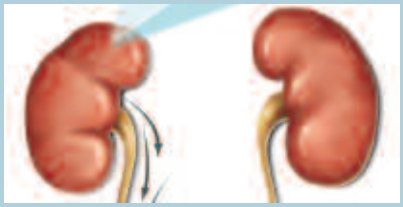
abstract



Chronic kidney disease (CKD) is increasingly common among older adults. In the older individual, the presence of CKD is predictive of cardiovascular death, increased all-cause mortality, and progression to end-stage renal disease and the need for dialysis. Early identification of these high-risk individuals may prevent or delay such adverse outcomes. The Canadian Society of Nephrology (CSN) released a position statement in September 2006 suggesting that screening be limited to those at high risk. We recommend that clinicians follow the CSN algorithm for screening for CKD among older adults.

Key words: *chronic kidney disease, estimated glomerular filtration rate, older adults, renal function, screening*

Screening for and Staging Chronic Kidney Disease

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Introduction

Chronic kidney disease (CKD) is increasingly common among older adults.[1] In the older individual, the presence of CKD is predictive of cardiovascular death, increased all- cause mortality, and, less so, progression to end-stage renal disease (ESRD) and the need for dialysis.[2,3] Early identification of these high-risk individuals may prevent or delay such adverse outcomes. The purpose of this review is threefold—to define and classify CKD, to discuss how best to measure renal function in clinical practice, and to discuss the health impact of CKD on our aging population.

CKD Staging

In 2002, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) led the way by developing a staging system and classification for CKD.[4] This staging system had the advantage of being clearly defined, reminding physicians that, with time, a large proportion of patients progress through the five stages of CKD and become at risk of requiring dialysis or kidney transplantation; it replaced loosely used terms such as *chronic renal failure, kidney failure, end-stage renal disease,* and *renal insufficiency*. Stages are based largely upon either the measured glomerular filtration rate (GFR) or estimated GFR (eGFR) and are divided into five levels, with each stage suggesting a higher degree of irreversibility and scarring (Table 1, Figure 2). Often forgotten are those at risk of renal disease (stage 0) for whom screening is essential, such as individuals with a >5-year history of diabetes or those with a family history of hereditary renal disease. Staging has been adopted widely throughout the nephrology community and is often used to develop specialized clinics that provide the necessary multidisciplinary team care.

Screening for CKD

The Canadian Society of Nephrology (CSN) released a position statement in September 2006 (www.csnscn.ca) that suggested that screening be limited to those at high risk, such as individuals with diabetes or hypertension or those with vascular disease (Figure 1). Furthermore, CSN acknowledged that many patients with CKD stages 1–3 have low risk of progression. Based on the latter observation, CSN currently recommends that patients with CKD stage 3, in whom eGFR has remained stable over 6–12 months, be managed without immediate nephrology referral unless there are additional symptoms or signs of concern. These individuals require serial measurements at regular intervals (3–6 monthly would be most appropriate for most cases).

The definition of "normal" renal function in the aged population is difficult; however, the Baltimore Longitudinal Study on Aging estimated the mean creatinine clearance of individuals aged 60–69 years, 70–79 years, and 80+ years

Table 1: Stages of Chronic Kidney Disease

Stage of CKD	Description	GFR mL/min/1.73 m^2	Evaluation and Management
0	At risk of renal disease	>60	Screening CKD risk reduction
1	Kidney damage with normal or increased GFR	>90	Diagnosis and treatment Treatment of coexisting conditions Delaying progression Cardiovascular disease risk reduction
2	Kidney damage with mild decrease in GFR	60–89	Estimate risk of progression
3	Moderate decrease in GFR	30–59	Evaluate and treat complications
4	Severe decrease in GFR	15–29	Referral to nephrologist Consideration of renal replacement therapy
5	End-stage renal disease	<15	Renal replacement therapy, if indicated

CKD = chronic kidney disease; GFR = glomerular filtration rate.

Source: American Journal of Kidney Disease, 2002.[4] Reproduced by permission.

to be 119 ± 3 mL/min, 107 ± 3 mL/min, and 94 ± 6 mL/min, respectively.[5] Renal function has been shown to decline with age in a fairly linear manner, with only a minimal acceleration in the rate of renal decline when aged over 70 years.[6] These studies were based upon insulin clearance, which is not a practical tool, and estimating equations are now recommended.

Serum creatinine has a nonlinear relationship with renal function and is therefore an inaccurate measure. Furthermore, individuals with a low muscle mass or poor dietary intake of meat will have erroneously low serum creatinine values (Table 2).[7] This is especially important among older adults as many older individuals may have a lower muscle mass, amputations, or protein-poor diets. Other assessments, such as timed urine collections or nuclear renal scans, are time consuming, expensive, or simply too difficult to perform (as in the case of collecting urine from an individual with incontinence). As a result, both the CSN and NKF KDOQI guidelines recommend the estimation of renal function using an equation based on measured serum cre-

Table 2: Factors Affecting Creatinine Generation*

Factor	Effect on Serum Creatinine
Aging	↓
Female sex	↓
Race or ethnic group†	
African ancestry	↑
Hispanic	↓
Asian	↓
Body habitus	
Muscular	↑
Amputation	↓
Obesity	↔
Chronic illness	
Malnutrition, inflammation, deconditioning (e.g., cancer, severe cardiovascular disease, hospitalized patients)	↓
Neuromuscular diseases	↓
Diet	
Vegetarian diet	↓
Ingestion of cooked meat	↑

*Variation in muscle mass accounts for the predominant proportion of creatinine generation.
†White race served as the reference group.

Source: Stevens LA et al., 2006.[8]

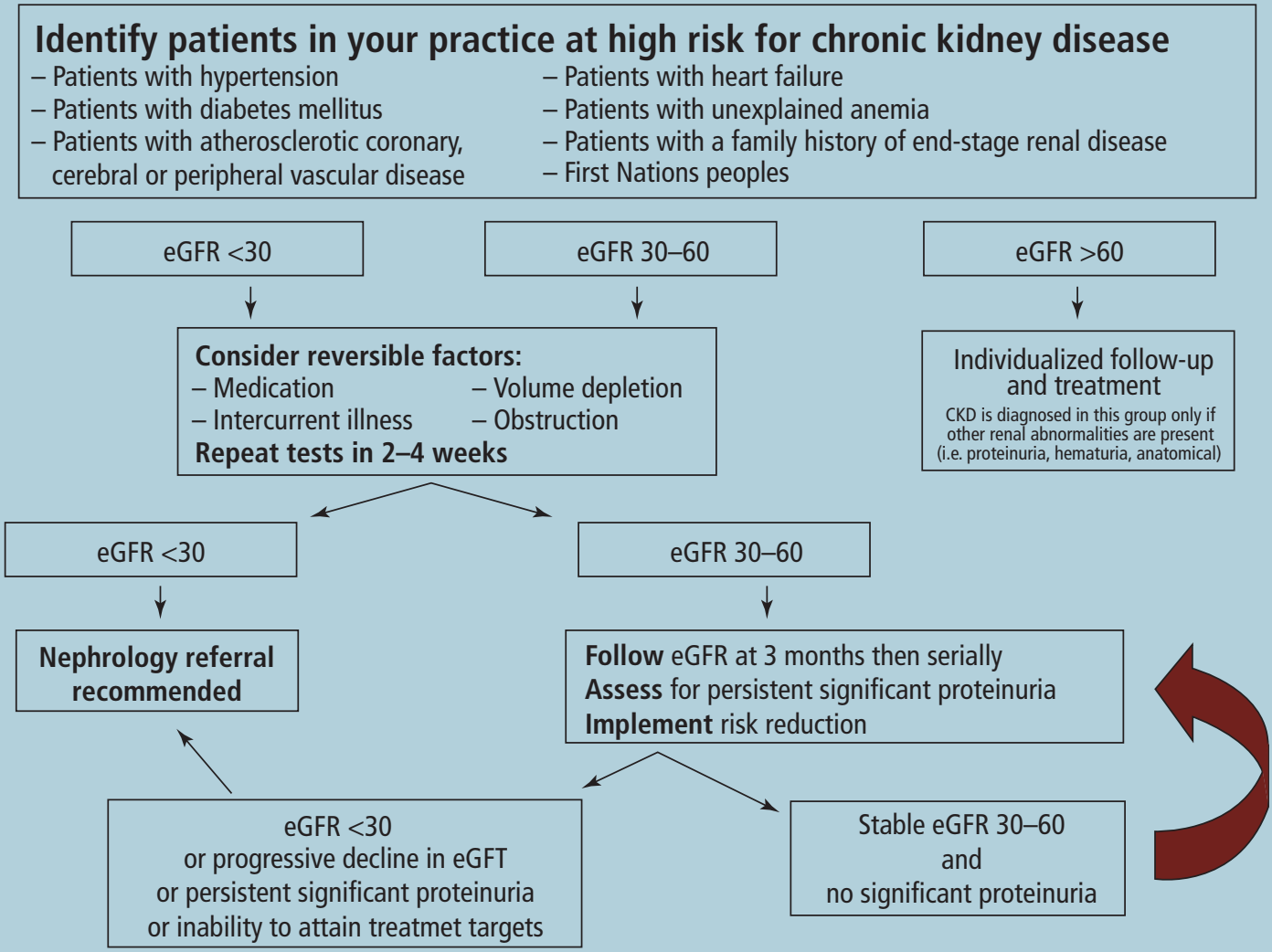
atinine. Estimating equations such as the Cockcroft-Gault and the Modification of Diet in Renal Disease (MDRD) study equations are the most commonly used tools. Both are easily calculated and depend only on serum creatinine measurement in the laboratory. Unlike the MDRD equation, which estimates GFR, the Cockcroft-Gault equation reports the estimated creatinine clearance. While, in many cases, this is not of clinical importance, the creatinine clearance may overestimate renal function at lower levels and underestimate at higher levels.[7] In the older individual, particularly those living in long-term care facilities, it remains unclear which of the two formulas is best, and many physicians choose to use the MDRD equation for simplicity.[8] Newer assays such as that for cystatin C are available in Europe and appear promising (Table 3).[9]

Recently in Ontario, most laboratories have started to report the MDRD estimate for eGFR together with the absolute serum creatinine value. As with lipid guidelines, guidelines helping with interpretation of these data should be made available with each result. However, in practice these data are particularly useful for clinicians following patients over time in the outpatient setting. For example, a patient with an eGFR of 90 mL/min who on retesting some months later has an eGFR of 60 mL/min is more concerning than a patient with a stable eGFR of 35 mL/min for 2 years. In acute care settings, the use of the MDRD equation to estimate acute changes in renal function is inappropriate as serum creatinine values (on which the eGFR is based) are not stabilized and are in continuous flux.

Prevalence of CKD

The prevalence of CKD has been estimated from data obtained through the Third National Health and Nutrition Examina-

Figure 1: Canadian Society of Nephrology Flow Chart for Identifying Patients with CKD



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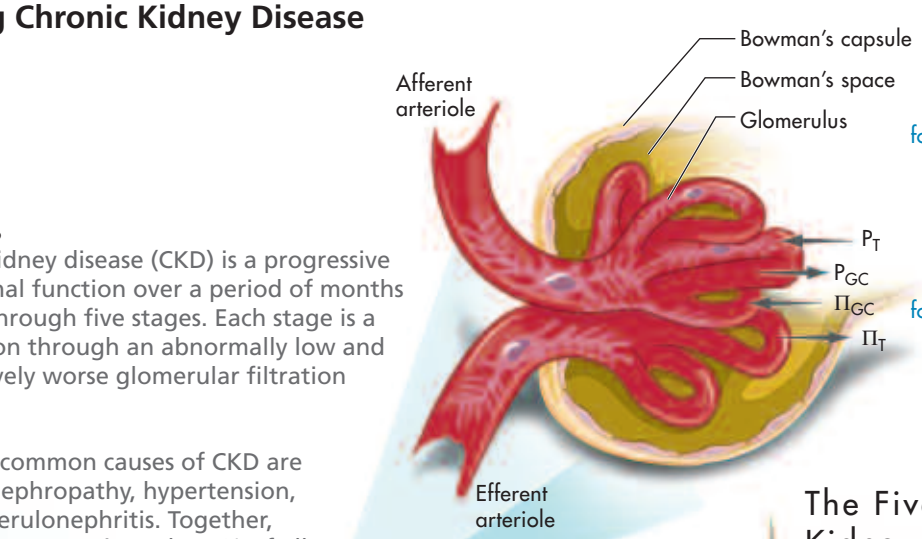
CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

Figure 2:
Staging Chronic Kidney Disease



forces favouring filtration

P_{GC}	= mean capillary hydraulic pressure
Π_T	= tubular oncotic pressure

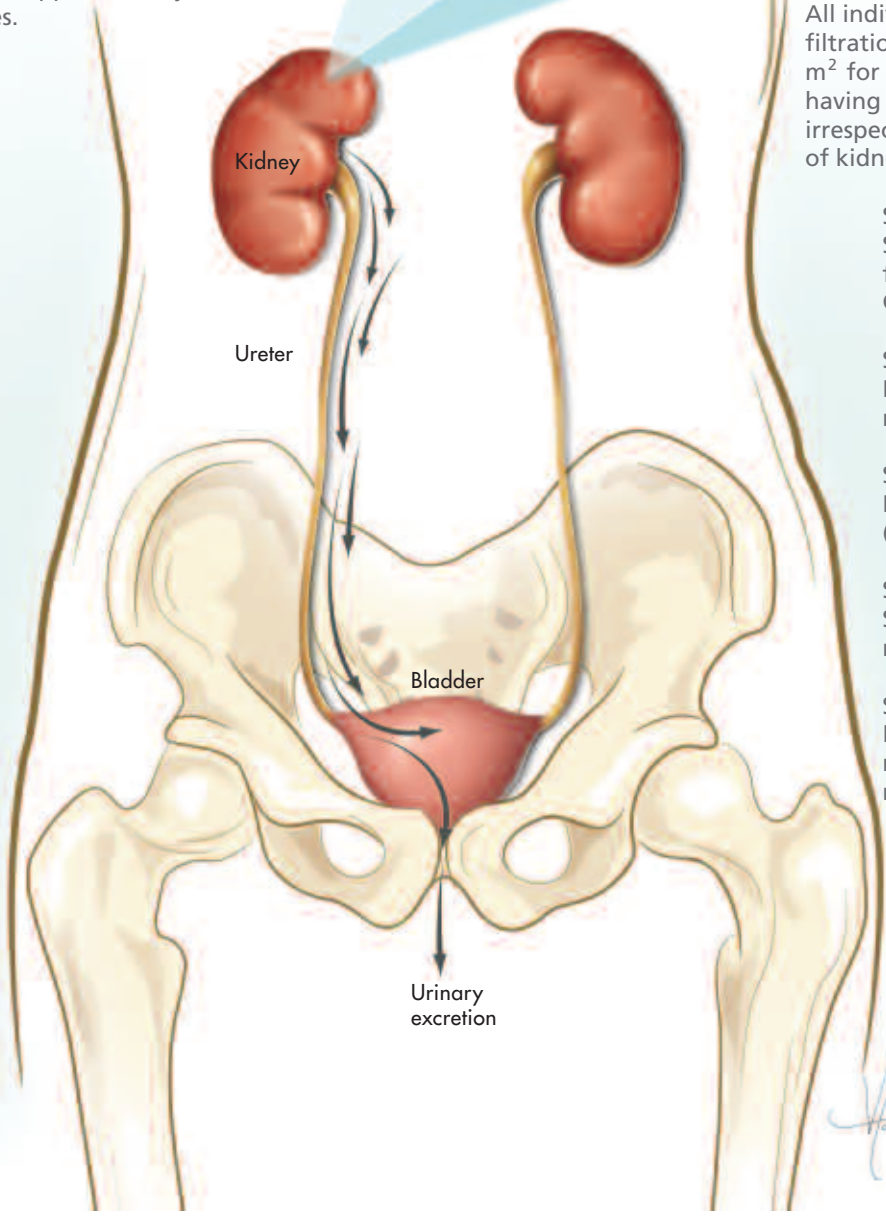
forces opposing filtration

P_T	= mean tubular hydraulic pressure
Π_{GC}	= capillary oncotic pressure

Causes

Chronic kidney disease (CKD) is a progressive loss of renal function over a period of months or years through five stages. Each stage is a progression through an abnormally low and progressively worse glomerular filtration rate.

The most common causes of CKD are diabetic nephropathy, hypertension, and glomerulonephritis. Together, these cause approximately 75% of all adult cases.



The Five Stages of Chronic Kidney Disease

All individuals with a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for 3 months are classified as having chronic kidney disease, irrespective of the presence or absence of kidney damage.

Stage 1 CKD
Slightly diminished kidney function—normal or increased GFR (>90 mL/min/1.73m^2)

Stage 2 CKD
Mild reduction in GFR (60–89 mL/min/1.73m^2)

Stage 3 CKD
Moderate reduction in GFR (30–59 mL/min/1.73m^2)

Stage 4 CKD
Severe reduction in GFR (15–29 mL/min/1.73m^2)

Stage 5 CKD
Kidney failure—severe reduction in GFR (<15 mL/min/1.73m^2)

tion Survey (NHANES III) in the U.S.[10,11] Prevalence estimates show strikingly high rates, particularly among those over 70 years of age, with >45% of individuals having some form of CKD (Figure 3). More importantly and regardless of stage, the prevalence of CKD appears to be increasing over time, with recent data showing that the prevalence of severely reduced GFR rose from 0.21 to 0.35% (a 30% increase, 95% CI 19–43%) over a 10-year span.[12] Older persons with diabetes and those with hypertension are, as expected, at higher risk of CKD; in addition, women—particularly those who are not African ancestry—are at higher risk.

As stated above, the Baltimore Longitudinal Study on Aging has demonstrated that renal function in healthy older individuals is similar to that in young persons.[5] Furthermore, renal functional reserve appears to be preserved, even with aging.[13] On average, residual renal function declines were estimated at 0.8 mL/min/1.73 m^2 creatinine clearance per year. The Baltimore data, however, also show that some individuals have little to no loss of renal function over time, while others have a steady but relatively fast rate of renal function loss. Interestingly, each individual's rate remained relatively stable over time provided there was no disease-associated renal injury. The progressive loss of kidney function was further studied in community-dwelling older individuals by a group in Alberta who used data from individuals who had had serum creatinine levels drawn during two time periods, July–December 2001 and July–December 2003.[14] Renal decline was found to be fastest among individuals with diabetes compared with persons without diabetes and among men compared with women (Table 4).

Identifying CKD remains important to the clinician as impaired renal function is associated with a higher risk of death and, in some situations, a need for dialysis.[2,15] Among individuals aged 65 years or more, the risk of death is significantly higher than the risk of progression to ESRD.[2] In an elegant analysis of data drawn from U.S. veterans attending Veterans Affairs facilities, O'Hare *et al.* plotted the ratio of the risk of progression to ESRD and the risk of death for different ages and for different levels of CKD. They demonstrated that for each stage of CKD, younger individuals were older

Table 3: Methods Used to Estimate Renal Function

Methods Used in Research but Impractical in Clinical Practice	Methods Used in Clinical Practice
Nuclear GFR scan with two-time blood sampling	Cockcroft-Gault formula for creatinine clearance (CrCl in mL/min/1.73m^2) **Men:** $\frac{(140 - \text{age [yr]}) \times \text{ideal body weight (kg)}}{\text{SCr (µmol/L)} \times 0.81}$ **Women:** $\frac{(140 - \text{age [yr]}) \times \text{ideal body weight (kg)} \times 0.85}{\text{SCr (µmol/L)} \times 0.81}$
Insulin clearance	MDRD formula for glomerular filtration rate (GFR in mL/min/1.73m^2) $= 186 \times (\text{SCr} \times 0.0113)^{-1.154} \times (\text{age [yr]})^{-0.203}$ **if** female, multiply by 0.742 **if** African ancestry, multiply by 1.210
Cystatin C	Timed urine collections

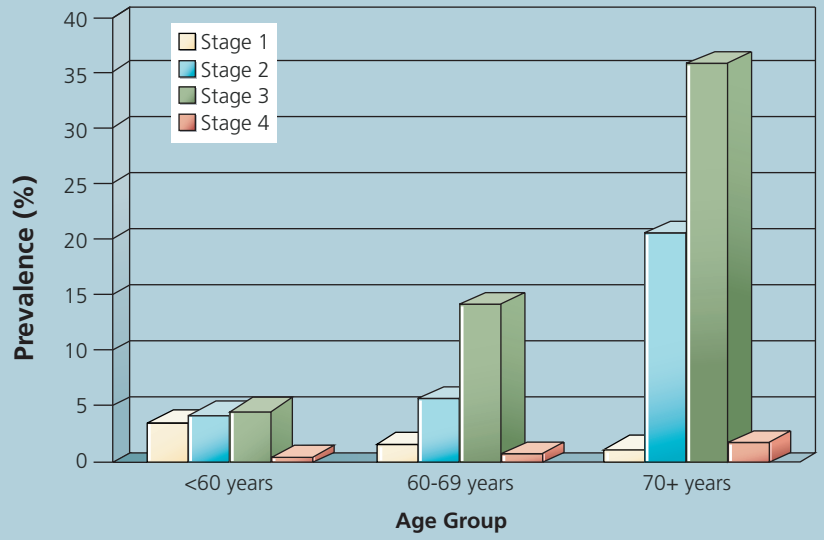
CrCl = creatinine clearance; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; SCr = serum creatinine.

Table 4: Age-Adjusted Rate of Renal Decline*

Subject Characteristics	Study Mean eGFR 60–89 Years (95% CI)	Study Mean eGFR 30–59 Years (95% CI)	Study Mean eGFR<30 Years (95% CI)	Overall
Females without diabetes mellitus	0.6 (0.3–0.9)	1.1 (0.8–1.4)	1.8 (1.2–2.4)	0.8 (0.6–1.0)
Males without diabetes mellitus	1.1 (0.8–1.4)	1.9 (1.5–2.3)	2.0 (1.3–2.7)	1.4 (1.2–1.6)
Females with diabetes mellitus	1.6 (1.0–2.1)	2.8 (2.3–3.3)	2.9 (2.2–3.7)	2.1 (1.8–2.5)
Males with diabetes mellitus	2.1 (1.6–2.6)	3.6 (3.1–4.2)	3.2 (2.3–4.0)	2.7 (2.3–3.1)

*As measured using estimated glomerular filtration rate (eGFR) mL/min/1.73m2/yr.
Source: Hemmelgarn BR et al., 2006.[16]

Figure 3: The Proportion of Patients aged ≤60, 60–69, and 70+ Years with Each Stage of CKD



Source: Coresh J et al., 2003.[13] Copyright © 2003 Massachusetts Medical Society. All rights reserved.

likely to progress to ESRD while older individuals were more likely to die before needing renal replacement therapy. Therefore, from the clinician's perspective, it is important to consider the individual's age in relation to the degree of CKD to understand the implications for outcome.

Conclusion

In conclusion, we suggest that clinicians follow the CSN algorithm for screening for CKD among older adults. Once detected, a repeat assessment after a few months is useful prior to referral to a nephrologist. In a large proportion of cases, renal function will not decline rapidly, and the nephrologist may choose to review the patient only infrequently. Under these circumstances, the most valuable measures are cardiopreventive interventions, 6-monthly creatinine and urine testing, and avoidance of nephrotoxins such as nonsteroidal anti-inflammatory drugs.

Dr. Tanna has no competing financial interests.
Dr. Jassal has been involved in the executive steering committee for the Amgen-funded study looking at Anaemia Correction and HRQoL Outcomes in Elderly CKD Patients (STIMULATE); held investigator led funding from OrthoBiotec and received speaker fees from Pfizer, Amgen, OrthoBiotec and Bristol Myers Squibb. She has also attended advisory board meetings for Novartis and INEOS Healthcare in the past 5 years.

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