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CKD: A Call for an Age-Adapted Definition

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ABSTRACT

Current criteria for the diagnosis of CKD in adults include persistent signs of kidney damage, such as increased urine albumin-to-creatinine ratio or a GFR below the threshold of 60 ml/min per 1.73 m^2. This threshold has important caveats because it does not separate kidney disease from kidney aging, and therefore does not hold for all ages. In an extensive review of the literature, we found that GFR declines with healthy aging without any overt signs of compensation (such as elevated single-nephron GFR) or kidney damage. Older living kidney donors, who are carefully selected based on good health, have a lower predonation GFR compared with younger donors. Furthermore, the results from the large meta-analyses conducted by the CKD Prognosis Consortium and from numerous other studies indicate that the GFR threshold above which the risk of mortality is increased is not consistent across all ages. Among younger persons, mortality is increased at GFR <75 ml/min per 1.73 m^2, whereas in elderly people it is increased at levels <45 ml/min per 1.73 m^2. Therefore, we suggest that amending the CKD definition to include age-specific thresholds for GFR. The implications of an updated definition are far reaching. Having fewer healthy elderly individuals diagnosed with CKD could help reduce inappropriate care and its associated adverse effects. Global prevalence estimates for CKD would be substantially reduced. Also, using an age-specific threshold for younger persons might lead to earlier identification of CKD onset for such individuals, at a point when progressive kidney damage may still be preventable.

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The current criteria used for the definition of CKD in adults are: (*1*) signs of kidney damage, most often determined by an elevated urine albumin (or protein)-to-creatinine ratio (ACR); or (*2*) reduced kidney function, indicated by GFR <60 ml/min per 1.73 m^2. GFR is considered the best determinant of kidney function,[1] and CKD is staged according to six GFR categories (G1, G2, G3a, G3b, G4, and G5) and three categories for urine ACR levels (A1, A2 and A3) (Table 1). There is a broad agreement that abnormal urine ACR should trigger a diagnosis of CKD, but controversy remains regarding the most appropriate diagnostic criteria regarding GFR.

In this article, we will focus on the role of GFR in the definition of CKD. Laboratory thresholds for disease identification are commonly determined in two ways.[2–4] First, the distribution of the laboratory results in a representative population of healthy persons is obtained and thresholds for defining disease are calculated according to extreme values based on this distribution (typically 95th or 97.5th percentile for "too high" and 2.5th or fifth percentile for "too low"). Second, a threshold associated with an adverse outcome is identified through epidemiologic studies. We will discuss these two strategies (reference distribution and prognosis) in the specific case of using GFR for CKD definition.

CURRENT CKD DEFINITION AND RELATED CAVEATS

The current and widely adopted definition of CKD in adults is based on the 2013 Kidney Disease Improving Global Outcomes (KDIGO) guidelines.[1] Although not entirely undisputed, we do recognize the merit of these guidelines, as they standardized the definition of CKD.[5–11] Not only is GFR one of the two main criteria for diagnosis of CKD, an isolated GFR <60 ml/min per 1.73 m^2 (confirmed

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Table 1. Current CKD staging according to GFR and urine ACR

CDK Stage	Measurement
GFR category	GFR (ml/min per 1.73 m^2)
G1	≥90
G2	60–89
G3a	45–59
G3b	30–44
G4	15–29
G5	<15
ACR category	Urine ACR (mg/g)
A1	<30
A2	30–300
A3	>300

with a second value after at least 90 days) suffices for the diagnosis of CKD. In other words, anyone with a GFR <60 ml/min per 1.73 m^2 persisting for at least 3 months, by definition, has CKD, even if the urine ACR and structure or kidney morphology (ascertained by imaging or biopsy) are normal (*e.g.*, category G3a GFR/stage A1 level of albuminuria), and irrespective of an individual's age.

The considerations in favor of a fixed threshold at 60 ml/min per 1.73 m^2 in the current CKD definition proposed by KDIGO are as follows:[1]

1. Simplicity. Only one number needs to be kept in mind. This argument is understandably relevant for non-nephrologists and patients, but carries the risk of oversimplification of the complexities of kidney pathophysiology.

2. Biology. A GFR <60 ml/min per 1.73 m^2 is believed to represent <50% of the kidney function measured in healthy young adults.[1] The choice of 50% of normal function is, however, arbitrary, and whether GFR in healthy young adults is actually about 120 ml/min per 1.73 m^2 is debatable. This value was originally based on measured GFR (mGFR) values compiled and published in 1969 by Wesson.[12] More recent studies have shown that median GFR values in healthy young adults are <120 ml/min per 1.73 m^2.[13–15] Indeed, one meta-analysis of mGFR data in 5482 living kidney donors found normal mean GFR values of 106.7 ml/min per 1.73 m^2 at ages 20–30 years.[14] Such values were also observed in a large cohort of 2007 French living kidney donors <40 years of age, with a mean mGFR of 107.2 ml/min per 1.73 m^2.[15]

3. Prognosis. The third argument for a threshold at 60 ml/min per 1.73 m^2 was based on the association of lower GFR values with increased morbidity and mortality. Many large epidemiologic studies, especially from the CKD Prognosis Consortium, have seemingly supported the choice of the 60 ml/min per 1.73 m^2 threshold for CKD. We will discuss this argument in depth below.

THE PROGNOSTIC ARGUMENT FOR AN AGE-ADAPTED DEFINITION OF CKD

Absolute risks of mortality are typically higher in older patients simply because of the limited human life span. Regarding relative risk, several studies from the CKD Prognosis Consortium have demonstrated that GFR <60 ml/min per 1.73 m^2 was independently associated with adverse outcomes, particularly cardiovascular events and all-cause mortality,[16–28] thereby confirming findings from the seminal study published by Go *et al.*[29] in 2004. Of note, most of the Consortium analyses of GFR and risk of adverse events in both high-risk and general populations use as the reference group participants with only a single eGFR available (hence, no confirmation of chronicity) of ≥95 ml/min per 1.73 m^2.[16–28] However, the Consortium's 2012 meta-analysis, which was dedicated to age and included more than 2-million individuals from 46 different cohorts (33 from the general population and 13 CKD cohorts), used 80 ml/min per 1.73 m^2 as the reference group eGFR rather than 95 ml/min per 1.73 m^2.[17] The associations with mortality and ESKD remained significant when eGFR was <60 ml/min per 1.73 m^2 in all age categories, although hazard ratios were much lower in older people.[17] Although the risk of ESKD was increased, the progression to ESKD in elderly patients with an eGFR of 45–59 ml/min per 1.73 m^2 and no abnormal urine ACR is very rare (<1% risk in 5 years using the Kidney Failure Risk Equation).[30]

Given the critical importance of the choice of the reference group in such analyses, others have reanalyzed the data from the CKD Prognosis Consortium for mortality using different reference groups based on age (Figure 1).[31–34] In these analyses,[31,34] the reference eGFR group in each age category was defined as the one with the lowest mortality risk (in subsets with urine ACR <10 or 10–29 mg/g). The results revealed that, in the 55–64 years age category (reference eGFR 90–104 ml/min per 1.73 m^2), the mortality risk began to increase when GFR fell below 60 ml/min per 1.73 m^2. However, for people older than 65 years (reference eGFR 75–89 ml/min per 1.73 m^2), the risk was trivial until the eGFR had fallen below 45 ml/min per 1.73 m^2. In the youngest age category of 18–54 years (reference eGFR >105 ml/min per 1.73 m^2), the risk of mortality started to increase when eGFR was <75 ml/min per 1.73 m^2.[31–34] Therefore, an age-specific analysis of the data used by the CKD Prognosis Consortium provides a strong argument for an age-adapted definition of CKD using appropriate prognostic strata for age.

Tables 2 and 3 summarize the studies on associations between eGFR and risk of adverse events outside of the CKD Prognosis Consortium. The analysis considered only published full-length articles. We included studies that used creatinine-based equations (Modification of Diet in Renal Disease study or CKD Epidemiology Collaboration [CKD-EPI] equations) and reported adjusted risks of cardiovascular or all-cause mortality.[29,35–55] We excluded studies that had only participants with eGFR categories G3–G5 and those without older individuals. Instead, we focused on studies that were performed in elderly individuals or reported results in separate age categories. Our main hypothesis was that the increased risk of mortality associated with lower eGFR differs across age categories and, notably, that an eGFR of 45–60 ml/min

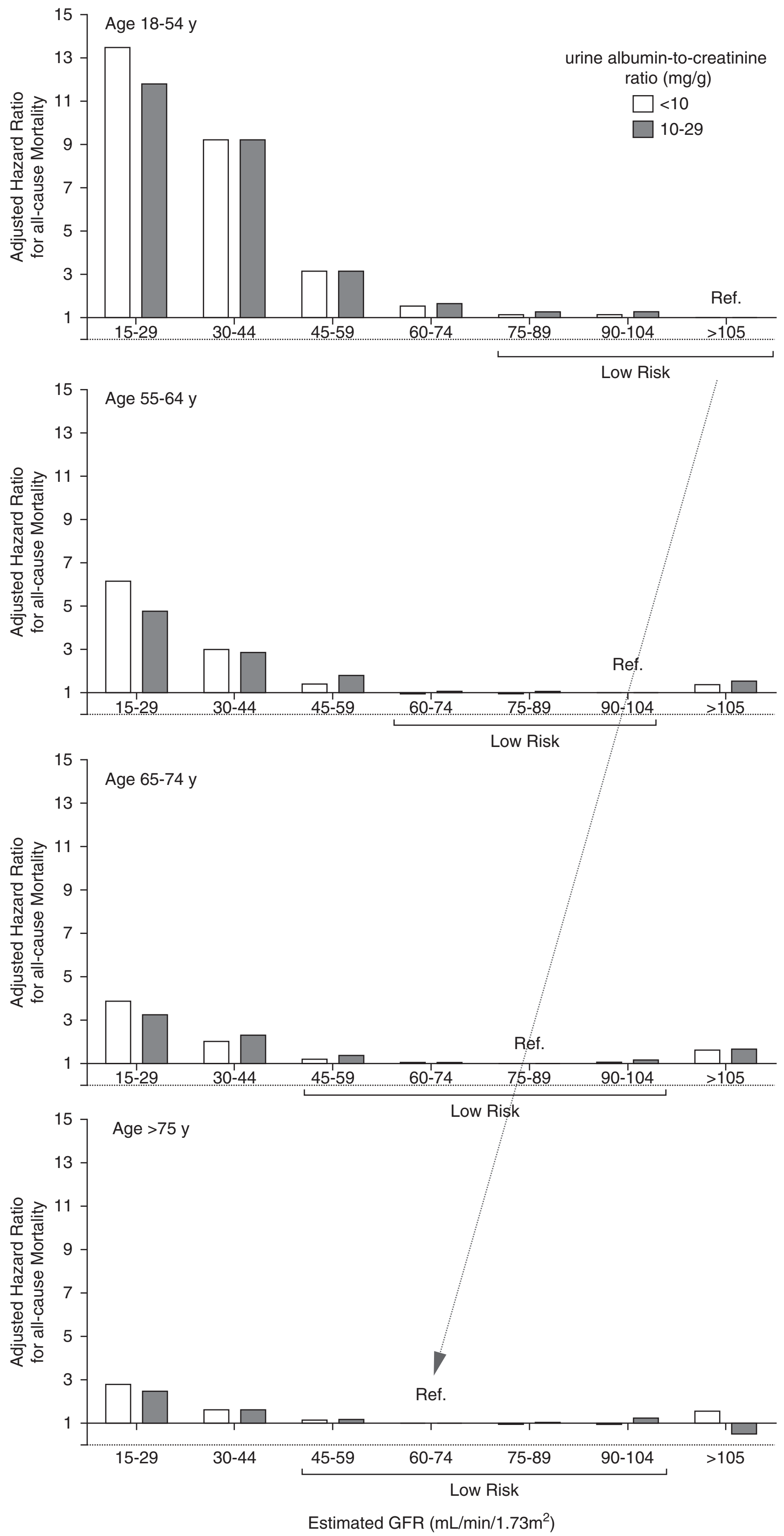

Figure 1. The association between eGFR and all-cause mortality depends on the age group. Hazard ratio for mortality when the reference group is the one with the lowest risk. eGFR ranges are within the brackets (low risk) and are not significantly different from the reference group (from Denic *et al.*[34]).

per 1.73 m^2 in older age groups is not associated with excess mortality.

When looking at studies that presented a separate eGFR category of 45–60 ml/min per 1.73 m^2 and used eGFR >60 ml/min per 1.73 m^2 as a reference category, only a few studies demonstrated an increased risk,[43,45,49,56] whereas others did not.[40,41,47,48] The largest study to date included a separate analysis of individuals with an eGFR of 50–60 ml/min per 1.73 m^2 in the older age categories. The results showed that, in this eGFR category, the risk of death was not higher than in the category eGFR>60 ml/min per 1.73 m^2.[36] In addition, the Renal Risk in Derby study deserves particular attention, as it included follow-up data on eGFR.[55] A total of 1741 participants, most with confirmed CKD, were prospectively followed for 5 years. The mean age of the cohort was 72.9±9 years, the mean eGFR using the CKD-EPI equation was 54±12 ml/min per 1.73 m^2, and most participants had normal urine ACR. After 5 years, 34.1% of the cohort was considered to be stable and 19.3% had even improved their GFR category. Nearly all of the participants who improved their CKD status had been classified as category G3a/A1 at baseline.[55] Interestingly, the age- and sex-standardized mortality rates of those with category G3a GFR were similar to those in the general population, whereas those with category G3b or G4 at baseline had higher mortality rates.[55,57]

Regarding the prognosis argument, we acknowledge that our proposal of an age-adapted definition for CKD is mainly based on mortality risk. We did not consider other outcomes, even though other publications have reported the risk of lower GFR with classic metabolic complications of CKD (anemia, hyperparathyroidism, acidosis, hyperphosphoremia)[58,59] and other clinical complications (such as frailty, impaired quality of life, and fracture).[60,61] These studies, unfortunately, are of little utility in informing our proposal of an age-adapted threshold. Although higher risk of these complications is frequently observed when eGFR is <45 ml/min per 1.73 m^2,[58] results are much more variable at higher eGFRs (unlike mortality, the

Table 2. Characteristics of studies that investigated outcomes in relation to GFR in general populations

Author (reference)	Study Name	Country	Time Period of Data Collection	Number of Subjects (*N*)	Age in years (mean±SD/ median and IQR) and Other Potentially Relevant Characteristics	Follow-Up Time (years)	Clinical Cohort/ General Population
Manjunath *et al.*[35]	Cardiovascular Health Study	United States	1989–1990	4893	73.4 (mean)	5.05 (maximum)	GP
Go *et al.*[29]	Kaiser Permanente Renal Registry	United States	1996–2000	1,120,295	52.2±16.3 (mean±SD)	2.84 (median) 1.65–4.01 (IQR)	GP (health insurer)
O'Hare *et al.*[36]	Department of Veterans Affairs	United States	2001–2002	2,583,911	63.6±14 (mean±SD) 95% men	3.17±0.62 (mean±SD)	GP (health care provider)
Maaravi *et al.*[37]	Jerusalem Seventy-Year-Old Longitudinal Study	Israel	1990–1991	441	70 (all)	12 (maximum)	GP
Hallan *et al.*[38]	HUNT II	Norway	1995–1997	9709	All with DM or treated HT plus 5% random sample. DM/HT age 65.9±11.9 (mean±SD); random non-DM/HT age 49.6±16.0 (mean±SD)	8.3 (median)	GP (health survey); population based, but in fact a "high-risk" study population
Raymond *et al.*[56]	NA	United Kingdom	2000–2003	106,366	57.7±19.1 (mean±SD)	3 (maximum)	GP
Brantsma *et al.*[39]	PREVEND	Netherlands	1997–1998	8495	49.2±12.7 (mean±SD)	7.5 (median) 6.9–7.8 (IQR)	GP (oversampling of individuals with elevated ACR levels)
Hwang *et al.*[40]	Elderly Health Examination Program	Taiwan	2002–2004	35,529	75.7±5.3 (mean±SD)	From 2.6±0.3 (mean±SD) for eGFR ≥60 ml/min to 2.3±0.7 (mean±SD) for stage 5	GP
Roderick *et al.*[41]	MRC General Practice Research Framework	United Kingdom	1994–1999	13,177	80.2 (median) IQR 6.9	7.3 (median) IQR 5	GP (primary care)
Van der Velde *et al.*[42]	PREVEND	Netherlands	1997–1998	8047	49±13 (mean±SD)	7.0±1.6 (mean±SD)	GP (oversampling of individuals with elevated ACR levels)
Muntner *et al.*[43]	REGARDS	United States	2003–2007	24,350	≥45	4.5 (median)	GP (oversampling of black people)
Stengel *et al.*[44]	Three-City	France	1999–2001	8705	74.3±5.5 (mean±SD)	6 (maximum)	GP
Van Pottelbergh *et al.*[45]	BELFRAIL	Belgium	2008–2009	539	84.7±3.6 (mean±SD)	2.9±0.3	GP (primary care)
Oh *et al.*[46]	KloSHA	Korea	2005–2006	949	75.8±9.0 (mean±SD)	5.3±1.4 (mean±SD)	GP

Table 2. Continued

Author (reference)	Study Name	Country	Time Period of Data Collection	Number of Subjects (*N*)	Age in years (mean±SD/ median and IQR) and Other Potentially Relevant Characteristics	Follow-Up Time (years)	Clinical Cohort/ General Population
Minutolo *et al.*[47]	Health Search/ Cegedim Strategic Data Longitudinal Patient Database	Italy	2003–2005	30,326	71.0±11.0 (mean±SD)	7.2 (median) 4.7–7.7 (IQR)	GP (primary care); population without nephrology consultation at baseline
Malmgren *et al.*[48]	OPRA	Sweden	NA	1011	75.2±0.2 (mean±SD) 100% women	10 (all)	GP
Chowdhury *et al.*[49]	ANBP2	Australia	NA	6083	71.9±4.9 (mean±SD)	10.8 (median) 9.6–11.4 (IQR)	RCT participants; hypertensive population
Nagai *et al.*[50]	Ibaraki Prefecture	Japan	1993	89,547	Men 60.2 (mean) Women 57.8 (mean)	17.1 (mean)	GP (exclusion of those with history of CVD)
Corsonello *et al.*[51]	InChianti	Italy	1998–2000	828	74.4±6.9 (mean±SD)	9 (maximum)	GP
Wu *et al.*[52]	Kailuan Study	China	2006–2007	95,391	52.0±12.6 (mean±SD)	8 (maximum)	GP

GP, general population; IQR, interquartile range; DM, diabetes mellitus; HT, hypertension; NA, not available; HUNT, Nord-Trøndelag Health Study; PREVEND, Prevention of Renal and Vascular Endstage Disease; MRC, Medical Research Council; REGARDS, Reasons for Geographic and Racial Differences in Stroke; KloSHA, Korean Longitudinal Study on Health and Aging; OPRA, Osteoporosis Risk Assessment; ANBP2, Second Australian National Blood Pressure Study; RCT, randomized controlled trial; CVD, cardiovascular disease.

Table 3. Findings of studies that investigated outcomes in relation to GFR in general populations

Author (reference)	Study Name	eGFR/ACR (GFR equation)	Outcome Studied (ACM or CVM)	Comparison Made and Reference Category	Adjusted Hazard Ratios in Exposure Categories	Comments
Manjunath *et al.*[35]	Cardiovascular Health Study	MDRD	ACM	90–130 ml/min per 1.73 m^2	60–89 ml/min 1.05 (0.78–1.41) 15–59 ml/min 1.47 (1.05–2.06)	
Go *et al.*[29]	Kaiser Permanente Renal Registry	MDRD	ACM CV events	≥60 ml/min per 1.73 m^2	ACM: 45–59 ml/min 1.2 (1.1–1.2) 30–44 ml/min 1.8 (1.7–1.9) 15–29 ml/min 3.2 (3.1–3.4) <15 ml/min 5.9 (5.4–6.5) CV events: 45–59 ml/min 1.4 (1.4–1.5) 30–44 ml/min 2.0 (1.9–2.1) 15–29 ml/min 2.8 (2.6–2.9) <15 ml/min 3.4 (3.1–3.8)	In a subgroup where chronicity was confirmed (repeated serum creatinine measurements) (*n*=172,144), eGFR at 45–59 ml/min was not associated with ACM 1.0 (1.0–1.1)
O'Hare *et al.*[36]	Department of Veterans Affairs	MDRD	ACM	≥60 ml/min per 1.73 m^2	18–44 yr: 50–59 ml/min 1.56 (1.30–1.88) 40–49 ml/min 1.90 (1.35–2.67) 30–39 ml/min 3.58 (2.54–5.05) 45–54 yr: 50–59 ml/min 1.27 (1.19–1.36) 40–49 ml/min 1.89 (1.74–2.06) 30–39 ml/min 2.89 (2.63–3.18) 55–64 yr: 50–59 ml/min 1.18 (1.13–1.23) 40–49 ml/min 1.75 (1.65–1.85) 30–39 ml/min 2.43 (2.27–2.59) 65–74 yr: 50–59 ml/min 1.02 (0.99–1.05) 40–49 ml/min 1.35 (1.32–1.39) 30–39 ml/min 1.81 (1.75–1.87) 75–84 yr: 50–59 ml/min 1.02 (0.99–1.04) 40–49 ml/min 1.21 (1.18–1.23) 30–39 ml/min 1.55 (1.51–1.58) 85+ yr: 50–59 ml/min 1.02 (0.97–1.06) 40–49 ml/min 1.10 (1.05–1.15) 30–39 ml/min 1.36 (1.29–1.44)	In younger age categories, adjusted HRs were higher and statistically significant already from 50 to 59 ml/min. In younger people and elderly with stable eGFR adjusted HRs were lower in all eGFR categories, 50–59 ml/min was not associated with ACM. Findings suggest that mortality risk stratification in younger and elderly people should not be based on the same eGFR cut-off points

Table 3. Continued

Author (reference)	Study Name	eGFR/ACR (GFR equation)	Outcome Studied (ACM or CVM)	Comparison Made and Reference Category	Adjusted Hazard Ratios in Exposure Categories	Comments
Maaravi *et al.*[37]	Jerusalem Seventy-Year-Old Longitudinal Study	MDRD CG Mayo Clinic	ACM	≥60 ml/min per 1.73 m^2 Results presented for MDRD	<60 ml/min 1.19 (0.83–1.71)	
Hallan *et al.*[38]	HUNT II	MDRD	CVM	≥75 ml/min per 1.73 m^2 and optimal ACR; ACR below sex-specific median (<5 and 7 mg/g in men and women)	<70 yr: Optimal ACR: 60–74 ml/min 1.17 (0.35–3.91) 45–59 ml/min 0.73 (0.26–2.02) <45 ml/min 1.08 (0.19–6.10) High normal ACR: 60–74 ml/min 1.53 (0.55–4.26) 45–59 ml/min 3.29 (1.02–10.6) <45 ml/min 2.57 (0.88–7.51) Micro-albuminuria: 60–74 ml/min 1.92 (0.71–5.16) 45–59 ml/min 2.22 (0.87–5.70) <45 ml/min 5.94 (2.06–17.2) ≥70 yr: Optimal ACR: 60–74 ml/min 0.79 (0.30–2.10) 45–59 ml/min 2.48 (0.76–8.13) <45 ml/min 1.49 (0.46–4.86) High normal ACR: 60–74 ml/min 1.68 (0.61–4.69) 45–59 ml/min 1.93 (0.63–5.92) <45 ml/min 4.70 (1.57–14.1) Micro-albuminuria: 60–74 ml/min 3.80 (1.33–10.80) 45–59 ml/min 4.09 (1.52–10.90) <45 ml/min 8.38 (2.83–24.9)	

Table 3. Continued

Author (reference)	Study Name	eGFR/ACR (GFR equation)	Outcome Studied (ACM or CVM)	Comparison Made and Reference Category	Adjusted Hazard Ratios in Exposure Categories	Comments
Raymond *et al.*[56]	NA	MDRD	ACM	≥60 ml/min per 1.73 m^2	20–44 yr: Stage 3a 13.6 (6.2–29.8) Stage 3b 12.1 (4.0–36.5) Stage 4 17.4 (5.9–51.4) Stage 5 26.1 (9.1–74.8) 45–54 yr: Stage 3a 7.5 (4.4–12.6) Stage 3b 13.6 (7.5–24.7) Stage 4 4.6 (1.2–17.4) Stage 5 28.6 (17.4–47.2) 55–64 yr: Stage 3a 3.0 (2.2–4.1) Stage 3b 5.9 (3.9–8.9) Stage 4 9.3 (6.1–14.2) Stage 5 18.2 (13.9–23.9) 65–74 yr: Stage 3a 1.8 (1.5–2.1) Stage 3b 3.2 (2.6–3.9) Stage 4 5.2 (4.1–6.5) Stage 5 7.6 (5.7–10.1) 75–84 yr: Stage 3a 1.2 (1.0–1.3) Stage 3b 1.9 (1.7–2.1) Stage 4 3.3 (2.9–3.8) Stage 5 4.4 (3.7–5.3) 85+ yr: Stage 3a 0.9 (0.8–1.0) Stage 3b 1.3 (1.2–1.5) Stage 4 1.8 (1.7–2.0) Stage 5 2.5 (2.3–2.8)	
Brantsma *et al.*[39]	PREVEND	MDRD ACR	CVM and CV hospitalization combined	No CKD	Stage 1 2.2 (1.5–3.3) Stage 2 1.6 (1.3–2.0) Stage 3 1.3 (1.0–1.7) Stage 3 with UAE <30 mg/24 h 1.0 (0.7–1.4) Stage 3 with UAE >30 mg/24 h 1.6 (1.1–2.3)	
Hwang *et al.*[40]	Elderly Health Examination Program	MDRD	ACM CVM	≥60 ml/min per 1.73 m^2	ACM: 45–59 ml/min 1.10 (1.0–1.2) 30–44 ml/min 1.52 (1.3–1.8) 15–29 ml/min 2.1 (1.7–2.6) <15 ml/min 2.55 (1.8–3.6) CVM: 45–59 ml/min 1.30 (1.0–1.7) 30–44 ml/min 2.42 (1.7–3.4) 15–29 ml/min 3.62 (2.3–5.8) <15 ml/min 3.22 (1.3–8.3)	

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Table 3. Continued

Author (reference)	Study Name	eGFR/ACR (GFR equation)	Outcome Studied (ACM or CVM)	Comparison Made and Reference Category	Adjusted Hazard Ratios in Exposure Categories	Comments
Roderick *et al.*[41]	MRC General Practice Research Framework	MDRD Dipstick proteinuria	ACM CVM in those without CVD at baseline	≥60 ml/min per 1.73 m^2; proteinuria negative	ACM after 0–2 yr: Men: 45–59 ml/min 1.13 (0.93–1.37) 30–44 ml/min 1.69 (1.26–2.28) <30 ml/min 3.87 (2.78–5.38) Women: 45–59 ml/min 1.14 (0.93–1.40) 30–44 ml/min 1.33 (1.06–1.68) <30 ml/min 2.44 (1.68–3.56) CVM after 0–2 yr: Men: 45–59 ml/min 1.67 (1.15–2.43) 30–44 ml/min 1.60 (0.94–2.73) <30 ml/min 2.89 (1.22–6.84) Women: 45–59 ml/min 1.59 (1.01–2.50) 30–44 ml/min 1.45 (0.93–2.28) <30 ml/min 3.80 (1.87–7.75) ACM: Men: Proteinuria positive >60 ml/min 1.29 (1.07–1.56) 45–59 ml/min 1.25 (1.02–1.52) 30–44 ml/min 1.08 (0.82–1.42) <30 ml/min 0.95 (0.56–1.59) Women: Proteinuria positive >60 ml/min 1.19 (0.96–1.47) 45–59 ml/min 0.94 (0.77–1.15) 30–44 ml/min 1.39 (1.10–1.77) <30 ml/min 1.70 (1.15–2.52) CVM: Men: Proteinuria positive >60 ml/min 1.05 (0.70–1.57) 45–59 ml/min 1.31 (0.91–1.89) 30–44 ml/min 0.83 (0.47–1.46) <30 ml/min 0.97 (0.35–2.68) Women: Proteinuria positive >60 ml/min 1.18 (0.80–1.74) 45–59 ml/min 0.93 (0.65–1.32) 30–44 ml/min 1.34 (0.88–2.03) <30 ml/min 2.79 (1.40–5.54)	Short-term (0–2 yr) eGFR-related risk is higher than long term (>2 yr) risk (not shown)

Table 3. Continued

Author (reference)	Study Name	eGFR/ACR (GFR equation)	Outcome Studied (ACM or CVM)	Comparison Made and Reference Category	Adjusted Hazard Ratios in Exposure Categories	Comments
Van der Velde *et al.*[42]	PREVEND	MDRD CKD-EPI SCr CysC SCr-CysC Creatinine clearance	Fatal and nonfatal CV events	+10 ml/min per 1.73 m^2 increase in eGFR. Results presented for CKD-EPI	<60 yr: 0.70 (0.62–0.79) ≥60 yr: 1.02 (0.92–1.13)	The association between eGFR and risk of CV events is weaker in elderly subjects than in younger subjects
Muntner *et al.*[43]	REGARDS	CKD-EPI ACR	ACM	≥60 ml/min per 1.73 m^2	45–59 yr: 45–60 ml/min 2.5 (1.3–4.6) <45 ml/min 3.5 (1.8–6.8) 60–69 yr: 45–60 ml/min 1.7 (1.3–2.3) <45 ml/min 2.2 (1.6–3.0) 70–79 yr: 45–60 ml/min 1.1 (0.9–1.3) <45 ml/min 1.9 (1.5–2.4) ≥80 yr: 45–60 ml/min 1.3 (1.0–1.7) <45 ml/min 1.5 (1.1–2.0)	If ACR is <10 mg/g, the results are similar: 45–59 yr: 45–60 ml/min 4.5 (1.8–11.1) <45 ml/min 4.7 (0.7–34.2) 60–69 yr: 45–60 ml/min 1.9 (1.2–3.1) <45 ml/min 2.5 (1.0–6.1) 70–79 yr: 45–60 ml/min 1.1 (0.8–1.6) <45 ml/min 2.1 (1.2–3.6) ≥80 yr: 45–60 ml/min 1.4 (0.9–2.2) <45 ml/min 1.6 (0.9–2.8)
Stengel *et al.*[44]	Three-City	CKD-EPI MDRD	ACM CVM	≥75–89 ml/min per 1.73 m^2; results presented for CKD-EPI	ACM: 60–74 ml/min 0.9 (0.8–1.1) 45–59 ml/min 1.1 (0.9–1.3) 30–44 ml/min 2.0 (1.5–2.7) <30 ml/min 3.3 (2.0–5.5) CVM: 60–74 ml/min 0.9 (0.6–1.3) 45–59 ml/min 1.6 (1.1–2.3) 30–44 ml/min 3.1 (1.8–5.0) <30 ml/min 4.3 (1.8–10.2)	
Van Pottelbergh *et al.*[45]	BELFRAIL	MDRD CKD-EPI SCr CKD-EPI CysC CKD-EPI SCr-CysC BIS-2 SCr-CysC	ACM and RRT combined	60–90 ml/min per 1.73 m^2; results presented for CKD-EPI SCr	45–60 ml/min 1.65 (1.05–2.61) 30–45 ml/min 1.72 (1.03–2.88) <30 ml/min 5.04 (2.95–8.60)	

Table 3. Continued

Author (reference)	Study Name	eGFR/ACR (GFR equation)	Outcome Studied (ACM or CVM)	Comparison Made and Reference Category	Adjusted Hazard Ratios in Exposure Categories	Comments
Oh *et al.*[46]	KLoSHA	CKD-EPI Disptick proteinuria	ACM	≥90 ml/min per 1.73 m^2; proteinuria negative	60–89 ml/min 1.37 (0.75–2.52) 45–59 ml/min 1.65 (0.84–3.25) <45 ml/min 2.36 (1.17–4.75)	If proteinuria: Trace 1.24 (0.78–1.96) ≥1+1.73 (1.13–2.63)
Minutolo *et al.*[47]	Health Search/ Cegedim Strategic Data Longitudinal Patient Database	MDRD	ACM	≥60 ml/min per 1.73 m^2	ACM: Stage 3a 1.11 (0.99–1.23) Stage 3b 1.66 (1.49–1.86) Stage 4 2.75 (2.41–3.13) Stage 5 2.54 (2.01–3.22)	
Malmgren *et al.*[48]	OPRA	CKD-EPI MDRD Revised Lund-Malmö BIS-1 CG	ACM	≥60 ml/min per 1.73 m^2; results presented for CKD-EPI	75–80 yr: 45–60 ml/min 1.1 (0.6–2.0) 0–45 ml/min 4.5 (2.2–9.2) 75–85 yr: 45–60 ml/min 1.4 (1.0–1.9) 0–45 ml/min 3.5 (2.1–5.8) 80–85 yr: 45–60 ml/min 1.7 (1.1–2.6) 0–45 ml/min 2.6 (1.4–5.0)	
Chowdhury *et al.*[49]	ANBP2	MDRD CKD-EPI	ACM CVM	≥60 ml/min per 1.73 m^2; results presented for CKD-EPI	ACM: 45–59 ml/min 1.13 (1.01–1.27) 30–44 ml/min 1.65 (1.37–1.99) <30 ml/min 5.16 (3.17–8.42) CVM: 45–59 ml/min 1.05 (0.89–1.23) 30–44 ml/min 1.64 (1.27–2.13) <30 ml/min 5.60 (2.32–13.51)	

Table 3. Continued

Author (reference)	Study Name	eGFR/ACR (GFR equation)	Outcome Studied (ACM or CVM)	Comparison Made and Reference Category	Adjusted Hazard Ratios in Exposure Categories	Comments
Nagai *et al.*[50]	Ibaraki Prefecture	MDRD	ACM CVM	≥60 ml/min per 1.73 m^2	ACM: Men: 40–69 yr: 45–49 ml/min 1.33 (1.06–1.67) 30–44 ml/min 1.53 (1.20–1.96) 70–80 yr: 45–49 ml/min 1.02 (0.82–1.25) 30–44 ml/min 1.63 (1.33–2.00) Women: 40–69 yr: 45–49 ml/min 1.50 (1.27–1.78) 30–44 ml/min 2.21 (1.81–2.71) 70–80 yr: 45–49 ml/min 1.19 (1.02–1.38) 30–44 ml/min 1.53 (1.31–1.79) CVM: Men: 40–69 yr: 45–49 ml/min 1.82 (1.23–2.69) 30–44 ml/min 1.65 (1.04–2.62) 70–80 yr: 45–49 ml/min 1.03 (0.72–1.48) 30–44 ml/min 1.37 (0.93–2.02) Women: 40–69 yr: 45–49 ml/min 1.34 (0.98–1.82) 30–44 ml/min 2.24 (1.58–3.17) 70–80 yr: 45–49 ml/min 1.43 (1.14–1.79) 30–44 ml/min 1.57 (1.23–2.00)	
Corsonello *et al.*[51]	InChianti	CKD-EPI SCr BIS-1 SCr FAS CKD-EPI SCr-CysC BIS-2 SCr-CysC	ACM	≥90 ml/min per 1.73 m^2; results presented for CKD-EPI SCr	60–89.9 ml/min 1.63 (0.84–3.17) 45–59.9 ml/min 2.50 (1.21–5.15) 30–44.9 ml/min 5.44 (1.10–27.7) <30 ml/min 7.42 (1.79–30.6)	

Table 3. Continued

Author (reference)	Study Name	eGFR/ACR (GFR equation)	Outcome Studied (ACM or CVM)	Comparison Made and Reference Category	Adjusted Hazard Ratios in Exposure Categories	Comments
Wu *et al.*[52]	Kailuan Study	CKD-EPI Dipstick proteinuria	ACM	≥ 90 ml/min per 1.73 m^2	All: 60–89 ml/min 1.01 (0.93–1.09) 45–59 ml/min 1.11 (0.99–1.24) <45 ml/min 1.51 (1.30–1.74) Men: 60–89 ml/min 1.01 (0.94–1.10) 45–59 ml/min 1.11 (0.99–1.23) <45 ml/min 1.35 (1.17–1.57) Women: 60–89 ml/min 1.65 (1.16–2.34) 45–59 ml/min 1.92 (1.25–2.96) <45 ml/min 4.11 (2.50–6.76)	

ACM, all-cause mortality; CVM, cardiovascular mortality; MDRD, Modified Diet in Renal Disease Study equation; CV, cardiovascular; HR, hazard ratio; CG, Cockcroft and Gault formula; MRC, Medical Research Council; CVD, cardiovascular disease; HUNT, Nord-Trøndelag Health Study; PREVEND, Prevention of Renal and Vascular Endstage Disease; CysC, cystatin C; REGARDS, Reasons for Geographic and Racial Differences in Stroke; KLoSHA, Korean Longitudinal Study on Health and Aging; NA, not available; OPRA, Osteoporosis Risk Assessment; ANBP2, Second Australian National Blood Pressure Study; SCr, serum creatinine; BIS1, Berlin Initiative Study; FAS, full age spectrum.

definitions of specific complications or of clinical status are not uniform).

In summary, most studies showed no or a trivial additional mortality risk for older adult participants with an eGFR of 45–59 ml/min per 1.73 m^2 and normal urine ACR. Prognostic arguments thus favor an age-adapted threshold for eGFR in the CKD definition.

KIDNEY SENESCENCE AS AN ARGUMENT FOR AN AGE-ADAPTED DEFINITION OF CKD

Another concern with a GFR threshold fixed at 60 ml/min per 1.73 m^2 is that it fails to account for the distinct microstructural and macrostructural differences between the aging kidney and kidneys affected by CKD. It also does not take into account the fact that a substantial proportion of healthy older people have an mGFR of <60 ml/min per 1.73 m^2.

Structural Differences Between Aging Kidney and CKD

Among healthy kidney donors, aging is reflected by an indolent nephrosclerosis, characterized by arteriosclerosis, ischemic globally (but not segmentally) sclerotic glomeruli, and interstitial fibrosis and tubular atrophy.[62] Although the interstitial fibrosis and tubular atrophy that occur with aging are fairly minimal,[62] there is a substantial nephron loss and dropout (from about 1,000,000 nephrons per kidney in healthy adults aged 18–29 years to 500,000 per kidney in healthy individuals aged 70–75 years).[63] Despite this substantial nephron loss with age, there is no compensation by the remaining nephrons because glomerular volume, single-nephron GFR, and single-nephron glomerular filtration capacity remain stable.[63–65]

CKD, on the other hand, is often characterized by disease-specific pathology that differs from age-induced nephrosclerosis. CKD can include unique microstructural findings (such as specific immunofluorescence staining patterns) or macrostructural findings (such as polycystic kidney or renal artery stenosis) that are not seen with aging alone. Although risk factors for CKD such as obesity, diabetes, and hypertension are associated with nephrosclerosis, they are also associated with glomerular enlargement, segmental glomerulosclerosis, and higher single-nephron GFR in intact nonsclerotic glomeruli.[63,64] Only when the degree of global glomerulosclerosis exceeds that expected for age or when there is increased metabolic demand (*e.g.*, obesity and hyperglycemia) is there an increase in single-nephron GFR. Therefore, application of age-adapted thresholds for glomerulosclerosis is also useful with kidney biopsies performed in clinical care, as only glomerulosclerosis exceeding that expected for age is a risk factor for CKD progression.[66,67]

Decline of GFR with Aging

As already stated, the definition of normality for laboratory results can also be obtained by the distribution of the results in healthy populations. Establishing reference interval values with a fixed threshold, as per the KDIGO guidelines, would mean that the GFR reference values are constant across all age categories.[13,14,68–81] However, more reliable studies, using mGFR and living kidney donors or healthy individuals selected from the general population, indicate a clear decrease in GFR with age[13–15,64,68–90] and show that the rate of mGFR decline becomes significant after age 40 years.[2,12–15,73,76,80,85,88,91,92] Importantly, such a decline in mGFR with aging has been established on different continents and in different ethnic groups.[68,77,79–81,87,89] From these data, it is obvious that a substantial proportion of healthy older people have an mGFR of <60 ml/min per 1.73 m^2, despite the paucity of studies focusing on the elderly and using mGFR.

Regarding eGFR,[93–95] available cross-sectional studies from different parts of the world confirmed that many people older than 65 years of age have an eGFR value <60 ml/min per 1.73 m^2, suggesting a rather ubiquitous decline of eGFR with age.[13,68,96–101] Unfortunately, the few published longitudinal studies have shown discrepancies in the rate of kidney function decline or suffered from methodological limitations, such as use of eGFR or 24-hour creatinine clearance, inclusion of nonhealthy individuals, limited follow-up duration, and study attrition, making it difficult to draw a definitive conclusion about the magnitude of the average rate of GFR decline with aging.

Despite these limitations, all studies have shown a significant decline in GFR with aging in the majority of healthy participants.[48,96,102–114] The only longitudinal study using mGFR in a healthy general population is the Renal Iohexol Clearance Survey in Tromsø 6, which included a representative sample of 1594 white people aged 50–62 years from the general population without CKD, diabetes, or cardiovascular disease. The iohexol clearance measurement was repeated in 1299 (81%) patients after a median period of 5.6 years. The authors showed a mean GFR decline rate of 0.84±2.00 ml/min per year (or 0.95±2.23 ml/min per 1.73 m^2 per year). Although this may be the most valid study to date, it nevertheless was limited by its inclusion of only middle-aged white people and by its relatively short follow-up, with only two measurements in the majority of participants.[114]

PROPOSALS FOR AN AGE-ADAPTED CKD DEFINITION

The concept of an age-adapted definition of CKD is not new and has been proposed by a number of authors.[2,3,8,10,31,33,34,36,64,98,99,115–124] Such adaptation could be achieved in different ways. We emphasize that the suggested change in CKD definition should pertain only to people without other evidence of kidney damage (notably those with normal urine ACR).

Age-Related Percentiles of GFR

One way to achieve an age-adapted definition of CKD is to refer to percentiles of GFR in the healthy population, which are available in the literature for mGFR or eGFR in different ethnic groups.[13,68,96–99] In practice, this would mean interpreting a GFR result in light of age-specific GFR percentiles, and defining CKD as a value below a given percentile in healthy persons (Figure 2). By relating measurements to percentiles using different mGFR or eGFR methods, this approach may overcome differences in mGFR measurement techniques[125,126] or eGFR equations.[93,94,127] Using percentiles for each year of age minimizes the "birthday paradox," in which healthy people can become classified as having a disease or individuals with a disease can "recover" simply by becoming 1 year older; this problem is inherent to a single -threshold approach or an age-based approach with only a few thresholds.

By employing age-specific means and SDs, the individual patient levels can be transformed into a SD score (SDS), a metric commonly used in pediatrics (or even in adults for diagnosing diseases like osteoporosis, using bone mass density). An SDS value of ≤ -2 corresponds to an mGFR/eGFR at the 2.5th percentile or lower. Calculation of an SDS requires well characterized reference values across the entire age spectrum. Using these data, GFR SDS can be reported directly by the laboratory, analogous to reporting the eGFR results. The SDS is independent of age and method and is therefore ideal for follow-up. Furthermore, reference values may be included in the laboratory report (Figure 2).

A Limited Set of Age-Specific Thresholds

One can consider the CKD staging based on three pivotal age categories (Figure 3): <40 years, 40–65 years, and >65 years. We suggest GFR cut-offs of 75 ml/min per 1.73 m^2 for the youngest group, 60 ml/min per 1.73 m^2 for individuals aged 40–65 years, and 45 ml/min per 1.73 m^2 for those older than 65 years. In other words, in individuals older than 65 years, the current CKD category G3a/A1 (GFR 45–60 ml/min per 1.73 m^2) would not be considered to have CKD. Moreover, younger adults with a GFR <75 ml/min per 1.73 m^2 would be considered to have CKD, as their kidney function is below what would be expected for their age.[31,34,97,120,123,128,129] The choice of the different GFR thresholds can be justified by associations of these thresholds with prognosis (Figure 1).

POTENTIAL EFFECT OF AN UPDATED DEFINITION OF CKD

A modification of the CKD definition would have a substantial effect on the estimation of CKD prevalence. The KDIGO guidelines used the data from the National Health and Nutrition Examination Survey (NHANES) study (1999–2006) and estimated the CKD prevalence in the US adult general population at 11.5%. Individuals with a GFR of 45–59 ml/min per 1.73 m^2 and normal urine ACR represented 3.6% of the general population, and 75% of patients that are classified with CKD solely by the GFR criterion. Individuals with category G3a/A1 represented >30% of all people with CKD.[1] CKD categories 3 or 3a are unequivocally the largest or second largest group in terms of CKD prevalence in other studies as well.[47,48,55,56,97,123,130–139] The epidemiologic literature clearly shows that CKD prevalence increases with age when using the fixed-threshold CKD definition of 60 ml/min per 1.73 m^2.[1,48,56,97,101,123,130–134,138–143] Most older subjects defined as having CKD have a GFR of 45–59 ml/min per 1.73 m^2 and normal urine ACR, whereas the younger individuals more frequently have elevated urine ACR and GFR >60 ml/min per 1.73 m^2.[53,97,134,144] Thus, among the 3.6% of the general population with normal urine ACR and a GFR of between 45–59 ml/min per 1.73 m^2 in the NHANES (1999–2006) cohort, a large proportion are adults older than 65 years, without any other signs of kidney damage. These individuals would be considered free of disease with the age-adapted definition proposed above. Likewise, results from the MAREMAR (Maladies Rénales Chroniques au Maroc) study crucially illustrate the important effect of an age-adapted definition on the CKD prevalence. Among the 10,524 individuals screened, 2.7% had a confirmed eGFR <60 ml/min per 1.73 m^2. However, almost half of those with eGFR <60 ml/min per 1.73 m^2 had an eGFR above the third percentile of the population. These people, all older than 55 years and with normal dipstick analysis, would not be considered to have CKD with the age-adapted definition (using age-related percentiles) and the estimated CKD prevalence based on GFR would decrease from 2.7% to 1.8%, a 33% decrease.[97]

The current fixed GFR threshold of 60 ml/min per 1.73 m^2 not only results in overdiagnosis of CKD in the older adults, it may also lead to missed diagnoses of CKD in younger individuals who lack overt signs of kidney damage and have a GFR above the fixed threshold of 60 ml/min per 1.73 m^2 but below the lowest percentile for their age. This group may include young people with low-nephron endowment, such as individuals born with a single kidney,[145] those born preterm[146] or at a low birth weight, patients with Down syndrome,[147] or young people with a past history of treatment with nephrotoxic drugs.[148] Such individuals are at risk for developing progressive CKD over their remaining lifetime, and may experience associated comorbidities and adverse events, including an increase in mortality.[33,97,123,129]

Because the availability of curative therapies is limited, treatment of CKD rests on the prevention of progressive kidney damage. The sooner younger people with CKD are identified, the greater the likelihood that poor health outcomes may be prevented. In the MAREMAR study, young individuals with a low-for-age GFR represented 1.3% of the population.[97] These persons remain unrecognized in most epidemiologic studies that use a fixed GFR threshold of 60 ml/min per 1.73 m^2.[97,123] Using SDS, percentiles, or age-adapted staging in the definition of CKD would result in classifying these patients as having a disease. Further research, with a focus on long-term follow-up data, is warranted to elucidate whether such patients should be considered at risk for adverse renal or other disease-related outcomes.

Moving from a CKD definition with a fixed GFR threshold to a definition based on GFR adapted to age has several advantages. These include:

1. taking into account the physiologic age-related decline in GFR.

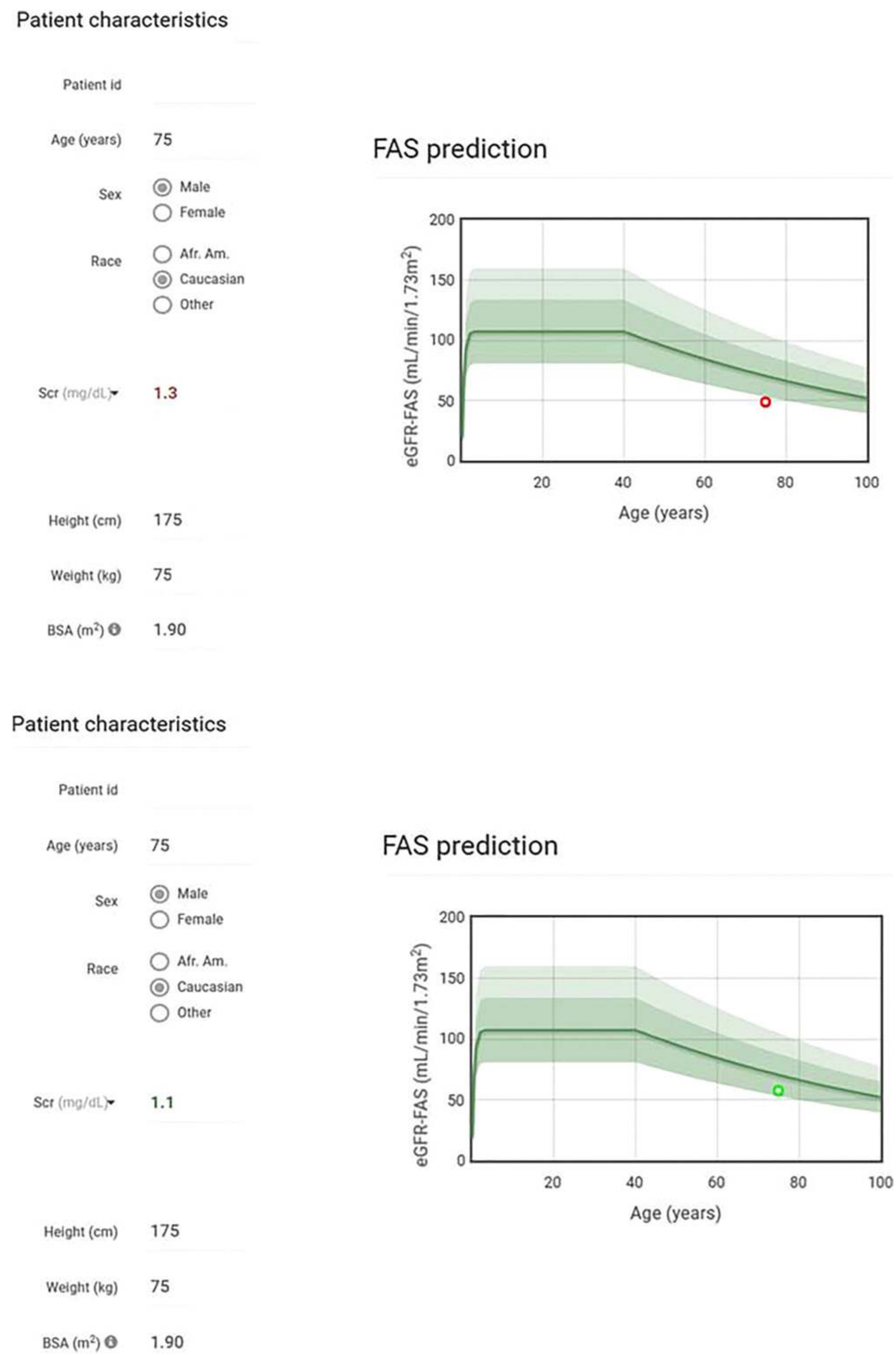

Figure 2. The interpretation of GFR results depends on age. Examples of interpretation of GFR (here GFR estimated using the FAS equation but the same can be applied to measured GFR or eGFR using other estimating equations) according to age and normal percentiles: abnormal (bottom) and normal (below) GFR result. The red circle corresponds to FAS=48 ml/min per 1.73 m^2 (serum creatinine [SCr]=1.3 mg/dl corresponds to SCr/Q=1.3/0.9=1.44>1.33) and the green circle corresponds to FAS=58 ml/min per 1.73 m^2 (SCr=1.1 mg/dl corresponds to SCr/Q=1.22<1.33). These results are abnormally low and normal predicted eGFR-FAS results with the age-adapted staging, respectively. Dark green shaded area corresponds to reference intervals for mGFR±SD and symmetrical limits for FAS based on SCr/Q=1 (middle line) and SCr/Q=1.33 (lower limit) (14). Light green area corresponds to the upper limit for FAS, based on SCr/Q=0.67. The interval (0.67 to 1.33) is considered the reference interval for SCr/Q. FAS, full age spectrum. Q, median SCr from healthy populations to account for age and sex.

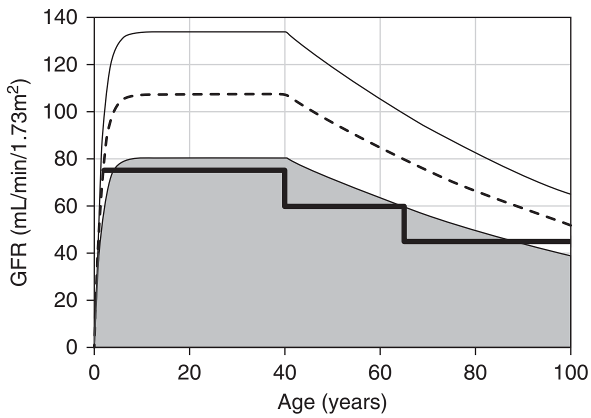

Figure 3. Age-specific thresholds in relation to age-specific GFR percentiles. GFR cut-off values and percentiles according to age (here percentiles of eGFR are calculated using the FAS equation). The bold line represents an age-adapted threshold for CKD: 75 ml/min per 1.73 m^2 for age below 40 years, 60 ml/min per 1.73 m^2 for age between 40 and 65 years, and 45 ml/min per 1.73 m^2 for age above 65 years. The dashed line represents the median (50th percentile) and the thin solid lines represent the 97.5th and 2.5th percentiles. The shaded zone is considered as below the normal reference intervals for GFR (<2.5th percentile).

2. fitting with reference distributions of mGFR and eGFR in healthy individuals.

3. consistency with the observed associations between low GFR and prognosis.

4. reconciling the two ways to define a disease—namely, the distribution of laboratory findings and the prognostic approach.

5. facilitating the identification, evaluation, and treatment of younger patients with a GFR that is too low for their age.

6. avoiding overdiagnosis of CKD in elderly patients.

Use of an age-adapted definition of CKD will also result in a much lower global CKD prevalence (perhaps by as much as 50%), particularly for elderly individuals. However, given that older adults without increased urine ACR or other signs of kidney damage usually have slightly decreased GFR that is physiologic and will on average remain stable (or could even improve) during follow-up, and have a mortality risk similar to those with higher GFR, there is no reason to consider such older individuals as living with a disease that requires investigations, referrals, and even therapeutic interventions with potential side effects.[149] At an individual level, applying a CKD status to older people ("D" meaning "disease") can sometimes be a source of unjustified stress. In some countries, this diagnosis can also lead to adverse consequences in terms of insurance. Using the age-adapted CKD definition could eventually result in more appropriate attention and directing resources to those who are at higher risk of adverse outcomes associated with CKD.

DISCLOSURES

Dr. Jager declared speaker honoraria from Fresenius and received grant support from European Renal Association – European Dialysis and Transplant Association. Dr. Schaeffner declared speaker honoraria from Fresenius Medical Care, Fresenius Kabi, and Siemens Health Care. Dr. White received grant support from Academic Health Science Center Alternate Funding Plan Innovation Fund. Dr. Melsom declared speaker honoraria from Astellas, Norwegian evening summit, American Society of Nephrology, 2018, and grants from Boehringer Ingelheim AS, outside the submitted work. Dr. van Londen declared speaker honoraria from Fresenius Medical Care. Dr. Rule declared royalties as "UpToDate" author on "The Aging Kidney." Dr. van der Giet reports personal fees from Novartis, personal fees from Bayer, personal fees and "other" from IEM, personal fees and other from Charité Research Organization, grants from Deutsche Forschungsgemeinschaft, grants from Else Kröner Freseniusstiftung, personal fees from Berlin Chemie, personal fees from Otsuka, personal fees from Servier, and personal fees from CVRX, outside the submitted work. Dr. Glassock reports other from Wolters-Kluwer, outside the submitted work. Dr. Rule reports grants from National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, during the conduct of the study. All authors are members of the ERA-EDTA European Kidney Function Consortium.

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See related perspectives, "Does eGFR by Any Number Mean the Same?" and "Modification of eGFR-Based CKD Definitions: Perfect, or Enemy of the Good?" on pages 1806–1807 and 1807–1809, respectively.

AFFILIATIONS

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