Trends and perspectives for improving quality of chronic kidney disease care: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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Chronic kidney disease (CKD) affects over 850 million people globally, and the need to prevent its development and progression is urgent. During the past decade, new perspectives have arisen related to the quality and precision of care for CKD, owing to the development of new tools and interventions for CKD diagnosis and management. New biomarkers, imaging methods, artificial intelligence techniques, and approaches to organizing and delivering healthcare may help clinicians recognize CKD, determine its etiology, assess the dominant mechanisms at given time points, and identify patients at high risk for progression or related events. As opportunities to apply the concepts of precision medicine for CKD identification and management continue to be developed, an ongoing discussion of the potential implications for care delivery is required. The 2022 KDIGO Controversies Conference on Improving CKD Quality of Care: Trends and Perspectives examined and discussed best practices for improving the precision of CKD diagnosis and prognosis, managing the complications of CKD, enhancing the safety of care, and maximizing patient quality of life. Existing tools and interventions currently available for the diagnosis and treatment of CKD were identified, with discussion of current barriers to their implementation and strategies for improving the quality of care delivered for CKD. Key knowledge gaps and areas for research were also identified.

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In its first chronic kidney disease (CKD) guideline, published in 2002, the Kidney Disease Outcomes Quality Initiative outlined the importance of identifying and staging CKD according to the level of glomerular filtration rate (GFR).[1] In 2009, Kidney Disease: Improving Global Outcomes (KDIGO) commissioned a meta-analysis of 45 cohorts that included over 1.5 million adults, to examine the association of estimated GFR (eGFR) and albuminuria with kidney outcomes and mortality and sponsored an international Controversies Conference to discuss these findings.[2–6] Conference participants agreed to modify CKD classification by adding urine albumin categories to each CKD stage and to subdivide CKD stage G3 into 2 stages, and they created the KDIGO heat map. KDIGO's 2012 CKD guideline[7] recommended determining CKD status and its prognosis via clinical diagnosis, as well as CKD classification based on etiology and GFR and albuminuria categories. Use of the best GFR estimating equation validated in the population of interest was encouraged. Guidance was provided for managing CKD

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progression and its complications, with rapid CKD progression defined as a sustained decline in GFR of greater than 5 ml/min per 1.73 m^2 per year. Patient safety and timing of nephrology referral were also discussed.

In the decade following the 2012 guideline, the range of tools available to clinicians for diagnosing and treating CKD expanded, and clinicians now have more opportunities to assess and manage CKD. Emerging concepts of precision medicine can be applied to CKD and potentially may direct therapies, but this will require significant changes in nephrology care. New drugs, such as the sodium-glucose cotransporter 2 (SGLT2) inhibitors and a nonsteroidal mineralocorticoid antagonist, can delay or potentially even prevent kidney failure and reduce cardiovascular disease events in patients with CKD. However, implementation of these new therapies appears to be slow. Also, there is an increasing recognition for the need to address other clinical outcomes and patient symptoms that affect the well-being and quality of life of individuals living with kidney disease.

The 2022 KDIGO Controversies Conference on Improving CKD Quality of Care: Trends and Perspectives examined and discussed best practices for improving the precision of CKD diagnosis and prognosis, managing the complications of CKD, enhancing the safety of care, and maximizing patient quality of life. The goals were to identify tools and interventions currently available for the diagnosis and treatment of CKD, determine the barriers to their implementation, and discuss a pathway for improving the quality of care delivered for CKD. The conference agenda, scope of work, and plenary presentations can be found at the KDIGO web site https://kdigo.org/conferences/ckd-quality-of-care/.

THE GROWING IMPACT OF CKD

CKD affects approximately 9% of the global population,[8] and its impact is substantial and rising.[9] Given the growing population of older adults and the increasing incidence of obesity and diabetes, the number of individuals with CKD will continue to increase.[10,11] Now the tenth-leading cause of mortality globally,[12] CKD contributes to approximately 5–10 million deaths annually, in part due to lack of access to kidney replacement therapy and the increased risk for acute kidney injury associated with CKD.[13–15] An additional 1.2 million deaths due to cardiovascular disease are also attributed to CKD.[13,16,17]

Although CKD for most individuals will not progress to kidney failure,[18–20] complications of CKD are common. CKD complicates the management of and heightens the mortality associated with many chronic conditions, such as cardiovascular disease and cancer, and with acute infections, including human immunodeficiency virus and severe acute respiratory syndrome coronavirus 2 (SARS-COV2).[16–19,21] Climate conditions, including heat waves and extreme cold, increase risk of mortality from CKD.[22,23] Populations with limited resources, poor access to healthcare, and low health literacy are at highest risk for kidney disease and related complications.[8] Given the increasing impact of CKD on population health and healthcare systems, preventing CKD and its progression is an urgent problem of growing global importance.

DIAGNOSIS, STAGING, AND PROGNOSTICATION IN CKD

Existing challenges

A CKD diagnosis increases the likelihood of treatment to slow CKD progression.[23a] Due to low rates of screening in high-risk populations, lack of patient symptoms, and the fact that creatinine-based measures of kidney function have low sensitivity to detect early kidney damage, most kidney disease remains undiagnosed and untreated until its later stages, when interventions are less effective.[24–29a] Moreover, in many cases of CKD, the etiology remains unclear. A kidney biopsy, the current gold standard for assessing renal microstructure, is performed in only a small proportion of cases. Also, a large degree of variability is present in eGFR trajectories, based in part on genetic factors and the burden of systemic chronic disease, including diabetes.[30,31] Early identification of patients with CKD at high risk of progression is therefore difficult, given that eGFR trajectories are usually not quantified, and rapid decline in eGFR may not be recognized.[30,31]

GFR evaluation

The best measure of kidney function is GFR, which is currently the basis for defining and staging CKD, as well as determining treatment plans. However, GFR cannot be measured easily in clinical practice, and all methods for measuring GFR (mGFR) and estimating GFR (eGFR) are subject to bias and imprecision.[32–35] Given the widespread availability and low cost of measuring serum creatinine, ascertaining estimated glomerular filtration rate based on serum creatinine ($eGFR_{cr}$) will likely remain the initial method for evaluating GFR. Non-GFR determinants of serum creatinine include factors influencing muscle mass, such as limb amputation, spinal cord injury, neuromuscular disease, severe malnutrition, advanced heart failure, cirrhosis, and diet and differences that have been attributed to race. Using serum cystatin C for estimating GFR ($eGFR_{cys}$ or $eGFR_{cys,cr}$) improves accuracy over $eGFR_{cr}$[36] and would be useful, in particular when precision is critical, such as when determining appropriateness for kidney donation, facilitating drug dosing within a narrow therapeutic index, or prescribing drugs with serious toxicity.

Meeting participants felt that clinicians need guidance on approaching GFR estimation and evaluation in the context of availability, standardization, and cost. Irrespective of the filtration markers used to estimate GFR, eGFR values always should be viewed within a broader context of body composition and comorbidities. Ideally, a single equation for each marker or combination of markers would be used uniformly within regions (e.g., continent or country). However, individual physicians may choose specific equations in certain circumstances. Although the output from GFR estimating equations is typically indexed to a body surface area of 1.73 m^2, the best approach to adjusting GFR for adults of different body sizes remains controversial.

Albuminuria evaluation

The presence and severity of albuminuria are equally important for defining and staging CKD, and change in the severity of albuminuria is a putative surrogate marker for risk of CKD progression. Spot morning urinary albumin–creatinine ratio (UACR) and random UACR are the best methods for assessing albuminuria and are preferred to more-demanding (24-hour urine collections) and less-standardized (protein–creatinine ratio; dipstick urinalysis) alternatives.

Factors that should influence the recommended frequency for evaluation of albuminuria include the risk of albuminuria-associated complications, available interventions, cost and cost-effectiveness, feasibility of implementation, and alignment with other guidance. The European Society of Hypertension recommends baseline UACR testing for all patients with hypertension, with follow-up measures at least annually for those who already have CKD.[37] The American Diabetes Association recommends UACR testing at least annually for most patients with type 2 diabetes, and more frequent testing for those with severely increased albuminuria or CKD stages G3–G5.[38]

Meeting participants agreed that data on the incidence of albuminuria are missing and/or highly variable, rendering evidence-based recommendations for testing frequency in specific populations difficult. For example, the median incidence of UACR ≥30 mg/g (≥3 mg/mmol) at 5 years among people with diabetes was 23.9% in 23 studies, with a range from 4.3% to 44.8%.[39] The incidence of increased UACR is similar among people with hypertension but without diabetes (median incidence 21.7% [range: 3.5%–31.7%]). This finding suggests that the potential benefits of repeat testing of UACR are likely similar for people with hypertension in the absence of diabetes, versus those with diabetes with or without hypertension.

Meeting attendees agreed that thresholds for testing should be context-specific and that there is considerable value of future studies determining the optimal populations for UACR testing, the ideal testing frequency within these populations, and the percent change in albuminuria that would be clinically meaningful to guide therapy (Table 1[40]). Until further data are available, annual testing appears to be a reasonable approach to take for all people with hypertension or CKD, with more frequent testing being conducted among those with CKD A3, G4–G5, or diabetes.

Evaluation of tubular function

Although clinical practice focuses on assessing glomerular function, kidney tubules support multiple other kidney functions, including concentration and acidification of the urine, hormone production, and metabolite excretion. A wide range of plasma- and urine-based biomarkers have been proposed for assessing tubular functions and damage, but few, if any, have compelling clinical advantages at present.[41] Possible clinical applications for markers of tubular function include treatment selection (matching a treatment to a mechanism of injury), monitoring for effectiveness of treatment or medication safety, and distinguishing kidney cell injury from hemodynamic causes of reduced GFR.

Meeting participants agreed that despite the huge potential to better assess tubular function, currently, no rationale exists for routinely measuring markers of tubular function in the general population, or in people with CKD. More information is required to define the clinical value of tubular biomarker(s) for specific settings, as well as what such biomarkers represent at the cellular and molecular levels (Table 1).

Remaining controversies in staging

Whether age and sex should be considered in defining thresholds for CKD and CKD stages, and whether such stratification would lead to clinically meaningful improvement in patient care, remains controversial.[42,43]

Race is included in current guideline-recommended $eGFR_{cr}$ equations because historically, evidence indicated that Black individuals have a higher average serum creatinine concentration than non-Black individuals for the same measured GFR.[44–46] Yet inclusion of race in GFR estimating equations is increasingly questioned, given that race is not a biologic construct, that its inclusion ignores diversity within other racial groups, and that the practice might contribute to inequities in CKD diagnosis and treatment.[47,48] New equations without race coefficients have been developed using plasma creatinine and/or cystatin C as filtration markers.[36,49] The implementation of equations without a race-coefficient has been recommended in the US,[50] but not in Europe.[51]

Further risk stratification

Following CGA staging (identifying the cause of CKD [C] and assigning GFR [G] and albuminuria [A] categories), further disease-specific stratification is possible. Examples include classification of IgA nephropathy according to MEST scoring (mesangial [M] or endocapillary [E] hypercellularity, segmental sclerosis [S]; and interstitial fibrosis/tubular atrophy [T]), measurement of serum anti-phospholipase A2 receptor (PLA2R) antibodies in membranous nephropathy, *APOL1* (apolipoprotein L-1) testing in glomerular diseases, and evaluation of the underlying gene defect (polycystin-1 vs. polycystin-2) in autosomal dominant polycystic kidney disease (ADPKD) and autosomal dominant tubulointerstial kidney disease (ADTKD).[52,53]

Although diabetes is a leading cause of CKD worldwide,[11] participants felt that currently, no rationale exists for staging based on the presence or absence of diabetes. Given that many large randomized controlled trials have focused on including people with diabetes, many drugs are presumably effective in the absence or presence of diabetes, and thus an alternative staging pathway for treatment is not needed at this time.

Risk prediction tools can help integrate various risk factors into actionable clinical indicators.[54–56] In using risk prediction to guide individualized clinical care and treatment planning, the primary outcomes of focus (e.g., kidney failure,

Table 1 | Key questions and research needs for improving care in CKD

CKD care considerations	Key questions and knowledge gaps	Research and translation needs
Use of point-of care-devices	• What are advantages and implementation barriers globally (cost, access to devices, standardization, flow of information, integration into busy clinical practice)	• Investigation of sufficiently robust and accessible point-of-care tools to measure creatinine and albuminuria in specific populations • Investigation of point-of-care tools to assess CKD-associated comorbidities and complications (glucose, potassium, hemoglobin)
GFR evaluation	• How best to globally standardize and calibrate measures of serum creatinine and mGFR • How to overcome laboratory and reimbursement barriers to cystatin C use • What is the value of non-indexed eGFR under specific circumstances • How eGFR can best be used in combination with markers of tubular function • How to best promote the GFR evaluation paradigm	• Standardization of mGFR ◦ Existing studies—individual participant analyses are preferable to systematic reviews ◦ New studies—cross-sectional studies in representative populations across regions or countries ◦ New studies—longitudinal studies in representative populations to assess impact of age and disease progression • Optimization of eGFR ◦ Ascertain accuracy, variation, and determinants of eGFR based on established and novel endogenous filtration markers ◦ Discovery of novel endogenous filtration markers for equitable and precise GFR estimations • Use of non-indexed GFR estimates
Albuminuria	• What changes in albuminuria warrant intensive treatment • What is the true cost-effectiveness of repeat testing in different populations (and thus the priority for emphasizing such testing when resources are limited) • How to improve adherence to recommended testing frequency	• Determining the optimal populations for UACR testing and the ideal frequency of testing within these populations
Tubular function	• What are the optimal biomarker(s) for each clinical setting • What do biomarkers represent at the cellular and molecular levels	• Methodological improvements, such as assay standardization, as well as understanding of how biomarkers can be used in combination to inform clinical diagnosis (much as the liver panel is currently used) • Determining normal levels of tubular biomarkers in the absence of CKD. Leverage existing resources such as the NHANES studies and the UK biobank • Longitudinal studies that assess sequential measures of tubular function as risk factors for CKD progression outcomes and other complications related to CKD. Use well-phenotyped CKD cohorts with repeated biosample collection, such as those gathered in the International Network of CKD Cohorts (iNETCKD)
Risk classification	• How to implement the Kidney Failure Risk Equation across clinical settings • What are the best risk equations for specific populations and settings	• Refinement and comparison of various risk equations
Imaging	• What is the biological validity of new imaging measures • What is the optimal frequency of serial renal imaging	• Cross-sectional studies of imaging biomarkers compared against kidney biopsy or biomarkers that are known to represent specific pathophysiological processes • Prospective longitudinal patient cohort studies to evaluate an imaging method's ability to predict progression and measure change in response to treatment • Serial imaging should test which parameters change over time in association with CKD progression or regression • Exploration of radiological techniques for early detection of chronicity • Health economic evaluations of costs and benefits of new imaging methods for CKD • Data and original images should be made available for secondary research and/or educational or commercial purposes when possible

(*Continued on following page*)

Table 1 | (Continued) **Key questions and research needs for improving care in CKD**

CKD care considerations	Key questions and knowledge gaps	Research and translation needs
Biomarkers	• How to develop platforms to study biomarkers • What is the validity of biomarkers for predicting disease progression and therapy response in different settings • How should one integrate results in a comprehensive clinical action plan • How should one integrate biomarkers, imaging, and biopsies into the diagnosis and monitoring of CKD in a comprehensive way	• Conducting development of biomarkers in parallel with therapeutic development • Developing a systemic approach to measure and use biomarkers in clinical trials • In clinical trials include untargeted samples to be used in biomarker discovery • Advocating for access to samples collected by clinical trials • Developing a catalog of biomarkers with ratings based on performance with respect to specific applications
Individualization of therapy	• Does individualization of therapy add value in the clinical management of CKD globally • For which patients and in which situations is individualization of care of relevance • How to improve communication with patients • How to assess information recall among patients with CKD, including those with impaired cognitive function	• Evaluating individualized treatment approaches based on biomarkers and pathophysiological considerations • Evaluating real-world evidence focusing on short- and long-term effectiveness and safety of new drugs and combination therapy, particularly in subgroups not well represented in clinical trials • Evaluating changes in patient awareness and communication • Developing a CKD-specific communication curriculum that is translatable across different settings and languages • Evaluating use of existing electronic applications for reinforcing important discussion points
Patient-reported outcome measures (PROMs)	• Which instruments are appropriate for routine use in CKD care and which are appropriate under specific circumstances	• Comparative effectiveness studies to assess whether using PROMs in CKD care significantly improves patient-prioritized outcomes compared with usual patient–clinician interactions • Developing practical tools focusing on these prioritized PROMs, including measurement of life participation, and evaluating them in the routine clinic • Of note, patients strongly promote implementation of studies to evaluate the most promising nontherapeutic interventions (e.g., exercise, diet) to improve prioritized PROMs
Polypharmacy	• When to discontinue certain medications and for how long • Which medications should be paused during acute illness and for how long ("sick day guidance") • What is the effect of "sick day guidance"[40] (discontinuation of certain medication during acute illnesses to avoid side effects, including acute kidney injury) on clinical outcomes	• Evaluating the safety and efficacy of combinations of medications • Evaluating the safety and efficacy of combining fixed doses of different drug classes in pills ("polypill") in the setting of CKD • Conducting pharmacoepidemiologic studies and consensus methods to identify and deprescribe potentially harmful or ineffective medications in patients with CKD, including in low-resource settings • Designing clinical trials to assess the effect of deprescribing on clinical outcomes (mortality, hospitalizations, and PROMs) • Analyzing data from observational studies to identify patient factors that may increase risk associated with specific medications • Evaluating polypill strategies to reduce medication burden
Models of care	• What are the optimal management plans for CKD based on the CGA classification • How should nephrology referral be integrated into regional management plans (especially given wide global variation in local resources) • What is the optimal approach to case identification, i.e., under which circumstances is screening for CKD justified • How to leverage the expertise of nephrologists for enhancing the management of patients who have not been (or who cannot be) referred • What are best practices for supporting care of CKD patients in primary care, including task-shifting and delegation by nephrologists, as appropriate	• Conducting studies to describe the clinical and economic benefits of multidisciplinary CKD care • Exploring opportunities for synergy and co-management between specialist nephrology care and other specialist services

Table 1 | (Continued)

CKD care considerations	Key questions and knowledge gaps	Research and translation needs
Digital support	• What are current deficiencies/shortcomings in the use of electronic health records with respect to diagnosis and management of CKD • How can machine learning be used to optimize detection, prognostication, and management of CKD • Can natural language processing help to better capture patient-reported experience measures	• Defining gaps in CKD diagnosis in current care • Evaluating algorithms for automatic detection and flagging of patients with CKD • Evaluating automatic delivery of alerts and management recommendations in patients with CKD • Evaluating automatic links to specific CKD guideline recommendations in relevant clinical settings

CGA classification, identifying the cause of CKD (C), assigning a GFR category (G), and assigning an albuminuria category (A); CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; mGFR, measured glomerular filtration rate; NHANES, National Health and Nutrition Examination Survey; PROM, patient-reported outcome measure; UACR, urinary albumin–creatinine ratio.

CKD progression, cardiovascular events) should be used to guide clinical decision-making, such as intensification of care or referral. Modeling of multiple outcomes, such as cardiovascular disease and CKD, can be useful in these instances and may lead to overlapping recommendations (e.g., SGLT2 inhibitors and nonsteroidal mineralocorticoid antagonists) or distinct recommendations (e.g., statins).

Further development of risk models for various acute and chronic comorbid outcomes (e.g., infection, mental health decline, gastrointestinal dysfunction, genitourinary dysfunction, musculoskeletal disorders, substance abuse, etc.) based on routine clinical data enriched by patient-reported information could enable and promote a proactive rather than a reactive approach to managing CKD.

Meeting participants considered how to best integrate risk prediction into communications with patients. Patient education, counseling, and understanding are important for appreciation of a diagnosis and its relevance to personally meaningful endpoints, including survival and reaching social milestones, such as attending celebrations. Understanding kidney and cardiovascular disease and their interactions can help inform an understanding of cardiorenal risk. Graphical illustration of risks and how they change with intervention can be helpful.[57]

Technology expansion and development

Application of home or decentralized assessments that are cost-effective can be feasible across different economic and resource-limited settings. Home or decentralized assessment of eGFR/UACR could be used to increase awareness and access, while optimizing the frequency of CKD screening and monitoring. In addition, it may lead to better understanding of the dynamics of kidney function (e.g., response to injury, challenge, treatments), and point-of-care platforms may be expandable to blood pressure, glucose, potassium, hemoglobin, etc. Integration of this approach with clinical trial design may lead to improvements in trial efficiency (e.g., outcome ascertainment). Current challenges to global implementation include standardization, integrating information with e-health systems, and potential shifts in interpreting results or action plans.

Additional opportunities to improve care do exist, and they include evaluating the functional kidney reserve via a kidney "stress test" through imaging or through the use of new isotopes or other biomarkers of kidney function. Determining functional kidney reserve could expand the understanding of the incidence and progression of kidney disease, leading to earlier identification and treatment. However, additional research is needed before implementation.

Kidney biopsies remain integral for diagnosis and provide insights into the unique pathways and patterns of disease, ultimately to guide therapies and inform trials. Kidney biopsies are essential in the development of imaging and blood/urine biomarkers, and their integration into current research or existing studies will lead to a better mechanistic understanding of disease progression and response to therapy. For example, the Nephrotic Syndrome Study Network (NEPTUNE),[58] an observational cohort of people with focal segmental glomerulosclerosis, membranous nephropathy, or minimal change disease undergoing biopsy, is partnering with ongoing clinical trials to facilitate participant recruitment for molecular phenotyping, which may provide molecular insights that can be used to differentiate unique pathways and patterns of disease. The European Biomarker Enterprise to Attack Diabetic Kidney Disease (BEAt-DKD) Consortium[59] and the US Kidney Precision Medicine Project[60] are obtaining kidney biopsies from adults with CKD or acute kidney injury to create a reference kidney atlas and characterize disease subgroups to identify critical pathways and targets for novel therapies and preventive strategies.

Technologies currently in development have the potential to improve the identification of CKD etiologies in individual patients and assess dominant pathologic mechanisms (Figure 1). These technologies include advancements in biopsy analysis, liquid biomarkers, imaging methods, artificial intelligence, and learning health systems for data integration to facilitate timely, optimally suited interventions. Genetic markers also play an important role in improving diagnostics, disease surveillance, and choice of therapy; KDIGO's 2021 Controversies Conference on Genetics in Chronic Kidney Disease[53] covered this topic in detail, and therefore it was not discussed in depth in the present conference.

Biomarkers. Multiomics approaches to identifying new biomarkers are needed to apply precision medicine to kidney

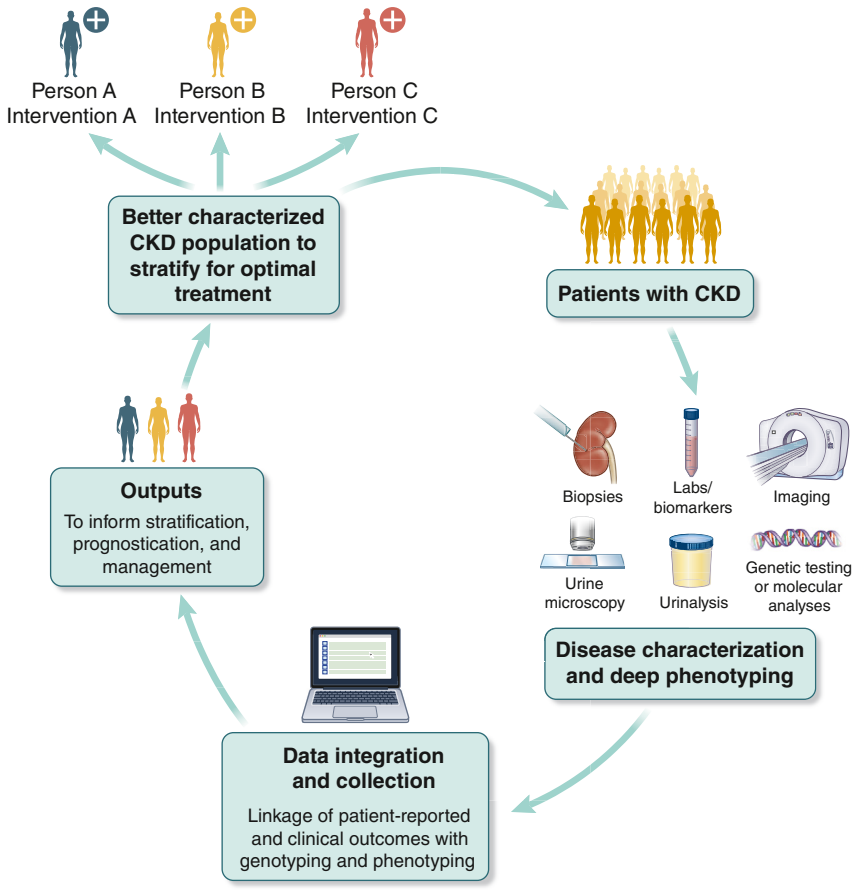

Figure 1 | Precision medicine framework for optimizing treatment of chronic kidney disease (CKD). Existing and developing technologies have the potential to improve the characterization of CKD in individual patients and assess etiologies and dominant pathologic mechanisms. Such technologies include advancements in analysis of tissues, biomarkers in blood or urine, imaging methods, genetic or molecular analyses, and data integration through artificial intelligence and learning health systems. Combining the information gained from characterization of disease and deep phenotyping, along with clinical and patient-reported outcome data, and integrating it with clinical trial design, the ultimate goal is to provide the right therapy for a given person at the right time. This framework may contribute to improving the lives of patients with CKD.

diseases. Biomarkers can be diagnostic (categorizing the presence/absence of a certain disease or type of disease), prognostic (indicating risk for disease occurrence and progression; to treat or not), predictive (predicting the likelihood of patient response to a particular treatment before its administration[48]; indicating what type of treatment), or dynamic (indicating a biological response [long-term effect] after short treatment; indicating whether to continue or not).[61]

Artificial intelligence (AI)–enabled algorithms can integrate information from biomarkers, imaging, biopsies, demographic and clinical characteristics, and patient-reported outcomes.[62] Such platforms would lead to a new set of risk scores and patient treatment-matching scores, ultimately supporting clinical decision-making.

Several recent examples of applications hold promise to serve as prognostic biomarkers for CKD progression. The urinary excretion of epidermal growth factor (uEGF) was identified as a biomarker of CKD progression using a kidney biopsy transcriptome-driven approach.[63] This biomarker was further identified as an independent predictor of kidney function decline in subsequent observational prospective cohort studes.[64,65] Molecular profiling has identified a patient subgroup within nephrotic syndrome with poor outcome as well as kidney tumor necrosis factor (TNF) pathway activation[66] identified by urine biomarkers, monocyte chemoattractant protein-1 (MCP1), and tissue inhibitor matrix metalloproteinase 1 (TIMP1).[66] Based on these findings, clinical trials utilizing noninvasive biomarkers of pathway activation to target therapies, improve response rates, and facilitate personalized treatment in nephrotic syndrome have been initiated (ClinicalTrials.gov identifier NCT04009668).

Urinary T cells in patients with inflammatory kidney diseases have potential to identify patients with active nephritis earlier,[67,68] monitor treatment response,[67] and predict treatment outcome.[69] Urinary kidney epithelial cells reflect extent of tubular damage in acute kidney injury and may help

predict outcome.[70] Urinary flow cytometry techniques have the potential to monitor inflammatory disease activity and tubular damage, guide treatment, and define need for biopsy. Single-cell sequencing of urinary cells could identify driving pathomechanisms for individualized treatment and potentially provide a substitute for biopsy in selected cases.

Imaging. Advanced imaging is part of routine clinical practice in other internal medicine specialties, whereas a majority of patients with acute or chronic kidney disease undergo limited imaging assessment, which in many cases does not contribute to clinical decision-making.

Fortunately, renal imaging, with a range of different modalities, is rapidly evolving (magnetic resonance imaging [MRI], computed tomography, newer ultrasound techniques, isotopes, etc.). In particular, with kidney MRI, a number of noninvasive, quantitative, and functional measures are now available that can inform different aspects of CKD pathophysiology without the need of contrast agents. Kidney MRI can clearly differentiate healthy from diseased kidneys[71–73] and provides multiparametric measures of hemodynamics, oxygenation, and microstructure.[74,75] An analysis of blood oxygen level–dependent (BOLD) MRI using a specialized 12-layer analysis technique showed that reduced cortical oxygenation predicts a progressive decline of kidney function in patients with CKD.[76] Several measures differentiate between high and low fibrosis,[75,77] possibly at different thresholds. Kidney volume has been accepted by the US Food and Drug Administration as an enrichment biomarker and surrogate outcome for trials in ADPKD.[78]

Given the rapid progress in the field, the need for standardization of measurements and reporting, independent of imaging modality, is clear. New imaging measures must be shown to be valid tools for testing hypotheses in a research setting, and then shown to be clinically useful and cost-effective in the routine management of patients (Table 1).

COMPREHENSIVE CARE FOR CKD

Dimensions of quality of care

Individuals with CKD often experience increasing symptom burden and reduction in quality of life as CKD progresses to advanced stages (Figure 2), similar to the progression seen in individuals with advancing malignancy.[79–82] The most

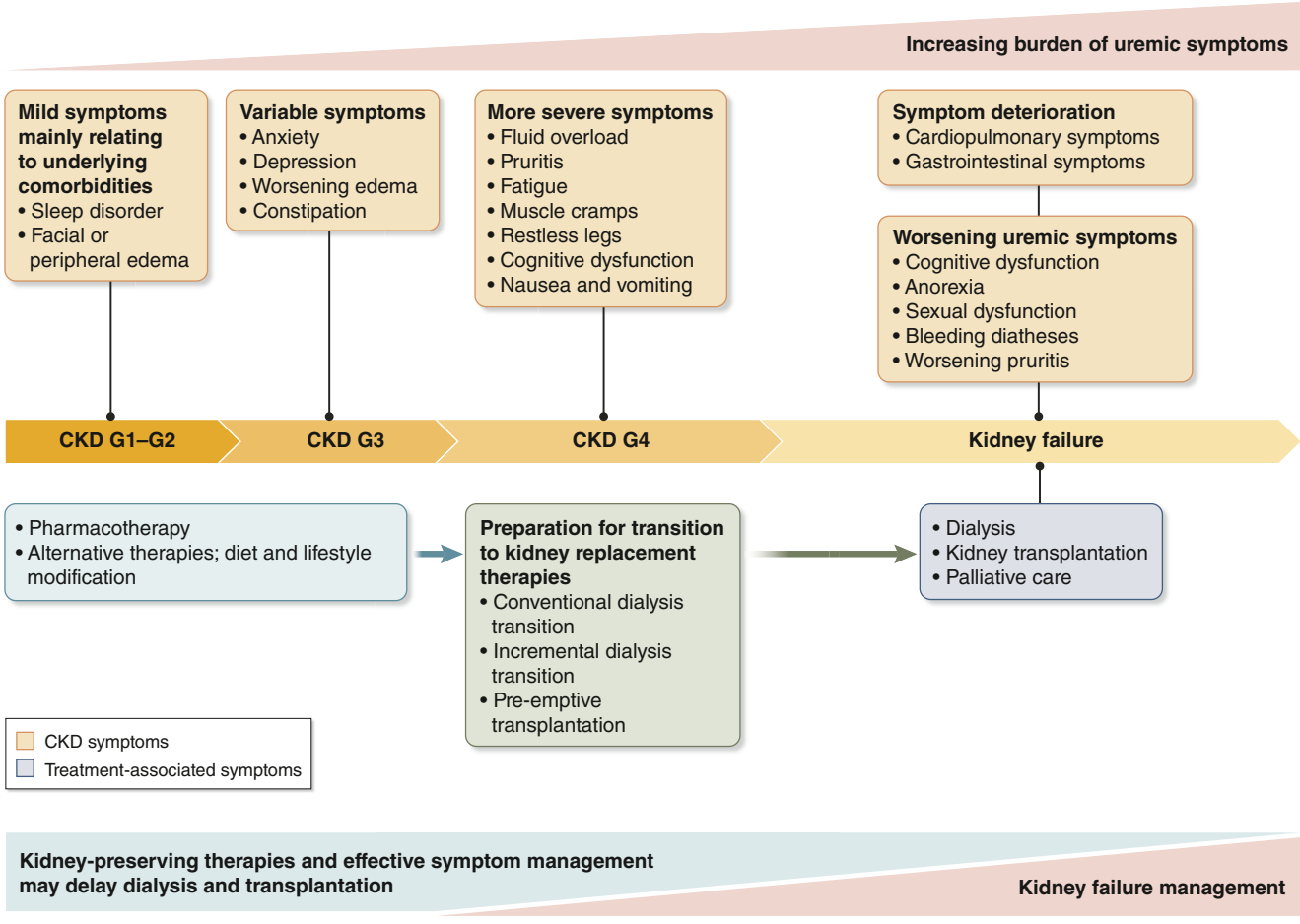

Figure 2 | Symptom burden progression with chronic kidney disease (CKD). Symptoms associated with chronic kidney disease and/or its treatment often increase in severity and frequency with progression of disease. Kidney failure management includes palliative care, supportive care, and hospice. Adapted from Kalantar-Zadeh K, Lockwood MB, Rhee CM, et al. Patient-centred approaches for the management of unpleasant symptoms in kidney disease, *Nature Reviews Nephrology*, volume 18, pages 185–198, 2022, with permission from Springer Nature.[81] This licensed material is not part of the governing Open Access license but has been reproduced with permission from SNCSC.

frequently mentioned CKD-associated symptoms are pain/discomfort, lack of energy/fatigue, sleep-related problems, and itching/skin problems. Yet effective symptom management remains a major unmet need. An imbalance exists between health professionals' almost exclusive focus on clinical events and laboratory results and patients' expressed need for holistic care and support in coping with daily activities and their wide array of symptoms.[83] Life participation (the ability to participate in meaningful activities of daily living) is a critically important outcome among individuals with CKD.[84,85]

Patient-centeredness, including shared decision-making, emerged as a critical dimension for maximizing the quality of care based on patient-valued outcomes. Patient-reported outcome measures (PROMs) aid in determining well-being as related to symptoms, functional status, health perceptions, and health-related quality of life.[86] Evidence from other chronic diseases suggests that regular PROM use with clinician follow-up serves to focus care on what matters to patients. PROMs can facilitate patient–clinician communication, enhance patient activation (in adherence to treatment and healthy behaviors), and prompt treatment and follow-up of previously unrecognized symptoms.

A variety of generic and disease-specific instruments may be used in CKD to assess patient priorities.[79,87–89] In contrast with oncology, a field in which randomized controlled trials and real-life interventions have shown that clinical use of PROMs improves quality of life and reduces healthcare use, evidence is needed to identify which instruments would be appropriate for use in routine CKD care.[86,90] Key considerations include the following: PROM psychometric properties and their validation for the target population; burden of measurement (length and frequency of administration); potential patient-level barriers (language, culture, cognition, health literacy); potential system/clinician-level barriers (lack of evidence-based interventions, lack of time and support); and role of technology and availability of electronic tools.

Evidence for interventions that improve CKD symptoms is limited, except for data indicating that treating anemia may reduce fatigue.[81] In addition, knowledge about PROM trajectories during the course of CKD is currently insufficient to determine the optimal frequency of administering PROM questionnaires.[82,91,92]

Numerous studies call for consideration of PROMs as a critical dimension of CKD care. However, concerns remain about the potential for harm when using PROMs in clinical practice without demonstrating their clinical value to health professionals and the feasibility of their incorporation into routine workflow, with appropriate technology, organization, and preparedness of stakeholders. Therefore, including PROMs as endpoints in clinical or intervention trials and raising awareness about PROMs among health professionals are of utmost importance (Table 1).

Models of care

Models of care broadly refers to the delivery of care and services across all stages of a disease or condition,[93] with a goal of ensuring that people get the right care, at the right time, delivered by the right team, and in the right place. Management of CKD has historically been dichotomized into the care that is provided before versus after referral to nephrologists. Over time, 4 factors have changed the scope and nature of nephrology practice. as follows: (i) data on the clinical and economic benefits of preventing kidney function loss and complications of CKD, as opposed to simply treating kidney failure; (ii) recognition of the high and growing burden of CKD; (iii) growing emphasis on allowing all health professionals to work to their full scope of practice; and (iv) demand for patient-centered care. These changes have led to reconceptualization of CKD care as a continuum that reflects the capacity, contributions, and needs of the health system, patients and families, and providers. Multidisciplinary care teams are recognized as being the best approach to deliver care across the continuum, with team composition and structure driven by local needs and resources, as well as patient characteristics, such as complexity or severity of illness.

Multidisciplinary CKD care is associated with lower rates of kidney function loss and emergent initiation of dialysis, better control of biochemical markers (e.g., calcium or phosphate), and possibly with other favorable outcomes, such as increased time to kidney replacement therapy, or lower mortality incidence, although data from randomized trials are lacking.[94,95] Limited data suggest that electronic infrastructure, such as clinical decision support, may enhance the success of multidisciplinary CKD teams.[96,97] Data from management of other chronic conditions, such as diabetes, suggest potential benefits of electronic tools (e.g., telehealth, mHealth applications, electronic medical record–based prompts); evidence-based strategies for quality improvement; and encouragement of self-management.[98–100]

In primary care, optimal models of care will have capacity to detect CKD and its complications; provide appropriate monitoring and management; and arrange timely referral as needed—based on clinical characteristics, patient preferences, as well as the local context, including health systems capacity. To optimize care, primary care teams should be provided with the following: clear guidance on who to test for CKD and how to manage identified cases; tools that can predict risk of progressive kidney function loss or other complications; criteria and pathways for specialist referral; and appropriate financing mechanisms. Delivering on these objectives to optimize care requires a broad range of professionals, which may include those from outside the traditional health sector (Table 2). In many settings, teams will be led by physicians, although alternative models (e.g., nurse-led, pharmacist-led) may be more appropriate in others. The correct mix of personnel is context-dependent and requires careful consideration to capitalize on potential benefits of task shifting or task strengthening.

Additional factors that can facilitate patient-centered primary care include the following: mechanisms for integrating CKD management with treatment of comorbidities (e.g., diabetes, heart failure, mental illness, or substance misuse);

Table 2 | Individuals who may help deliver comprehensive multidisciplinary care for patients with CKD

- General practitioner
- Nephrologist
- Other medical specialist
- Nurse
- Nurse practitioner, clinical officer, physician assistant
- Medical administrative staff member
- Dietician
- Psychologist
- Physio/occupational therapist
- Exercise physiologist
- Pharmacist
- Information technology staff member
- Translator
- Community health worker
- Social worker
- Other patient
- Member of patient self-help group
- Lay person to act as a care navigator or for peer support
- Health-trained worker
- Homecare worker
- Educator
- Facilitator

CKD, chronic kidney disease.

translation services where language is an issue; and resources for culturally sensitive care of disadvantaged populations.

For patients with social challenges and/or low health literacy, a patient navigator may be useful for making and attending appointments, translating language, and assisting with any other patient needs.[101,102] Electronic medical records may be leveraged to access plain-language description of information. Clinicians require training in communication and support in building therapeutic alliances. Education level, language skills, and ethnicity are considerations in communication strategies.

In addition to encountering a large number of patients with CKD, primary care providers can experience a number of barriers to providing optimal care, including lack of resources[103] or capacity, inadequate financing or reimbursement structures, complexity of CKD guidelines, inappropriate clinical guidance (e.g., is not accessible or culturally acceptable; conflicts with other disease-specific guidance), patient mistrust, and lack of interdisciplinary support for the treating clinician.

The goals of care for CKD patients after first nephrology referral are similar to those for patients managed solely in primary care, but they include treatment of specific kidney diseases (e.g., glomerulonephritis, ADPKD), attention to CKD-specific complications (e.g., anemia, metabolic bone disease), as well as choices and adequate timing of kidney replacement therapy (KRT), including consideration of living-donor kidney transplantation. Given the typically greater complexity of those patients who have advanced CKD, the benefits of multidisciplinary care appear to be greater for them than they are for those managed solely in primary care. Again, local context is critical for selecting the appropriate model. Special considerations are relevant for the care of children with CKD and their transition into adulthood.[104] As the number of participating professionals increases, communication within and between disciplines becomes increasingly important.

Before and after referral, increasing the degree of integrated care using a team approach; prioritizing the patients' concerns, values, and preferences; and empowering patients and families through education should be the 3 guiding principles for devising or revising models of care.

Individualized pharmacotherapy

Examples of individualized pharmacotherapy in nephrology include the following: dose adjustments for kidney function (considering pharmacokinetic and pharmacodynamic alterations, dialysis clearance, and therapeutic drug monitoring); thresholds for initiating pharmacotherapy for management of CKD and its complications; individualized parameter targets, such as less-stringent HbA1c values in CKD; medication changes at transitions of care; and deintensification or deprescribing of treatment. Interventions include the following: comprehensive medication management, review, and reconciliation[105]; improving communication during transitions of care (for example, between hospital and community pharmacists); interventions at the community level[106]; utilizing multidisciplinary programs (including nurses, pharmacists, and nephrologists); utilizing communication technologies (mobile health applications, virtual visits); and home-monitoring. For example, among individuals at high risk for cardiovascular events in rural Indonesia,[107] a multifaceted mobile technology–supported primary health care intervention was associated with greater use of preventive cardiovascular medication and lower blood pressure levels.

Goals or benefits of interventions would be lower rates of readmission, lower numbers of medication-related hospitalizations, reduced numbers of medication errors, cost-savings, increased use of preventive CKD medication, and lower blood pressures.

Disease-modifying medications

Disease modification is a concept in which the primary focus is on the disease process and main outcomes (e.g., long-term remission or prevention of progression) rather than on symptoms and complications (e.g., anemia or hyperphosphatemia). Although this therapeutic concept is well established in a number of disease areas,[108,109] it is yet to be defined for CKD. The consensus among conference participants is that interventions that have a positive effect on kidney disease trajectory (i.e., slow or reverse kidney damage and functional decline) and reduce risk of kidney failure may be defined as a chronic kidney disease−modifying treatment.

Use of available disease-modifying medications for CKD currently is not optimized. For example, in the US, only 25%–40% of eligible patients with CKD receive generic, low-cost angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.[110,111] Several studies in CKD/hemodialysis/transplant and general populations support implementation of comprehensive medication management to impact health

outcomes, healthcare cost, and patient and provider satisfaction.[105,112–115] As the number of disease-modifying medications increases, questions arise about the optimal use of combination therapies in individual patients, based on diagnosis and risk of progression. Treatment recommendations for related diseases such as arterial hypertension and heart failure have recently undergone a paradigm shift, with parallel initiation of medications with different mechanisms now being recommended rather than incremental prescription using escalation schemes.[116,117] Ideally, prescription and deprescription should be individualized and response-driven, with decision strategies defined in clinical trials.

Novel combinations in the absence of trial data

Participants considered the question of whether more than 1 disease-modifying drug should be used if a positive benefit-to-risk ratio has been established for the drugs individually but not in combination. Key questions are as follows: (i) can drugs be safely combined; (ii) are the drug effects additive or sub-additive; (iii) for whom and when should drugs be combined. A large variation is present in the baseline risk and absolute benefits of drugs. For instance, studies that tested the effect of SGLT2 inhibitors on top of angiontensin-converting enzyme inhibitors or angiotensin receptor blockers indicated that the absolute benefit in reducing kidney failure was larger in those with a higher baseline UACR.[118] In the absence of dedicated data from randomized controlled trials, combination therapies may be acceptable in high-risk patients (in whom the absolute effects are highest) if drugs have different mechanisms of action and if the safety profile is compatible. In particular, in cases in which residual risk remains high (e.g., with high UACR), combining individual agents appears to be advisable. Ongoing reassessment and medication reconciliation and review are key to this approach.

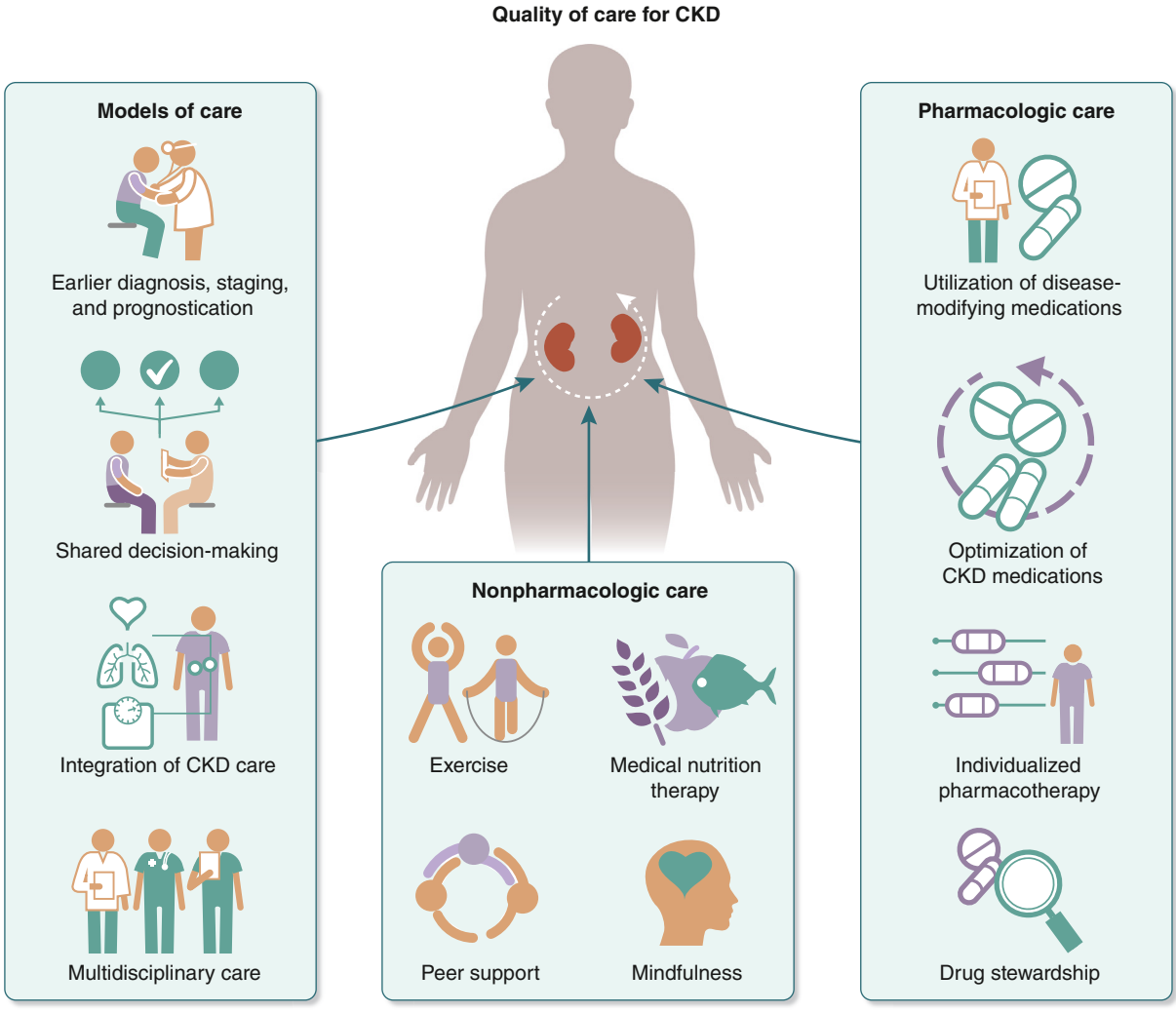

Figure 3 | Components of quality care for chronic kidney disease (CKD). Conference participants identified 3 overarching components for improving quality of care: models of care, nonpharmacologic care, and pharmacologic care.

Avoiding the adverse consequences of polypharmacy

Although the term has no standard definition, "polypharmacy" is often used to mean the routine use of 5 or more medications, including over-the-counter, prescription, and/or traditional and complementary medicines.[119] In patients with CKD, the prevalence of having a high pill burden ranges from 38% to over 80%, and it is more common among women, elderly patients, and those with more severe disease.[120–122] The average number of different medications taken every day by patients with CKD is reported to be between 8 and 9,[120,123] and in this population, having a high pill burden has been associated with increased risk for kidney failure, hospitalization, adverse drug reactions, and mortality.[121,124–126]

Although this high pill burden is widely considered problematic, as is the inappropriate prescribing of multiple medications, a causal relationship between polypharmacy and adverse outcomes has not been demonstrated. In fact, polypharmacy may be appropriate when medication use is in accordance with best evidence and is optimized for patients with complex and/or multiple conditions.[127] This concept applies to patients with CKD, particularly with the recent incorporation of multiple therapies with evidence of benefit for CKD progression and management of complications.

Strategies of deprescribing. Computerized alerts and pharmacist support can improve quality of care by reducing medication errors and inappropriate prescription in patients with CKD.[128,129] However, whether such interventions improve outcomes in patients with CKD is uncertain. Nevertheless, the importance of communication between providers and medication reconciliation is paramount, especially during transitions of care, including during and after hospitalizations, kidney transplantation, and dialysis initiation, to avoid potentially inappropriate prescriptions and optimize medication dosage. A list of medications that need to be avoided or dose-modified in patients with CKD has been published elsewhere[130] and should be updated frequently. In addition, the American Society of Geriatrics and other international organizations have developed specific guidance for identifying potentially inappropriate medications among elderly patients, including those with CKD.[131–134]

In addition to ensuring adequate medication prescription practices, and weighing risks versus benefits when prescribing a medication for the first time, deprescription of medications is also important to consider once their benefit becomes limited or if their associated risks increase, based on patient age and/or kidney function.[135,136] Although the benefits of deprescribing have not been well studied among patients with CKD not on dialysis therapy, it has been associated with decreased pill burden and increased satisfaction among patients with kidney failure receiving maintenance hemodialysis,[137,138] and with decreased mortality in community-dwelling older adults.[139] Approaches to medication assessment and deprescribing among patients with CKD, as well as a summary of currently available deprescribing tools, have been recently published.[130,135] These deprescribing protocols and algorithms should be tailored to individual clinical and healthcare settings. The use of polypills that include several key medications may be another strategy to reduce pill burden.[140]

Drug stewardship. Because of the heterogeneity of medication prescribing practices, an action plan to avoid the use of potentially inappropriate medications and decrease pill burden needs to be tailored, depending on the healthcare setting and available resources. In addition, mechanisms are needed to improve communication among prescribers, based on the resources available (e.g., electronic health record systems). Furthermore, patients need to be engaged in the process of medication prescribing to increase adherence and self-efficacy.

Nonpharmacologic therapy

Nonpharmacologic interventions include medical nutrition therapy, exercise, cognitive behavioral treatment, social or peer support, mindfulness, and meditation. Nonpharmacologic approaches have fewer adverse effects and no potential for interactions relative to medications. Meeting participants recognized nonpharmacologic approaches as being contributors to well-being, but discussion of these was beyond the scope of this meeting.

SUMMARY AND CONCLUSIONS

The expansion of available tools for diagnosing and treating CKD since the publication of KDIGO's 2012 CKD guideline is cause for optimism. Clinicians have more opportunities to assess and manage CKD by focusing on the models of care delivered and via utilization of both pharmacologic and nonpharmacologic interventions (Figure 3). Over the next decade, the emergence of more opportunities to improve the diagnosis and treatment of CKD is anticipated, but care delivery still needs to be adapted to take full advantage of the advances. Approaching change proactively versus reactively will best serve expansion of diagnostic measures and treatment options. A key area for research is development of blood and urine biomarkers, and partnerships with large clinical trials can be used to aid molecular phenotyping. Ongoing recognition of patient experiences should inform research strategies and changes to care delivery.

APPENDIX

Other Conference Participants

Ziyad Al-Aly, USA; Gloria E. Ashuntantang, Cameroon; Peter Boor, Germany; Viviane Calice da Silva, Brazil; Jill Coleman, USA; Josef Coresh, USA; Pierre Delanaye, Belgium; Natalie Ebert, Germany; Philipp Enghard, Germany; Harold I. Feldman, USA; Lori Fisher, Jamaica; Jennifer E. Flythe, USA; Akira Fukui, Japan; Morgan E. Grams, USA; Joseph H. Ix, USA; Meg J. Jardine, Australia; Vivekanand Jha, India; Wenjun Ju, USA; Robert Jurish, USA; Robert Kalyesubula, Uganda; Naoki Kashihara, Japan; Andrew S. Levey, USA; Adeera Levin, Canada; Valerie A. Luyckx, Switzerland; Jolanta Małyszko, Poland; Jo-Anne Manski-Nankervis, Australia; Sankar D. Navaneethan, USA; Gregorio T. Obrador, Mexico; Alberto Ortiz, Spain; John Ortiz, USA; Bento Fortunato Cardoso Dos Santos, Brazil; Mark J. Sarnak, USA; Elke Schaeffner, Germany; Nick M. Selby, UK; David Simpson, USA; Laura Solá, Uruguay; Wendy L. St. Peter, USA; Paul E. Stevens, UK; Navdeep Tangri, Canada; Elliot Koranteng Tannor, Ghana; Irma Tchokhonelidze, Georgia; Nicola Wilck, Germany; and Michelle M.Y. Wong, Canada.

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