# KDIGO Controversies Conference on Early Identification & Intervention in CKD
# - Public Review Comments -

**As of September 10, 2019**
**Industry comments are highlighted in blue**

**Jay Shubrook - Touro University California (Doctor / Physician)**
I have a primary care and Diabetology background and have been working on better training the primary care workforce on managing diabetes and its complications. I am very interested in learning more about your initiative.
Thank you! Jay Shubrook

**Celeste Boucher - Albany Medical Center Dialysis (RN, CDN)**
I work with both the pediatric and adult populations. I believe early detection by means of specific targeted tests & medications is crucial in treating and delaying kidney disease progression to ESKD. Dialysis dependency has so many potential complications and the impact on lives and healthcare system is astronomical. Research is imperative to develop more improved earlier testing and also potential for development and transplantation of kidneys grown from stem cells reducing immunosuppressant therapies for improved life spans and outcomes.

**Carmen Peralta - Cricket Health (Doctor / Physician)**
Thank you for tackling this great topic. One major piece that is missing is to tackle the question of HOW DO WE EVALUATE SUCCESS? To that end, what clinical outcomes should be followed after detection and interventions? (slow progression of disease, delay dialysis, reduce cardiovascular events, for example). Specifically, more work is required to define how to measure these outcomes with real world data.

**Magdy Elsharkawy - Ain-Shams University (Doctor / Physician)**
Topics should focus on: Media and governmental involvement into every screening and prevention program. Food industry should be involved in all preventive programs It is of at most importance to address school students and their teachers

about kidney disease. Screen young adults in the schools every 3 years with urine and blood pressure measurement.

**Rumeyza Kazancioglu - Bezmialem Vakif University (Doctor / Physician)**
I really liked your topic but please pay attention to geographical and resource differences worldwide.

**Mona Alrukhaimi - Dubai Medical College (Doctor / Physician)**
Excellent scope. Nothing to add

**Jessie Pavlinac - Oregon Health & Science University (Renal Dietitian)**
There is one comment about diet in the Scope and no references concerning nutrition intervention in slowing the progression of CKD and managing DM. Also I hope your invited attendees include experts in the area of nutritional assessment and intervention in this population.

**Rodrigo Bueno de Oliveira - University of Campinas (Doctor / Physician)**
Who it concern, I would address some comments/suggestions for workgroup 1: Early CKD Detection Measures.
1. CKD diagnosis and classificaton is largely based on measurements of eGFR;
2. GFR can be afected by drugs with intrarenal hemodynamic effects (SGLTi, ACEi, etc.);
3. Residual renal function can be affect by the same drugs plus dietary habits (protein load);
4. GFR can be assessed in different condictions: "basal" GFR (hipoproteic diet) or "stressed GFR" (AA infusion, dopamine or glucagon infusion);
Based on the statments above one could argue:

- Is RRF determination important to evaluation of true GFR?
- Is RRF important to predict progression rate?
- What are the implications of RRT at clinical setting?
- Should doctors access RRF?

References
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**Richard Glassock - Geffen School of Medicine at UCLA (Doctor / Physician)**
1) be sure to take a very careful and critical look at the estimates of the global burden of CKD - I think they are very much overstated
2) be sure to take a very critical look at CKD l screening strategies, especially those based on eGFR. The evidence that they do very much to improve the lives of patients with CKD is very, very weak and almost all observational or theoretical. It is time to move onto RCT of screening in a serious way.
3) since CKD is largely a disease (or diseases) of the elderly awareness programs should focus on this group- using age-adapted criteria for CKD definition.
4) will better recognition of HTN reduced the prevalence of CKD or ESRD in non-diabetics? I think not - the message from SPRINT needs to be carefully examined.
5) don't forget mGFR - don't spend too much time on eGFR - Cystatin C. It is no better than an eGFR-creatinine + a C-RP.

**Diana Garcia - Private Practice & Teaching (Doctor / Physician)**
It will be very interesting to hear something about nephrology specific in Latinos. Also I think it's necessary to update the CKD guidelines, and I hope you show us the new updates about this. I will be waiting the details.

**Arif Khwaja - Sheffield Kidney Institute (Doctor / Physician)**
i) The scope of work takes it as a given that early detection of CKD de facto leads to improved outcomes. It would be good to review the evidence for this the impact of early detection on other diseases (eg prostate cancer) remains far from certain.
ii) For the vast majority of people CKD is effectively a surrogate for age and vascular disease and so important that the scope of work focuses on a comprehensive CV strategy of which CKD is a part of rather than a separate strategy for CKD
iii) We have a number of sister renal centres in developing countries and its clear that the problems are very different. In those countries there is no early detection - just crashlanding at CKD 5 - it is pleasing to see the scope of work seems to recognise that there needs to be fundamentally different models of care according to resource setting

**Linda McCann – No current affiliation (Dietitian)**
This is a very ambitious undertaking, very well thought out and comprehensive. Well done. This may be a little off the grid, but a question I have been wondering about is related to dietary patterns. When I was in practice I saw a couple examples of patients who were likely stage 4 or heading into stage 5 who seemed to precipitate their decline in kidney function with protein sparing fast for weight loss. I am wondering if the strong reimergence of high protein, very low carbohydrate weight loss efforts have had an effect on progression to needing kidney replacement

therapy. We have always had a bit of a mixed message about the benefit of reducing protein intake to preserve function (after confirming someone eats a lot of protein more than suggested amounts). Does the expanded use of Keto diet, Atkins type diets create any problems. It might be of interest to at least suggest that a dietary history ask the question about recent use of such diets. My practice always included a full diet history including a detailed assessment of usual and recent dietary intake to understand what modifications might be warranted. The process of obtaining an accurate diet history is time consuming and needs a definitive process. One downfall of a majority of studies trying to define optimal nutrient intake seems to be that we struggle to get accurate information about actual intake (i.e. using estimates of protein intake to estimate phosphorus intake which doesn't necessarily consider the phosphorus content or digestibility of the protein source) - but also recognizing that food composition data bases are not that accurate for some nutrients. Sorry - long diatribe just to say it might be interesting to begin a discussion or suggest some research question related to use of fad diets. Again, the scope of work seems very comprehensive and complete and promises to help clinical practice and patient understanding of the disease and its complexity. Thank you for your efforts on behalf of those who have kidney disease.

**James Tattersall - UK National Health Service (Healthcare Artificial Intelligence Consultant)**

I think the extent and mechanisms for patient engagement should be discussed explicitly. For example, in Group 1, early detection measures, there should be an item to discuss whether and how screening should be accessed by patients directly (e.g. by home test kit, or as an open access service provided by pharmacy) or administered by the patients healthcare provider as at present. Should screening be advertised using AI-targeted methods as currently used by google, facebook etc. ?
In group 2: The item "What promising emerging opportunities or technologies (e.g.,AI) exist for automated and targeted surveillance approaches to identify at-risk individuals?' is far too timid. This should be at top position and titled "How should we be using AI to facilitate identification and surveillance of at-risk individuals?"
In group 3: The item "What is the role of self-management and new technologies (mobile apps) when detecting/managing CKD?" is far too timid. It should be a top position and titled "How can we facilitate self management in detecting and managing CKD using mobile and web applications?"
In Group 4: I suggest an additional item with high priority "To what extent should patients be able to access CKD management tools directly, independently of healthcare providers?"

**Rukshana Shroff Consultant in Paediatric Nephrology (Doctor / Physician)**
Some areas to consider are:
1. with reference to pediatric practice:
- school screening programmes to detect hematuria/ proteinuria
- follow-up of children with multiple UTIs or UTIs caused by resistant / unusual organisms
- follow-up of patients with abnormal antenatal scans
2. For adults and children:
- follow-up for survivors of AKI (eg ICU patients who required CVVH)
Thank you for this opportunity to submit comments.

**Kevin Fowler - Kidney Health Initiative (Patient)**
I would like the workgroup to consider adding these meeting topics: Compare nephrology's adoption of novel medications and therapies to other specialties. Acknowledge that there are multiple up stream interventions for Diabetic Kidney Disease, ADPKD, FSGS, IGAN, Alport syndrome, etc and that the global nephrology community is for the most part treating the downstream consequences of kidney disease. If nephrology does not change their care models, then the pharmaceutical industry may cut back on their investment. I suggest that the adoption of ACEs/ARBs be included as part of the discussion because a January 30, 2019 JASN article noted that the use of ACES/ARBs have plateaued. This is significant and disconcerting because these medications have been off patent for over a decade. There needs to be a discussion about reimbursement incentives that support dialysis rather than early intervention.

**Irene Mewburn - BEAT-CKD and AKTN (Patient)**
If invited I have a strong interest in Groups 1 and 3. After attending the AKI Conference, I am becoming more affiliated with different ones. From an Allied Health perspective I have a very strong interest in Mental Health as an early follow-up (Group 3). From a Patient Perspective with early detection, the problems associated with Uraemia were strongly overlooked. If this had been detected earlier I may not have ended up with Renal Failure (Group 1). I was under Dr P. Danby in Melbourne at that time and had my Biopsy for diagnosis done at Monash.

**Laura Sola - CASMU-IAMPP (Doctor / Physician)**
It is a very comprehensive agenda. I would only ad for GROUP 3: Additionally, to asking when, how, and how often to monitor preventive interventions, we should know which would be an appropriate way to monitor the effectiveness of the interventions regarding CKD progression. How should we monitor progression, Δ estimated glomerular filtration rate? defining stabilization or progression of CKD?

**Cibele Isaac Rodrigues - Pontifícia Universidade Católica de São Paulo (Doctor / Physician)**

Considerations: Group 1: Early CKD Detection Measures: cystatin C is not a possibility marker of CKD in our country (Brasil), on the other hand serum creatinine and GFRe is easily available and is a low cost laboratory marker with well-known limitations. Proteinuria and albuminuria creatinine ratio is also available, but not in all states. Group 3: For the implementation of the guideline it has to be translated by the local nephrology societies and be reliable. Diagrams and flow charts are more likely to be read and to be follow by clinicians. In Brasil the majority of the population has mobile phone. Detection and management of CKD and its risk factors with Apps will be possible. Agree with the scope.

**Eiichiro Kanda - Kawasaki Medical School (Doctor / Physician)**

Thank you very much for your asking for my comments, which are below: Background The number of chronic kidney disease (CKD) patients has been increasing. To prevent the progression of CKD, and improve their prognosis, early identification of CKD patients and intervention are necessary. There are about 334,000 dialysis patients in Japan. The underlying diseases requiring dialysis are diabetic kidney disease (DKD) (42.5%), chronic nephritis (16.3%), and nephrosclerosis (14.7%), which have been increasing with aging in Japan. For CKD prevention, it is a key strategy to identify DKD and nephrosclerosis patients and treat them at an early stage. However, because in nephrosclerosis and in some cases of DKD, proteinuria is not observed, it is difficult to identify these patients at early stage. My previous investigations of early CKD I conducted several cohort studies of early CKD. Here, I describe the results of two studies.

① ・Importance of glomerular filtration rate change as surrogate endpoint for the future incidence of end-stage renal disease in general Japanese population: community-based cohort study (Clin Exp Nephrol (2018) 22:318–327) ・ Guidelines for clinical evaluation of chronic kidney disease (Clinical and Experimental Nephrology (2018) 22:1446–1475) This cohort study in Japan for 15 years included 58,292 healthy persons with high eGFR (>60 ml/min/1.73m2) and 10,946 persons with low eGFR (<60 ml/min/1.73m2). In high eGFR group, which is the target of this KGIDO project, end-stage kidney disease (ESKD) was only observed in 186 persons (20.8/100,000 person-years). The risk of ESKD and eGFR changes showed a U-shaped relationship. That is, because the persons with high risks of ESKD may show not only a decrease in eGFR but also an increase in eGFR (improved eGFR). This is our aim to identify these patients with an increase in eGFR

at an early CKD stage. The following difficulties of analysis were encountered: (1) Because the number of the events are very small, large sample size and a long observation period are required. (2) The small number of events makes analysis using classical statistics (frequentist) difficult. (3) Because eGFR often changes (increase or decrease), a long observation period is needed to confirm the trend of decrease in eGFR.

② ・Identifying progressive CKD from healthy population using Bayesian network and artificial intelligence: A worksite-based cohort study (Scientific Reports volume 9, Article number: 5082 (2019)) Considering the study ①, we conducted another cohort study in Japan to identify persons with a high risk of early CKD. In this study, enrolled persons (eGFR>60), 7465, were enrolled, and they were followed up for 9 years. Trajectory analysis showed that their GFR fluctuated (increase or decrease). Most of the persons at stages G1 A1 (70.8%) and G2 A1 (81.4%) showed stable CKD. On the other hand, 10.6% of the persons, who were initially at stage G2 A1 at the start showed improvement in CKD stage (G1 A1), and 2.3% were at stage G3 A1 one year later. Moreover, 9 years later, 6.6% of the persons at stage G2 A1 showed improvement in eGFR (G1 A1), and 7.2% showed progression of CKD (G3a A1). Persons at CKD stage G1 A1 showed greater progression than those at stage G2 A1. Then, the factors associated with early CKD progression were investigated using the Bayesian network, because the "frequentist analysis" was inapplicable. The time-series changes in the prognostic category of CKD were more related to the outcome than the baseline characteristics, such as hypertension and diabetes mellitus. Moreover, support vector machines including time-series data of the prognostic category of CKD detected the high possibility of the progression of CKD not only in persons at very high risks but also in those at low risks at baseline (G1 A1 and G2 A1). This study showed that (1) eGFR and proteinuria often change for many years. (2) Time-series observation is necessary to identify persons with a high risk of early CKD. (3) After the evaluation of kidney function at a health checkup, it is necessary to follow up not only patients at high risks but also those at low risks at baseline for many years.

Comments Considering the background, my comments are as follows. Group 1: Early CKD Detection Measures >What are strengths and weaknesses of currently available measures to identify and categorize CKD; values of discriminating risk; specificity; and costs? As described above, eGFR changes markedly, which makes it difficult to predict CKD progression. Prediction of CKD progression using support vector machines including time-series data on CKD stage showed a high accuracy of 88% (logistic regression model could not identify persons at high risks). >What

are the ideal CKD detection measures and the influence of demographic characteristics on; the relative value of creatinine only versus adding cystatin C, albuminuria/proteinuria, or a triple-marker strategy? eGFR based on creatinine (eGFRcr) alone is insufficient to identify persons at high risks of CKD. Because measured GFR cannot be measured frequently, it is not appropriate for clinical settings at medical facilities. eGFR based on cystatin C (eGFRcyc) is inaccurate at stage 5 (GFR<10). Moreover, there are limitations of measurement of mGFR and eGFRcyc depending on the health insurance coverage. Therefore, the combination of eGFRcr and proteinuria is useful for evaluating kidney function. >What criteria should be used to evaluate potential screening strategies: accuracy versus measured GFR; prediction of adverse outcomes; sensitivity versus specificity; stage classification? The criteria should be selected on the basis of its purpose. To screen persons with high risks, high sensitivity criteria are appropriate. For definitive diagnosis, high-specificity criteria are better. >What are the costs of commonly used kidney health measures, including creatinine, cystatin C, proteinuria, dipsticks and albuminuria? >What are the relative yields (utility) from testing proteinuria versus albuminuria; and are dipsticks adequate? >Is there a potential role for point-of-care (POC) testing, such as novel POCs for real-time GFR or creatinine measurements, or measures of urine albumin, in a public health CKD program? In Japan, at health checkups, dipsticks are used for the general population. Then, a person found to have proteinuria is further examined for serum creatinine level (eGFR) and proteinuria level. Albuminuria is examined only in diabetes mellitus patients in accordance with the Japanese National Health Insurance System. >Where should testing be conducted and how often should it be repeated in a CKD detection and intervention program? What new tests or biomarkers are being developed that might expand diagnosis beyond glomerular measures in order to detect and monitor kidney tubule health? As described above, time-series measurements of eGFR and proteinuria (once a year) for more than 3 years are required to identify persons with high risks of CKD. >Propose research agenda related to this section A large-scale retrospective cohort study. Group 2: Populations to Screen and Identifying At-Risk Individuals >Should screening for occult CKD in an early detection program be directed to populations or targeted to high-risk individuals, using any combination of kidney measures? Combination of eGFR and proteinuria are useful to evaluate kidney function. >What are the optimum settings (community based vs primary care practices) for capturing at risk individuals? It depends on the purpose. To screen persons with high risks of early incident CKD, a community-based study is better. To prevent the progression of CKD, a primary-care-practice-based study is better. >What is the difference between a surveillance program and a screening/detection intervention, and what can we learn from prior programs including the prevalence of CKD? A surveillance

program is useful for investigating the prevalence of CKD as a public health concern. On the other hand, screening is important for treating CKD at the individual level. > Should the prevalence of CKD or the absolute risk of CKD complications and ESKD be used as the first step for an early detection intervention program? A cross-sectional study of the prevalence of CKD can easily be carried out than a research (cohort study) on the absolute risks of CKD complications and ESKD. >If high-risk groups are to be identified, should the absolute risk estimate be based on lifetime risk or within a finite interval of time (e.g., 10-yr risk), and should the risk estimates be dependent on laboratory measures? For early incident CKD, a finite interval of time (e.g., 10-yr risk) is appropriate. Studies of lifetime risk take a longer time than studies of the finite interval of time. >How do early detection strategies apply at extremes of age, such as in pediatrics or among older adults? Aging is a growing problem. In Japan, the population of people aging more than 80 years has been increasing. >How might we identify individuals that need re-screening after an initially negative screen? As described above, an increase in eGFR does not always indicate an improvement of kidney function. Time-series data are needed to screen for persons with high risks. >Are there social, behavioral, occupational or environmental exposures that would warrant population screening rather than individual risk-based targeting? In Japan, school and workplace health checkups are carried out. >Should there be a role for reflex family screening if ancestral factors, such as high-risk APOL1 genotype, are present among screened individuals? This should be considered from the viewpoint of cost effectiveness. >What promising emerging opportunities or technologies (e.g., AI) exist for automated and targeted surveillance approaches to identify at-risk individuals?' As described above, I have conducted a cohort study of early CKD using AI (support vector machine). If you will give me a chance, I will be glad to present the results of our study in the conference. >Propose research agenda related to this section. A large-scale retrospective cohort study including time-series data of healthy population such as community-based health checkup. Group 3: Optimal Interventions and Implementation after CKD Detection >What Interventions (e.g., lifestyles, diet, pharmaceuticals) should we adopt to prevent CKD onset and/or slow CKD progression and to prevent CVD and HF? A combination of these therapies should be adopted. It is difficult for only a single therapy to prevent the progression of CKD. >Beyond BP, glycemic and lipid control, what are other risk factors that we should be targeting? (e.g., metabolic acidosis, hyperuricemia, inflammation, anemia, etc.) >What additional risk factors/interventions should we consider among individuals with CKD and other comorbidities (e.g., ASCVD, heart failure, etc.)? Malnutrition is an additional risk factor. Protein energy wasting is a risk factor for ESKD and death, and is often observed in CKD patients. With aging, the prevalence of PEW has been increasing. >When, how, and how often to monitor preventive

interventions among people at risk or with CKD? It depends on a person's health condition. When a person has a severe comorbid condition, monthly monitoring is required. When a person has no comorbid condition, yearly or half-yearly monitoring is sufficient. >How can we improve dissemination of guideline-based care via implementation or knowledge translation efforts? Conducting lectures to medical staff members and doctors is effective. >What risk algorithms can we use to stratify risk levels among persons at risk for or with CKD? How about developing a risk score to predict ESKD or progression of CKD? >How do patient perspectives and values affect decisions around detection efforts, such as the relative benefits from early awareness balanced with concerns of overdiagnosis, medication side effects, monitoring, and living with a disease label? This is affected by the social and cultural background of patients, which may be different among countries, and may be affected by the awareness of activities that may prevent CKD. >What is the role of patient education and CKD awareness programs to prevent CKD onset and progression, and to prevent CVD? Patient education has an impact on CKD patients in terms of adherence to CKD therapy such as dietary therapy, which is especially difficult for them to adhere to, because of restriction on salt, protein, potassium, and phosphorus. >What is the role of self-management and new technologies (mobile apps) when detecting/managing CKD? Mobile applications are effective for CKD patients to adhere to the dietary therapy. I have developed and released a mobile application for dietary therapy in Japan called "gohan coach (meal coach)", which is effective for monitoring dietary intake. If you will give me a chance, I will be glad to present the system. >What does successful implementation of early detection/management of CKD programs look like, and what constitutes a proof of concept for such programs? Detection of persons with high risk of early CKD and/or progression of CKD. At individual level, the proof is slow-down of decrease in eGFR speed or prevention of ESKD. At public health, decrease in number of ESKD patients and improvement in their prognosis. >Propose research agenda related to this section. How about a prospective cohort study using propensity score matching of patient education? Group 4: Health System and Economic Factors: Mapping the Cascade of Care for Successful Implementation of Screening/Detection and Interventions >Are early CKD detection and monitoring strategies cost-effective, and how does this determination differ in developing vs developed countries, and what inputs/metrics drive the cost-effectiveness assessment? >What models of chronic disease detection and management could be applied to CKD detection and management, such as screening, treating or preventing CVD, diabetes, and HIV? In Japan, at health checkups, dipsticks are used for the general population. Then, a person found to have proteinuria is further examined for serum creatinine level (eGFR) and urinary protein level. Dipsticks are cheap for screening, and can be used in developing countries. >What are the

barriers and facilitators of implementation of evidence–based CKD detection strategies, including the role of primary care providers, integrated care teams, specialist engagement, and community partners? >What is the role of health systems in improving use of evidence-based treatments in CKD, and how can cost-effectiveness be projected and monitored? Nephrologists and Nephrology associations such as the Japanese Society of Nephrology (JSN) take part in providing evidence-based medicine. JSN provides CKD guidelines for specialists and general practitioners, and gives lectures on CKD to general practitioners and general population. >What is the role of information technology and other innovations in improving early CKD detection, monitoring and clinical decision-making; how can technology be integrated; and how will cost-effectiveness be demonstrated? JSN established a large database of CKD patients (>150,000) using ICT technology, which is used for a real-world database. It is cost-effective. (I am one of the persons in charge.) >What is the role of socioeconomic factors in early CKD detection and management, and what strategies and interventions can be used to bridge gaps across socioeconomic groups? In Japan, the cost of school, workplace and elderly health checkups is minimal. The items measured at a health checkup are determined by each municipality or company, and the treatment of CKD is covered by the national health insurance on the basis of CKD guidelines. Standardized CKD guidelines are useful for bridging the gaps. >What incentives could improve early CKD detection/ management, such as financial and non-financial incentives and alternate payment models? As an example, partial coverage of medical fees by health insurance or municipalities can be an incentive. >What are some successful implementation strategies that we can learn from other disciplines and how did they demonstrate their cost-effectiveness? In Japan, hypertension and diabetes mellitus are screened at health checkups. The cost-effectiveness of such screening is evaluated by the decrease in medical fees. >Proposed research agenda related to this section How about a survey among countries to investigate health system and health insurance?

**Hans Pottel - KULeuven Kulak (Researcher / Biostatistician)**

"The worldwide prevalence is currently estimated at 7.2% to 13.4%." Comment: this prevalence is based on eGFR and the fixed threshold of 60mL/min/1.73m$^2$. An age-dependent threshold will increase the prevalence in the young and decrease the prevalence in an older population, resulting in an overall decrease of the worldwide prevalence. "Another study found that only 14 to 28% of patients with an initial eGFR < 60 ml/min/1.73 m2 have a documented diagnosis of CKD." Comment: this will certainly depend on the age of the cohort in the study. As said before, older adults with stable eGFR below 60 mL/min/1.73m$^2$ may not have CKD.
"Applicability of measurements across age and race/ethnicity may change the

preferred measurements according to setting." Comment: this should be a call to apply and/or develop eGFR equations applicable for all ages, sexes and race/ethnicities. The current KDIGO-strategy to use the CKiDScr equation combined with the CKD-EPI equation should be abandoned. Also, the preference should be on height-independent eGFR equations since height is normally not available in the clinical laboratory databases. "To this end, the objectives of this conference are to determine the optimal strategies for early detection and intervention of CKD" Comment: the topics defined are nice but I am missing the discussion on fixed versus age-adapted thresholds to define CKD. The application of an age-dependent threshold has a major effect on the diagnosis of CKD. "The goal of this KDIGO conference is to identify best practices and areas of uncertainties, review key relevant literature, address ongoing controversial issues, …" Comment: 1. Fixed versus age-dependent threshold and their impact on the prevalence of CKD 2. switching eGFR-equations at the transition from pediatric to adult nephrology care 3. flaws of the current eGFR-equations and how to remediate them 4. setting up a central repository of GFR-related data "Group 2:" "How do early detection strategies apply at extremes of age, such as in pediatrics or among older adults?" Comment: use of an age-dependent threshold would increase the detection in pediatrics, since the threshold will be 75 mL/min/1.73m$^2$ rather than 60 mL/min/1.73m$^2$

**Michelle Mazuranic – AstraZeneca (Pharma / Sponsor)**

A few comments to please be considered for incorporation into the agenda if appropriate: What are the current/historical barriers to implementation of testing and diagnostic recording recommendations I presume section 2 will ultimately arrive at recommendations on who, how, when and how often to test identified at risk individuals or populations? For patients with comorbidities should joint multi-disciplinary care pathways be addressed (eg. Joint Endo, Neph, Cardio) Where available and supported by evidence are recommendations for preventative strategies in at risk individuals or populations in scope? Will CKD awareness address the importance of both public (patient) awareness and clinical (Endo/PCP) awareness around the importance of CKD and the appropriate methods and recommendations for testing? The role of prevention and HCP intervention Regards, Michelle

**Barbara Philips - Brighton and Sussex Medical School (Doctor / Physician)**

Reading through the 4 groups and the scope of work planned, I cannot see a section on the relationship between AKI and CKD. At how much greater risk of AKI is an acutely ill patient with underlying mild to moderate CKD compared to patients with no underlying renal pathology? Can any risk be predicted or quantified? Can the risk

be mitigated and if so how? Similarly, what are the risk factors for developing severe CKD from episodes of AKI? I know you have separate conferences for AKI but where is the interrelationship discussed?

**Joanna Hudson - The University of Tennessee (Pharmacist)**
As a professor of pharmacy at the University of Tennessee College of Pharmacy and Medicine (Division of Nephrology) and a pharmacist specializing in nephrology from the research, teaching and patient care aspects, I have had the opportunity to be involved in the nephrology community and work with other health care professionals to provide care to patient with chronic kidney disease and ESRD. When reading the scope of work for the Identification and Intervention in CKD, I was excited to see the multidisciplinary component emphasized. I was disappointed, however, that pharmacists were not identified as a key member of the team to be involved in this conference. There was mention of involving an individual with expertise in pharmacology, but this is not a clinical pharmacist involved in the day to day care of CKD patients. I hope the group considers including an individual clinical pharmacist who can provide a prospective on comprehensive medication management in the CKD patient. Doing so will help meet the goal of this conference in determining the best methods to deliver integrated coordinated care for CKD patients and incorporating an interdisciplinary approach. I am happy to provide recommendations of individuals who can provide a perspective of a clinical pharmacist and be involved in this conference.

**Jyothi Nayak - Manipal College of Nursing (PhD Scholar)**
I appreciate your contribution for the care of CKD patient. Your hard work helped me to gain in-depth knowledge on CKD. I would like to add something if it is discussed in the workshop. Some of the complementary therapy used for the prevention of progression of the CKD such as Yoga. Thanking you. With Regards, Jyothi Ph D Scholar Manipal College of Nursing, MAHE, Manipal Karnataka, India Email: jyothikuledu@gmail.com

**Deepak Sharma – Ketav Kalp Healthcare & Research PVT LTD (Doctor / Physician)**
Well thought of and researched scope of work.

**Maarten Taal - University of Nottingham (Doctor / Physician)**
The scoping document is extremely well written and provides a clear framework for the Controversies Conference on Early Identification & Intervention in CKD. My main comment is that I would like to suggest more specific focus on the issues of CKD in older persons and comorbidity in the context of CKD. This is certainly

implied in the current scope but because of the importance of these issues, perhaps should be made more explicit. CKD in the elderly: The prevalence of CKD rises sharply with age but the risks associated with CKD also change with advancing age. The risk of ESKD declines due to the competing risk of death but the risks of hospitalisation and cardiovascular events remain high. For example in one cohort study of older persons (mean age 73 years) with CKD stage 3 at baseline, the incidence of ESKD after 5 years was only 0.2% (Shardlow A et al. PLOS Med 2016; 13(9): e1002128). In older persons CKD is also frequently associated with other chronic conditions (see below). These considerations should inform the approach to both detection and optimal management of CKD in older people. Comorbidity: CKD is associated with a very high prevalence of comorbid conditions. In one large population-based study 25% of persons with CKD had 3 or more comorbidities (Tonelli M et al. Kidney Int 2015; 88:859-66) and in a cohort study of older persons (mean age 73 years) with CKD stage 3, only 4% had no comorbidities and 40% had 3 or more comorbidities (Fraser SDS et al. BMC Nephrology 2015; 16:193). In both studies a greater number of comorbidities was associated with reduced survival. Comorbidities are important because they impact a person's quality of life and ability to engage with health care interventions. Treatment guidelines should include consideration of how to manage CKD in the context of other chronic conditions and how these conditions may negatively impact the optimal management of CKD.

**Kunitoshi Iseki - Nakamura Clinic (Doctor / Physician)**

In Japan, we have high incidence and prevalence of ESRD, in particular DKD. Since 2008, Nationwide screening program on early detection and intervention for metabolic syndrome has started. In this programn the target is those covered by National Insurance Holders. It covers people; house-wife, farmers, fishemen, and non-employees (Age 40-74). One third of them have been paricipatng one a year (Total nember>30 miilions). We have been working on the database since 2008. Follwing papers are related to the cost-benefit analysis on CKD screening. 1. Kondo M, Yamagata K, Hoshi SL, et al. Cost-effectiveness of chronic kidney disease mass screening test in Japan. Clin Exp Nephrol 16:279-291, 2012 2. Kondo M, Yamagata K, Hoshi SL, et al. Budget impact analysis of chronic kidney disease mass screening test in Japan. Clin Exp Nephrol 18(6): 885-891, 2014 3. Nagai K, Iseki C, Iseki K, et al. Higher medical costs for CKD patients with a rapid decline in eGFR: A cohort study from the Japanese general population. PLoS One (in press)

**Eisei Noiri - UTokyo / NCGM (Doctor / Physician)**

Group 1: Early CKD Detection Measures Q: What are strengths and weaknesses of currently available measures to identify and categorize CKD; values of

discriminating risk; specificity; and costs? A: KDIGO based CKD categorization is easy indicator to understand basal kidney function of individuals. However, we cannot tell who may get worse from one category to the next with the current classification and thinking way. This is because the indicators such as serum creatinine, albuminuria and cystatin C, do not have any data. Proteinuria reported from Okinawa, named OCHID study, that highly positive protein level shows worse outcome. This is epidemiological analysis. Studies of DKD in Europe and Japan shows that high urine L-FABP level can distinguish the progressor better than albuminuria. This will be tips to the next stage of CKD staging. I can give a small data as a hint about it including recent data in UK and South-East Asia. Q: What are the ideal CKD detection measures and the influence of demographic characteristics on; the relative value of creatinine only versus adding cystatin C, albuminuria/proteinuria, or a triple-marker strategy? A: There is no recommendation to this question. Instead, we can learn from the evidence in DKD. In addition, there are small studies which demonstrate the efficacy of L-FABP to predict the progressor in glomerular diseases in JPN. l Q: What criteria should be used to evaluate potential screening strategies: accuracy versus measured GFR; prediction of adverse outcomes; sensitivity versus specificity; stage classification? A: I would prefer to use current KDIGO criteria in combination with the data of cyctatin C. This way will tell the potentiality of cystatin C to distinguish the progressor if real. Likewise, the combination of albuminuria and L-FABP will tell the progressor. The combination of serum and urine will tell the cohort who need closer management presumably showing faster eGFR decline. Q: What are the costs of commonly used kidney health measures, including creatinine, cystatin C, proteinuria, dipsticks and albuminuria? A: Dipstick including proteinuria < serum creatinine < dipstick albuminuria = dipstick L-FABP < quantitative albuminuria < cystatin C = quantitative L-FABP However, frequency will be once in a couple of month depending on the above mentioned considerations. Q: What are the relative yields (utility) from testing proteinuria versus albuminuria; and are dipsticks adequate? A: Proteinuria negative and albuminuria positive is mostly non-progressor. I would recommend to measuring urine L-FABP three times a year to detect the change of phenotype. Proteinuria positive cases should not measure albuminuria in dipstick. I would recommend to compare quantitation of proteinuria and dipstick for just in case to miss myeloma related kidney diseases. l Q: Is there a potential role for point-of-care (POC) testing, such as novel POCs for real-time GFR or creatinine measurements, or measures of urine albumin, in a public health CKD program? A: Yes. We have a small data in Vietnam and Bangladesh. Using L-FABP dipstick, we can provisionally show CKD disease burden as NCD. Q: Where should testing be conducted and how often should it be repeated in a CKD detection and intervention program? What new tests or biomarkers are being developed that

might expand diagnosis beyond glomerular measures in order to detect and monitor kidney tubule health? A: In Japan, we have already developed the product, urine L-FABP both for POC and clinical laboratory. This product is reimbursed for the use every 3 month. L-FABP is considered as the monitor of proximal tubular stress and injury. So, I recommend L-FABP measure 3 times a year, if stable CKD. If a patient is suspected as progressor concerning the development of AKI with CKD, physicians are allowed to use with their own decision for their patients. Q: Propose research agenda related to this section A: As I mentioned earlier, CKD patients of stage 2 and 3a will be the candidate for the study. I would prefer to place 3 year period with the use of inulin clearance or equivalent every year. This is because serum creatinine level in lower resource country is not the level of high resource country. Then 5 indicators, serum creatinine, serum cystatin C, urine albumin, urine L-FABP, urine protein, are candidates for the follow up study. Both serum creatinine and cystatin C (2x2) high group is definitely the progressor. Both low is presumably non-progressor. Other two conditions are the target of urine albumin and L-FABP (2x2) based on the previous data of DKD.

**Alvaro Garcia – Internista Nefrologo (Doctor / Physician)**

Group 1: Early CKD Detection Measures  What are strengths and weaknesses of currently available measures to identify and categorize CKD; values of discriminating risk; specificity; ¿and costs? The CKD still persists with a very high incidence and prevalence, especially in developing countries and Latin Americans; in which 50 to 70% of patients consult in late stages of CKD (G5), to initiate RRT programs, for complications that precipitate the onset of this type of high-cost therapies (Hemodialysis, peritoneal dialysis); The most common complications of the patient with CKD are: congestive heart failure, acute coronary event, stroke, hydro electrolytic or metabolic disorders, which increase the costs of initiation of therapy by a high% due to the need for: intensive care ICU, catheter for onset of dialysis, treatment by intensives, cardiologist, nephrologist, nursing etc., and also with a very poor patient survival expectations in the first 3 months after starting RRT. Hassan R. shows this beginning of RRT, not controlled in his work on: Risk factors for Unplanned Dialysis initiation: A systematic review of the Literature: where it is shown that (10.4%) of dialysis began during hospitalization, or dialysis began without prior vascular access (18.8%), or by medical emergency (14,6), other 27%, etc. (3). Although pre-dialytic therapy is an epidemiological, medical, social, and economic solution, etc., which avoids a disorderly and unscheduled admission of patients with CKD to RRT in stage G5, and provides a comprehensive medical therapy to patients at different stages of CKD and their comorbidities; Health providers are not convinced of the economic / medical benefits of this type of therapy due to the lack of well-designed studies (RTCs), in which these benefits are

revealed. The study Canadians sober, the cost of care for people with chronic kidney disease. On a court of 219,641 patients with CKD, for a year on average pre-dialysis the cost of the integral treatment of US$ 14,634 per patient / year in the initial stages and shows how this cost is increasing as the CKD progresses, up to reach an exponential value of US$ 95,000, to US$ 100,000 according to the therapy used HD or PD patient / year in stage G5. That is why: Is it important that the treatment of the pre-dialysis patient be part of the RRT of the patient with CKD?  What are the ideal CKD detection measures and the influence of demographic characteristics on; the relative value of creatinine only versus adding Cystatin C, albuminuria/proteinuria, or a triple-marker strategy? – Quantify the glomerular filtration rate (GFR ≥ or ≤ of 60 ml / min / 1.73 $m^2$) in the patient with CKD; It is the starting point to stratify it into 6 subgroups according to the GRF, which is directly proportional to the degree of kidney damage the patient has. There are several markers used to determine GFR, either measured (m) or estimated (e), by means of validated formulas (MDRD; CKD-EPI); these markers can be divided into exogenous: Inulin, Cr-51-EDTA, Iothalamate, iohexol and others; its use is complex, high cost and difficult to implement in clinical practice, despite having a very high specificity value. The most common markers in medical practice are endogenous (Cr, Cystatin C, and albuminuria). Creatinine (Cr), is a 113-Da breakdown, a product of muscle metabolism, identified in 1847, proposed as a marker of glomerular filtration 1926. The eGFRcr is a mathematical formula which combines not only blood levels but age, sex, race; to try to correct these variables. Cystatin C (CysC) is a 13-kDa cysteine protease, ubiquitous in all nucleated cells that is produced at a constant rate, freely filtered, not reabsorbed, and not secreted in renal tubules. It was identified in 1979 and proposed as a marker of glomerular filtration in 1985. Cystatin C is less influenced with the patient's muscle mass, and eGFR is better correlated, especially in special groups of the population such as: vegetarians, muscle wasting, diseases chronicles, or limb amputation; The clearance of Cystatin C (eGFRcys) is not more significant than that determined with eGFRcr, in standard populations, but the combination of eGFRcr-cys is superior to either (Cr or Cys). Determine GRF only with creatinine (Cr), eGFRcr levels in blood; This may be underestimated especially in those patients with muscular disorders, diet and medications that alter the concentration of Cr in blood; The UK guidelines recommend determining renal clearance using Cystatin C, eGRFcys or e-GRFcr-cys, especially in those patients, classified as G3aa1, (clearance between 45 to 59 ml / min / 1.73 $m^2$, without proteinuria). The eGRFcr -cys reclassifies a small proportion (7.7%) of patients not classified with the e-GRF-cr, but does not predict higher % mortality from all causes, or % in the progression of CKD. The increase in costs is 23 pounds' patient / year, therefore more studies are recommended to clarify its implementation Triple-marker strategy: as a marker of chronic renal damage very little has been used, the

works on this subject demonstrate a high degree of superiority when compared with any of the other markers. The combination of Cr, Cystatin C, and urine albumin-to-creatinine ratio (ACR), would improve not only identifying patients with CKD but the risks associated with CKD compared with Cr alone. The Reasons for geographic and Racial Differences in stroke (REGARDS), is a prospective study in 26,643 patients and the Main outcome measure: All –cause mortality and incident in-stage renal disease with median follow-up of 4.6 years, the conclusion was: adding cys C to the combination of Cr and ACR measures improved the predictive accuracy for all-cause mortality and end-stage renal disease.  What criteria should be used to evaluate potential screening strategies: accuracy versus measured GFR; prediction of adverse outcomes; sensitivity versus specificity; ¿stage classification? It is important to plan the strategies to follow when measuring GFR. The quantification of this test, by means of urinary, blood collection, or other techniques, may not be specified by the collection bias or too expensive and not practical. At present, the eGFR estimate, through formulas, which have been perfected over time, adding a series of variables such as age, sex, body mass, ethnicity, makes them more precise and is a way to determine the GFR is used throughout the world. Due to the costs and ease of the tracer to determine GFR, to date endogenous markers such as Cr and Cys are the most used. The method used to determine the GFR must be highly sensitive, rather than specific; this allows us a high negative predictive power, which we can correct with other more specific tests; in the case of eGRFcr, using the eGFRcys which corrects problems in special populations in which Cr levels are altered as in vegetarians, amputees, or in those with muscle problems etc. The pressure power of eGRF increases significantly in either of the two formulas when we add the albumin / creatinine radio ACR, but despite this, there are several combinations that have been made to evaluate and classify patients in stage 1 and 2, and the G3aa1 (GFR between 45-59ml / min) without proteinuria, with poor results, that is why precise markers are needed.  What are the costs of commonly used kidney health measures, including Creatinine, Cystatin C, proteinuria, dipsticks and albuminuria? The costs of the different markers used in the diagnosis of CKD and its control over time vary, in different countries; It depends on the health provider that makes it state or private entity: A single determination of Cr $ 3.8 US, Cys C $ 73.3 US, proteinuria $ 5.8 US, Albuminuria / creatinine (ACR): $ 14.2 US, dipsticks $ 3.1 US, for a total of $ 100 US The Canadian study on costs per year in pre-dialysis is US $ 14,630  What are the relative yields (utility) from testing proteinuria versus albuminuria; ¿and are dipsticks adequate? Dip-stik proteinuria is only sensitive to albuminuria and is poorly correlated with the quantification of proteinuria in 24h. Dip-stik is used in RTCs of renopro-tective character. Decide urine protein to creatinine radio (UPCR) or albumin to creatinine radio (UACR), correlates with excretion in 24 hours, Dip-stik correlates poorly with UPCR, and

moderately with UACR. The UCAR and UPCR, increase the diagnosis of eGFR, and are associated with cardiovascular risk and high mortality in the patient with CKD. Proteinuria or albuminuria not only increases the diagnosis of CKD, when we use eGFR as a method, but also determines the risk for RRT and cardiovascular risk. The UACR is a more sensitive marker in the diagnosis and follow-up in diabetics, hypertensive patients, glomerular disease; but when we use UPCR we can identify 16% more patients with CKD, who also have a high risk of all causes of mortality  Is there a potential role for point-of-care (POC) testing, such as novel POCs for real-time GFR or creatinine measurements, or measures of urine albumin, in a public health CKD program? A simple screening method to determine the presence or not of CKD is to measure Creatinine levels, with on dry blood spot on filter paper followed by the clearance quantification estimated by eMDRDcr or eCKD-EPIcr. Patients with GFR <60 ml / min, could be determined in 76% of hypertensive patients, 30% in diabetics, 37% of patients with a family history of CKD. The sensitivity using the equation: e-MDRD was 96%, and its specificity was 55%. By the e-CKD-EPI equation the sensitive positive value was 94%, specificity 55%. This simple method can be applied as screening in communities with high risk of CKD. The Iwate –KENCO is a prospective study, in a community of 22,975 patients with 5.6 years of follow-up, the diagnosis of CKD, determined by eGFR, improved significantly when the UACR was added, rather than when the Dip-stick proteinuria was used, this was not so blunt, but both predicted the possibility of cardiovascular events in the future. Finding highly simple / specific diagnostic methods to evaluate populations at risk of CKD is the challenge we have to face in the coming years.  Where should testing be conducted and how often should it be repeated in a CKD detection and intervention program? What new tests or biomarkers are being developed that might expand diagnosis beyond glomerular measures in order to detect and monitor kidney tubule health? A program for the promotion and prevention of CKD should be developed in each of the countries of the world, with locations fully identified or similar to hemodialysis or peritoneal dialysis units, and make pre-dialysis a part of the patient's RRT with CKD. These renal health entities would be the places where the development of CKD is diagnosed and followed at the same time (stages / interventions); they must have all the programs of the integral treatment of the patient which will be derived in a phased manner to RRT in stages 5. Primary or secondary involvement at the glomerular, tubular or interstitial level can lead to a CKD over time; that is why we must have simple markers of easy application that allow us to identify this commitment early: 1-The saliva urea nitrogen (SUN) dipstick, has been suggested as a screening tool for acute or chronic kidney disease diagnosis, is highly sensitive in CKD 2-Asymmetric Dimethylarginine (ADMA), is a novel biomarker in CKD, is an analogue of L-arginine, its high levels inhibit the production of nitric oxide (NO), causing endothelial

dysfunction typical of patients with CKD 3-Symmetric Dimethylarginine (SDMA), is a product of the metabolism of methyl arginine that is eliminated by the kidney, blood levels and glomerular filtration correlate with the degree of CKD. 4-Uromodulin (Tamm-Horsfall protein), it is produced for the tubular cells of the thick ascending limb- is a promising marker for the number of intact nephrons. 5-Kidney Injury molecule-1 (KIM-1) is known as a regulator of the differentiation of proximal tubule cells after an ischemic or toxic injury, this marker is used to identify glomerular tabular damage and is a predictor of time damage of the KCD. 6-Neutrophil Gelatinase-associated lipocalin (NEGAL) - it is a first molecule that helps the embryogenetic formation of the kidney is part of the mesenchyme cell and tubular epithelial cells - its levels frequently increase in tubulointerstitial diseases 7-mi RNA, ncRNa, IncRNA and licRNA biomarkers- epigenetic approaches towards the examination of regulation of genes involved in disease detection and progression are now wide interest.8-Proteomic and Metabolomics Biomarkers: Serum Cr and urinary albumin-proteomic biomarkers may facilitate more accurate and earlier detection of renal pathology

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**Pierre Delanaye - University of Liège (Doctor / Physician)**

I agree with the efforts of KDIGO to improve early detection of CKD at the population level. In this view, several points need to be discussed. First the CKD definition is based on a fixed, unique threshold of 60 mL/min/1.73m$^2$. This point is however very debatable. Several authors have argued that an age-adapted definition is required, notably to better reflect the natural trend of GFR with aging 1–21. With such age-adapted definition, less old subjects will be diagnosed as CKD, but many young patients will be diagnosed earlier than with the fixed definition 19,22. For example: just consider a 35-years old man (or woman) with GFR at 65 ml/min/1.73m$^2$: is this GFR level really "normal"? A change in the CKD definition is needed (see a review paper that will be soon published in JASN, 10th September). This is also very important for developing countries where CKD is important and frequent in young people (demographic repartition of emerging countries being different from developing countries). It is also time to reconsider the equation promoted until now by the KDIGO: the CKD-EPI equations 23. The performance of the CKD-EPI equation is very questionable at the transition between adolescence to adults 24. The ethnic factor in the MDRD or CKD-EPI equations is questionable in African people 25–29, but also in African-Americans 29,30. There are reasons to think that the "too high" ethnic factor in African Americans leads to late referral (their GFR being "too high", "too good"). Other equations (revised Lund Malmö/CAPA equations 31,32 and Full Age Spectrum 33,34) are better than CKD-EPI in Africans 26,35, and also solve the problem due to transition 24. Eventually, the metrics used in the current literature to test the potential superiority of one given equation on another should be debated.

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**Alvaro Garcia – Internista Nefrologo (Doctor / Physician)**

Group 2: Populations to Screen and Identifying At-Risk Individuals  Should screening for occult CKD in an early detection program be directed to Populations or targeted to high-risk individuals, using any combination of kidney Measures  It has been estimated that 40%, of the population with CKD, is not diagnosed (hidden population), especially in the initial stages 1, 2, 3, this population will be subject to presenting, cardiovascular morbidity and mortality by 20%, more frequent that the general population and they will consult for CKD at late stages, which increases the costs of their treatment for the implementation of RRT. All of the above conditions to identify and to intervene this population as quickly as possible.  All the guides agree that it is more practical, of greater coverage, and more economical to identify high-risk populations: HT, Diabetics 2, cardiovascular disease, hereditary kidney diseases or with family associations (glomerulopathies, interstitial nephropathies), indigenous communities, blacks etc.; this in order to classify the stage of the CKD and be able to intervene them medically; ideally, make a low-cost rapid screening test: eGFR + Dipsticks for Urine proteins or a UPCR determination, which increases the power of sensitivity and specificity  What are the optimum settings (community based vs primary care practices) for capturing at risk individuals? Community practices on diseases related to CKD such as diabetes day, hypertension, heart disease, kidney day, are very useful not only to promote the educational part about them, but it is a timely and key moment to evaluate patients on CKD, using fast and simple screening methods; activities that can increase the incidence of CKD and know the socio-economic and cultural environment of the population.  Primary care programs are optimal for diagnosing new patients with CKD, they have defined evaluation and stratification technology, but the number of patients who attend these programs is not high and is subject to the health programs of each country or region.  What is the difference between a surveillance program and a Screening/detection intervention, and what can we learn from prior programs including the prevalence of CKD?  An epidemiological surveillance program of the CKD implies a systematic and permanent collection of the essential data of the CKD (age, sex, race, most frequent etiology, stages according to the GFR, etc.), to perform an analysis and interpretation of your data; which will allow us to elaborate a well-defined planning, this allows to implement and evaluate the strategies to follow in a CKD program.  Detention and intervention goes beyond identifying the incidence

and prevalence of CKD. An intervention program must establish prevention strategies, management of CKD and its complications by primary health care; fully defined criteria must be taken to refer patients to a level of greater complexity and treatment by nephrology, which will improve the renal health and prognosis of our patients. There are several aspects that must be taken into account in this program among others: Susceptibility factors: which increase the possibility of kidney damage? Initiating Factors: those that directly initiate kidney damage. Progression factors: worsen kidney damage and accelerate its deterioration Final stage factors: Increase morbidity in renal failure situations (Spanish model). The high prevalence of this entity (CKD), its treatment costs and the associated cardiovascular complications make it necessary to develop screening and intervention programs. Should the prevalence of CKD or the absolute risk of CKD complications and ESKD be used as the first step for an early detection intervention program? CKD is a public health and for public health problem, due to its high prevalence estimated between 7 and 14% of the world's population; due to its high morbidity and mortality in the advanced stages G4, G5; It is also an important consumer of health resources in all countries of the world, due to the high costs of RRT. Finally it is associated as the main cause of cardiovascular disease, vascular brain and peripheral vascular in a short time. All these situations make the CKD, an important global health problem, which should be a priority intervention in primary health care programs in the initial stages 1, 2, 3; where their diagnosis, their possible etiology and the events that perpetuated or accelerate the deterioration of renal function over time are fully defined, to correct and treat them medically If high-risk groups are to be identified, should the absolute risk estimate be based on lifetime risk or within a finite interval of time (e.g., 10-yr risk), and should the risk estimates be dependent on laboratory measures? Given the prevalence of CKD, the variety of its etiology, and the need for a classification in different stages (G6); It is important to determine if during the whole journey of CKD from stage 1 to 5, the same factors of progression of CKD act, which can worsen or accelerate the deterioration of renal function and evaluate whether we can measure or quantify these factors with lab tests? But although many of these factors called traditional risk, have abundant RCTs on cardiovascular risk and death, in the general population and initial stages of CKD, many of them do not influence the progression of the disease, in the advanced stages. Traditional markers of risk quantification, BUN, CR, glycemia, uric acid, k, Ca, P, urine cytochemical, albuminuria / proteinuria, Hb levels, Hto, arterial gases, Cholesterol-triglycerides, HDL, LDL etc., are important in the initial stages of the CKD, GFR> of 30 ml / min / 1.73mts$^2$; but in stages G4, G5, they are other important factors that influence the morbidity and mortality of the patient with CKD: (hyperparathyroidism, coronary heart disease, and vascular calcifications, especially at the coronary level). Their determination not

only helps the diagnosis but they are markers clarify the pathophysiology of comorbidity; quantify the % risk, and survive at this stage of the CKC; these markers are totally different: blood levels of Phosphorus, Ca, vitamin D3, PTH, 23FGF, MO, Carbamylated LDL, ADMA, P-Cresylsultato Fetuin, Osteopontin, osteocalcin, matrix gla- protein, matrix metalloprotease 3, 24 hydroxylase, homocysteine, among others, are blood level markers that are associated with the risk of CKD in advanced stages.  How do early detection strategies apply at extremes of age, such as in pediatrics or among older adults?  The strategies to follow in extreme ages are totally different. In populations at risk, eGFR and albuminuria should be performed every year (if it is positive, it must be confirmed 2 or 3 times in 3 months). This determination should be made in populations such as: type 2 DM, HTa, or established cardiovascular disease. It is advisable to evaluate renal function in people over 60, obese (BMI> 35kg / $m^2$) with type 1 DM, with more than 5 years of evolution, relatives in 1 degree of hereditary kidney diseases, obstructive urinary tract disease, treatment prolonged with nephrotoxic drugs (nonsteroidal anti-inflammatory drugs, antineoplastic drugs); patients with cardiovascular risk (hyperlipidemia, metabolic syndrome, smokers), history of AKI, chronic infections, autoimmune diseases and malignancies associated with CKD. The CKD stage (from G1 to G5), plus the determination of albuminuria (<30, 30-299,> 300 mg / g), allows us to monitor patients and refer to the nephrologist for progression of CKD,> than normal deterioration over time, for example: decrease in eGFR> 5 ml / min / year or> 10 ml / min in 5 years. You should always determine your progression with two variables: impairment of the GFR> 25% or increase> 50% of the UACR.  The criteria for referral to the nephrologist are determined by the GFR or UACR, a GFR <30 ml / min / 1.73mts$^2$ or a proteinuria> 300 mgr / gr, except in patients> 80 years of age, without progression of CKD. RRT candidates must be sent to the nephrologist 1 year before starting this therapy. Patients <70 years with GFR between 30-45ml / min / 1.73mts$^2$, should be monitored every 3-6 months and those with less than 30ml / min / 1.73mts$^2$ every 3 months; In addition, all patients with an accelerated deterioration of GFR or albuminuria, who are outside the proposed range, should be referred.  We have little experience in pediatrics, but children with a history of family inherited diseases (Allport syndrome, Ochoa facial uro syndrome, ADPKD, congenital glomerulopathies etc.) should be evaluated, their follow-up must be fully defined by nephron pediatricians.  How might we identify individuals that need re-screening after an initially negative screen?  In general e-GFR, it is inadequate in a series of clinical situations which must be taken into account for example: patients with an extreme BMI body weight <19 kg / mts$^2$ or> 35 kg / mts$^2$, people with special diets ( vegetarians, creatine supplements), malnutrition, impaired muscle mass, <18 years, liver disease, ascites, AKI, adjustment of renal elimination drugs, metabolic syndrome etc. Many of these GFR

determinations can be corrected with a second test, UACR, or use of cys C. A second re-screening scenario can occur in patients with clinical conditions in which renal involvement is fully demonstrated in a high percentage over time: type DM with more than 10 years of evolution, or DM 1 with more than 5 years, poorly controlled hypertension, cardiovascular disease, rheumatic diseases, neoplasms associated with kidney damage, family inherited disease (Allport syndrome, ADPKD, uro facial uro syndrome, some glomerulopathies,), black patients, special ethnicities, etc. In which, it is necessary to monitor your renal function to determine your GFR.  Are there social, behavioral, occupational or environmental exposures that would warrant population screening rather than individual risk-based targeting? The social, cultural environment and the work environment are important, as contributing factors, which can act on a genetic basis, to configure renal damage over time leading the patient to CKD; A clear example of this is in the so-called Balkan nephropathy, or Mesoamerican nephropathy of Central America, where the triggers of them are fully studied. In Colombia recently a Nephrologist Dr. Edgar San Clemente, did an excellent job (book), on environmental toxic, medicines and CKD. Through renal biopsy taken in miners who exploit rivers and quarries in search of gold using mercury and cyanide, he was able to relate the presence of glomerulopathies in these patients; The use of pesticides at the level of the agricultural industry (Cañaduzales) was another important scenario to evaluate factors that induce renal damage; finally air pollution in large cities in the number of dissolved particles in the environment, not only cause diseases of the airway, but possible kidney damage. We suggest to KDIGO a special segment in the guidelines on CKD, including the work environment, and nephrotoxins as a possible etiology of CKD, on a previous genetic basis  Should there be a role for reflex family screening if ancestral factors, such as high-risk APOL1 genotype, are present among screened individuals? At the literature level there are many articles, which relate genetic factors, to the environment; this allows us to explain why there are regions with a higher incidence of CKD when compared to others (3) Both genomic factors and environmental factors contribute to this complex heterogeneous disease. CKD heritability has been estimated at 30 to 75%. Genome-wide association studies (GWAS) and GWAS Meta-analyzes ham identification genetic loci associated with CKD (1) In a Canadian study (2), on genetic risk factors of CKD, I conclude that 5 SNPs is a protein related to (Osteopontin, osteocalcin, matrix gla protein, matrix metalloprottease3 and 24 hydroxylase) which is associated with an increase in CKD, producing vascular calcifications typical of stages G4, G5. As we can see in addition to the APOL-1 gene, there are many studies that show a high association between the genetic part and environmental factors as an adjunct in the development of CKD.  What promising emerging opportunities or technologies (e.g., AI) exist for automated and targeted surveillance approaches to identify at-risk individuals?'

The AI, in cellular tablets, PC, others; which have small programs for monitoring blood pressure, heart rate, electrocardiograms; or estimate the GFR or possibility of reaching the CKD in a while; they are important electronic measures; which must be corrected, make them more sensitive and effective in their measurements. A place of formal consultation of the user must be provided to resolve their concerns, this approach must be used to capture these patients, and determine if they have or CKD, to enter them into a formal program. We only have one doubt, these electronic resources are not so popular in third world countries because of the costs, and strategies for their endowment should be studied.

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**Lingyun Li - Relypsa (Medical Director)**

Thank you for providing us an opportunity to comment on the Scope of Work for the KDIGO Controversies Conference on Early Identification & Intervention in CKD. We have reviewed the selected topics that will be covered during the meeting and would like to recommend that the following topic be addressed during the controversies conference. RAAS inhibitor use in delaying CKD progression and management of the associated risk of hyperkalemia Group 3 Topic 1 in the proposed Scope of Work comment on interventions (e.g., lifestyles, diet, pharmaceuticals) we should adopt to prevent CKD onset and/or slow CKD progression and to prevent CVD and HF. A part of this discussion should focus on the utility and optimization of renin-angiotensin-aldosterone-system (RAAS) inhibitors in delaying disease progression in this patient population, the associated risk of hyperkalemia, and management strategies for hyperkalemia. RAAS inhibitors, including angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-receptor-blockers (ARBs) are recommended by KDIGO guideline as first-line agents to prevent CKD progression in diabetic and non-diabetic adults with CKD and urine albumin excretion >300 mg/24 hours (1B) and in diabetic adults with CKD and urine albumin excretion 30–300 mg/24 hours (2D) (KDIGO 2012 CKD guideline). RAAS inhibitors have been shown to significantly reduce the degree of proteinuria and the rate of loss of renal function, reduce the risk of developing end-

stage renal disease, and most importantly, reduce the risk for kidney failure, cardiovascular events, and all-cause mortality in CKD patients (Brenner et al, 2001; Lewis et al, 2001; Xie et al, 2016). In addition, mineralocorticoid receptor antagonists (MRA) have been shown to decrease urine albumin excretion when added to ACEi or ARB therapy in patients with CKD (KDIGO 2012 BP guideline). Many patients with CKD have co-morbid heart failure; in this setting, MRA are also Class 1A recommended therapies to reduce morbidity and mortality for symptomatic patients with HF-REF, and Class IIB recommended therapies to reduce hospitalizations in patients with HF-PEF (Yancy et al, 2013; Yancy et al, 2017; Ponikowski, 2016). Despite the benefits of RAAS inhibitors in CKD patients, hyperkalemia has been reported in clinical trials with RAAS inhibitors and constitutes the major barrier for the utilization of guideline-recommended RAASi treatment (Epstein, 2016). Sub-maximum doses and discontinuation of RAASi therapy result in worse patient outcomes (Epstein, 2015). Recently, the emerging new potassium binders (patiromer and SZC) provide options for safe and effective treatment of hyperkalemia (Bakris et al, 2015; Weir et al, 2015; Kosiborod et al, 2014; Spinowitz et al, 2019), and may facilitate maintaining patients on optimal doses of RAAS inhibitors as recommended in the current treatment guidelines. For these reasons, we suggest that the following questions be addressed within the proposed Scope of Work: • How do we improve use of RAAS inhibitors to slow CKD progression, and use of MRA at the guideline recommended doses among individuals with CKD and HF-rEF? • Does discontinuation of RAAS inhibitors as the method of correction for hyperkalemia affect patient outcomes in CKD and HF? If yes, how do we ensure that the patients get optimal RAASi treatment? • What are the recommendations for the management of hyperkalemia for CKD patients on RAAS inhibitors?

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**Francesco Locatelli - Alessandro Manzoni Hospital (Doctor / Physician)**

I fully agree with the very good questions for the 4 groups: you did a wonderful job! I would like to underline that the present methods for measuring GFR are able to detect a kidney damage only when there is already an important damage of the

kidneys.Therefore, we need new methods for evaluating the renal function. The sceening for albuminuria is much more important for detecting early kidney damage. Eventualy the markers of tubular damage could be more important for detecting renal damage related to the worker activities. The workers in the agicolture (and the products they are using (Kidney Int Rep (2018) 3, 271–280; https://doi.org/10.1016/j.ekir.2017.10.006) and the climate where they are working) should be carefully considered, taking into account the prevalence of CKD in different populations and considering their life expectancy ( in population without apparent reasons for different life expectancy ) for selecting the priorities among the population to be tested. The possible kidney damage associated with plastic contamination is another interesting topic for research (DOI: 10.1056/NEJMc1907676).

**Joseph Vassalotti - National Kidney Foundation & Icahn School of Medicine at Mount Sinai (Doctor / Physician)**

Overall, this is a clear, well-organized and comprehensive Scope of Work for Early Identification & Intervention in CKD. I commend KDIGO and the organizers for addressing this topic. The most important aspect of this work is that the target population is not the general population, nor is it restricted to interventions in CKD. Methods that CKD identification & intervention can be integrated into population health, quality improvement and other systematic approaches to care in chronic diseases or risk conditions is clearly described in this scope of work. This allows CKD identification and interventions to be integrated into existing workflows, rather than creating de novo CKD care plan. This is crucial for dissemination and scale. Specific comments to consider for strengthening an already excellent scope of work.

Major

Page 3: Dietitians and nutrition is important enough to early CKD intervention to be noted specifically.

Page 5: Group 1 early CKD detection measures - a bullet on the status of international standardization of laboratory methods is important - sCr standarized - international implementation status?, uACR (pending status?), sCystatin C (pending status?), uPCR (likely not feasible).

Page 6: Group 2 Populations to Screen and Identifying At-Risk Individuals

Introducing the concept of perceived-risk for CKD here is worth considering. This is a concept that could be systematically promoted or assessed. In other words, does the population with DM and or HTN know that they are at risk for subsequent CKD? (See 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(10):1123-9.) This is distinct from the concept of CKD awareness.
Page 7: Group 3 Optimal Interventions and Implementation after CKD Detection. The distinction between slowing progression and preventing CV events and particularly preventing HF is important. Accordingly, CKD metabolic acidosis is important to note as small RCTs support alkali treatment slows progression, whereas hyperuricemia, inflammation, CKD anemia therapies are important but have no compelling RCT data that demonstrate treatment slows CKD progression.
Page 8: Health system and economic factors - the conditions that are listed here as models for integration of CKD care are CVD, DM and HIV. These are important. Obesity is not mentioned anywhere in this scope of work and may be worth including here and/or elsewhere. Also, there is an obvious inter-dependence of this discussion with the Group 2 at-risk populations to screen. Ideally, all the conditions noted in the disease management section group 4 would be addressed by the screening group 2. Although the list of the latter could be more extensive or complete.

Minor
Page 1: US CDC describes 15% of the population with CKD in the 2019 kidney disease fact sheet. See hyperlink: https://www.cdc.gov/kidneydisease/pdf/2019_National-Chronic-Kidney-Disease-Fact-Sheet.pdf Additional References to consider other than the 8 in the SoW - pdf provided on request, as applicable. I am genuinely honored and excited to be able to participate and contribute to this discussion.

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**Cesar Loza - Peruvian University Cayetano Heredia (Doctor / Physician)**
All questions or questions are very well focused: But I think that an important question that could be incorporated would be; If the national health surveys implemented by some countries to periodically assess the prevalence of CKD is a recommended practice, to be implemented in all countries of the world

**Guillermo Garcia Garcia - University of Guadalajara (Doctor / Physician)**
Some additional questions: and one comment. Role of Integration of CKD into NCDs programs? Any progress since the Bangkok KDIGO Conference? Role of CKD detection as part of National Health Surveys. Role of mandatory CKD detection by dialysis providers (the example of Colombia) What is the role of kidney foundations, especially in LMIC? Role of fragmented, dysfunctional Health Systems (Mexico, India, South Africa) as barriers to successful implementation) Main barriers in LMIC are those linked to poverty (so called social determinants of health): lack or cost to access to health care, including medications and lab tests; geographic barriers; health literacy; cultural beliefs; barriers imposed by the health

system (ie. en Mexico, patients with Seguro Popular are denied treatment when they are identified as having kidney disease), losing the opportunity to intervene to retard CKD progression)

**Sijie Zheng - Kaiser Permanente/The Permanente Medical Group (Doctor / Physician)**

Group 3: Optimal Interventions and Implementation after CKD Detection

• What Interventions (e.g., lifestyles, diet, pharmaceuticals) should we adopt to prevent CKD onset and/or slow CKD progression and to prevent CVD and HF?

1. Stop smoking
2. Stop NSAIDs
3. Avoid processed food,
4. Avoid dairy product
5. Plant based diet
6. Weight loss
7. Exercise as tolerates
8. ACE-I/ARB
9. Low salt diet
10. Statin
11. Not sure about SGLT-2 inhibitors yet, especially in low resource countries.
12. Control DM
13. Treat OSA

• Beyond BP, glycemic and lipid control, what are other risk factors that we should be targeting? (e.g., metabolic acidosis, hyperuricemia, inflammation, anemia, etc.) Metabolic acidosis, the others have no strong evidence

• What additional risk factors/interventions should we consider among individuals with CKD and other comorbidities (e.g., ASCVD, heart failure, etc.)? ASCVD, CHF, OSA, Obesity, smoke cessation,

• When, how, and how often to monitor preventive interventions among people at risk or with CKD? CKD 3a: every 6 months CKD3b-4: every 4 months CKD 5: every 2-3 months

• How can we improve dissemination of guideline-based care via implementation or knowledge translation efforts? Not understanding the question

• What risk algorithms can we use to stratify risk levels among persons at risk for or with CKD? PCR/ACR

• How do patient perspectives and values affect decisions around detection efforts, such as the relative benefits from early awareness balanced with concerns of overdiagnosis, medication side effects, monitoring, and living with a disease label? If there is resource that able to change the progression of CKD, then early detection

can be done. In resource challenged situation, when intervention is not feasible, early detection may not be beneficious.
• What is the role of patient education and CKD awareness programs to prevent CKD onset and progression, and to prevent CVD? Very important, high yield
• What is the role of self-management and new technologies (mobile apps) when detecting/managing CKD? Yes, need easy use mobile apps
• What does successful implementation of early detection/management of CKD programs look like, and what constitutes a proof of concept for such programs? Kaiser Permanente has a very good upstream CKD management program, focus on blood pressure control, avoid nephrotoxins, cholesterol control, measure Urine protein, make sure CKD patients are on ACE-I/ARB.
• Propose research agenda related to this section

**Radica Alicic - Providence Health Care (Doctor / Physician)**
Thank you for developing clear objectives and excellent discussion questions. I'm thrilled to see health systems, care delivery and economic factors included in discussion. Recognition of obstacles for implementation of any major initiative is crucial for its success, but it is frequently missing form our discussions . Inclusion of this topic will help establish clear pathway for implementation of suggested measures. I would like to make suggestion for including few references for suggested review
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**Jose Ernesto Lopez-Almaraz - Fresenius Medical Care (Doctor / Physician)**
Group 1: it is fundamental to differentiate between screening and "confirm and categorize" CKD, perhaps with an algorithm that makes clear the implications of the process (i.e. the screening won't allows us to provide a prognosis, but to catch early stages and promote interventions to stop/slow progression. The group should work on simple guides in order to make it easier to decide (for PCP's) what studies they should use in the diagnosis and stratification of CKD. Serum Creatinine (with

eGFR), ACR (spot or 24H), urinary output, urinary sediment, renal ultrasound should be considered as a second step after screening for confirmatory (and classification) purposes.
Group 2: geographical, ethnical and etiology factors should be considered when addressing screening for CKD since in high risk populations (i.e. diabetes) should lead to support community based programs whereas less prevalent etiologies should be directed to primary care - based screening.
Group 3: - An algorithm and/or a "checklist" for modifiable risk factors that may be used should be considered, perhaps with focus on (a) Primary Care, (b) Internal Medicine / Pediatritian, (c) Nephrologist (Adult & Pediatric). - Self management should include in the discussion tools related to self-monitor progression of CKD (eGFR and proteinuria) once the disease is established, along with Educational Programs both from HCP's and also with collaboration of Patient's groups or associations.
Group 4: - Instead of "developing vs. developed countries" we should talk about Healthcare Systems and Coverage for Early (and therefore Advanced) CKD. Screening programs may be "uncomfortable" for those countries lacking of Universal Health Coverage since these programs may increase the prevalence of the disease and the requirement for treatment. - What would be the implications of being classified as CKD patient during a screening process for Insurance eligibility and cost related to it? Should we consider other kidney disease markers (ACR, hematuria, structural) before label and classify a patient with CKD based solely on the eGFR?