ACEi/ARBs may be beneficial. In resource-poor settings with elevated risk of proteinuric kidney disease, such as populations with prevalent *APOL1* high-risk variants, widespread screening with urine dipstick may be beneficial, ideally accompanied by eGFR measurement. Individuals identified by such screening approaches could then be evaluated with assessment of both eGFR (by creatinine, cystatin C, or both) and UACR to confirm the diagnosis of CKD and accurately risk stratify.

In communities with limited availability of primary care clinicians, community-based screening using nonphysician health care workers may be an option for CKD screening, risk stratification, and treatment. In some settings, treatments for late stages of CKD, such as dialysis or transplantation, may not be widely available, underscoring the importance of early CKD identification and intervention.[7]

Conclusions

The KDIGO Controversies Conference participants were unanimous that the bulk of evidence supports systematic approaches to screen for, risk stratify, and treat persons with CKD. Because interventions to slow CKD progression and reduce cardiovascular risk are evidence based and have been shown to improve outcomes, conference attendees agreed that the focus should be on strategies to maximize deployment of CKD screening, risk stratification, and treatment efforts. Ideally, these implementation efforts will be launched across multiple countries and myriad health systems. A worldwide effort will generate lessons learned and opportunities to share and disseminate strategies that are successful. Pragmatic trials should be designed to test CKD early-identification and intervention programs across various high-risk populations using different combinations of measures. Implementation efforts should engage policy makers, local clinicians, the community at large, and broader stakeholders in an iterative process. Ultimately, we call for large-scale randomized controlled trials to evaluate the effects of CKD screening, risk-stratification, and treatment programs compared with usual care on clinical endpoints. Implementing and evaluating systematic CKD screening efforts across large health care systems will build definitive evidence regarding their effectiveness to reduce morbidity and mortality from kidney disease for the global population.

APPENDIX

Other Conference Participants

Georgi Abraham, India; Zanfina Ademi, Australia; Radica Z. Alicic, USA; Ian H. de Boer, USA; Raj Deo, USA; Xiaoqiang Ding, China; Natalie Ebert, Germany; Kevin J. Fowler, USA; Linda F. Fried, USA; Ron T. Gansevoort, The Netherlands; Guillermo Garcia-Garcia, Mexico; Brenda R. Hemmelgarn, Canada; Jessica Lee Harding, USA; Joanna Q. Hudson, USA; Kunitoshi Iseki, Japan; Vasantha Jotwani, USA; Leah S. Karliner, USA; Andrew S. Levey, USA; Adrian Liew, Singapore; Peter J. Lin, Canada; Andrea O.Y. Luk, Hong Kong; Verónica Martínez, Mexico; Andrew E. Moran, USA; Mai Nguyen, USA; Gregorio T. Obrador, Mexico; Donal O'Donoghue, UK; Meda E. Pavkov, USA: Jessie Pavlinac, USA; Neil R. Powe, USA; Jesse C. Seegmiller, USA; Jenny I. Shen, USA; Rukshana Shroff, UK; Laura Solá, Uruguay; Maarten W. Taal, UK; James Tattersall, UK; Joseph A. Vassalotti, USA; Matthew R. Weir, USA; and Ella Zomer, Australia

DISCLOSURE

MGS declared having consultancy fees from Intercept Pharmaceuticals and University of Washington; stock equity from Cricket Health and TAI Diagnostics; research support from Booz Allen Hamilton; and future research support from Bayer U.S. SLT declared having consultancy fees from Bayer AG and research support from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). MEG declared having research support from the National

Kidney Foundation/National Institutes of Health (NIH). JHI declared having consultancy fees from AstraZeneca; future consultancy fees from Ardelyx; research support from NIDDK; and serving as Data and Safety Monitoring Board (DSMB) member for Sanifit. VJ declared having consultancy fees from AstraZeneca and Baxter Healthcare; and research support from Baxter Healthcare and GSK. A-PK declared having research support from European and Developing Countries Clinical Trials Partnership and future research support from the NIH. MM declared having consultancy fees from AstraZeneca and Bayer; future consultancy fees from AstraZeneca and Bayer; and research support from Fundación Gonzalo Río Arronte. NT declared having consultancy fees from AstraZeneca, Boehringer Ingelheim-Lilly, Janssen, and Otsuka; stock equity from Mesentech, Pulsedata, Rénibus, and Tricida; and research support from AstraZeneca, Janssen, Otsuka, and Tricida. MJ declared having consultancy fees from Amgen, AstraZeneca, Boehringer Ingelheim, Mundipharma, Merck Sharp & Dohme (MSD), and Vifor Fresenius Medical Care Renal Pharma; future consultancy fees from Astellas; speakers bureaus from Amgen, AstraZeneca, Menarini, Mundipharma, and MSD; research support from Amgen, MSD, and Otsuka; and future research support from AstraZeneca. WCW declared having consultancy fees from Akebia, AstraZeneca, Bayer, Janssen, Merck, Relypsa, and Vifor Fresenius Medical Care Renal Pharma; and research support from the NIH. All the other authors declared no competing interests.

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REFERENCES

1. Bikbov B, Purcell CA, Levey AS, et al. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2020;395:709–733.
2. Palmer Alves T, Lewis J. Racial differences in chronic kidney disease (CKD) and end-stage renal disease (ESRD) in the United States: a social and economic dilemma. *Clin Nephrol*. 2010;74(suppl 1):S72–S77.
3. Caskey FJ. Prevalence and incidence of renal disease in disadvantaged communities in Europe. *Clin Nephrol*. 2016;86:34–36.
4. Garcia M, Hernandez B, Ellington TG, et al. A lack of decline in major nontraumatic amputations in Texas: contemporary trends, risk factor associations, and impact of revascularization. *Diabetes Care*. 2019;42:1061–1066.
5. Crews DC, Bello AK, Saadi G, World Kidney Day Steering Committee. Burden, access, and disparities in kidney disease. *Kidney Int Rep*. 2019;4:372–379.
6. Curtis S, Komenda P. Screening for chronic kidney disease: moving toward more sustainable health care. *Curr Opin Nephrol Hypertens*. 2020;29:333–338.
7. Li PK, Garcia-Garcia G, Lui SF, et al., World Kidney Day Steering Committee. Kidney health for everyone everywhere-from prevention to detection and equitable access to care. *Kidney Int*. 2020;97:226–232.
8. Moyer VA. Screening for chronic kidney disease: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2012;157:567–570.
9. Qaseem A, Hopkins RH Jr, Sweet DE, et al. Screening, monitoring, and treatment of stage 1 to 3 chronic kidney disease: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2013;159:835–847.
10. American Diabetes Association. 11. Microvascular complications and foot care: standards of medical care in diabetes—2020. *Diabetes Care*. 2020;43(suppl 1):S135–S151.
11. Wilson JMG, Jungner G, World Health Organization. Principles and practice of screening for disease. 1968. Available at: https://apps.who.int/iris/handle/10665/37650. Accessed October 22, 2019.
12. Andermann A, Blancquaert I, Beauchamp S, Dery V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. *Bull World Health Organ*. 2008;86:317–319.
13. Xie X, Liu Y, Perkovic V, et al. Renin-angiotensin system inhibitors and kidney and cardiovascular outcomes in patients with CKD: a bayesian network meta-analysis of randomized clinical trials. *Am J Kidney Dis*. 2016;67:728–741.
14. Herrington WG, Emberson J, Mihaylova B, et al. Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. *Lancet Diabetes Endocrinol*. 2016;4:829–839.
15. Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103–2116.
16. Ruospo M, Saglimbene VM, Palmer SC, et al. Glucose targets for preventing diabetic kidney disease and its progression. *Cochrane Database Syst Rev*. 2017;6:CD010137.
17. Coca SG, Ismail-Beigi F, Haq N, et al. Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus: systematic review and meta-analysis intensive glucose control in type 2 diabetes. *Arch Intern Med*. 2012;172:761–769.
18. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380:2295–2306.
19. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644–657.
20. Tuot DS, Plantinga LC, Hsu CY, et al. Chronic kidney disease awareness among individuals with clinical markers of kidney dysfunction. *Clin J Am Soc Nephrol*. 2011;6:1838–1844.
21. White SL, Yu R, Craig JC, et al. Diagnostic accuracy of urine dipsticks for detection of albuminuria in the general community. *Am J Kidney Dis*. 2011;58:19–28.
22. Wright Nunes J, Roney M, Kerr E, et al. A diagnosis of chronic kidney disease: despite fears patients want to know early. *Clin Nephrol*. 2016;86:78–86.
23. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296–1305.
24. Tangri N, Grams ME, Levey AS, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. *JAMA*. 2016;315:164–174.
25. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013;3:1–150.
26. Wanner C, Tonelli M. KDIGO clinical practice guideline for lipid management in CKD: summary of recommendation statements and clinical approach to the patient. *Kidney Int*. 2014;85:1303–1309.
27. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73:3168–3209.
28. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:1269–1324.
29. Boulware LE, Jaar BG, Tarver-Carr ME, et al. Screening for proteinuria in US adults: a cost-effectiveness analysis. *JAMA*. 2003;290:3101–3114.
30. Komenda P, Ferguson TW, Macdonald K, et al. Cost-effectiveness of primary screening for CKD: a systematic review. *Am J Kidney Dis*. 2014;63:789–797.
31. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA Cancer J Clin*. 2018;68:250–281.
32. Grams ME, Chow EK, Segev DL, Coresh J. Lifetime incidence of CKD stages 3–5 in the United States. *Am J Kidney Dis*. 2013;62:245–252.
33. Nelson RG, Grams ME, Ballew SH, et al. Development of risk prediction equations for incident chronic kidney disease. *JAMA*. 2019;322:2104–2114.
34. Crews DC, Liu Y, Boulware LE. Disparities in the burden, outcomes, and care of chronic kidney disease. *Curr Opin Nephrol Hypertens*. 2014;23:298–305.

35. Morton RL, Schlackow I, Mihaylova B, et al. The impact of social disadvantage in moderate-to-severe chronic kidney disease: an equity-focused systematic review. *Nephrol Dial Transplant*. 2016;31:46–56.
36. Nicholas SB, Kalantar-Zadeh K, Norris KC. Socioeconomic disparities in chronic kidney disease. *Adv Chronic Kidney Dis*. 2015;22:6–15.
37. United States Renal Data System. 2018 USRDS annual data report: epidemiology of kidney disease in the United States. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health; 2018. Available at: https://www.usrds.org/annual-data-report/previous-adrs/.
38. Essue BM, Laba T-L, Knaul F, et al. Economic burden of chronic ill health and injuries for households in low-and middle-income countries. In: Jamison DT, Gelband H, Horton S, et al., eds. *Disease Control Priorities: Improving Health and Reducing Poverty*. 3rd ed. Washington, DC: International Bank for Reconstruction and Development/World Bank; 2017. chapter 6.
39. Zelnick LR, Weiss NS, Kestenbaum BR, et al. Diabetes and CKD in the United States population, 2009–2014. *Clin J Am Soc Nephrol*. 2017;12:1984–1990.
40. United States Renal Data System. *2019 USRDS annual data report: epidemiology of kidney disease in the United States*. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health; 2019. Available at: https://www.usrds.org/annual-data-report/.
41. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007;298:2038–2047.
42. Hallan SI, Matsushita K, Sang Y, et al. Age and association of kidney measures with mortality and end-stage renal disease. *JAMA*. 2012;308:2349–2360.
43. Matsushita K, Ballew SH, Coresh J, et al. Measures of chronic kidney disease and risk of incident peripheral artery disease: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol*. 2017;5:718–728.
44. Delanaye P, Jager KJ, Bokenkamp A, et al. CKD: a call for an age-adapted definition. *J Am Soc Nephrol*. 2019;30:1785–1805.
45. Seidu S, Barrat J, Khunti K. Clinical update: the important role of dual kidney function testing (ACR and eGFR) in primary care: identification of risk and management in type 2 diabetes. *Prim Care Diabetes*. 2020;14:370–375.
46. Litvin CB, Hyer JM, Ornstein SM. Use of clinical decision support to improve primary care identification and management of chronic kidney disease (CKD). *J Am Board Fam Med*. 2016;29:604–612.
47. Perkins RM, Chang AR, Wood KE, et al. Incident chronic kidney disease: trends in management and outcomes. *Clin Kidney J*. 2016;9:432–437.
48. Abdel-Kader K, Greer RC, Boulware LE, Unruh ML. Primary care physicians' familiarity, beliefs, and perceived barriers to practice guidelines in non-diabetic CKD: a survey study. *BMC Nephrol*. 2014;15:64.
49. Stevens PE, O'Donoghue DJ, de Lusignan S, et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. *Kidney Int*. 2007;72:92–99.
50. Shlipak MG, Matsushita K, Arnlov J, et al. Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med*. 2013;369:932–943.
51. Lees JS, Welsh CE, Celis-Morales CA, et al. Glomerular filtration rate by differing measures, albuminuria and prediction of cardiovascular disease, mortality and end-stage kidney disease. *Nat Med*. 2019;25:1753–1760.
52. Ebert N, Shlipak MG. Cystatin C is ready for clinical use. *Curr Opin Nephrol Hypertens*. 2020;29:591–598.
53. Ismail OZ, Bhayana V, Kadour M, et al. Improving the translation of novel biomarkers to clinical practice: the story of cystatin C implementation in Canada: a professional practice column. *Clin Biochem*. 2017;50:380–384.
54. Vassalotti JA, Centor R, Turner BJ, et al. Practical approach to detection and management of chronic kidney disease for the primary care clinician. *Am J Med*. 2016;129:153–162.
55. Vassalotti JA, Thavarajah S. Combined albuminuria and estimated GFR laboratory reporting impacts primary care management of CKD. *Kidney Med*. 2020;2:235–238.
56. Xia J, Wang L, Ma Z, et al. Cigarette smoking and chronic kidney disease in the general population: a systematic review and meta-analysis of prospective cohort studies. *Nephrol Dial Transplant*. 2017;32:475–487.
57. Thompson S, Wiebe N, Padwal RS, et al. The effect of exercise on blood pressure in chronic kidney disease: a systematic review and meta-analysis of randomized controlled trials. *PLoS One*. 2019;14:e0211032.
58. vanden Wyngaert K, van Craenenbroeck AH, van Biesen W, et al. The effects of aerobic exercise on eGFR, blood pressure and VO_2 peak in patients with chronic kidney disease stages 3–4: a systematic review and meta-analysis. *PLoS One*. 2018;13:e0203662.
59. Bach KE, Kelly JT, Palmer SC, et al. Healthy dietary patterns and incidence of CKD: a meta-analysis of cohort studies. *Clin J Am Soc Nephrol*. 2019;14:1441–1449.
60. Kelly JT, Palmer SC, Wai SN, et al. Healthy dietary patterns and risk of mortality and ESRD in CKD: a meta-analysis of cohort studies. *Clin J Am Soc Nephrol*. 2017;12:272–279.
61. Bress AP, Bellows BK, King JB, et al. Cost-effectiveness of intensive versus standard blood-pressure control. *N Engl J Med*. 2017;377:745–755.
62. Messow CM, Isles C. Meta-analysis of statins in chronic kidney disease: who benefits? *QJM*. 2017;110:493–500.
63. Sanguankeo A, Upala S, Cheungpasitporn W, Ungprasert P, Knight EL. Effects of statins on renal outcome in chronic kidney disease patients: a systematic review and meta-analysis. *PLoS One*. 2015;10:e0132970.
64. Schlackow I, Kent S, Herrington W, et al. Cost-effectiveness of lipid lowering with statins and ezetimibe in chronic kidney disease. *Kidney Int*. 2019;96:170–179.
65. Zoungas S, Arima H, Gerstein HC, et al. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. *Lancet Diabetes Endocrinol*. 2017;5:431–437.
66. Neuen BL, Ohkuma T, Neal B, et al. Effect of canagliflozin on renal and cardiovascular outcomes across different levels of albuminuria: data from the CANVAS program. *J Am Soc Nephrol*. 2019;30:2229–2242.
67. Heerspink HJL, Stefánsson BV, Correa-Rotter R. DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383:1436–1446.
68. Wheeler DC, Stefansson BV, Jongs N, et al. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. *Lancet Diabetes Endocrinol*. 2021;9:22–31.
69. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311–322.
70. Mann JF, Ørsted DD, Brown-Frandsen K, et al. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med*. 2017;377:839–848.
71. Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol*. 2018;6:605–617.
72. Raphael KL, Isakova T, Ix JH, et al. A randomized trial comparing the safety, adherence, and pharmacodynamics profiles of two doses of sodium bicarbonate in CKD: the BASE pilot trial. *J Am Soc Nephrol*. 2020;31:161–174.
73. Novick TK, Surapaneni A, Shin JI, et al. Prevalence of opioid, gabapentinoid, and NSAID use in patients with CKD. *Clin J Am Soc Nephrol*. 2018;13:1886–1888.
74. Muanda FT, Weir MA, Bathini L, et al. Association of baclofen with encephalopathy in patients with chronic kidney disease. *JAMA*. 2019;322:1987–1995.
75. Lopez-Vargas PA, Tong A, Howell M, Craig JC. Educational interventions for patients with CKD: a systematic review. *Am J Kidney Dis*. 2016;68:353–370.
76. Narva AS, Norton JM, Boulware LE. Educating patients about CKD: the path to self-management and patient-centered care. *Clin J Am Soc Nephrol*. 2016;11:694–703.
77. Kramer H, Jimenez EY, Brommage D, et al. Medical nutrition therapy for patients with non-dialysis-dependent chronic kidney disease: barriers and solutions. *J Acad Nutr Diet*. 2018;118:1958–1965.
78. Teasdale EJ, Leydon G, Fraser S, et al. Patients' experiences after CKD diagnosis: a meta-ethnographic study and systematic review. *Am J Kidney Dis*. 2017;70:656–665.
79. Sperati CJ, Soman S, Agrawal V, et al. Primary care physicians' perceptions of barriers and facilitators to management of chronic kidney disease: a mixed methods study. *PLoS One*. 2019;14:e0221325.
80. Narva AS, Briggs M. The National Kidney Disease Education Program: improving understanding, detection, and management of CKD. *Am J Kidney Dis*. 2009;53(3 suppl 3):S115–S120.

81. Kidney Health Initiative. Technology roadmap for innovative approaches to renal replacement therapy. October 2018. Available at: https://www.asn-online.org/g/blast/files/KHI_RRT_Roadmap1.0_FINAL_102318_web.pdf. Accessed December 10, 2020.
82. Diamantidis CJ, Becker S. Health information technology (IT) to improve the care of patients with chronic kidney disease (CKD). *BMC Nephrol*. 2014;15:7.
83. National Kidney Disease Education Program. Available at: http://www.nkdep.nih.gov. Accessed September 16, 2020.
84. Tuot DS, Boulware LE. Telehealth applications to enhance CKD knowledge and awareness among patients and providers. *Adv Chronic Kidney Dis*. 2017;24:39–45.
85. Singh K, Diamantidis CJ, Ramani S, et al. Patients' and nephrologists' evaluation of patient-facing smartphone apps for CKD. *Clin J Am Soc Nephrol*. 2019;14:523–529.
86. Siddique AB, Krebs M, Alvarez S, et al. Mobile apps for the care management of chronic kidney and end-stage renal diseases: Systematic search in app stores and evaluation. *JMIR Mhealth Uhealth*. 2019;7:e12604.
87. Lewis RA, Lunney M, Chong C, Tonelli M. Identifying mobile applications aimed at self-management in people with chronic kidney disease. *Can J Kidney Health Dis*. 2019;6, 2054358119834283.
88. Lambert K, Mullan J, Mansfield K, Owen P. Should we recommend renal diet-related apps to our patients? An evaluation of the quality and health literacy demand of renal diet-related mobile applications. *J Ren Nutr*. 2017;27:430–438.
89. Rogers D. Patient perspective of smartphone-based apps for CKD self-care. *Clin J Am Soc Nephrol*. 2019;14:483–484.
90. Tuttle KR, Alicic RZ, Duru OK, et al. Clinical characteristics of and risk factors for chronic kidney disease among adults and children: an analysis of the CURE-CKD registry. *JAMA Netw Open*. 2019;2:e1918169.
91. Fraser SD, Parkes J, Culliford D, et al. Timeliness in chronic kidney disease and albuminuria identification: a retrospective cohort study. *BMC Fam Pract*. 2015;16:18.
92. Ravera M, Noberasco G, Weiss U, et al. CKD awareness and blood pressure control in the primary care hypertensive population. *Am J Kidney Dis*. 2011;57:71–77.
93. Razavian M, Heeley EL, Perkovic V, et al. Cardiovascular risk management in chronic kidney disease in general practice (the AusHEART study). *Nephrol Dial Transplant*. 2012;27:1396–1402.
94. Nash DM, Brimble S, Markle-Reid M, et al. Quality of care for patients with chronic kidney disease in the primary care setting: a retrospective cohort study from Ontario, Canada. *Can J Kidney Health Dis*. 2017;4, 2054358117703059.
95. Boulware LE, Carson KA, Troll MU, Powe NR, Cooper LA. Perceived susceptibility to chronic kidney disease among high-risk patients seen in primary care practices. *J Gen Intern Med*. 2009;24:1123–1129.
96. Boulware LE, Troll MU, Jaar BG, Myers DI, Powe NR. Identification and referral of patients with progressive CKD: a national study. *Am J Kidney Dis*. 2006;48:192–204.
97. Greer RC, Liu Y, Cavanaugh K, et al. Primary care physicians' perceived barriers to nephrology referral and co-management of patients with CKD: a qualitative study. *J Gen Intern Med*. 2019;34:1228–1235.
98. Tsang JY, Blakeman T, Hegarty J, et al. Understanding the implementation of interventions to improve the management of chronic kidney disease in primary care: a rapid realist review. *Implement Sci*. 2016;11:47.
99. Hallan SI, Rifkin DE, Potok OA, et al. Physicians' recognition and management of kidney disease: a randomized vignette study evaluating the impact of the KDIGO 2012 CKD classification system. *Kidney Med*. 2020;2:258–266.
100. Tangri N, Stevens LA, Griffith J, et al. A predictive model for progression of chronic kidney disease to kidney failure. *JAMA*. 2011;305:1553–1559.
101. Smekal MD, Tam-Tham H, Finlay J, et al. Patient and provider experience and perspectives of a risk-based approach to multidisciplinary chronic kidney disease care: a mixed methods study. *BMC Nephrol*. 2019;20:110.
102. Reilly R, Evans K, Gomersall J, et al. Effectiveness, cost effectiveness, acceptability and implementation barriers/enablers of chronic kidney disease management programs for indigenous people in Australia, New Zealand and Canada: a systematic review of mixed evidence. *BMC Health Serv Res*. 2016;16:119.
103. Flodgren G, Hall AM, Goulding L, et al. Tools developed and disseminated by guideline producers to promote the uptake of their guidelines. *Cochrane Database Syst Rev*. 2016;8:CD010669.
104. Gagliardi AR, Alhabib S, members of Guidelines International Network Implementation Working G. Trends in guideline implementation: a scoping systematic review. *Implement Sci*. 2015;10:54.
105. Mytton OT, Jackson C, Steinacher A, et al. The current and potential health benefits of the National Health Service Health Check cardiovascular disease prevention programme in England: a microsimulation study. *PLoS Med*. 2018;15:e1002517.
106. Centers for Medicare and Medicaid Services, Health and Human Services. Medicare PROGRAM; revisions to payment policies under the physician fee schedule and other revisions to Part B for CY 2018; Medicare Shared Savings Program requirements; and Medicare Diabetes Prevention Program. Final rule. *Fed Regist*. 2017;82(219):52976–53371.
107. Farmer AJ, Stevens R, Hirst J, et al. Optimal strategies for identifying kidney disease in diabetes: properties of screening tests, progression of renal dysfunction and impact of treatment—systematic review and modelling of progression and cost-effectiveness. *Health Technol Assess*. 2014;18:1–128.
108. Yarnoff BO, Hoerger TJ, Simpson SK, et al. The cost-effectiveness of using chronic kidney disease risk scores to screen for early-stage chronic kidney disease. *BMC Nephrol*. 2017;18:85.
109. Sutton AJ, Breheny K, Deeks J, et al. Methods used in economic evaluations of chronic kidney disease testing—a systematic review. *PLoS One*. 2015;10:e0140063.
110. Lunney M, Alrukhaimi M, Ashuntantang GE, et al. Guidelines, policies, and barriers to kidney care: findings from a global survey. *Kidney Int Suppl*. 2018;8:30–40.
111. Jha V, Arici M, Collins AJ, et al. Understanding kidney care needs and implementation strategies in low- and middle-income countries: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. *Kidney Int*. 2016;90:1164–1174.
112. George C, Mogueo A, Okpechi I, et al. Chronic kidney disease in low-income to middle-income countries: the case for increased screening. *BMJ Glob Health*. 2017;2:e000256.
113. Bello AK, Levin A, Tonelli M, et al. Assessment of global kidney health care status. *JAMA*. 2017;317:1864–1881.