

# Chapter 2: Definition, identification, and prediction of CKD progression

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## 2.1: DEFINITION AND IDENTIFICATION OF CKD PROGRESSION

**2.1.1: Assess GFR and albuminuria at least annually in people with CKD. Assess GFR and albuminuria more often for individuals at higher risk of progression, and/ or where measurement will impact therapeutic decisions (Figure 17). (Not Graded)**

### RATIONALE

The statement is worded this way to remind the practitioner to use both GFR and albuminuria in order to assess progression and is consistent with the definition offered in Chapter 1 regarding definitions of CKD which include both parameters. There is increasing evidence which supports that both parameters are valuable. Lower GFR and greater

albuminuria are both associated with an increased rate of progression and are synergistic.

More frequent measures of eGFR and albuminuria should be considered in patients with a lower GFR and greater albuminuria as these people are more likely to progress. Frequency of measurement should also be individualized based on the patient history and underlying cause of kidney disease.

In specific conditions (e.g., GN or increased levels of albuminuria), frequent (every 1–3 months) assessment may guide therapeutic decisions. Regular monitoring of stable patients may include more frequent monitoring than annually, but will be dictated by underlying cause, history, and estimates of GFR and ACR values obtained previously.

### Evidence Base

There is variability in the presence of or rate of decline of kidney function in those with CKD. The rate at which

Guide to Frequency of Monitoring (number of times per year) by GFR and Albuminuria Category				Persistent albuminuria categories		
				Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30mg/mmol
GFR categories (ml/min/1.73 m <sup>2</sup> ) Description and range	G1	Normal or high	≥90	1 if CKD	1	2
	G2	Mildly decreased	60–89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45–59	1	2	3
	G3b	Moderately to severely decreased	30–44	2	3	3
	G4	Severely decreased	15–29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

**Figure 17 | GFR and albuminuria grid to reflect the risk of progression by intensity of coloring (green, yellow, orange, red, deep red).** The numbers in the boxes are a guide to the frequency of monitoring (number of times per year). Green reflects stable disease, with follow-up measurements annually if CKD is present; yellow requires caution and measurements at least once per year; orange requires measurements twice per year; red requires measurements at 3 times per year while deep red may require closest monitoring approximately 4 times or more per year (at least every 1–3 months). These are general parameters only based on expert opinion and must take into account underlying comorbid conditions and disease state, as well as the likelihood of impacting a change in management for any individual patient. CKD, chronic kidney disease; GFR, glomerular filtration rate. Modified with permission from Macmillan Publishers Ltd: *Kidney International*. Levey AS, de Jong PE, Coresh J, et al.<sup>30</sup> The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. *Kidney Int* 2011; 80: 17–28; accessed <http://www.nature.com/ki/journal/v80/n1/full/ki2010483a.html>

**Table 20 | Decline in kidney function in various populations (longitudinal studies only)**

Reference	Population	N	GFR decline
<b>Healthy</b>			
Slack TK <sup>216</sup>	Healthy kidney donors	141	0.40 ml/min/year
Rowe JW et al. <sup>217</sup>	Healthy males	293	0.90 ml/min/1.73 m <sup>2</sup> /year (CrCl)
Lindeman RD <sup>218</sup>	Healthy males	254	0.75 ml/min/year (CrCl)
Halbesma N et al. <sup>219</sup>	PREVEND cohort (all participants)	6894	0.55 ml/min/1.73 m <sup>2</sup> /year
Imai E et al. <sup>220</sup>	Annual health exam participants in Japan	120,727	0.36 ml/min/1.73 m <sup>2</sup> /year
Matsuchita K et al. <sup>221</sup>	Atherosclerosis Risk In Communities Cohort	13,029	0.47%/year (median)
Kronborg J et al. <sup>222</sup>	Healthy adults from Norway	4441	1.21 ml/min/1.73 m <sup>2</sup> /year (men) 1.19 ml/min/1.73 m <sup>2</sup> /year (women)
<b>With comorbidity</b>			
Lindeman RD <sup>218</sup>	Males with renal/urinary tract disease	118	1.10 ml/min/year (CrCl)
Lindeman RD <sup>218</sup>	Males with hypertension	74	0.92 ml/min/year (CrCl)
Halbesma N et al. <sup>219</sup>	PREVEND cohort – adults with macroalbuminuria (> 300 mg/24 hours)	86	1.71 ml/min/1.73 m <sup>2</sup> /year
Halbesma N et al. <sup>219</sup>	PREVEND cohort - Adults with impaired renal function (5% lowest CrCl/MDRD GFR)	68	0.05 ml/min/1.73 m <sup>2</sup> /year
Imai E et al. <sup>220</sup>	Annual health exam participants in Japan with hypertension	16,722	0.3 to 0.5 ml/min/1.73 m <sup>2</sup> /year
Imai E et al. <sup>220</sup>	Annual health exam participants in Japan with proteinuria (≥1+ dipstick proteinuria)	2054	0.6 to 0.9 ml/min/1.73 m <sup>2</sup> /year
<b>Older adults</b>			
Hemmelgarn B et al. <sup>223</sup>	Males age > 65 with diabetes	490	2.7 ml/min/1.73 m <sup>2</sup> /year
Hemmelgarn B et al. <sup>223</sup>	Males age > 65 without diabetes	2475	1.4 ml/min/1.73 m <sup>2</sup> /year
Hemmelgarn B et al. <sup>223</sup>	Females age > 65 with diabetes	445	2.1 ml/min/1.73 m <sup>2</sup> /year
Hemmelgarn B et al. <sup>223</sup>	Females age > 65 without diabetes	3163	0.8 ml/min/1.73 m <sup>2</sup> /year
Keller C et al. <sup>224</sup>	Cardiovascular Health Study	4128	1.83 ml/min/1.73 m <sup>2</sup> /year (based on cystatin C-based eGFR)

Abbreviations: CrCl, creatinine clearance; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; PREVEND, Prevention of Renal and Vascular End-Stage Disease.

this decline occurs also varies based on the underlying population, cause of CKD, presence of albuminuria/proteinuria, comorbidities and age. The Work Group searched the literature for longitudinal studies that evaluated decline in kidney function. As outlined in Table 20 the study populations included healthy adults, those with comorbidity, as well as a subgroup of adults aged 65 and older.

Data from the PREVEND study, a prospective, population-based cohort study, provides important information on decline in kidney function at the population level.<sup>219</sup> The PREVEND study evaluated 6894 people over a 4-year period and reported loss in eGFR of 2.3 ml/min/1.73 m<sup>2</sup>/4 years in the whole population, 7.2 ml/min/1.73 m<sup>2</sup>/4 years in participants with macroalbuminuria (> 300 mg/24 hours) and 0.2 ml/min/1.73 m<sup>2</sup>/4 year in participants with impaired renal function. The yearly decline in eGFR among a Japanese general population over 10 years was slightly lower at 0.36 ml/min/1.73 m<sup>2</sup>/year.<sup>220</sup> The rate of eGFR decline was approximately two times higher in participants with proteinuria, and about 1.5 times higher among participants with hypertension.<sup>220</sup> Among adults aged 65 and older, progression (median follow-up 2 years) varied by sex and presence of diabetes.<sup>223</sup> In general these studies suggest progression rates of approximately 0.3 to 1 ml/min/1.73 m<sup>2</sup>/year among participants without proteinuria or comorbidity and rates of approximately two to three times higher among participants with proteinuria or comorbidity. The somewhat surprising finding that eGFR had low rates of progression among the group with impaired renal function

at baseline<sup>219</sup> has been shown in other studies<sup>225</sup> and may relate to the statistical phenomenon of regression to the mean. There is also a concern that it is hard to maintain consistent calibration of the SCr assay over time and progression results are highly sensitive to drift in the creatinine assay.

Studies evaluating rate of decline in eGFR among populations with CKD specifically are outlined in Table 21 and typically demonstrate a slightly more rapid rate of decline in this subgroup, thus requiring more frequent assessment of GFR and albuminuria.

Data from the MDRD Study during a mean 2.2 year follow-up showed that the average rate of decline in GFR ranged from 2.3 to 4.5 ml/min/year, depending on the baseline GFR and protein/MAP treatment assignments.<sup>227</sup> Similarly, a more recent study of 4231 patients with GFR categories G3a-G5 (GFR < 60 ml/min/1.73 m<sup>2</sup>) referred to a nephrologist showed a mean decline in GFR of 2.65 ml/min/1.73 m<sup>2</sup>/year,<sup>231</sup> and variability in the rates of decline in this referred cohort.

Note that there have been no studies which evaluate the utility of more or less frequent monitoring in CKD cohorts.

### International Relevance

Frequency of measurements of GFR and albuminuria may vary by country and so are economic resources available to support such testing, and the ability to implement therapeutic strategies to address changes. Nonetheless, given the availability of simple monitoring tools like urine reagent

**Table 21 | Decline in kidney function in CKD populations**

Study	Study population	N	Baseline GFR ml/min/1.73 m <sup>2</sup>	Mean Follow-up years	GFR decline Mean (SD) or (95% CI) ml/min/1.73 m <sup>2</sup> /year
MDRD Study Group <sup>226</sup>	Study A: GFR 25-80 ml/min/1.73 m <sup>2</sup>	28	Mean (SD) 37.1 (8.7)	1.2	3.7 (7.6)
	Study B: GFR 7.5-24 ml/min/1.73 m <sup>2</sup>	63	15.0 (4.5)		4.3 (4.7)
Klahr S et al. <sup>227</sup>	Study 1: GFR 25-55 ml/min/1.73 m <sup>2</sup>		Mean (SD)	2.2 years	
	- Usual protein, usual MAP	145	37.6 (9.0)		4.5 (3.7 – 5.3)
	- Usual protein, low MAP	149	38.2 (8.6)		3.3 (2.5 – 4.1)
	- Low protein, usual MAP	140	38.9 (8.8)		3.3 (2.5 – 4.2)
	- Low protein, low MAP	151	39.7 (9.1)		2.3 (1.5 – 3.0)
	Study 2: GFR 13-45 ml/min/1.73 m <sup>2</sup>				
	- Low protein, usual MAP	62	18.7 (3.1)		4.9 (3.8 – 5.9)
- Low protein, low MAP	67	18.8 (3.3)		3.9 (3.2 – 4.7)	
- Very low protein, usual MAP	61	18.3 (3.7)		3.6 (2.8 – 4.4)	
- Very low protein, low MAP	65	18.4 (3.5)		3.5 (2.6 – 4.5)	
Wright J et al. <sup>228</sup>	African Americans with hypertension and GFR 20-65 ml/min/1.73 m <sup>2</sup>		Mean (SD)	4 years	Mean (SE)
	- Low MAP	380	46.0 (12.9)		2.21 (0.17)
	- Usual MAP	374	45.3 (13.2)		1.95 (0.17)
Eriksen B <sup>229</sup>	GFR categories G3a and G3b (GFR 30-59 ml/min/1.73 m <sup>2</sup> )	3047	Median (IQR) 55.1 (50.8 – 57.9)	Median 3.7 years	Mean 1.03 ml/min/1.73 m <sup>2</sup> /year
Jones C et al. <sup>230</sup>	Nephrology referrals with GFR categories G3a-G5 (GFR < 60 ml/min/1.73 m <sup>2</sup> )	726	Median (IQR) 29 (18-38)	Median (IQR) 2.9 years (1.3 – 4.1)	Median 0.35 ml/min/1.73 m <sup>2</sup> /year
Levin A et al. <sup>231</sup>	Nephrology referrals with GFR categories G3a-G5 (GFR < 60 ml/min/1.73 m <sup>2</sup> )	4231	Median 33 ml/min/1.73 m <sup>2</sup>	Median (IQR) 2.6 years (1.6-3.6)	Mean 2.65 ml/min/1.73 m <sup>2</sup> /year

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; GFR, glomerular filtration rate; IQR, interquartile range; MAP, mean arterial pressure; MDRD, Modification of Diet in Renal Disease; SD, standard deviation; SE, standard error.

strips, consideration may be given to implementation of this assessment in high-risk groups.

### Implications for Clinical Practice and Public Policy

Practitioners must incorporate underlying category of GFR and albuminuria as well as cause of kidney disease and individual patient characteristics in determining the frequency of ongoing assessment. The implications for practice include the incorporation of regular monitoring of both GFR and albuminuria into clinical care for patients with CKD.

There are no immediate implications for public policy of this statement.

### Areas of Controversy, Confusion, or Non-consensus

There are many who would like more definitive guidance on frequency of measurement according to specific categories of risk. However this is not possible at the current time given the lack of evidence to guide such statements and the extreme number of individual circumstances that would mitigate any proposed protocol.

We recommend further research to more accurately define the frequency with which GFR and albuminuria measure-

ments should be performed based on their ability to inform strategies which prevent adverse outcomes (e.g., progression of kidney disease and death).

### Clarification of Issues and Key Points

- Assessment of both GFR and albuminuria should be undertaken to evaluate progression.
- More frequent assessment is required as kidney disease progresses.
- Not all individuals with CKD require close surveillance and monitoring; clinical context remains an important modifier for all recommendations.
- While cause of CKD is an important predictor of progression, it is the values of GFR and albuminuria that are used to assess progression.

### Pediatric Considerations

Currently there is no evidence as to the value of increasing the frequency of assessment of either GFR or proteinuria in children with CKD. Eventually more complete longitudinal data from the CKiD cohort<sup>55</sup> and hence better granularity of individual and group rates of decline in GFR may provide the data required to strengthen proof of this guideline in children.

As described in detail in the *Pediatric Considerations* for Recommendation 1.3.1, there is good observational evidence acknowledging the importance of level of GFR and proteinuria at baseline on predicting rates of progression and it may be that interventional opportunities would exist if closer monitoring and earlier recognition of worsening in these values for the individual were available. Future studies may examine this.

**2.1.2: Recognize that small fluctuations in GFR are common and are not necessarily indicative of progression. (Not Graded)**

**2.1.3: Define CKD progression based on one of more of the following (Not Graded):**

- **Decline in GFR category ( $\geq 90$  [G1], 60-89 [G2], 45-59 [G3a], 30-44 [G3b], 15-29 [G4],  $< 15$  [G5] ml/min/1.73 m<sup>2</sup>). A certain drop in eGFR is defined as a drop in GFR category accompanied by a 25% or greater drop in eGFR from baseline.**
- **Rapid progression is defined as a sustained decline in eGFR of more than 5 ml/min/1.73 m<sup>2</sup>/year.**
- **The confidence in assessing progression is increased with increasing number of serum creatinine measurements and duration of follow-up.**

## RATIONALE

This statement serves to inform clinicians that some consistent definition of progression is required and should be implemented based on an appreciation of baseline values for an individual. There is considerable controversy as to what constitutes normal progression of CKD. The potential for biological and analytical variation associated with use of SCr measurements should be taken into account as they represent reversible fluctuations in GFR and are not necessarily indicative of progression. Further, it is important to recognize that the degree of precision with which progression is able to be estimated is highly dependent upon two factors: the number of SCr measurements used to define progression and the duration of follow-up. Estimating risk of ESRD based on extrapolation of the previous rate of change in GFR required substantial information ( $\geq 4$  measurements over  $\geq 3$  years in most cases) to add to the risk information in the most recent GFR. Further, it should be recognized that some reno-protective treatments (e.g., BP lowering and RAAS antagonists) result in a slower rate of GFR decline long-term but often lower GFR in a stepwise fashion as a result of hemodynamic effects. Even substantial (5-25%) reductions in GFR may be protective, complicating the interpretation of progression in these individuals. Finally, underlying disease activity should be considered when assessing patients for progression of kidney dysfunction.

The importance of determining the rate of decline in kidney function over time is to identify individuals who are

progressing at a more rapid rate than anticipated, which is associated with increased morbidity and mortality. Individuals who are “rapid progressors” should be targeted to slow their progression and associated adverse outcomes. A progressive decline in kidney function is influenced by baseline GFR category and albuminuria category.

## Evidence Base

Unfortunately few studies are available to guide us regarding the optimal definition of “rapid progression.” Such studies require serial follow-up of patients to calculate change in GFR over time, with more frequent measurements and longer duration of follow-up providing more accurate estimates. The Work Group reviewed cohort studies of the general population that have evaluated rapid progression of kidney function (Table 22).

Approaches to define decline in kidney function included absolute rate of loss<sup>232,233,235</sup> as well as percent change.<sup>221,234</sup> Studies consistently demonstrate that a more rapid rate of loss of kidney function was associated with an increased risk of adverse clinical outcomes including death and vascular related events. These studies have been limited however by relatively few patients with GFR levels  $< 60$  ml/min/1.73 m<sup>2</sup>, few measurements of SCr, and relatively short duration of follow-up to obtain accurate estimates of the rate of decline in kidney function. The precision of the estimate of the slope depends on a number of factors including the number of measurements of kidney function, biological variability, measurement error, and duration of follow-up. In general at least three measures of kidney function are required to permit an estimate of slope.<sup>1</sup>

None of these studies assessed the impact of albuminuria on rate of “rapid decline” in kidney function. However as noted in Recommendation 2.1.1, the presence of proteinuria has been associated with a faster rate of kidney function decline compared with people without proteinuria.<sup>236-238</sup> Two of the largest prospective cohort studies have shown an approximate two-fold increase in the rate of decline in GFR in the presence of proteinuria.<sup>219,220</sup> Further evidence regarding the potential adverse effects of albuminuria on outcomes has been reported among patients with diabetes. The AER is one of the best indicators of diabetic nephropathy risk in both type 1 and type 2 diabetes, and patients with microalbuminuria have been reported to have 200 to 400% higher risk for progression to proteinuria than patients with normal albuminuria.<sup>239,240</sup> Long-term follow-up studies have also demonstrated the increased risk of ESRD associated with albuminuria among patients with both type 1 and type 2 diabetes.<sup>241,242</sup>

Given the recognized limitations in defining rapid progression, the Work Group aimed to provide options for determination of progression, based on their clinical utility, and ease of use. One approach included an assessment of change in GFR category, combined with a minimal percent change. A criterion requiring both a change in GFR category (e.g., change from G2 to G3a) and percent change would

Table 22 | Studies evaluating rapid progression (general population studies only)

Study	Study population	N	Categories for decline in kidney function	Outcome	Follow-up	Results (95% CI)
Al-Aly Z et al. <sup>232</sup>	Veterans Affairs - GFR categories G3a and G3b (GFR 30–59 ml/min/1.73 m <sup>2</sup> ) with ≥ 2 eGFR measurements	4171	No decline: eGFR 0 ml/min/yr Mild decline: 0 to 1 Moderate decline: 1 to 4 Severe decline: > 4	Death	5.7 yrs (median)	HR (multivariate): No decline: 1.15 (0.99–1.24) Mild: Reference Moderate: 1.10 (0.98–1.30) Severe: 1.54 (1.30–1.82)
Shlipak et al. <sup>233</sup>	Cardiovascular Health Study - Age 65+ - eGFR measurements at baseline, years 3 and 7	4378	Rapid decline: eGFR > 3 ml/min/1.73 m <sup>2</sup> /yr Not rapid decline: ≤ 3 ml/min/1.73 m <sup>2</sup> /yr	Incident: HF MI Stroke PAD	Subsequent 8 years after enrollment in year 7	HR (multivariate): HF: 1.40 (1.20–1.65) MI: 1.42 (1.14–1.76) Stroke: 1.11 (0.89–1.37) PAD: 1.67 (1.02–2.75)
Matsushita et al. <sup>221</sup>	ARIC study - eGFR measurements at baseline and 3 years	13,029	Quartiles of % annual change in eGFR: Q1 (-52.76 to -5.65) Q2 (-5.65 to -0.47) Q3 (-0.47 to -0.33) Q4 (-0.33 to 42.94)	CHD & all cause mortality	Up to Jan 1, 2006 (Baseline 1987–89)	HR (multivariate): CHD: Q1: 1.30 (1.11–1.52) Q2: 1.16 (1.00–1.35) Q3: Reference Q4: 1.04(0.90–1.22)
Cheng et al. <sup>234</sup>	Taiwanese civil servant & school teachers	7968	% decrease: < 20% decrease ≥ 20% decrease	All cause, CVD, CHD, & stroke mortality	Up to Dec 31, 2005 (Baseline 1989–94)	HR (multivariate): All death: 1.45 (1.13–1.86) CVD death: 2.48 (1.58–3.89) CHD death: 2.14 (1.07–4.29) Stroke death: 2.79 (1.45–5.36)
Rifkin et al. <sup>235</sup>	Cardiovascular Health Study - Age 65+ - eGFR measurements at baseline, years 3 and 7	4380	Rapid decline: eGFR > 3 ml/min/1.73 m <sup>2</sup> /yr Not rapid decline: < 3 ml/min/1.73 m <sup>2</sup> /yr	All cause, & CVD mortality	Mean follow-up 9.9 yrs	HR (multivariate): All death: 1.73 (1.54–1.94) CVD death: 1.70 (1.40–2.06)

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; PAD, peripheral arterial disease; yr, year.



ensure that small changes GFR from 61 to 59 ml/min/1.73 m<sup>2</sup> for example, which represents a change in category but a minimal change in GFR, would not be misinterpreted to represent progression. A change of <25% in a pair of GFR estimates may reflect physiologic variation rather than true progression.

Additional work to inform this definition has been undertaken, using data from the Alberta Kidney Disease Network (AKDN).<sup>243</sup> In this analysis 598,397 adults with at least two out-patient measures of SCr spaced at least 6 months apart were included. Progression was defined as “certain” (rise or drop) if during the median follow-up time of 2.4 years there was a change in GFR category combined with a 25% or greater change in GFR from the baseline measurement (constituting a certain rise or a certain drop). Participants who changed GFR category but did not meet the criterion of 25% change in GFR were categorized as “uncertain” rise or drop. The reference group was comprised of participants who did not change GFR category over the follow-up period. As outlined in Table 23, compared to participants with stable eGFR, those with a certain drop had an almost two-fold increase in the risk of all-cause mortality

(HR 1.89; 95% CI 1.83–1.95)<sup>244</sup> and a five-fold increase in the risk of ESRD (HR 5.11; 95% CI 4.56–5.71).<sup>245</sup> Lesser degree of risk was present for those with an uncertain drop (reflecting a change in category only). It is worth noting that once progression occurs, the last eGFR which has a lower level often contains much of the information about risk of ESRD and extrapolation of progression using information from prior progression and the most recent eGFR is only useful if the information about progression is precise and the patient’s trajectory is linear.

The second approach to define progression takes into account the rate of change in kidney function based on a slope analysis. In this approach the rate of loss is defined by both the absolute rate of change and the percent change, as determined among a cohort of 529,312 adults who had at least 3 outpatient SCr measurements over a four year period (AKDN databases). Two indices of change in eGFR were estimated: the absolute annual rate of change (categorized as: increase, stable and -1, -2, -3, -4, and  $\geq -5$  ml/min/1.73 m<sup>2</sup>/year decline); and the annual percentage change (categorized as: increase, stable, -1 to -2, -3 to -4, -5 to -6, and  $\geq -7$  percent decline/year). The adjusted ESRD risk associated with each category of change in eGFR was estimated, using stable eGFR (no change in eGFR) as the reference. The results were adjusted in two ways: for eGFR and covariates at the time of the first eGFR measurement, and at the time of the last eGFR measurement. As outlined in Table 24, the risk of ESRD increased almost two-fold for every 1 ml/yr decline in eGFR, when adjusted for covariates and eGFR at the time of the first eGFR measurement. The risk remained significant, but was less pronounced, when adjustments were performed at the time of the last eGFR measurement. This suggests that extrapolation of kidney function beyond the last measurement of eGFR is still informative, but identifies a lesser risk. Similar results were obtained when change in eGFR was defined by a percentage.

**Table 23 | CKD progression and risk of all-cause mortality and ESRD using baseline (first) eGFR**

Definition of progression	All-cause mortality HR** (95% CI)	ESRD* HR** (95% CI)
Certain rise	1.51 (1.46–1.56)	0.33 (0.26–0.42)
Uncertain rise	1.12 (1.08–1.16)	0.39 (0.30–0.51)
Stable (reference)	Ref	Ref
Uncertain drop	0.98 (0.95–1.01)	2.13 (1.84–2.47)
Certain drop	1.89 (1.83–1.95)	5.11 (4.56–5.71)

Abbreviations: CI, confidence interval; eGFR, glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio.

Data from Turin et al.<sup>244,245</sup>

\*ESRD defined as requiring renal replacement therapy.

\*\*Adjusted for age, gender, hypertension, diabetes, proteinuria, Charlson comorbidities and baseline (first) eGFR.

**Table 24 | Association between absolute and percentage change in kidney function and risk of ESRD\*, based on adjustment for eGFR at the first and last measurement**

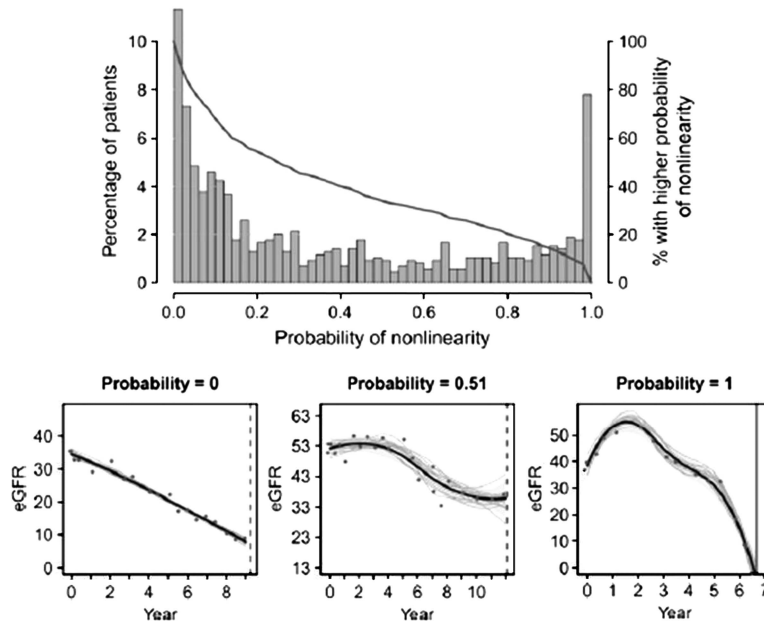
Absolute rate of change (over a median of 3.5 years)	Adjusted for eGFR at first creatinine measurement HR** (95% CI)	Adjusted eGFR at last creatinine measurement HR** (95% CI)
Increasing eGFR	0.64 (0.48–0.86)	1.20 (0.90–1.61)
Stable (0 ml/min/1.73 m <sup>2</sup> /year)	Ref	Ref
-1 ml/min/1.73 m <sup>2</sup> /year	2.05 (1.56–2.69)	1.45 (1.11–1.90)
-2 ml/min/1.73 m <sup>2</sup> /year	2.71 (2.08–3.53)	1.58 (1.21–2.06)
-3 ml/min/1.73 m <sup>2</sup> /year	3.98 (3.06–5.17)	1.63 (1.25–2.13)
-4 ml/min/1.73 m <sup>2</sup> /year	5.82 (4.45–7.61)	1.90 (1.45–2.48)
-5 ml/min/1.73 m <sup>2</sup> /year or more	12.49 (10.04–15.53)	1.70 (1.36–2.12)
Percentage Change:		
Increasing	0.76 (0.55–1.07)	1.11 (0.80 – 1.55)
Stable	Ref	Ref
-1 to -2%/year	1.17 (0.81–1.68)	0.97 (0.67–1.40)
-3 to -4%/year	1.79 (1.25–2.56)	1.19 (0.83–1.71)
-5 to -6%/year	2.26 (1.55–3.29)	1.21 (0.83–1.78)
-7%/year or more	11.30 (8.53–14.97)	2.17 (1.60–2.93)

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio.

Data from the Alberta Kidney Disease Network.

\*ESRD defined as requiring renal replacement therapy.

\*\*Adjusted for age, gender hypertension, diabetes, proteinuria, Charlson comorbidities and eGFR at the first or last measurement.



**Figure 18 | Distribution of the probability of nonlinearity (top) with three example trajectories demonstrating different probabilities of nonlinearity (bottom).** Reprinted from Li L, Astor BC, Lewis J, et al. Longitudinal Progression Trajectory of GFR Among Patients With CKD. *Am J Kidney Dis* 2012; 59: 504-512 with permission from the National Kidney Foundation.<sup>247</sup>; accessed <http://download.journals.elsevierhealth.com/pdfs/journals/0272-6386/PIIS0272638611017896.pdf>

With respect to the impact of changes in albuminuria over time, a study from the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint trial (ONTARGET) investigators showed that a greater than or equal to twofold increase in albuminuria from baseline to 2 years associated with a nearly 50% higher mortality (HR 1.48; CI 1.32-1.66), while a greater than or equal to twofold decrease in albuminuria associated with 15% lower mortality (HR 0.85; CI 0.74-0.98) compared with those with lesser changes in albuminuria, after adjustment for baseline albuminuria, BP, and other potential confounders. Increases in albuminuria also significantly associated with renal outcomes, defined as ESRD or doubling of SCr (HR 1.40; CI 1.11-1.78), while a decrease in albuminuria was associated with a decrease of the combined renal outcome (HR 0.73; CI 0.57-0.95).<sup>246</sup> However, preliminary analysis of cohort studies is limited and suggests that further research is required to more accurately determine the change in albuminuria associated with an increased risk of kidney disease progression.

There is accumulating evidence that the trajectories of GFR decline are non-linear, and may take a number of different courses over time. The longer an individual is followed over time, the more likely they are to experience non-linear change in trajectory.<sup>247,248</sup> The non-linearity of a trajectory may be due to intercurrent illness, changes in medication, intrinsic to the disease process, or any combination of these factors. Li et al.<sup>247</sup> described individual GFR progression trajectories over twelve years of follow-up among participants in the African American Study of Kidney Disease (AASK) (Figure 18). The authors reported that 41.6% of patients exhibited a greater than 90% probability

of having a non-linear trajectory; in 66.1% the probability of non-linearity was > 50%.

#### International Relevance

Studies to date evaluating rapid progression of kidney disease have been limited to North American (White and African American), European, and Asian populations. Given the differences in the prevalence of CKD by ethnic group, there may also be variations in rate of progression by ethnicity, and in particular ethnic groups with high rates of comorbid conditions leading to ESRD such as the Aboriginal population. Thus, the definition of rapid progression may vary according to country or region. However, by using a general definition of progression, which includes change of category of eGFR or albuminuria or both, as well as a numeric change over an established period of time, we believe that the definition of progression can be used in all cohorts.

#### Implications for Clinical Practice and Public Policy

Practitioners should monitor the GFR and albuminuria at regular intervals to identify rates of decline which exceed that normally demonstrated. The rate of GFR decline may be relatively constant over time in an individual; however the rate of GFR decline is highly variable among people and over long periods of observation, within individuals. Thus clinicians are encouraged to evaluate changes in GFR or albuminuria in the context of multiple observations over time, and with attention to clinical events which may have impacted the change. A number of factors influence assessment of rate of progression including frequency and duration of GFR and albuminuria measurements as well as

factors related to the patient (e.g., baseline GFR, comorbidities, age etc.).

There are no implications for public policy at this time.

### Areas of Controversy, Confusion, or Non-consensus

The practical issue in clinical practice and clinical trials is how to define progression (as inferring true deterioration in kidney function) with meaningful thresholds that are easy to understand for the non-nephrologist. While changes in proteinuria may signify change in clinical condition, there are no data yet to suggest that change in proteinuria is itself reliably associated with progression of CKD *per se*. This may be confusing to practitioners, since a change in quantity of proteinuria is an indication for referral.

We recommend research to confirm rates which can be classified as slow, moderate, and rapid progression of kidney disease. The rate to define “rapid progression” may vary depending on the outcome considered, such as kidney failure versus mortality for example. It will be important for researchers to determine methods by which reproducible classification systems for describing rates of progression can be developed. There are increasing data to suggest the non-linearity of progressive disease in many individuals. This makes extrapolation risky and warrants continued assessment of the slope on a regular basis.

### Clarification of Issues and Key Points

Small fluctuations in GFR are common and should not be misinterpreted to represent progressive decline in kidney function. Many factors can cause a small change in GFR including medications, volume status, measurement error, and biological variability. Assessment of progressive decline in GFR needs to take into account the number of measurements considered and time period of assessment.

In pediatrics, information about utility of serial creatinine measurements over periods of time during which growth (and muscle mass increase) is occurring, for the diagnosis of progression or regression, remains problematic.

### Pediatric Considerations

Applying strict GFR criteria in order to develop cutoff values associated with ‘true’ progression in terms of any one individual child is not currently possible. Conceptually the movement from various levels of renal function downward, in particular if that movement is associated with increasing comorbidities or intensity of such, is a reasonable approach.

The most informative data available in children comes from the longitudinal GFR data from CKiD.<sup>72</sup> Examination of the whole cohort reveals an annual decline in GFR of  $-4.2\%$ ; median GFR decline was  $-1.8 \text{ ml/min/1.73 m}^2$  (interquartile range [IQR]  $-6.6$  to  $1.6$ ); this can be expressed as a median absolute decline in GFR of  $-4.3 \text{ ml/min/1.73 m}^2$  (IQR  $-11.9$  to  $1.1$ ) and  $-1.5 \text{ ml/min/1.73 m}^2$  (IQR  $-5.0$  to  $1.8$ ).

Given that the lower IQR in each of the overall cohort and both sub-groups is equal to or exceeds the suggested decline of  $5 \text{ ml/min/1.73 m}^2$  as stated here, we suggest that it is

reasonable to adopt this definition at least for the purpose of classification as it relates to ‘rapid’ progression; note the above values all relate to measured GFR.

Increasing numbers of any given measurement of an event generally allow for greater precision and accuracy. However, the simple repeated measurements of creatinine over time are less likely to be valuable in children than in adults with CKD. Unlike adults with static muscle mass and hence expected stability in creatinine values, or adults with expected declining muscle mass and hence expectations of declining creatinine if renal function has remained stable, pediatric populations have a situation of increasing muscle mass with expectation of increasing creatinine in the otherwise normal child without CKD. In a child with CKD who is growing therefore, and in particular one going through puberty, the simple comparison of creatinine values over time will likely not be sufficient to presume CKD progression or regression has occurred. The two exceptions to this would be a) a series of creatinine measurements demonstrating significant increase over a short period of time wherein there is no demonstrable or expected gain of muscle mass; b) values of creatinine that over time demonstrate an increase to levels above that which is expected of the child’s age and sex based on population normative value for the lab and method of measurement.

**2.1.4: In people with CKD progression, as defined in Recommendation 2.1.3, review current management, examine for reversible causes of progression, and consider referral to a specialist. (Not Graded)**

### RATIONALE

This statement intends to reassure patients and practitioners that not all patients necessarily require referral to specialists, but that this should be considered in the event that the patient or clinician requires further guidance or prognostic information. CKD progression, contextualized for the individual circumstance, does not always require referral, and earlier guidelines may not have been so overt in stating this. Faster or unusual trajectories of progression should alert the patient and physician to assess for potentially reversible causes of progression.

Progressive kidney disease requires the need for more aggressive assessment and treatment, which may include referral to a nephrologist or specialist (if they are not currently being managed by a nephrologist).

### Evidence Base

Decline in GFR may not be constant, with acute decline superimposed on CKD (see Chapter 2.2 for discussion of factors associated with progression of a more chronic nature). The most common risk factors identified for acute decline in GFR for patients with established CKD include: obstruction of the urinary tract; volume depletion; nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 (COX 2) inhibitors; select antimicrobial agents



such as aminoglycosides and amphotericin B; radiocontrast agents; and angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin-receptor blockers (ARBs).<sup>249–252</sup> Readers are also referred to the *KDIGO Clinical Practice Guideline for Acute Kidney Injury*<sup>7</sup> which contains additional relevant details regarding risk factors for rapid progression and management strategies.

Rapid sustained decline in GFR could also be considered an indication for referral once potentially reversible factors as outlined above have been assessed and treated. The principles guiding referral include additional input from a nephrologist into management of CKD and preparation for RRT, such as that which may be required with rapidly declining GFR. The NICE guidelines for CKD also recommend referral for “rapidly declining GFR” although the definition of rapidly declining is not provided.<sup>186</sup> Most studies assessing nephrology referral have focused on early versus late referral, and not considered the impact or implications of nephrology referral in situations associated with rapid decline in GFR.<sup>253</sup> The evidence that such referral will change outcomes is not clear but given that nephrologists often have access to education and specialized services, which are essential for optimal preparation for RRT, referral to a specialist is recommended. Additional discussion of when to consider a referral to a nephrologist can be found in Chapter 5.

### International Relevance

Risk factors for acute deterioration in kidney function may vary slightly by country of origin, although the common categories in general (e.g., medications, volume depletion and urinary tract obstruction) would be relevant irrespective of country. This set of statements serves to ensure that attention to changes in kidney function in those identified with kidney disease is part of the usual care of these individuals.

### Implications for Clinical Practice and Public Policy

Practitioners should be aware of the common risk factors for acute-on-chronic kidney disease resulting in a rapid loss of kidney function. Acute rapid deterioration in kidney function should alert the practitioner to assess for these potentially reversible causes of progression. This assessment would include an evaluation for potential urinary tract obstruction as well as a volume assessment and detailed medication review.

### Areas of Controversy, Confusion, or Non-consensus

Readers are referred to the *KDIGO Clinical Practice Guideline for Acute Kidney Injury*<sup>7</sup> for a detailed discussion of issues related to definition, diagnosis, and treatment of rapid progression of kidney dysfunction, as defined by AKI.

### Clarification of Issues and Key Points

There are no specific numeric values to define “rapid loss” as this varies within and between disease states, individuals, and populations. The key point for practitioners is to serially review individual trajectories of changes in kidney function so as to determine stability or not, identify changes in

previous stable trajectories, and to be aware of the importance of circumstances where AKI changes the course of CKD. Further studies are required to determine the rate of loss of GFR that constitutes rapid loss of kidney function. In children, interpretation of serial changes in SCr requires understanding of normative value ranges and drivers of change in SCr which are different than in adults.

## 2.2: PREDICTORS OF PROGRESSION

**2.2.1: Identify factors associated with CKD progression to inform prognosis. These include cause of CKD, level of GFR, level of albuminuria, age, sex, race/ethnicity, elevated BP, hyperglycemia, dyslipidemia, smoking, obesity, history of cardiovascular disease, ongoing exposure to nephrotoxic agents, and others. (Not Graded)**

### RATIONALE

The rationale for estimating the risk of kidney failure is that it may inform referral, care plans, and other therapeutic strategies, including frequency of monitoring and follow-up. Previous guidelines have not been able to suggest risk equations or relative and absolute risks of specific outcomes but with the data currently available, this is now possible. There are several factors that influence the likelihood and rate of CKD progression including GFR and albuminuria category, the degree of albuminuria, the cause of kidney disease, ongoing exposure to nephrotoxic agents, obesity, hypertension, age, race/ethnicity and laboratory parameters such as Hb (hemoglobin), albumin, calcium, phosphate, and bicarbonate.

As some of these risk factors are modifiable they should be actively identified and, if present, be treated as they may impact long-term outcomes including cardiovascular conditions, QOL, and progression of CKD.

It is not yet clear what the relative weight of each of these factors is in predicting in an individual whether he/she will have progressive CKD.

### Evidence Base

As progression of CKD is defined as either a progressive decrease in GFR or a progressive increase in albuminuria, we should consider separately whether different factors would predict these two components of CKD differently. Given the limited evidence, this will not be discussed separately. It is however clear that a subject with a lower GFR to start with will progress more rapidly to a GFR  $< 15$  ml/min/1.73 m<sup>2</sup>, just as a subject with already elevated albuminuria will progress more rapidly to an ACR  $> 300$  mg/g ( $> 30$  mg/mmol). Similarly, it is well-known that a subject with membranous glomerulopathy is more likely to progress to nephrotic syndrome, while a subject with adult polycystic kidney disease is more likely to progress to ESRD.

Although there are many cross-sectional studies that describe factors associated with a low GFR and factors associated with a high albuminuria, the number of studies evaluating which

factors are associated with progressive decreases in GFR and progressive increases in albuminuria are more limited. In general, it can be argued that most of the above-mentioned factors are associated with a more progressive rise in albuminuria and a more progressive fall in GFR. Most recently, studies have focused on the development of risk scores for identifying progressive decreases in GFR and progressive increases in albuminuria. It has not yet been established which prediction formula could best be used. Some formulas use just simple demographic and clinical measures, while others also include laboratory tests. Some were developed for high-risk populations, such as people with known underlying CVD,<sup>254</sup> with CKD in general,<sup>255</sup> or with specific causes of CKD, such as IgA nephropathy,<sup>256</sup> diabetic nephropathy,<sup>257</sup> or renal artery stenosis.<sup>258</sup> Others developed a risk prediction model in the general population.<sup>259</sup> This latter model included age, race, gender, and in dichotomized version, the presence of anemia, hypertension, diabetes, and CVD history. More recently, two studies used more accurate laboratory parameters in addition to demographic characteristics. The first study was in patients with an eGFR of 15–60 ml/min/1.73 m<sup>2</sup>/year, and included age, gender, eGFR, albuminuria, and serum calcium, phosphate, bicarbonate and albumin.<sup>260</sup> The second study was in subjects from the general population and included age, eGFR, albuminuria, measured levels of BP and C-reactive protein (CRP).<sup>261</sup> The results from these predictive models require validation in future studies but they demonstrate the potential and the capabilities of developing clinically meaningful classification of risk for individual patients. Further research is required to establish whether prediction formulas may differ for different ethnicities.

### International Relevance

Studies describing factors associated with lower GFR and higher ACR have been described from all over the world. In general, there is much overlap between these data. It may be that in different parts of the world the relative weight of each of the factors predicting progressive increases in albuminuria or decreases in GFR may substantially differ.

### Implications for Clinical Practice and Public Policy

It is important to realize that some factors predicting progression of CKD are modifiable. This holds true for lifestyle measures such as cessation of smoking and prevention of obesity. It also subtends to lowering of BP, lowering of albuminuria and prevention of hyperglycemia. A further factor that may be modifiable is the underlying cause of CKD. As various causes may respond to targeted treatment, finding the cause of CKD is the starting point of the work-up of a subject with CKD. If this causal disease is modifiable, for example by immunosuppressive treatment, then such treatment is the first step to consider. Management of

patients with CKD and delay of progression are dealt with in Chapter 3 and more fully in other guidelines (see *KDIGO Clinical Practice Guideline for Glomerulonephritis*<sup>8</sup> and *KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update*.<sup>262</sup>)

### Areas of Controversy, Confusion, or Non-consensus

While there are prediction equations available using combinations of eGFR, albuminuria, cause of CKD, and some or all of the laboratory abnormalities listed, they have not been used in clinical practice to guide therapy as yet. Furthermore, while the associated abnormalities clearly increase in severity with worsening kidney function, normalizing them in some instances has not changed progression to ESRD. The need for prediction equations to take into account changes over time (trajectories) and stability or instability of specific factors has been raised by many. Nonetheless, the ability to determine progression versus stability should be of value for patients and clinicians.

### Clarification of Issues and Key Points

Clinicians should attempt to determine stability or progression of patients with CKD for the purposes of informing care. Further research is required to determine which formula best predicts who will have progressive increases in albuminuria and progressive decreases in GFR. The key components of prediction equations for ESRD may well be different than prediction equations for cardiovascular events or death.

### Pediatric Considerations

A more complete discussion of the evidence in children supporting these factors as potentially related to risk of progression, in addition to the pediatric specific risk of growth/puberty, can be found in the *Pediatric Considerations* for Recommendation 1.3.1.

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