Chronic kidney disease (CKD), defined by reduced glomerular filtration rate (GFR), proteinuria, or structural kidney disease, is a growing problem among the aging population (Figure 1). Although ESRD, defined as kidney failure treated with dialysis or transplantation, is less prevalent than earlier CKD stages, the number of patients who have ESRD and are older than 65 yr almost doubled during 25 yr, and the fastest growing segment of that population during the past decade is older than 75 yr.

Proteinuria, hypertension, diabetes, race, and ethnicity are strong risk factors for progression from CKD to ESRD, and the higher ESRD incidence among men than among women is most pronounced in older patients. Declines in renal function, measured by creatinine clearance, occur in approximately two thirds of “healthy” older adults over time but progresses to ESRD in only 1 to 2% of these patients, yet mortality rates are high among older patients with CKD. Few studies of older patients with CKD have addressed the mechanisms leading to ESRD or mortality.

MECHANISMS UNDERLYING CKD IN AGED PEOPLE

The cause of age-related increases in renal fibrosis, which leads to glomerulosclerosis, interstitial fibrosis, tubular atrophy, vascular sclerosis, and loss of renal function, is poorly understood; however, in animal models, collagen seems to accumulate with age in the glomerulus, peritubular capillary, and tubu-
lointerstitium because of increased transcription of the gene encoding type III collagen.\textsuperscript{12} Preliminary studies in aged rats showed a loss of polycomb-mediated (epigenetic) collagen gene silencing despite a significant decrease in histone modifications associated with repressed genes, suggesting that other polycomb-related abnormalities contribute to age-associated loss of gene regulation.\textsuperscript{13,14} Calorie restriction, a robust antiaging intervention in animal models, resulted in increases in histone modifications, similar to those seen in aged rats on a regular diet, but restored gene expression and prevention of kidney sclerosis in the calorie-restricted animals suggest the restoration of effective polycomb-mediated silencing. How increases in epigenetic silencing mechanisms are circumvented in these models is not known.

Telomere shortening and increased p16\textsuperscript{INK4A} expression, which are implicated in somatic cellular senescence pathways (Figure 2), are observed in aging human kidneys.\textsuperscript{15,16} Increased p16\textsuperscript{INK4A} expression is also observed in aging rodents,\textsuperscript{17} but telomere shortening is not.\textsuperscript{16} Cellular senescence is associated with several features of the aging kidney\textsuperscript{15} and accelerates in patients with progressive kidney disease,\textsuperscript{18,19} and transplant nephropathy,\textsuperscript{18} in biopsies from patients with hypertensive nephropathy,\textsuperscript{20} and in animal models of experimental hypertension\textsuperscript{20} and ischemia/reperfusion-induced injury.\textsuperscript{21,22}

**GENES AND CKD**

Efforts are under way to identify genes associated with CKD and diabetic nephropathy and to establish biomarkers of risk for CKD and likelihood of benefit from intensive treatment; however, replication of potential CKD candidate genes is inconsistent because of phenotype specificity, varying genotyping technologies, and challenges with study design. How genetic variation will predict CKD risk, how patients will respond to their individual risk assessment, and how genetic risk contribution differs across ancestral groups are not clear. Gene–gene and gene–environment interactions are also poorly understood. Several candidate age-associated genes have

**1. INTRINSIC: Telomere-dependent, “relicative senescence”**

**2. EXTRINSIC: Telomere-independent, “STASIS”**

(= stress or aberrant signaling induced senescence)

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**Figure 1.** Prevalence of CKD by age group in National Health and Nutrition Examination Survey (NHANES) data 1988 through 1994 and 1999 through 2004. Adapted from Coresh et al.\textsuperscript{65}

**Figure 2.** Senescence-associated changes in gene expression.\textsuperscript{145} Cellular senescence is marked by increased expression of cell-cycle inhibitors and extracellular matrix proteins and by decreased expression of proteins involved in cell-cycle progression. Redrawn from ref. 145 (Melk A: Senescence of renal cells: Molecular basis and clinical implications. *Nephrol Dial Transplant* 18(12): 2474–2478, 2003), by permission of Oxford University Press.
been identified, including genes involved in regulating metabolism and enhancing tissue integrity. Global age-associated changes in gene expression also have been observed for the kidney. Selection pressure, epigenetic mechanisms, and changes in telomere biology and the proliferative capacity of renal stem or progenitor cells also might modulate dysfunction in the aging kidney.

ACUTE KIDNEY INJURY AND CKD PROGRESSION

The incidence of acute kidney injury (AKI) is increasing, particularly among older patients. Patients with CKD are more likely to experience AKI, and AKI is a risk factor for progression to ESRD. In the rat ischemia/reperfusion model, AKI is characterized by a temporary but substantial decrease in GFR, compromised urine-concentrating ability, proteinuria and interstitial fibrosis, and impaired sodium processing. Injured kidneys in this model also show a dramatic increase in hypoxia and renal fibrosis. Glomerular capillary density and interstitial peritubular vascular density decrease with age in the absence of other insults and are exacerbated by acute injury, and the ability to repair and regenerate tissue after injury declines with age. Thus, progression of CKD might not be a smooth, continuous course so much as a stepwise function marked by repeated episodes of AKI.

MEASURING AND CLASSIFYING CKD

Although measured GFR is considered the best overall measurement of kidney function, it is often not practical in clinical or epidemiologic settings. Thus, there are few studies of measured GFR in older adults, and they have small sample sizes. GFR declines with age in the general population, but the rate of decline varies widely among individuals, and it is not clear whether declining GFR is part of “normal aging.” The annual rate of GFR decline was only 0.8 to 1.4 ml/min per 1.73 m² in one community-based cohort of adults who were older than 65 yr and did not have diabetes, and one third of “healthy” older patients in another study showed no appreciable declines in kidney function during 10 yr.

GFR is usually estimated (eGFR) from serum levels of endogenous filtration markers, most commonly creatinine and recently cystatin C; however, factors other than filtration, including generation, tubular secretion or reabsorption, and extrarenal elimination, affect these markers. Estimating equations, which incorporate some of these non-GFR determinants, yield more accurate estimates of kidney function than do serum marker levels alone; however, current creatinine-based estimating equations have been reported to be less accurate in patients without kidney disease, and muscle wasting and inflammation might interfere with the accuracy of creatinine or cystatin C–based estimating equations in older people with frailty or comorbid illnesses. Improved measures of kidney function in older patients are needed to estimate better the prevalence of CKD and AKI, to manage and diagnose comorbidities appropriately, and to dose medications properly.

A new creatinine-based estimating equation, developed in a pooled sample in which the mean age was 52 yr, reduces bias by 50% and offers small but consistent improvement in precision and accuracy, compared with the most commonly used equation. In addition, accuracy of creatinine-based equations does not differ significantly from that of cystatin C–based equations in populations studied thus far, but equations based on the combination of the two markers might provide the best accuracy. Non-GFR determinants affecting each marker, such as low muscle mass and possibly obesity, might lead to systematic over or underestimation of GFR in specific individuals.

The term “preclinical kidney disease” has been proposed to describe patients with a creatinine-based eGFR >60 ml/min per 1.73 m² and a cystatin C level >1.0 mg/L (equivalent to an eGFR of approximately 75 ml/min per 1.73 m²). On the basis of these criteria, 39% of the Cardiovascular Health Study sample, in which the mean age is 75 yr and patients do not meet the GFR-based criteria for CKD, have preclinical kidney disease. The incidences of death and CKD, defined on the basis of creatinine-based eGFR, is higher among these patients than it is among patients with eGFR >60 ml/min per 1.73 m² and low cystatin C (Figure 3).

Figure 3. Effects of preclinical kidney disease. Incidence for progression to CKD and for all-cause mortality is higher among patients with preclinical kidney disease, defined as GFR >60 ml/min per 1.73 m² and cystatin C >1.0 mg/L, than it is among patients with normal kidney function. Redrawn from ref. 43.
CKD, CARDIOVASCULAR DISEASE, AND ALL-CAUSE MORTALITY

Age-associated macrovascular changes include increased arterial diameter, wall thickness, and stiffness; changes in gene expression related to vascular elasticity and hypertension; increased migration of smooth muscle cells from the media to the epithelial space; and increased endothelial dysfunction.44–47 Similar changes have been observed in kidney disease45,48 and attributed to increased production of reactive oxygen species, decreased production of telomerase reverse transcriptase, and, ultimately, increased levels of C-reactive protein and oxidized LDL cholesterol.49 Impaired vasodilation has also been associated with proteinuria.50

Both aging and ESRD are independently associated with exponential increases in mortality from cardiovascular disease (CVD),51 but they exert an additive effect on mortality risk. The high rate of CVD is also a large factor in the high mortality rates seen among older patients with CKD.41 Among patients undergoing cardiac surgery, mortality risk increases even with a 0.2-mg/dl increase in serum creatinine,52 and patients with serum creatinine levels between 1.2 and 2.1 mg/dl before cardiovascular surgery are at increased risk for AKI requiring dialysis.53

The GFR threshold predictive of cardiovascular events and all-cause mortality has not been established. Several studies have shown increased risk with moderate chronic renal insufficiency or preclinical kidney disease in both older and younger patients.43,54–58 Other studies have observed that increasing age attenuates the association of eGFR with mortality.59–61 Consequently, the threshold eGFR at which mortality or cardiovascular risk increases might differ across the age spectrum, although risk for mortality is consistently increased at eGFR <45 ml/min per 1.73 m² in all age groups. Furthermore, the association between creatinine-based GFR62 and mortality differs slightly from that seen with cystatin C–based GFR (Figure 3).

Standard risk factors for CVD do not fully explain the increased risk for CVD seen in patients with CKD.63 Urti- nary albumin concentration, which is a strong risk factor for progression to ESRD64 and increases in prevalence with age,65 is an independent risk factor for CVD.66–67 GFR and albuminuria are poorly correlated, but they exert an additive effect on CVD outcomes,67–70 even in patients aged ≥70 yr.68 Microalbuminuria, defined as 30 to 300 mg/g albumin in the urine, has been associated with left ventricular abnormalities,71 increased inflammatory markers,72 insulin resistance,73 endothelial dysfunction,50,74 and abnormalities in fibrinolytic and coagulation pathways. Antihypertensive drugs used to reduce microalbuminuria might be associated with a lower risk for incident cardiovascular events.75,76

Vascular calcification and hyperphosphatemia are also independent risk factors for CVD in patients with CKD,77–80 as demonstrated by mechanistic data in animal81 and cell culture models.82 CKD bone mineral disorder is characterized by phosphorus, calcium, vitamin D, and pH values associated with abnormal bone turnover and vascular calcification. Higher phosphorus levels, even within the “normal reference range,” also might be associated with all-cause mortality in the general population.83,84 The osteoblastic transcription factor osterix might participate in the causative pathway involving phosphorus, vascular calcification, and CVD.82

Oxidized LDL correlates with increased mortality risk in dialysis patients83 and might play a role in endothelial injury.84 Vascular dropout occurs in patients with hypertension and even more so in patients with CKD,85 and endothelin production increases in animal models of CKD.86 Treatment with an endothelin inhibitor prevents podocyte injury, proteinuria, and glomerulosclerosis in animal models.87,88

Initiation of maintenance dialysis for ESRD is associated with significant improvement in BP and left ventricular mass,89 but common approaches toward management of CVD, including statins90 or reductions in calcification and phosphorus metabolism,92 may not be as successful in patients with CKD or ESRD. Although anemia is a risk factor for CVD in patients with CKD,93,94 data from recent randomized trials of erythropoietin treatment suggested that targeting specific hemoglobin levels might not be appropriate for treatment or prevention.95

CKD, COMORBID CONDITIONS, AND AGING

Frailty is more prevalent among older patients with CKD than it is among those with normal kidney function.96 Although a large proportion of dialysis patients are frail even at younger ages, frailty is common among older dialysis patients.97 The natural history of frailty in patients with CKD and the factors that increase risk are not known, which has stymied the identification and evaluation of interventions to address frailty in patients with CKD.

Physical activity decreases with age, particularly among patients on dialysis,98 and mortality risk during 1 yr is higher among sedentary than among nonsedentary dialysis patients.99 In older patients, physical performance–based measures predict falls, hospitalizations, length of hospital stay, discharge to a nursing home, or mortality.100 The significance of these measures for CKD or ESRD is not known. Low physical functioning, measured by objective laboratory tests or self-reported measures, predicts survival in ESRD.101–103 Sarcopenia is a significant problem in CKD and may contribute to low functioning and frailty. Although muscle size is comparable between healthy control subjects and dialysis patients, the proportion of contractile tissue in dialysis patients is only two thirds that in control subjects.104

Exercise training improves exercise capacity and physical performance–based measures,105 as well as CVD-related factors,106–110 protein uptake into skeletal muscles,111 dialysis efficiency,112 and quality of life.113 Cardiovascular training improves peak oxygen uptake
and muscle strength in patients with CKD, and resistance training increases muscle fiber size, improves muscle strength, and reduces inflammation. Thus, nephrology practice should include assessments of physical function and interventions to address low function in patients with CKD.

Although age-related criteria for defining anemia in older people are debated, anemia is highly prevalent among older people and associated with depression and impaired physical and cognitive function. The prevalence of anemia is much higher among patients with a GFR <30. The aging process may have an inflammatory component, and some clinical markers of inflammation-associated anemia overlap with those of iron deficiency. The role of inflammation in CKD-associated anemia in older people is poorly understood.

CKD is associated with an increased risk for cognitive decline and dementia. Accumulating data suggest that the prevalence of cognitive impairment begins to increase early in CKD, as GFR drops <60 ml/min per 1.73 m². Other CKD markers, including increased cystatin C and microalbuminuria, have also been linked with an increased risk for cognitive impairment. Thirty percent of dialysis patients overall and up to 70% of dialysis patients aged ≥55 yr have moderate to severe impairment. Cerebrovascular disease, both clinical (e.g., stroke) and subclinical, might play a large role in the development of cognitive impairment among patients with CKD and ESRD. Other factors that might contribute to cognitive impairment include anemia; accumulation of uremic toxins; and, in patients with ESRD, a dialysis delirium-like syndrome that, over time, might have deleterious effects on cognition.

GOALS FOR CLINICAL MANAGEMENT IN OLDER PATIENTS WITH CKD

Among older patients with CKD, mortality and cardiovascular events are more common than progression to ESRD. Studies suggest that hypertension therapy that preserves cardiac function might not prevent ESRD or a 50% decline in GFR. Thus, care for patients with CKD should focus more on reducing CVD risk than on progression to ESRD. Furthermore, functional outcomes, such as cognition and physical functioning, might be more meaningful outcomes in older patients with CKD. More study is needed to determine how CKD affects independent function, and interventions should be developed and assessed in terms of maintaining active life expectancy. Such approaches might facilitate intervention in older patients before disability develops.

The appropriate treatment of older patients with CKD is not clear. Among patients who had CKD and were not referred to a nephrologist, increasing age attenuated the association of serum creatinine with mortality risk, but in a multivariable analysis, reduced eGFR independently predicted death, whereas age did not. Other work demonstrated that early referral to nephrology care re-

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<th>Table 1. Questions for future research</th>
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<tr>
<td><strong>Mechanisms and biology</strong></td>
</tr>
<tr>
<td>Is CKD in elderly people the same condition as CKD in young adults?</td>
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<tr>
<td>How do age-related mechanisms such as fibrosis and cellular senescence interact with mechanisms underlying CKD progression?</td>
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<tr>
<td>How much risk for CKD progression is determined by age versus factors such as AKI?</td>
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<tr>
<td>How does fibrosis versus vessel dropout change with age?</td>
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<tr>
<td>Do age- and CKD-associated changes in vascular biology differ from other parenchymal kidney disease changes associated with age?</td>
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<tr>
<td><strong>Measurement and prognosis</strong></td>
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<tr>
<td>Are there better ways to estimate GFR in older adults to identify CKD?</td>
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<tr>
<td>What are the morphologic correlates of CKD in elderly people?</td>
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<td>Are there other markers that can contribute to assessment of CKD prognosis in elderly people, beyond eGFR and cystatin?</td>
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<tr>
<td><strong>CVD</strong></td>
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<tr>
<td>How do age-related changes in vascular biology contribute to CKD-associated increases in cardiovascular risk?</td>
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<td>What are the age-related changes in nontraditional cardiovascular risk factors in patients with CKD?</td>
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<tr>
<td><strong>Other comorbidities</strong></td>
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<td>How do comorbidities differ during the transition from CKD to ESRD and need for dialysis?</td>
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<td>Can the deterioration in physical functioning and subsequent frailty in patients with CKD be prevented by physical activity interventions?</td>
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<td>How does age interact with exercise in prevention or reduction of comorbidities associated with CKD progression?</td>
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<tr>
<td>What is the natural history of cognitive impairment associated with CKD progression, and what happens to cognitive function with the start of dialysis?</td>
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<td>What mechanisms link CKD with cognitive impairment in elderly people?</td>
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<td>Are there any interventions to attenuate the development of cognitive impairment in patients with CKD?</td>
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<td>How does preclinical kidney disease relate to other prefrailty risk factors?</td>
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<tr>
<td><strong>Management and care</strong></td>
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<tr>
<td>How can geriatricians, internists, general family practitioners, and nephrologists work together to optimize the care of elderly patients with CKD and ESRD?</td>
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<tr>
<td>Can age-related declines in kidney function and progression to CKD be modulated?</td>
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duced adverse CKD outcomes.\textsuperscript{135–138} The effects of multidisciplinary care are also debated. Two studies correlated multidisciplinary care with modest improvements in survival,\textsuperscript{39,139} but another study showed no differences in kidney function or mortality between patients who received multidisciplinary, intensive care and those who did not.\textsuperscript{140}

The benefits of long-term dialysis in older patients are controversial. Although one study suggested that dialysis improves survival in patients aged $\geq 65$ yr,\textsuperscript{141} mortality rates are exceedingly high among very old patients who initiate dialysis.\textsuperscript{141} In one small observational study of patients who were aged $\geq 75$ yr and had stage 5 CKD, those who initiated dialysis survived longer than those who did not; however, among the subgroup with a high number of comorbidities, survival was similar among those treated conservatively and those who initiated dialysis.\textsuperscript{142}

AREAS OF FUTURE RESEARCH

Potential research questions in the areas of CKD biology, measurement and prognosis, CVD, other comorbidities, and management are listed in Table 1.

The manifestations and prognosis of CKD differ between older and younger adults. Additional studies are needed to delineate age-related differences in the mechanisms and pathways that contribute to progression of CKD and adverse cardiovascular and metabolic events. Randomized clinical trials are also needed to explore novel therapeutic approaches to reduce CVD and mortality in older patients with CKD. More study is needed to determine not only whether aging and CKD mechanisms differ but also how they interact.

Measurement of GFR in representative populations without significant illnesses is needed to determine “normal” GFR and allow development of more accurate estimating equations for older people. Improved methods to estimate GFR in the frail and in sick older patients will likely require new filtration markers or combinations of markers, particularly those not affected by muscle or disease. In addition, more study is needed to determine the length of time needed to see decreases in the numbers of glomerular and functional tubular cells.

Additional information on CKD complications would facilitate greater understanding of the overall impact of CKD on the patient. Markers other than GFR, such as AKI markers, are needed to assess patients’ risk and to measure kidney damage more directly. Although proteinuria already has been identified as an important risk factor, other risk factors might include microalbuminuria, erythropoietin/anemia ratios, advanced glycation end products and their receptors, vitamin D metabolism, and serum phosphate. The identification of new measures that are clearly in the causal pathway for CKD and ESRD would be useful, as would studies including the long-term follow-up needed to distinguish true kidney disease from normal GFR declines in older people.

How age influences vascular biology and cardiovascular risk factors and how these changes contribute to CKD-associated increases in risk for CVD are not

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<th>Parameter</th>
<th>$\beta$ (SE)</th>
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<td>Total plasma PUFAs (mg/L)</td>
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</tr>
<tr>
<td>Plasma n-3 FA (mg/L)</td>
<td>6.28 (1.29)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plasma linolenic acid (mg/L)</td>
<td>0.19 (0.05)</td>
<td>0.0004</td>
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<tr>
<td>Plasma n-6 FA (mg*10/L)</td>
<td>3.62 (1.19)</td>
<td>0.0300</td>
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<tr>
<td>Plasma linoleic acid (mg*10/L)</td>
<td>0.08 (0.03)</td>
<td>0.0040</td>
</tr>
<tr>
<td>Plasma arachidonic acid (mg*10/L)</td>
<td>0.24 (0.06)</td>
<td>&lt;0.0001</td>
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$^*$Data adjusted for creatinine clearance at baseline, education, cigarette-smoking pack-years, Mini-Mental Status Exam score, energy intake, alcohol consumption, LDL cholesterol, HDL cholesterol, self-reported cancer, CVD, and hypertension. Covariates were selected using a Pearson correlation coefficient $<0.10$. PUFAs, plasma polyunsaturated fatty acid. Table is reproduced from ref. 144.
clear. The connection between CKD and other comorbidities, such as frailty and cognitive impairment, and how age influences these connections should be explored further. Further study is also needed to determine how age affects interventions to prevent or reduce these comorbidities in patients with CKD.

Geriatricians, internists, general family practitioners, and nephrologists should work together to optimize care for older patients with CKD and ESRD. Recent epidemiologic evidence correlated serum polyunsaturated fatty acid levels, which have a strong anti-inflammatory effect, with slower rates of decline in creatinine clearance in an aging population (Figure 4). How target BP and other surrogate markers can be used to preserve patients’ ability and independence, as opposed to preventing progression to ESRD, should be studied further. More study is also needed to determine how to identify patients most likely to benefit from dialysis, reduce the number of inappropriate dialysis starts, and aid patients and family members in decision-making regarding dialysis. More clinical trials are needed, particularly those that include physical and cognitive function as outcomes.

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DISCLOSURES
None.

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