Leonardo Bencivenga, MD, PhD
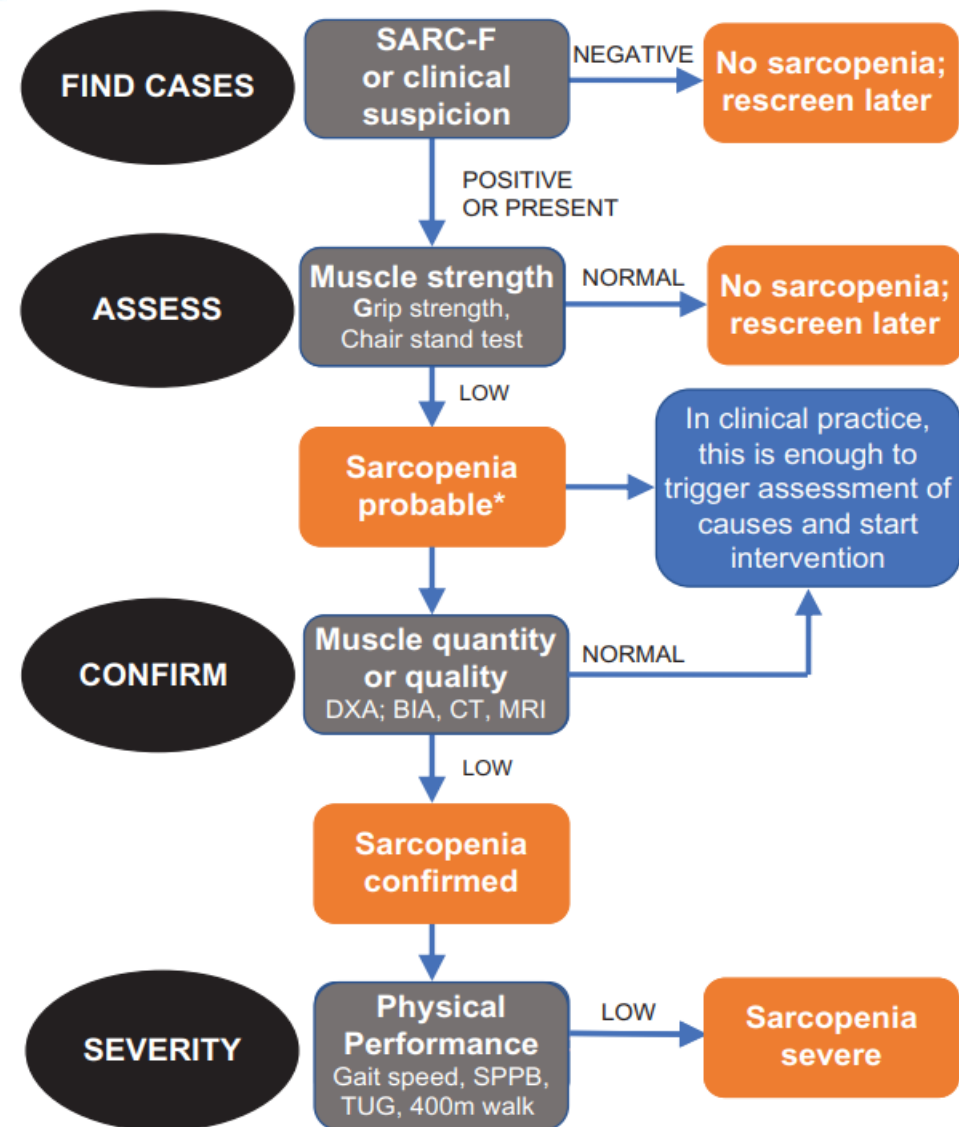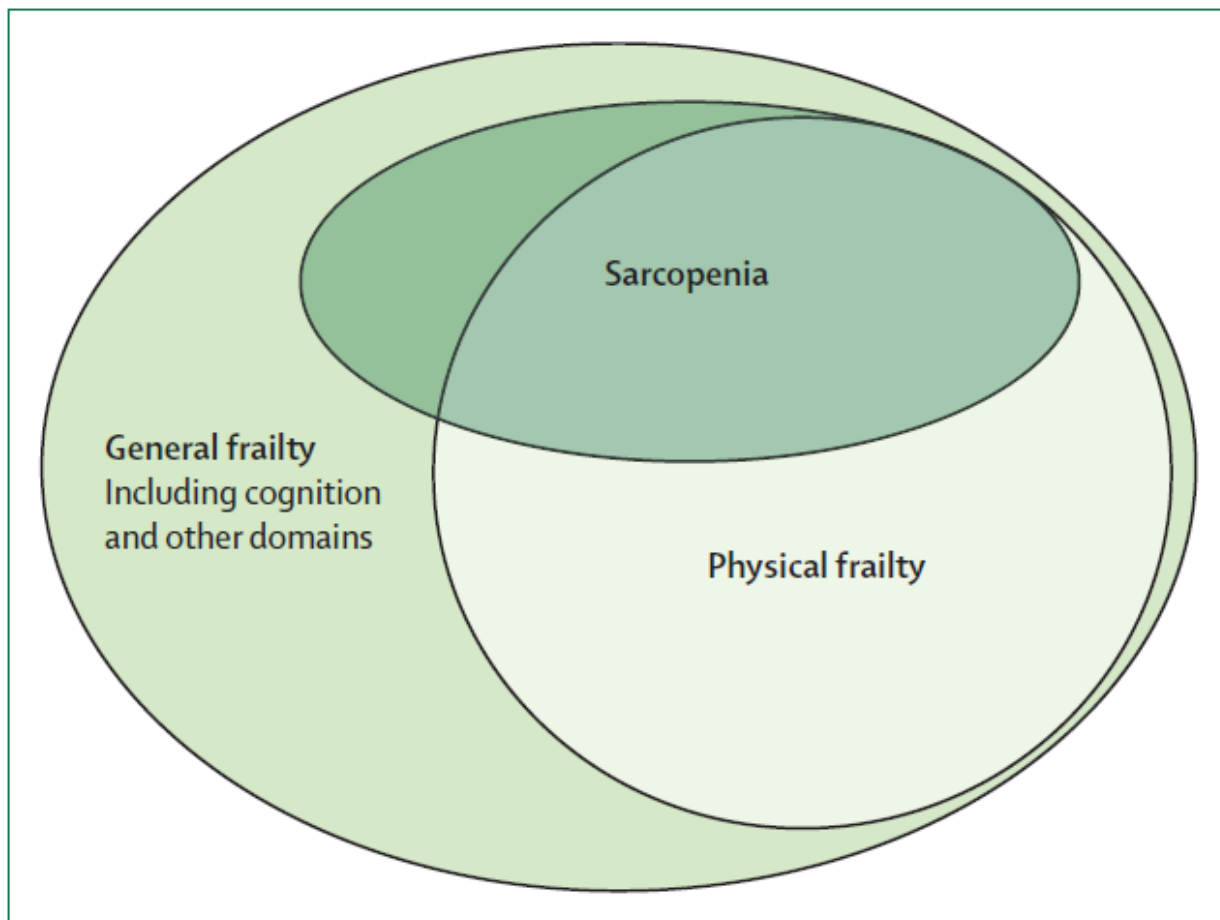*Università degli Studi di Napoli Federico II*

Funzionalità renale nel paziente sarcopenico:
come valutarla? Quali scale?

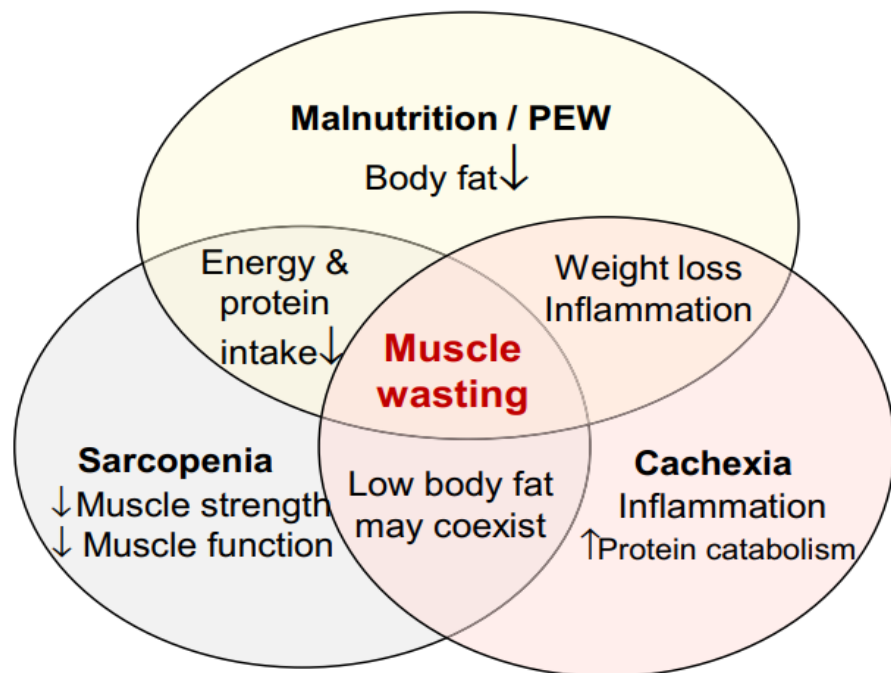# Loss of muscle mass and strenght

Cruz-Jentoft et al. The Lancet, 2019

EWGSOP . Age and Ageing, 2019

Common Etiological Factors

- Inflammation
- Increased protein catabolism
- Insufficient energy and nutrient intake
- Aging
- Comorbidities
- Decreased appetite
- Sedentarism
- Nutrient losses into the dialysate
- Resistance to anabolic hormones

Common Outcome

- Low quality of life
- Increased falls/fractures
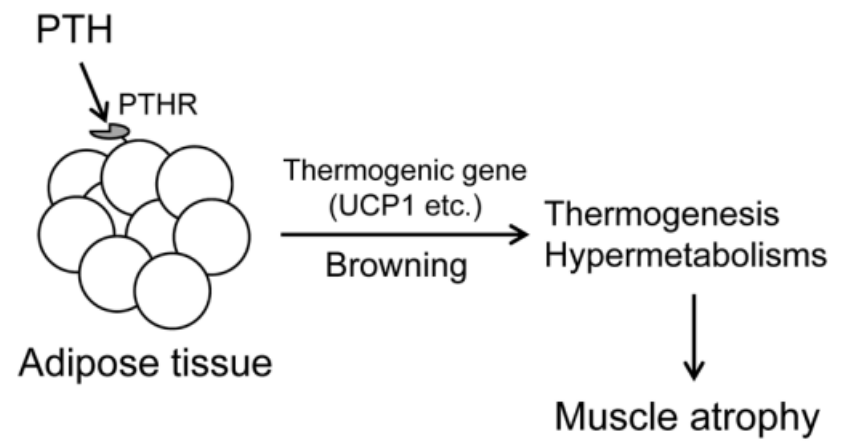- Increased hospitalization rate
- Increased mortality

Sabatino et al. Journal of Nephrology, 2022
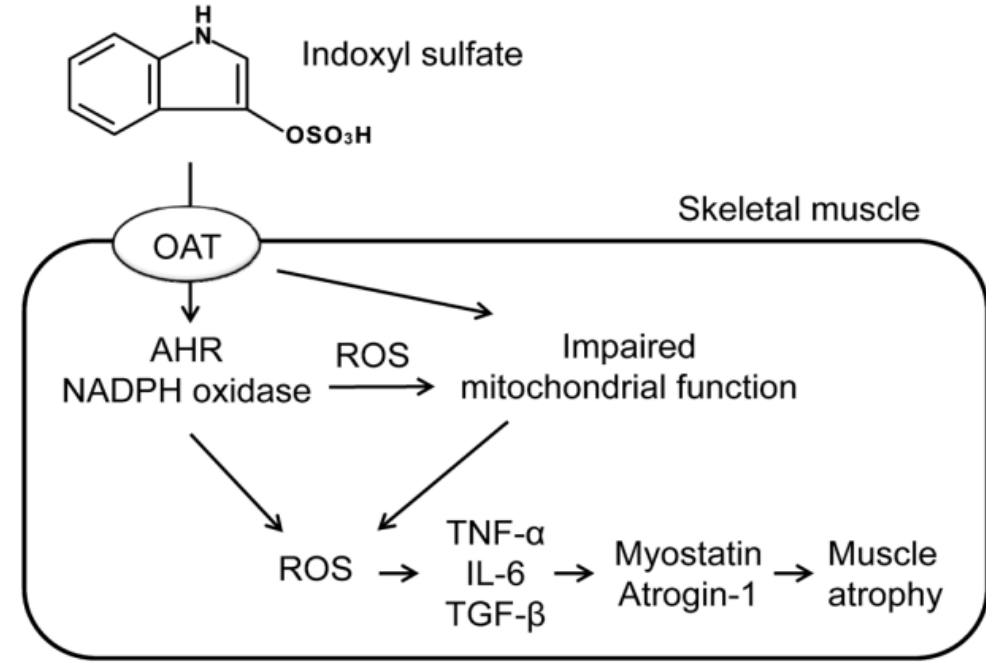
Wei et al. Front. Endocrinology, 2023
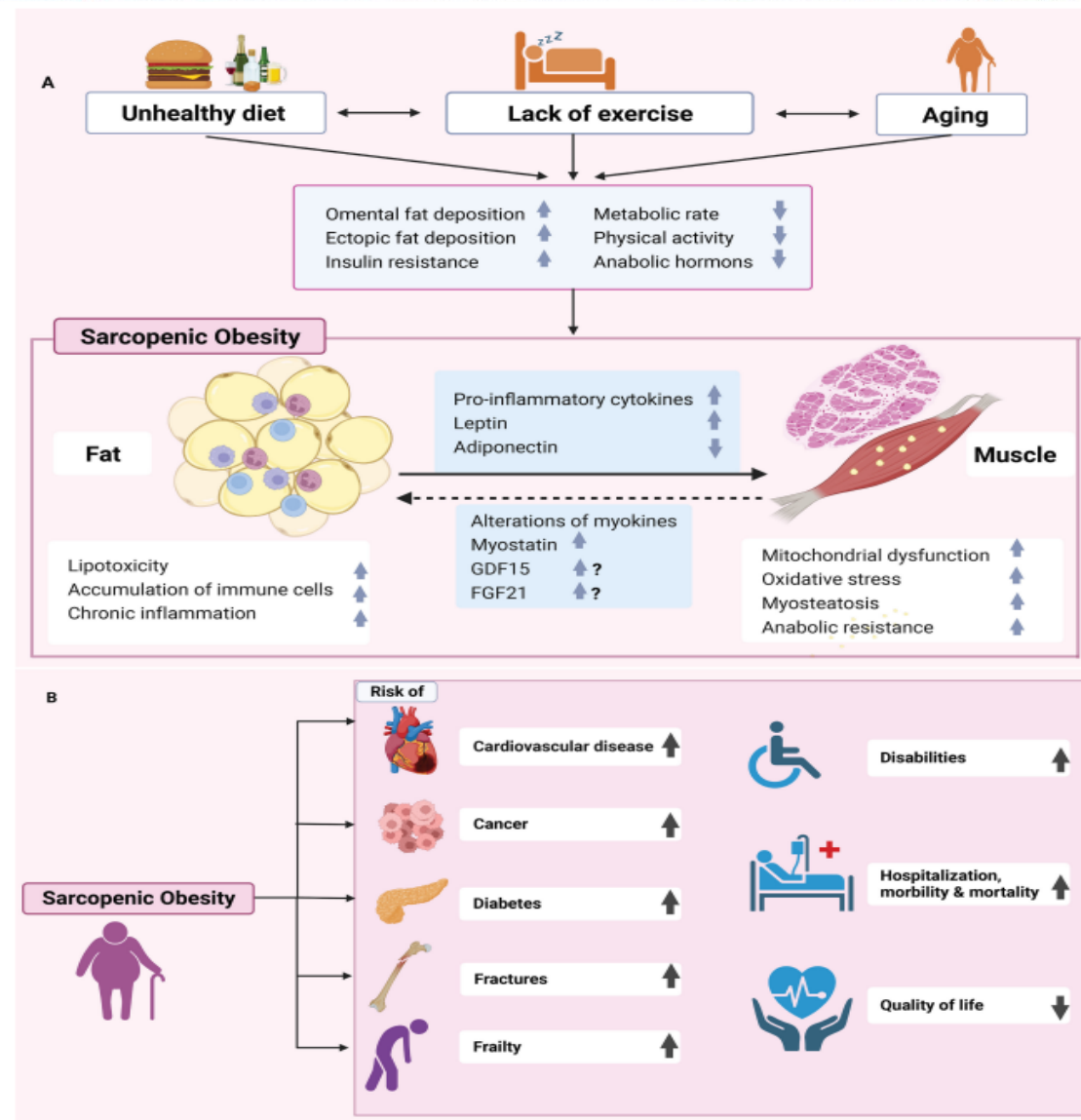
Muscle wasting in CKD

- Cachexia/PEW: 19-50%
- Sarcopenia: 4-42%
- Sarcopenic Obesity: 2-23%

Von Haehling et al. J Cachexia Sarcopenia Muscle, 2016
Chatzipetrou et al. Calcif Tissue Internat., 2022
Tomborelli Bellafronte et al. Med Princ Pract., 2021

	CKD-related sarcopenia	Ageing-related sarcopenia
Muscle protein degradation	Increased	No change
Muscle protein synthesis	Decreased	Decreased
Resting energy expenditure	Increased/unchanged	Unchanged
Inflammation	Increased	Increased or unchanged
Insulin resistance	Present	Present
Body fat	Unchanged, increased or decreased	Normally increased
Muscle fiber change	Atrophy in type I and II fibers	Preferential loss of type II fibers

Sabatino et al. Journal of Nephrology, 2022

Watanabe et al. Biol. Pharm. Bull., 2019

↓ Energy and protein intake

Inflammation

- Gut dysbiosis
- Dialysis membrane biocompatibility
- Obesity
- Ageing

Loss of amino acids and protein into the dialysate in PD;
Loss of amino acids during HD session

Insulin resistance

↓ Regenerative stimulus

↑ Protein degradation

Hormonal

Metabolic

Practice Point 3.3.1.1: Do not restrict protein intake in adults with sarcopenia, cachexia, or conditions that result in undernutrition.

Sedentary lifestyle

↑ Oxidative stress

↓ Energy and protein intake mainly on the HD day

Ageing

Negative protein balance

↓ Appetite Dietary restrictions

| Muscle loss = Muscle wasting | Weakness = Low muscle strengh | Low physical performance | Disability and frailty |

- Oxidative stress
- Changes in hormones, growth factors
- Neural plaque changes, motor neuron loss
- Satellite cell dysfunction
- Mitochondrial dysfunction
- Sarcopenia
- Apoptosis
- Microvascular changes
- Inactivity, disuse
- Inflammation
- Imbalance in protein metabolism

Sabatino et al. Journal of Nephrology, 2022

Cruz-Jentoft et al. The Lancet, 2019

Child/adolescent
• Growth
• Nutrition
• Weight/BSA-based drug dosing
• Neurocognitive development
• Supporting education
• Transition to adult care
• Holistic approach to care for the whole family unit

Sex
• Menopause
• Contraception
• Differential drug effects
• Differing epidemiology of risk factors and complications

Older adults
• Multidimensionality of chronic conditions/multimorbidity
• Frailty (including sarcopenia)
• Cognitive function
• Polypharmacy
• Prioritization
• End-of-life care

Pregnancy/lactation
• Drug pharmacokinetics and pharmacodynamics
• Drug teratogenicity
• Risk of CKD progression
• Increased risk of pregnancy complications, preterm birth and small for gestational age babies
• Fertility

Gender
• Gender identity
• Gender roles
• Gender relations
• Institutionalized gender

9,1%   28%

KDIGO, 2023 (under review)

Markers of kidney damage (one or more)	Albuminuria (AER ≥30 mg/g (≥3 mg/mmol)) Urine sediment abnormalities Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR <60 ml/min per 1.73 m^2 (GFR categories G3a-G5)

Table 1. Criteria for chronic kidney disease (CKD) (either of the following present for >3 months).
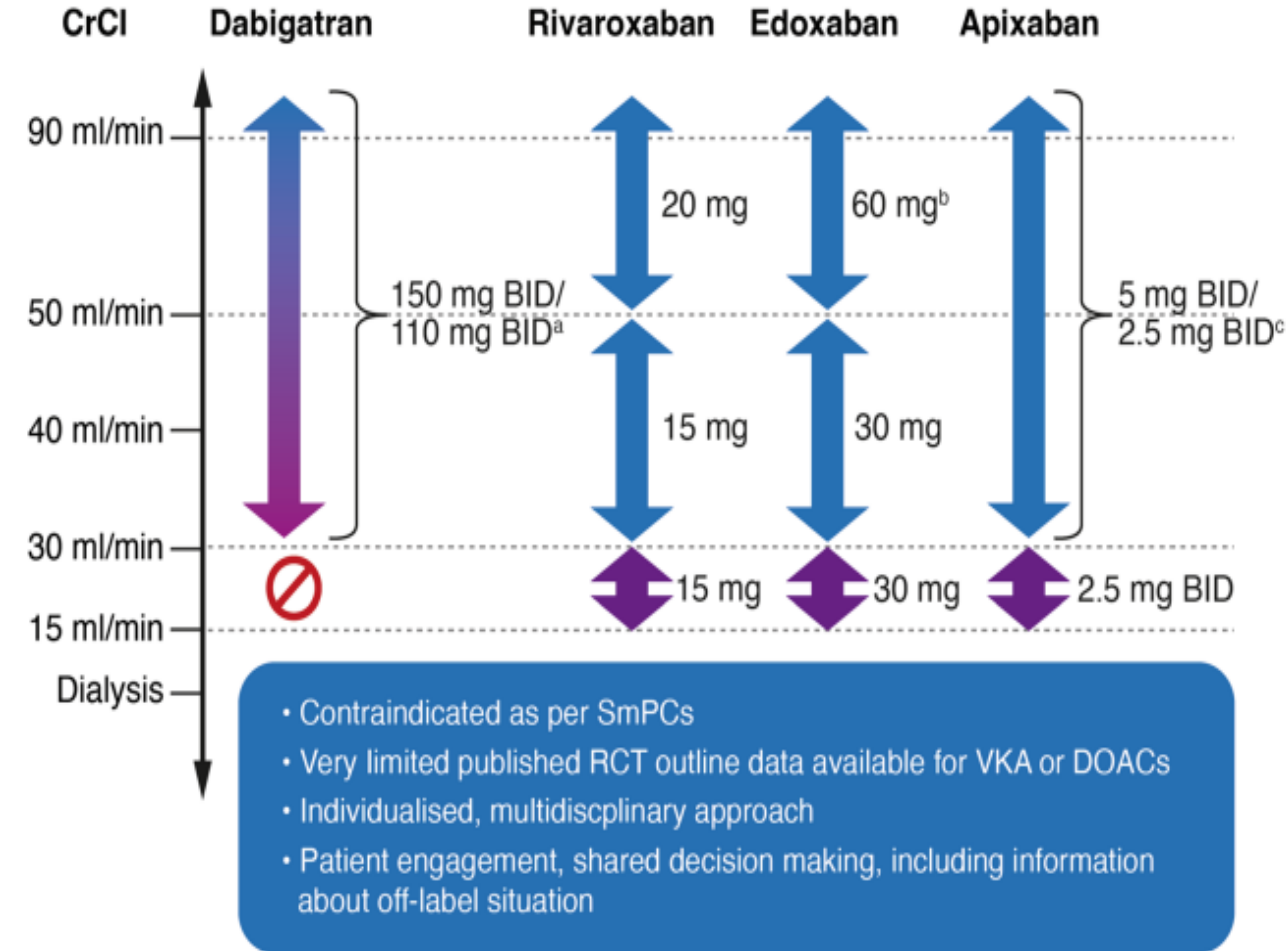AER, albumin excretion rate; GFR, glomerular filtration rate

↓ 0,8-1 mL/min/year after age 30 years

GFR category	GFR (ml/min per 1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60-89	Mildly decreased*
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

Table 3. Glomerular filtration rate (GFR) categories in chronic kidney disease (CKD). *Relative to young adult level. In the absence of evidence of kidney damage, neither G1 nor G2 fulfill the criteria for CKD.
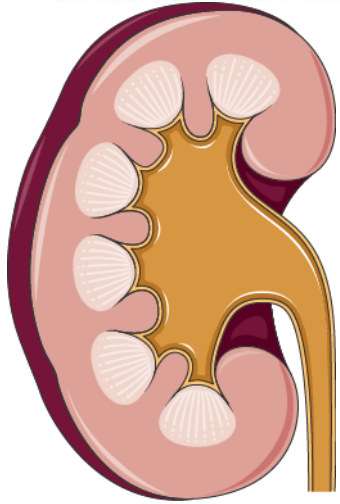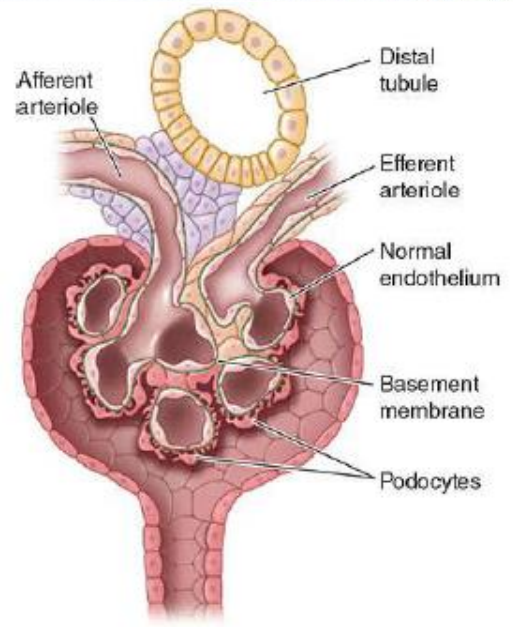
KIDNEY DISEASE · IMPROVING GLOBAL OUTCOMES · KDIGO®

Left figure:

CrCl — Dabigatran — Rivaroxaban — Edoxaban — Apixaban

- 90 ml/min
- 50 ml/min
- 40 ml/min
- 30 ml/min
- 15 ml/min
- Dialysis

Dabigatran: 150 mg BID / 110 mg BID[a]
Rivaroxaban: 20 mg
Edoxaban: 60 mg[b]
Apixaban: 5 mg BID / 2.5 mg BID[c]

Rivaroxaban: 15 mg
Edoxaban: 30 mg

Rivaroxaban: 15 mg
Edoxaban: 30 mg
Apixaban: 2.5 mg BID

- Contraindicated as per SmPCs
- Very limited published RCT outline data available for VKA or DOACs
- Individualised, multidiscplinary approach
- Patient engagement, shared decision making, including information about off-label situation

Right table:

Medication	> 50mL/min	30-50mL/min	10-30mL/min	< 10 mL/min (non-dialysis)	HD[1]	CAPD[2]	Comments
Amoxicillin	250-500mg TID	250-500mg TID	250-500mg BID	250-500mg daily to BID	250-500mg BID[3]	250-500mg BID	• Higher single doses (eg. 2 g po 1 hr prior to dental surgery) are fine for all CKD stages
Amoxicillin/ Clavulanate (Clavulin®)	250-500 mg TID or 875 mg BID	250-500 mg TID or 875 mg BID	250-500 mg BID	250-500mg daily to BID	250-500 mg BID	250-500 mg BID	
Azithromycin	250-500mg daily	No dosage adjustments					
Cefixime	400mg daily	400mg daily	200 mg daily	200 mg daily	200 mg daily	200 mg daily	• Give post HD on dialysis days
Cefuroxime axetil	250-500mg BID to TID	250-500mg BID to TID	250-500 mg BID	250-500 mg BID	250-500 mg BID	250-500 mg BID	
Cephalexin	250-500mg QID	250-500mg TID to QID	250-500mg BID to TID	250-500mg daily to BID	250-500mg BID	250-500mg BID	
Ciprofloxacin	250-750mg BID	250-750mg BID	500-750mg daily	250-500mg daily	500-750mg daily	500-750mg daily	• May prolong QTc • Space doses apart from Ca++, Iron and Al+++ by at least 3 hours • Give post HD on dialysis days
Clarithromycin/ Clarithromycin XL	250-500 mg BID (1g daily XL)	250-500 mg BID (1g daily XL)	500mg daily	250-500mg daily	250-500mg daily	250-500mg daily	• May prolong QTc • Use regular release format with eGFR < 30 mL/min (not XL)
Clindamycin	300 - 600mg TID	No dosage adjustments					
Cloxacillin	500 - 1000mg QID	No dosage adjustments					

Hahn et al. Advances in Therapy, 2023
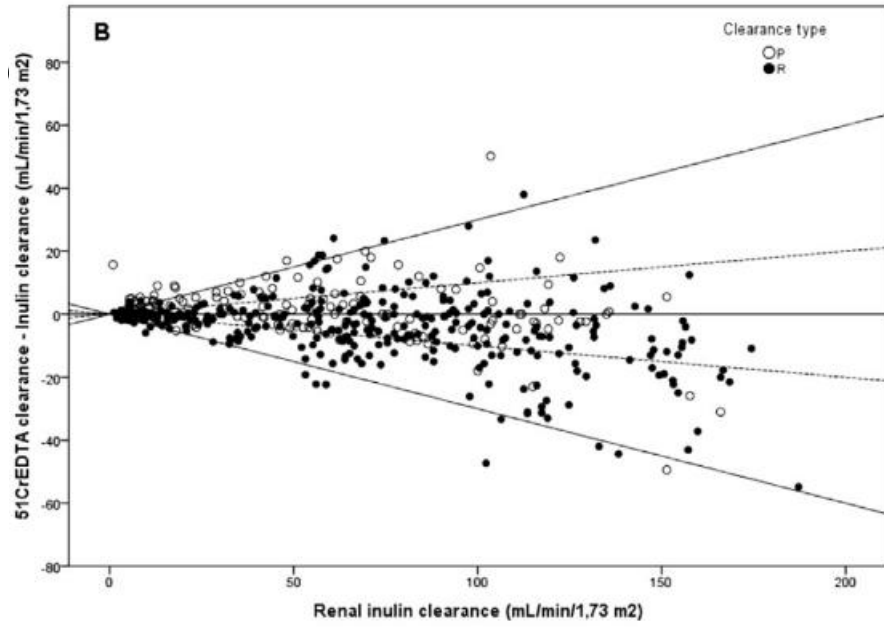
BCPRA Pharmacy and Formulary Committee, 2017

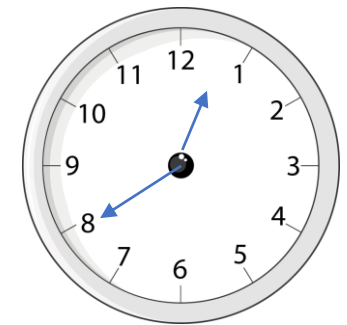True GFR cannot be measured directly in humans

$$CL_X = \frac{U_X \times \dot{V}}{P_X}$$

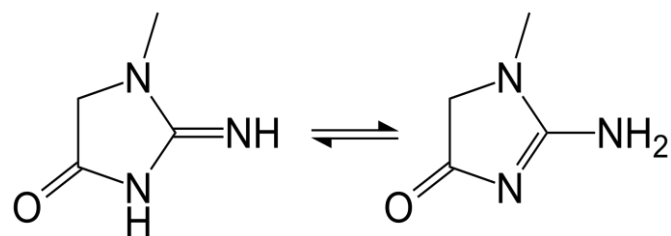Inulin

Multiple blood samples
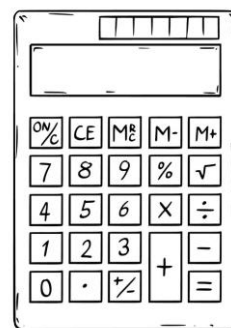Continuous intravenous infusion

51Cr-EDTA
Iothalamate
Iohexol

Timed urine collection

Soveri et al. Am J Kidney Dis., 2014

eGFR

Advise adults not to eat any meat in the 12 hours before having a blood test for eGFRcreatinine. Avoid delaying the despatch of blood samples to ensure that they are received and processed by the laboratory within 12 hours of venepuncture. [2008]

We recommend using eGFRcr-cys in clinical situations when eGFRcr is less accurate and GFR affects clinical decision-making
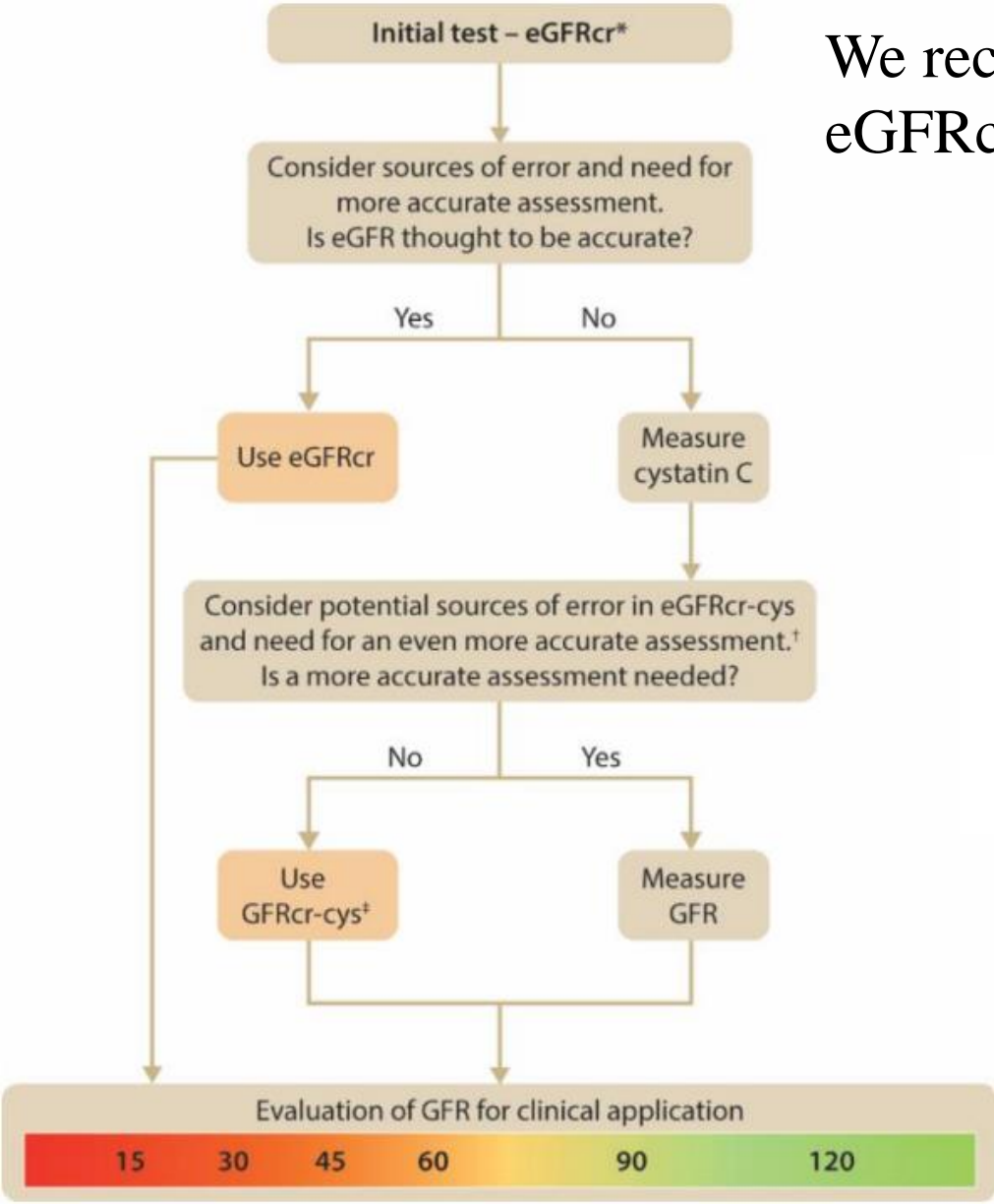

Specific clinical condition	Cause of decreased accuracy	Comments on GFR evaluation
Class III obesity (BMI>40 kg/m²)†	nonGFR determinants of SCr and SCys	eGFRcr-cys demonstrated to be most accurate
Muscle wasting diseases	nonGFR determinants of SCr	Suggest eGFRcys in those without other comorbid illness. eGFRcr-cys in those with other comorbid illness

Rationale for using cystatin C containing equations for CKD staging

The rationale for using cystatin C versus SCr, or a combination of both, in eGFR equations is that creatinine, which is directly linked to muscle mass, may be misleading at extremes of body habitus, or in specific conditions (spinal cord injuries, sarcopenia), and that cystatin C is impacted by different variables (steroid use, thyroid disease, cancer). Thus, since neither is a perfect marker to use for estimating clearance, the combination of the 2 compounds gives more accurate estimates of GFR when compared to measured values.

Very low levels of SCr often represent poor health status, such as frailty or sarcopenia, which limit the production of SCr. This biological feature of SCr (i.e., relation to muscle mass) has limited its prognostic utility, and results in reducing the risk associations for eGFRcr 45-60 ml/min per 1.73 m² and elevating risks for eGFRcr >110 ml/min per 1.73 m². These limitations are not observed when risk is estimated using eGFRcr-cys or cystatin C-based eGFR (eGFRcys) (Figure 6).
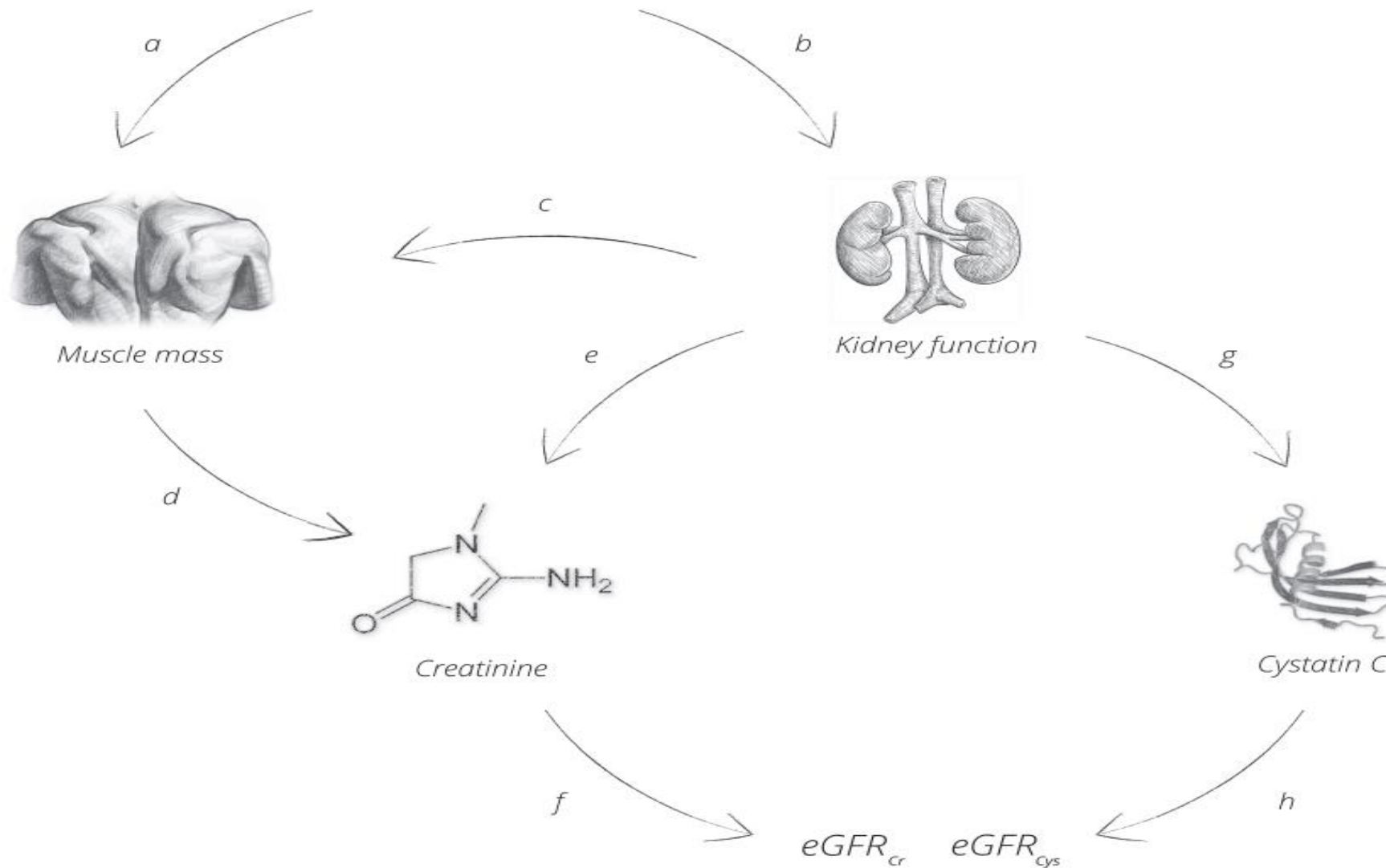
KDIGO, 2023 (under review)

Groothof et al. J Cachexia Sarcopenia Muscle., 2022

	Author - year	Country - subjects	N, Age (mean ± SD), Gender (%), BMI (mean ± SD)	Kidney function	Description
U/C	de Mutsert et al. - 2009[7]	The Netherlands - End-stage renal disease patients	1601, 59 ± 15, Men: 978 (61.1), Women: 623 (38.9), BMI 24.7 ± 4.1	Severe PEW (81) versus Moderate PEW (367) versus Normal nutrition (1153); rGFR 2.3 ± 2.2 versus 3.2 ± 2.9 versus 4.1 ± 3.0, $P < 0.001$	Severe PEW at baseline, as assessed with the 7-point SGA, was independently associated with a 2-fold increased mortality risk in 7 years of follow-up. In time-dependent analyses, this association was even stronger, 5-fold, indicating that PEW was associated with a remarkably high risk of short-term mortality.
nd	von Haehling et al. - 2016[3]	Europe, USA, Japan - Estimates based on data	No detailed data	Estimates for the prevalence of cachexia in CKD; Prevalence in population 0.1%, Patients at risk 50%, Prevalence in patients at risk 50%, Patients in Europe 190 000, the USA 80 000, Japan 30 000, 1-year mortality 20%	Given the high prevalence and very high mortality associated with cachexia, advances are urgently needed for patients worldwide.
C	Dai et al. - 2017[8]	Sweden - CKD patients	1031	Well-nourished (711) versus Malnourished (according to SGA, PEW_{SGA}, 320); Creatinine-based eGFR 6.1 (0–68.8) versus 5.6 (0–11.4), $P < 0.001$, Cr (µmol/L) 664 (95–1017) versus 627 (403–917), $P = 0.79$	SGA, a valid assessor of nutritional status, is an independent predictor of all-cause mortality both in CKD non-dialysis and dialysis patients that outperforms non-composite nutritional markers as prognosticator.
C	Hyun et al. - 2017[9]	Korea - Predialysis CKD patients	1834, 53.9 ± 12.2, Men: 1108 (60.4), Women: 726 (39.6)	Creatinine-based eGFR Stage 1 (≥90) (231) versus Stage 2 (60–89) (339) versus Stage 3a (45–59) (327) versus Stage 3b (30–44) (405) versus Stage 4 (15–29) (418) versus Stage 5 (<15) (114); PEW 2.2 versus 4.4 versus 8.3 versus 6.2 versus 15.6 versus 24.6, $P < 0.001$	PEW increases with advanced CKD stage. PEW is independently associated with renal function, low total CO_2, low physical activity, comorbid diabetes, and increased hs-CRP in adults with predialysis CKD.
C	Pérez-Torres et al. - 2017[10]	Spain - Patients attending the advanced CKD outpatient clinic	186, Men: 101 (54.3), Women: 85 (45.7) BMI 27.6 ± 5.1	Total versus Men versus Women; Cr 3.7 ± 1.1 versus 3.8 ± 1.3 versus 3.6 ± 0.9, Not significant, Cr clearance 17 ± 4 versus 18 ± 4 versus 17 ± 4, Not significant PEW (%) 56 (30) versus 23 (23) versus 33 (39), $P < 0.001$	Malnutrition was identified in Spanish advanced CKD patients measured by different tools. We consider it appropriate to adapt new diagnostic elements to PEW criteria.
nd	Koppe et al. - 2019[6]	Searched the publication in MEDLINE from February 2008 to September 2018	No detailed data	PEW prevalence increases when renal function declines, that is, from <2% in CKD stages 1–2 to 11–54% in CKD stages 3–5	The recent understanding of cachexia physiopathology during CKD progression suggests that PEW and cachexia are closely related and that PEW corresponds the initial state of a continuous process that leads to cachexia, implicating the same metabolic pathways as in other chronic diseases.
U/nd	McKeavency et al. - 2021[4]	United Kingdom - Adult haemodialysis patients	106, 67.62 ± 13.18, Men: 76 (71.7), Women: 30 (28.3), BMI, median (IQR) 28.0 (23.0–31.3)	Cachectic versus Not cachectic; URR, median (IQR) 0.75 (0.72–0.81) versus 0.73 (0.68–0.77), $P < 0.001$, eGFR, median (IQR) 6.8 (5.5–6.8) versus 8.6 (6.85–10.7), Not significant	This is the first study to apply the defined characteristics of cachexia to a representative sample of patients receiving HD. Further, more extensive studies are required to establish a phenotype of cachexia in advanced CKD.

BMI, body mass index; CKD, chronic kidney disease; Cr, creatinine; eGFR, estimated glomerular filtration rate; HD, haemodialysis; hs-CRP, high sensitivity C-reactive protein; IQR, inter-quartile range; PEW, protein-energy wasting; rGFR, residual glomerular filtration rate corrected for body surface area; SD, standard deviation; SGA, subjective global assessment; URR, urea reduction ratio.

Author, year	Country - subjects	N, Age (mean ± SD), Gender (%), BMI (mean ± SD)	Kidney function	Description
U/C Isoyama et al. - 2014[12]	Sweden - Incident dialysis patients	330, 53 ± 13, Men: 203 (61.5), Women: 127 (38.5)	Muscle mass; Appropriate versus Low; PEW 19 versus 43, $P < 0.001$, Serum creatinine 8.1 (5.3–11.7) versus 6.9 (4.2–10.4), $P < 0.001$ GFR calculated by renal urea and creatinine clearances 7 (4–9) versus 6 (4–10), $P = 0.80$ Muscle strength; Appropriate versus Low; PEW 16 versus 52, $P < 0.001$, Serum creatinine 8.3 (5.6–11.7) versus 6.46 (4.17–10.0), $P < 0.001$, GFR calculated by renal urea and creatinine clearances 7 (5–9) versus 6 (4–9), $P = 0.27$	Low muscle strength was more strongly associated with aging, protein-energy wasting, physical inactivity, inflammation, and mortality than low muscle mass.
C Hyun et al. - 2016[14]	Korea - General population	10 734, 49.5 ± 16.1, Men: 4691(43.7), Women: 6043 (56.3), BMI 22.21 ± 1.72	Normal (6325) versus Sarcopenia alone (1535) versus Obesity alone (16.0) versus Sarcopenic obesity (1152); Creatinine-based eGFR 97.0 ± 15.5 versus 98.7 ± 17.7 versus 94.7 ± 16.6 versus 94.1 ± 19.4, $P < 0.001$, CKD (%) 2.3 versus 2.9 versus 3.4 versus 6.5, $P < 0.001$	Sarcopenic obesity was associated with CKD and high eGFR. Sarcopenia alone was associated with high eGFR. BMI, which was used as an operational definition for classifying both obesity and underweight, has long been recognized as an important indicator of nutrition and chronic debilitating disease.
C Yang et al. - 2016[13]	China - Type 2 diabetes patients	1555	Without diabetes; Non-sarcopenia (420) versus Sarcopenia (342); Creatinine-based eGFR (mL/min) 111.49 ± 18.47 versus 100.95 ± 17.61, $P < 0.001$, Cr (μmol/L) 64.98 ± 12.86 versus 71.35 ± 15.15, $P < 0.001$ Diabetes; Non-sarcopenia (585) versus Sarcopenia (208), Creatinine-based eGFR (mL/min) 122.75 ± 29.20 versus 107.42 ± 30.95, $P < 0.001$ Cr (μmol/L) 61.57 ± 15.41 versus 77.31 ± 62.17, $P < 0.001$	Sarcopenia is associated with declining renal function, which in turn leads to lower eGFR and higher UACR in the non-diabetic population and type 2 diabetics.
C Fukuda et al. - 2020[15]	Japan - Type 2 diabetes patients	745, 64.6 ± 11.8, Men: 399 (53.6), Women: 346 (46.4)	Non-sarcopenic low A/G (205) versus Sarcopenic low A/G (168) versus Non-sarcopenic high A/G (287) versus Sarcopenic obesity (85); Creatinine-based eGFR 71.5 ± 20.6 versus 76.5 ± 29.3 versus 67.9 ± 22.1 versus 68.9 ± 24.6, $P = 0.003$, Annual decline rate in creatinine-based eGFR, −1.3 ± 3.1 versus −2.4 ± 4.0 versus −1.9 ± 3.7 versus −4.0 ± 4.8, $P < 0.001$	Sarcopenic obesity evaluated through a whole-body DEXA scan is significantly associated with decline in renal function in Japanese people with type 2 diabetes, even after adjustment for established risk factors of decline in renal function including eGFR, ACR and systolic blood pressure.
C Moreno-Gonzalez et al. - 2020[16]	Austria, Germany, Israel, Italy, the Netherlands, Poland, Spain - Community-dwelling older adults	1420, 79.5 (77.0–83.0), Men: 616 (43.4%), Women: 804 (56.6%), BMI 27.0 (24.4–30.0)	Sarcopenia was more prevalent in participants with more advanced stages of CKD according to BIS (9.6% in stages 1 and 2 and 13.9% in stages 3a, 3b and 4, $P = 0.042$), and also	Participants within poorer eGFR categories, irrespective of the equation used for its calculation, have a higher prevalence of sarcopenia and are more often severely sarcopenic.

(Continues)

Author, year	Country - subjects	N, Age (mean ± SD), Gender (%), BMI (mean ± SD)	Kidney function	Description
C/Cys Kusunoki et al. - 2021[20]	Japan - Healthy community-dwelling elderly individuals	949, 73.2 ± 5.9, Men: 302 (31.8), Women: 647 (68.2), BMI 22.7 ± 2.9	according to CKD-EPI (9.8% versus. 14.2%, $P = 0.042$). Men: Normal versus Sarcopenia, Cre 0.87 ± 0.17 versus 0.90 ± 0.19, $P = 0.374$, eGFRcre 68.4 ± 13.6 versus 65.0 ± 13.2, $P = 0.230$, eGFRcys 72.5 ± 15.5 versus 62.7 ± 16.9, $P = 0.003$, eGFRcys/eGFRcre 1.07 ± 0.17 versus 0.96 ± 0.14, $P = 0.002$ Women: Normal versus Sarcopenia, Cre 0.65 ± 0.13 versus 0.66 ± 0.14, $P = 0.670$, eGFRcre 69.5 ± 13.8 versus 67.6 ± 14.1, $P = 0.339$, eGFRcys 75.8 ± 15.1 versus 69.1 ± 17.1, $P < 0.001$, eGFRcys/eGFRcre 1.10 ± 0.17 versus 1.02 ± 0.14, $P < 0.001$	Low eGFRcys (CKDcys) was more frequent in participants with sarcopenia than in normal participants. In the multivariate logistic regression analysis adjusted for complications (hypertension, diabetes, dyslipidaemia, liver disease, and heart disease), CKDcys was clearly related to sarcopenia based on AWGS 2019 while CKDcre was not.
C Soraci et al. - 2021[17]	Italy - Elderly patients admitted to hospitals	504, Survived; 338, 79.6 ± 6.59, Men: 155 (45.9%), Women: 183 (54.1%), BMI 27.0 ± 5.02 Died; 166, 82.8 ± 6.23, Men: 86 (51.8%), Women: 80 (48.2%), BMI 25.9 ± 5.14	Survived versus Died; Creatinine-based eGFR 48.4 ± 15.3 versus 42.5 ± 17.2, $P < 0.001$ Sarcopenia 51 (15.1%) versus 57 (34.3%), $P < 0.001$	Our study demonstrates that eGFR, anaemia, sarcopenia, cognitive and physical impairment variably interact in predicting long-term survival of older patients discharged from acute care hospital.
Cys Wilkinson et al. - 2021[21]	United Kingdom - Individuals with chronic kidney disease	8767, 62.8 ± 6.8, Men: 4033 (46.0), Women: 4734 (54.0), BMI 29.3 ± 5.2	Sarcopenic versus Non-sarcopenic; Cystatin C 1.5 ± 0.5 versus 1.3 ± 0.4, $P < 0.001$	We found a probable sarcopenia prevalence of 9.7% among participants with reduced kidney function defined as an eGFR < 60 mL/min/1.73 m^2; this prevalence was approximately double that seen in those without CKD. The presence of sarcopenia increases the risk of mortality and end-stage renal disease.
C Yoshimura et al. - 2021[22]	Japan - Stroke patients	813, 73.5 ± 11.8, Men: 423 (52), Women: 390 (48)	Creatinine-based eGFR ≥90 (117) versus 60–89 (363) versus 30–59 (302) versus 15–29 (28) versus <15 (3); Sarcopenia (%) 60 (51.3) versus 173 (47.7) versus 144 (47.7) versus 8 (28.6) versus 0 (0.0), $P = 0.116$	Elevated creatinine-based eGFR is associated with sarcopenia, dysphagia, and adverse rehabilitation outcomes after stroke. Our findings highlight the limitations of assessing renal function using creatinine levels in patients with sarcopenia; therefore, future studies using cystatin C are needed to validate our findings.

A/G, android to gynoid fat ration; ACR, urinary albumin-to-creatinine ratio; BIS, Berlin initiative study; BMI, body mass index; CKD, chronic kidney disease; CKD-EPI, chronic kidney disease epidemiological collaboration; Cr, creatinine; Cre, creatinine; cys, cystatin C; CysC, cystatin C; DEXA, dual-energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; EWGSOP, the European working group on sarcopenia in older people; FNIH, the Foundation of the National Institutes of Health; GFR, glomerular filtration rate; PEW, protein-energy wasting; SD, standard deviation; UACR, urine albumin: creatinine ratio.
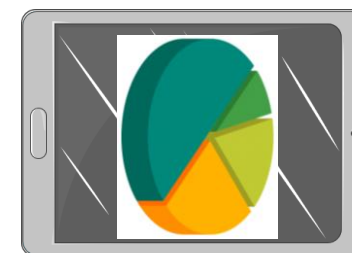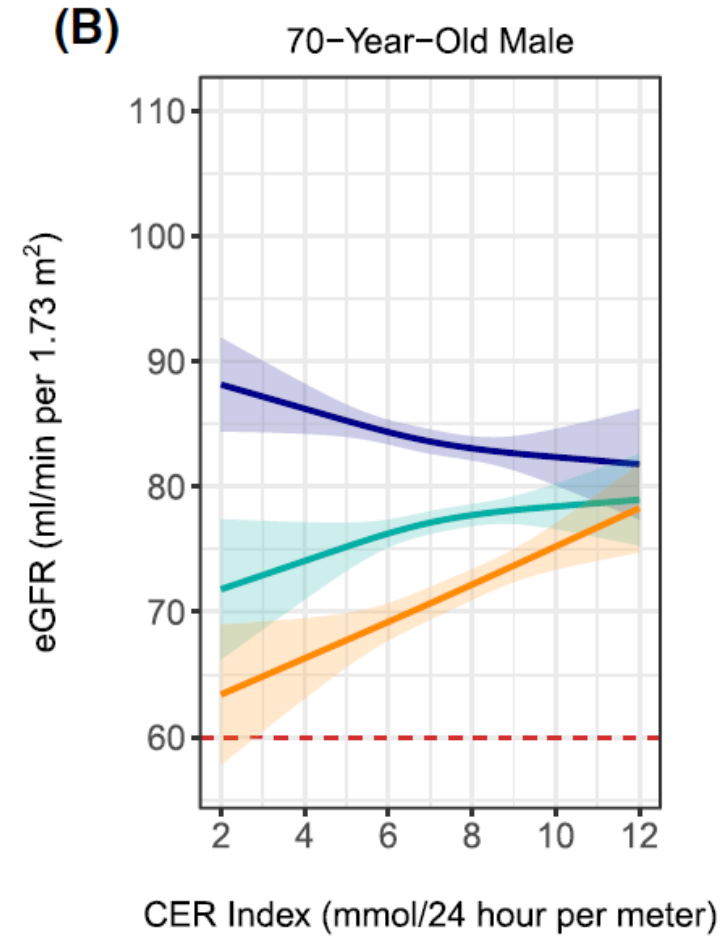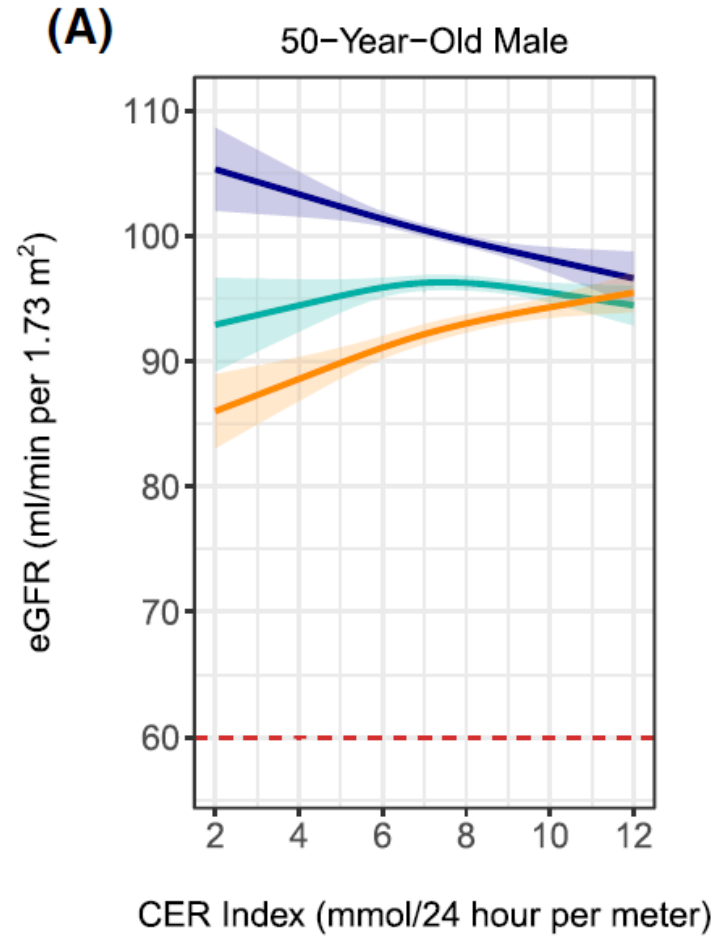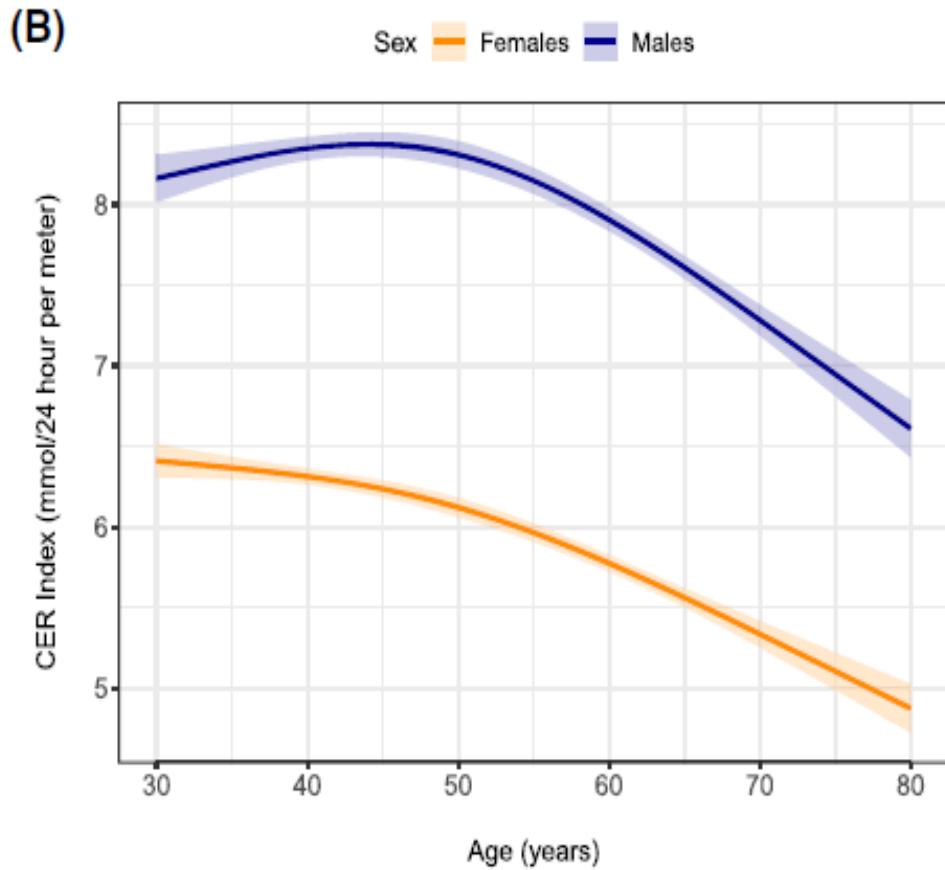
The committee agreed that in the absence of good evidence for their accuracy, <u>the 2014 recommendations that cystatin-c equations should be considered during diagnosis in certain circumstances, should be removed</u>. In particular, they noted that although using cystatin-c equations may reduce false-positive results, it is likely to also increase false negative results. This will avoid potentially misleading tests being conducted and the costs associated with these. They made a recommendation for research for a large study using UK data to evaluate the accuracy of cystatin-c equations

Other recommendations for research

Cystatin-C equations

What is the diagnostic accuracy of cystatin-C equations to estimate GFR as a measurement of kidney function in adults, young people and children in the UK? **[2021]**

NICE National Institute for Health and Care Excellence

Groothof et al. J Cachexia Sarcopenia Muscle., 2022

eGFR < 60 mL/min

(A)

CER index:
Males: <7, 7–9, >9
Females: <5.25, 5.25–6.75, >6.75

Groothof et al. J Cachexia Sarcopenia Muscle., 2022
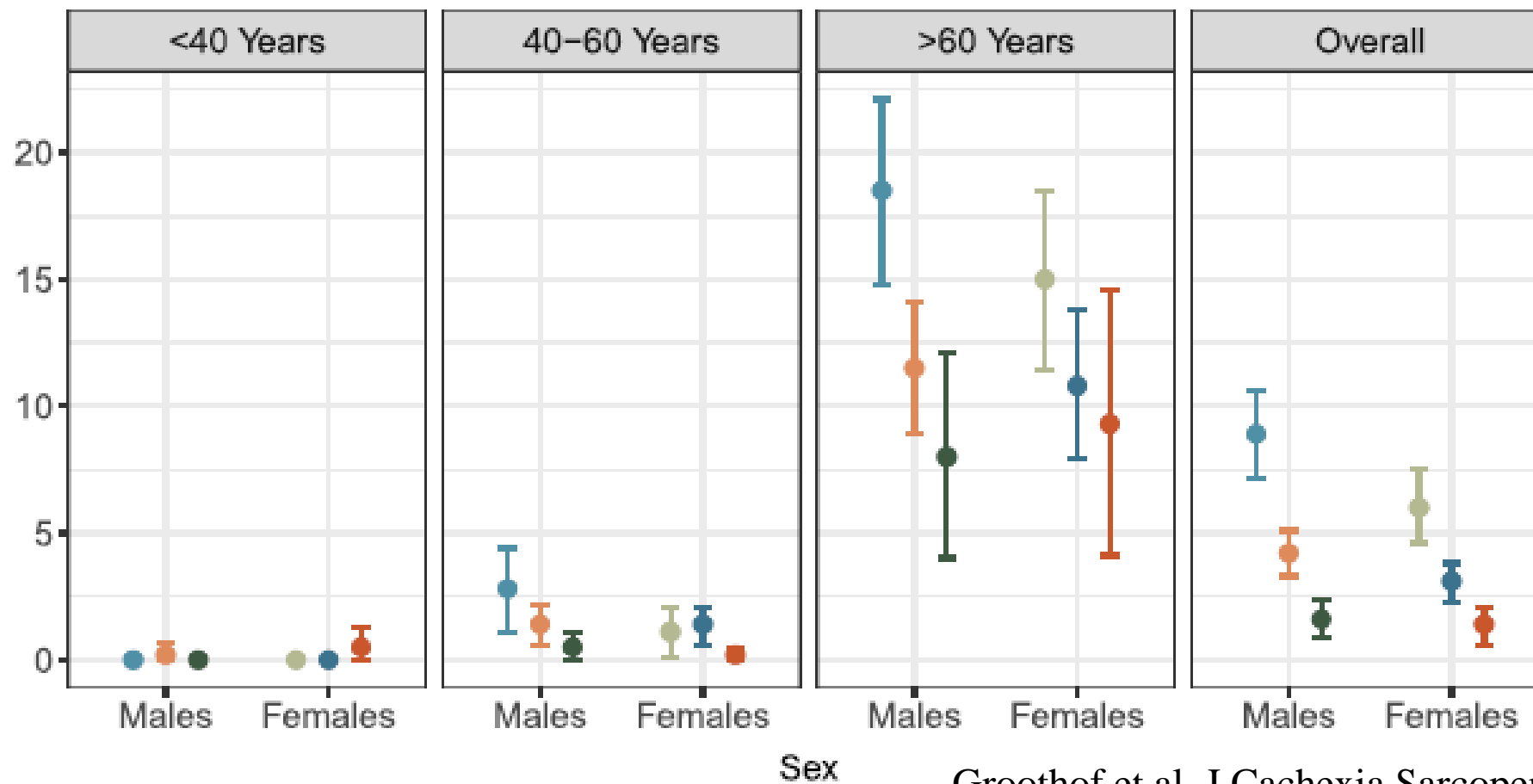
	Men			Women		
	Normal ($n=277$)	Sarcopenia ($n=25$)	p value	Normal ($n=597$)	Sarcopenia ($n=50$)	p value
eGFRcre (mL/min/1.73 m^2)	68.4 ± 13.6	65.0 ± 13.2	0.230	69.5 ± 13.8	67.6 ± 14.1	0.339
eGFRcys (mL/min/1.73 m^2)	72.5 ± 15.5	62.7 ± 16.9	0.003	75.8 ± 15.1	69.1 ± 17.1	<0.001
eGFRcys/eGFRcre	1.07 ± 0.17	0.96 ± 0.14	0.002	1.10 ± 0.17	1.02 ± 0.14	<0.001

A Men

AUC: 0.693
Cut off: 1.00
Specificity: 62.4%
Sensitivity: 72.0%
p=0.001

B Women

AUC: 0.630
Cut off: 1.09
Specificity: 48.9%
Sensitivity: 74.0%
p<0.001

eGFRcys/eGFRcre < 1

Kusunoki et al. Clinical and Experimental Nephrology, 2022
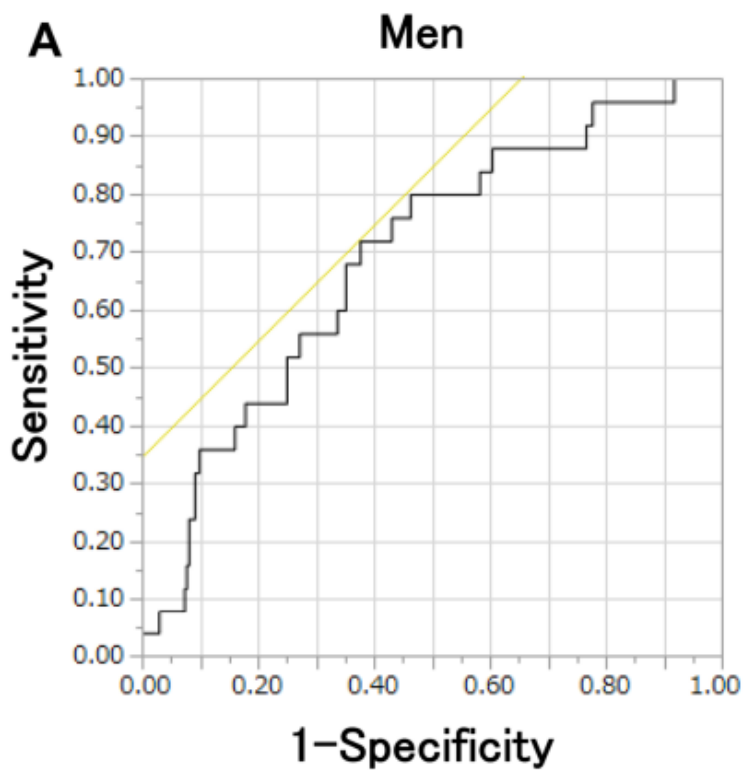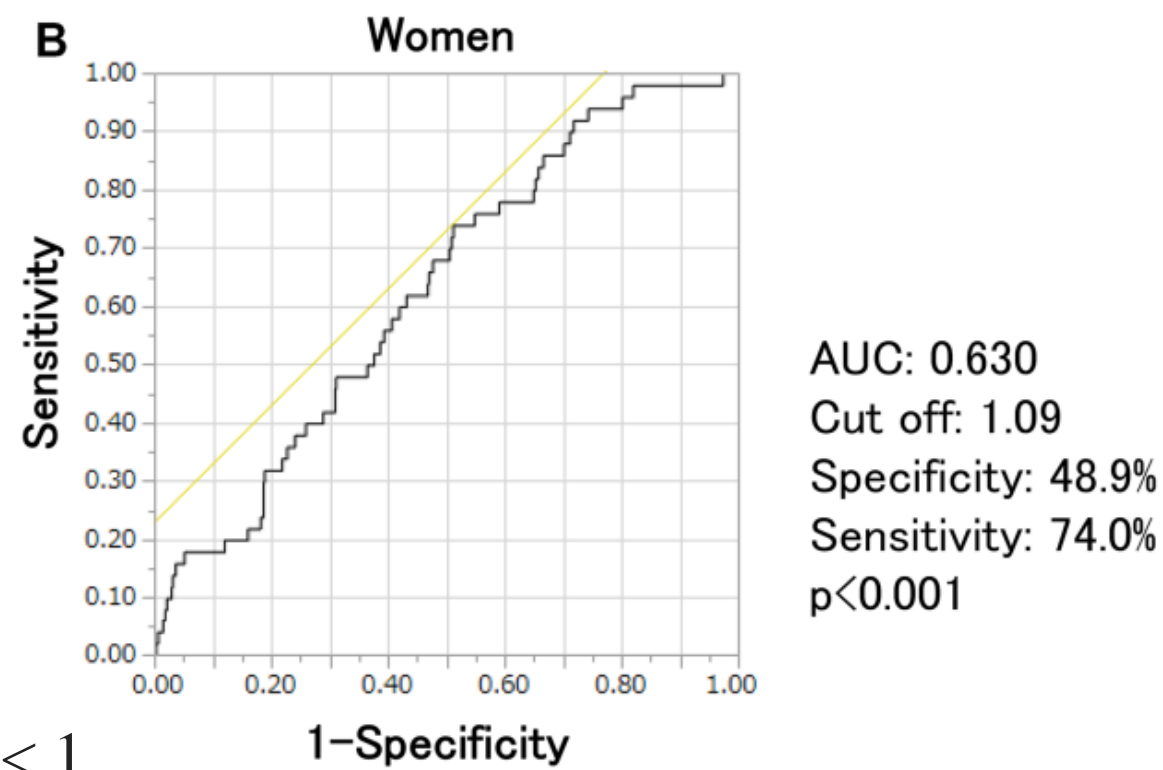
Equations for Assessing Estimated Glomerular Filtration Rate in Older Adults

Name		Equation
MDRD		$175 \times SCr^{-1.154} \times age^{-0.203} \times 1.212$ (if patient is black) $\times 0.742$ (if female)
CKD-EPI (2009)	Men (Scr ≤ 0.9)	$141 \times (Scr/0.9)^{-0.411} \times 0.993^{Age}$
	Men (SCr >0.9)	$141 \times (SCr/0.9)^{-1.209} \times 0.993^{Age}$
	Women (SCr ≤0.7)	$144 \times (SCr/0.7)^{-0.329} \times 0.993^{Age}$
	Women (SCr >0.7)	$144 \times (SCr/0.7)^{-1.209} \times 0.993^{Age}$
RLM		$e^{X-0.0158 \times Age + 0.438 \times \ln(Age)}$
	Men (SCr < 2.04)	$x = 2.56 + 0.00968 \times (180 - SCr)$
	Men (SCr ≥ 2.04)	$x = 2.56 - 0.926 \times \ln(SCr/180)$
	Women (SCr < 1.7)	$x = 2.50 + 0.0121 \times (150 - SCr)$
	Women (SCr ≥ 1.7)	$x = 2.50 - 0.926 \times \ln(SCr/150)$
BIS		$3736 \times SCr^{-0.87} \times age^{-0.95} \times 0.82$ (if female)
EKFC	Men (SCr/0.9 <1)	$107.3 \times (SCr/0.9)^{-0.322} \times 0.990^{(Age-40)}$
	Men (SCr/0.9 ≥1)	$107.3 \times (SCr/0.9)^{-1.132} \times 0.990^{(Age-40)}$
	Women (SCr/0.7 <1)	$107.3 \times (SCr/0.7)^{-0.322} \times 0.990^{(Age-40)}$
	Women (SCr/0.7 ≥1)	$107.3 \times (SCr/0.7)^{-1.132} \times 0.990^{(Age-40)}$

Abbreviations. MDRD: Modification of Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiological Collaboration; RLM: Revised Lund-Malmo; BIS: Berlin Initiative Study; EKFC: European Kidney Function Consortium; SCr: Serum Creatinine
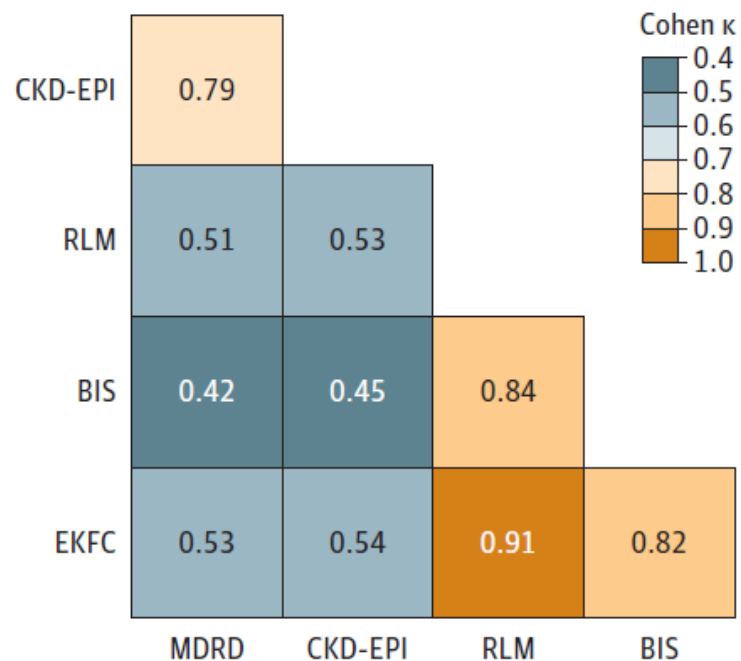
>3000 adults aged 60 years or older in Sweden

- Concordance
- Prognostic value (15 years)
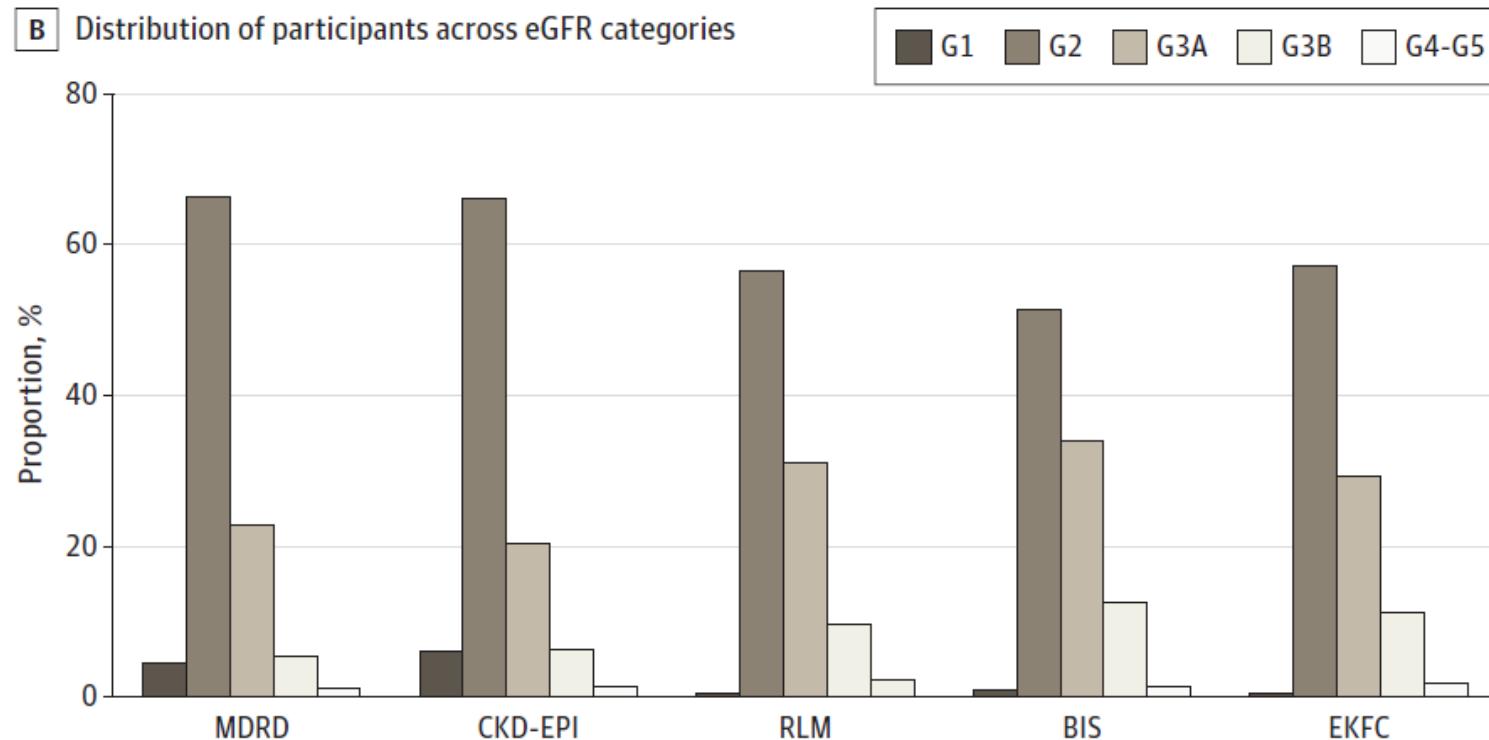- Sources of discrepancies

Beridze et al. JAMA Network, 2023

A Concordance among equations in the staging of CKD

B Distribution of participants across eGFR categories

Cohen κ: 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0

	MDRD	CKD-EPI	RLM	BIS
CKD-EPI	0.79			
RLM	0.51	0.53		
BIS	0.42	0.45	0.84	
EKFC	0.53	0.54	0.91	0.82

G1 represents eGFR ≥90 mL/min/1.73 m²; G2, 89.9-60 mL/min/1.73 m²; G3a, 59.9-45 mL/min/1.73 m²; G3b, 44.9-30 mL/min/1.73 m²; G4-5, <30 mL/min/1.73 m². BIS indicates Berlin Initiative Study; CKD-EPI, Chronic Kidney Disease Epidemiological Collaboration; EKFC, European Kidney Function Consortium; MDRD, Modification of Diet in Renal Disease; RLM, Revised Lund-Malmö.

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Table 2. Discriminative Capacity of Each Equation in Regard to 15-Year All-Cause Mortality[a]

Equation	Overall (n = 3094)		Low muscle mass (n = 407)[b]		Low BMI (n = 744)[c]		Age ≥78 y (n = 1369)	
	AUC (95% CI)	Harrel C (95% CI)	AUC (95% CI)	Harrel C (95% CI)	AUC (95% CI)	Harrel C (95% CI)	AUC (95% CI)	Harrel C (95% CI)
MDRD	0.66 (0.64-0.68)	0.62 (0.61-0.64)	0.72 (0.66-0.78)	0.61 (0.58-0.65)	0.66 (0.62-0.70)	0.62 (0.60-0.65)	0.58 (0.54-0.61)	0.56 (0.55-0.58)
CKD-EPI	0.72 (0.70-0.74)	0.67 (0.66-0.69)	0.78 (0.72-0.83)	0.64 (0.61-0.68)	0.73 (0.70-0.77)	0.67 (0.65-0.70)	0.60 (0.57-0.64)	0.58 (0.56-0.60)
RLM	0.78 (0.76-0.79)	0.71 (0.70-0.73)	0.81 (0.76-0.87)	0.67 (0.64-0.70)	0.79 (0.76-0.82)	0.72 (0.69-0.74)	0.63 (0.60-0.67)	0.60 (0.58-0.62)
BIS	0.80 (0.78-0.81)	0.73 (0.72-0.74)	0.82 (0.77-0.87)	0.68 (0.64-0.71)	0.81 (0.78-0.84)	0.73 (0.71-0.75)	0.64 (0.61-0.68)	0.61 (0.59-0.62)
EKFC	0.76 (0.74-0.77)	0.70 (0.69-0.71)	0.80 (0.75-0.86)	0.66 (0.63-0.69)	0.77 (0.74-0.81)	0.70 (0.68-0.73)	0.62 (0.58-0.65)	0.59 (0.57-0.61)

Abbreviations: AUC, area under the receiver operating characteristic curve; BIS, Berlin Initiative Study; BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiological Collaboration; EKFC, European Kidney Function Consortium; MDRD, Modification of Diet in Renal Disease; RLM, Revised Lund-Malmö.
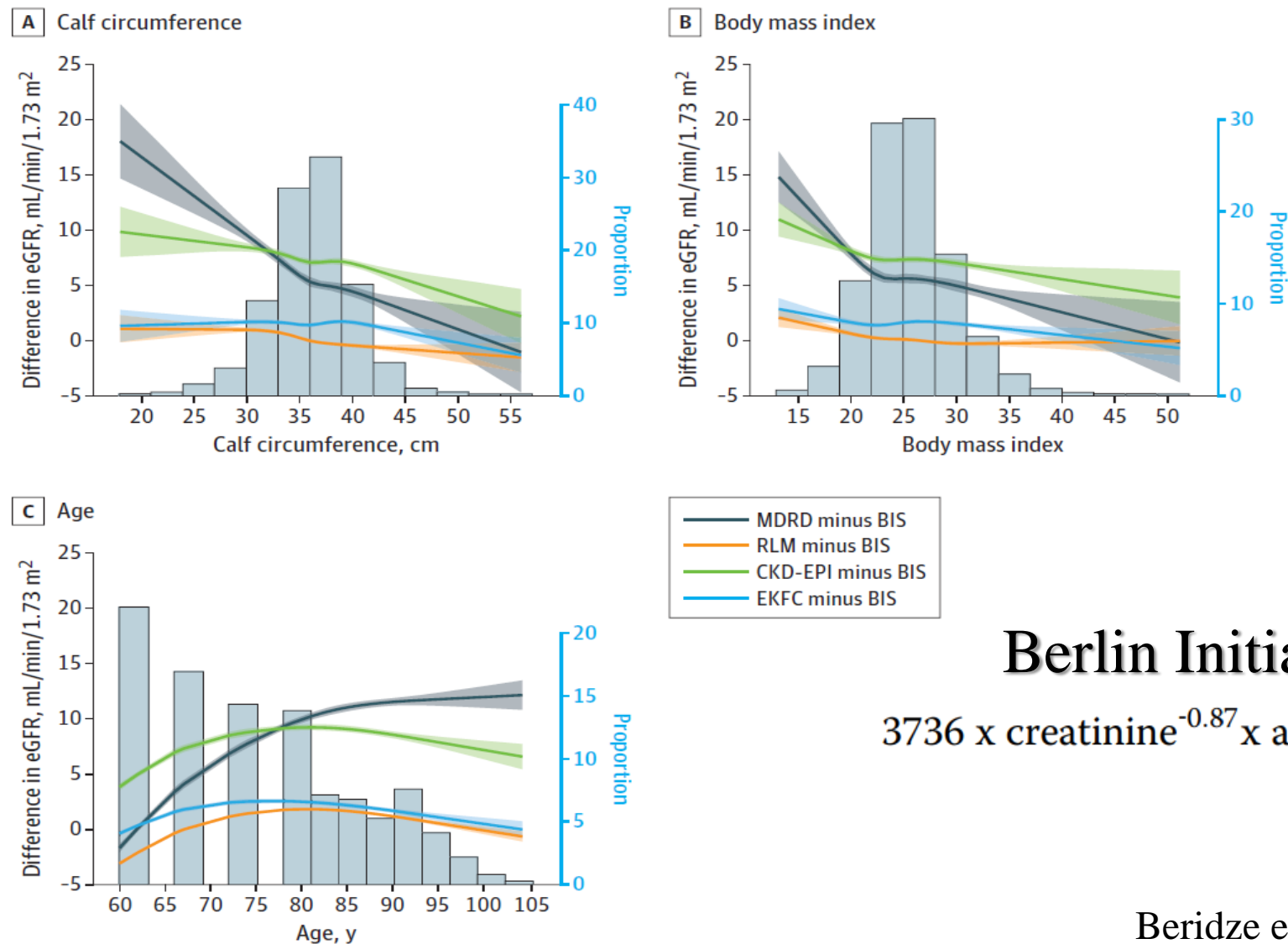
[a] AUC and Harrel C statistics obtained from crude logistic regression and Cox regression models, respectively.

[b] Low muscle mass included participants with calf circumference less than the 20th sex-specific percentile.

[c] Low BMI included participants with BMI below 23.

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Figure 2. Discrepancies Between Estimated Glomerular Filtration Rate (eGFR) Equations

A | Calf circumference
B | Body mass index
C | Age

Legend:
- MDRD minus BIS
- RLM minus BIS
- CKD-EPI minus BIS
- EKFC minus BIS

Berlin Initiative Study

$$3736 \times \text{creatinine}^{-0.87} \times \text{age}^{-0.95} \times 0.82(\text{if female})$$

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New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race

L.A. Inker, N.D. Eneanya, J. Coresh, H. Tighiouart, D. Wang, Y. Sang, D.C. Crews, A. Doria, M.M. Estrella, M. Froissart,
M.E. Grams, T. Greene, A. Grubb, V. Gudnason, O.M. Gutiérrez, R. Kalil, A.B. Karger, M. Mauer, G. Navis, R.G. Nelson,
E.D. Poggio, R. Rodby, P. Rossing, A.D. Rule, E. Selvin, J.C. Seegmiller, M.G. Shlipak, V.E. Torres, W. Yang, S.H. Ballew,
S.J. Couture, N.R. Powe, and A.S. Levey, for the Chronic Kidney Disease Epidemiology Collaboration*

Table 1. Characteristics of the Participants in the Development and Validation Data Sets.*

Characteristic	eGFRcr 2009 Development Data Set			eGFRcr-cys 2012 Development Data Set			2021 Validation Data Set		
	Overall (N=8254)	Black (N=2601)	Non-Black (N=5653)	Overall (N=5352)	Black (N=2123)	Non-Black (N=3229)	Overall (N=4050)	Black (N=579)	Non-Black (N=3471)
Percent of overall population	100	31.5	68.5	100	39.7	60.3	100	14.3	85.7
Age — yr	47.0±14.8	52.8±12.0	44.3±15.2	46.5±15.1	53.1±11.6	42.2±15.6	57.0±17.4	53.6±12.6	57.6±18.0
Age category — no. (%)									
<40 yr	2921 (35.4)	397 (15.3)	2524 (44.6)	2008 (37.5)	299 (14.1)	1709 (52.9)	715 (17.7)	59 (10.2)	656 (18.9)
40–65 yr	4309 (52.2)	1807 (69.5)	2502 (44.3)	2625 (49.0)	1463 (68.9)	1162 (36.0)	1989 (49.1)	417 (72.0)	1572 (45.3)
>65 yr	1024 (12.4)	397 (15.3)	627 (11.1)	719 (13.4)	361 (17.0)	358 (11.1)	1346 (33.2)	103 (17.8)	1243 (35.8)

GFR: Urinary iothalamate clearance

- **CRIC**: The CRIC Study is a prospective cohort study that examines risk factors for progression of CKD and CVD among patients with established CKD [16].
- **MDRD**: The MDRD consisted of two randomized trials that investigated if protein restriction and control of blood pressure had an effect on CKD progression [17].
- **AASK**: The AASK randomized trial investigated the effects of blood pressure control and the use of specific antihypertensive regimens on the progression of chronic kidney disease in African Americans [18], [19].
- **DCCT/EDIC**: DCCT/EDIC trial and prospective follow-up studied the effect of intensive vs. conventional diabetes therapy on development and progression of vascular and neurologic complications of type 1 diabetes [20], [21].
- **CRISP**: The CRISP longitudinal cohort makes prospective, longitudinal measurements of cyst and kidney growth in a large cohort of patients with Autosomal dominant polycystic kidney disease [22].
- **ALTOLD**: ALTOLD was a prospective cohort study designed to understand the pathophysiological effects of kidney donation [23], [24].
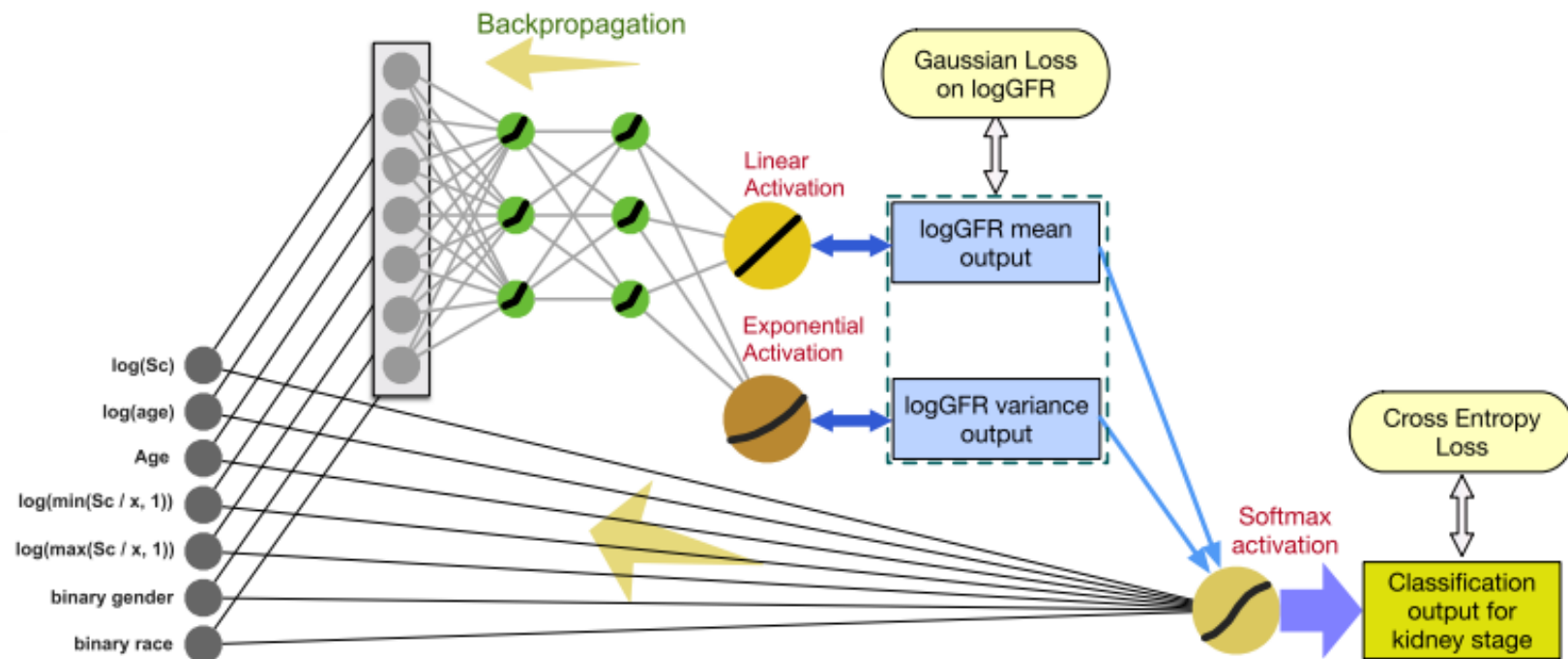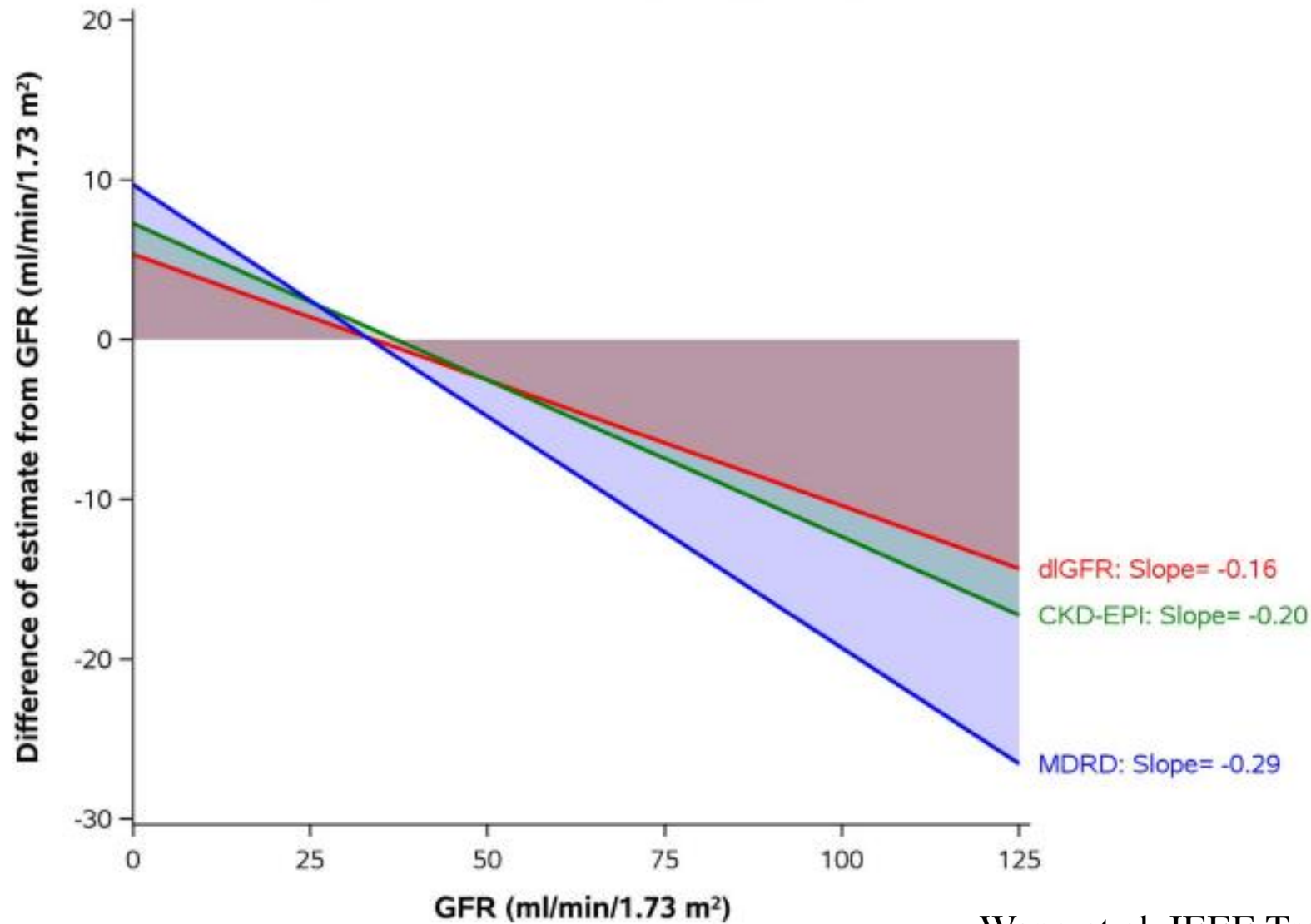

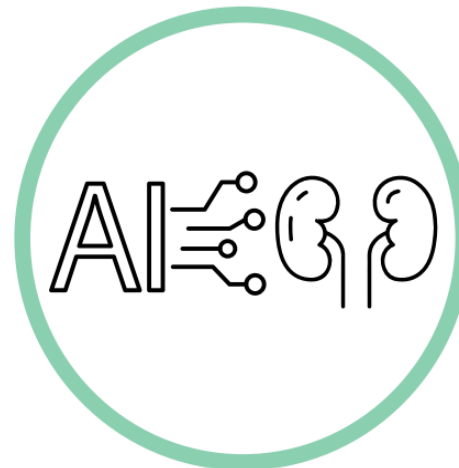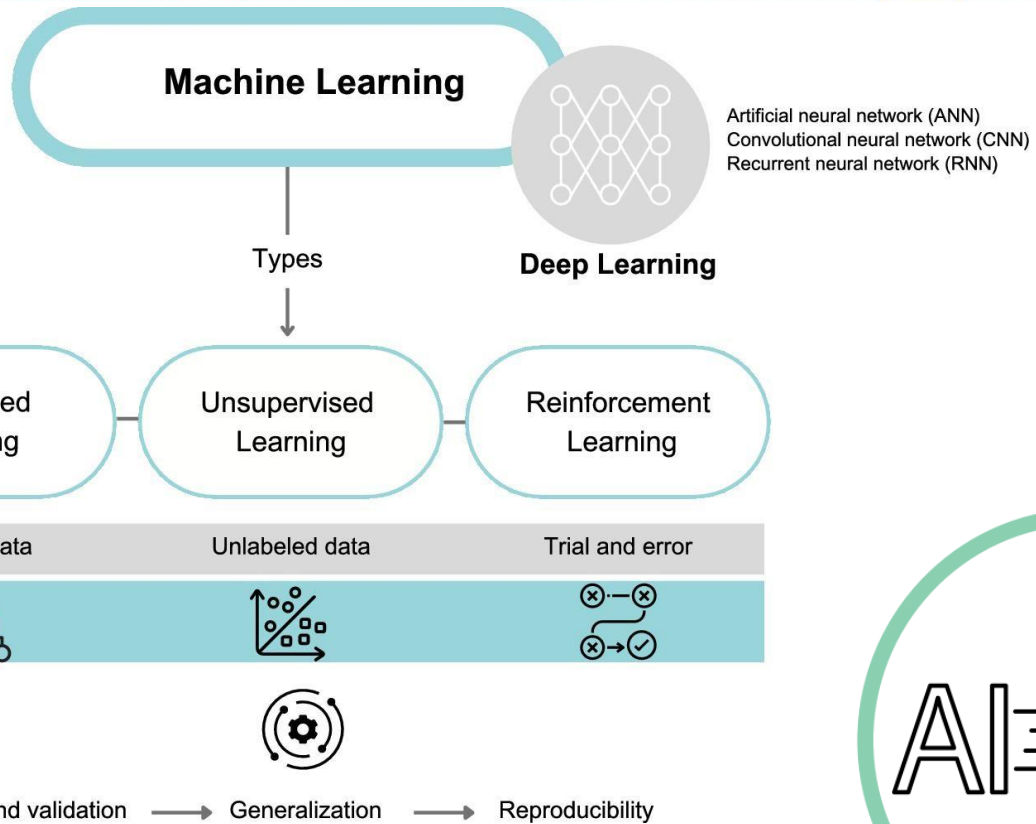PERFORMANCE OF GLOMERULAR FILTRATION RATES ESTIMATES

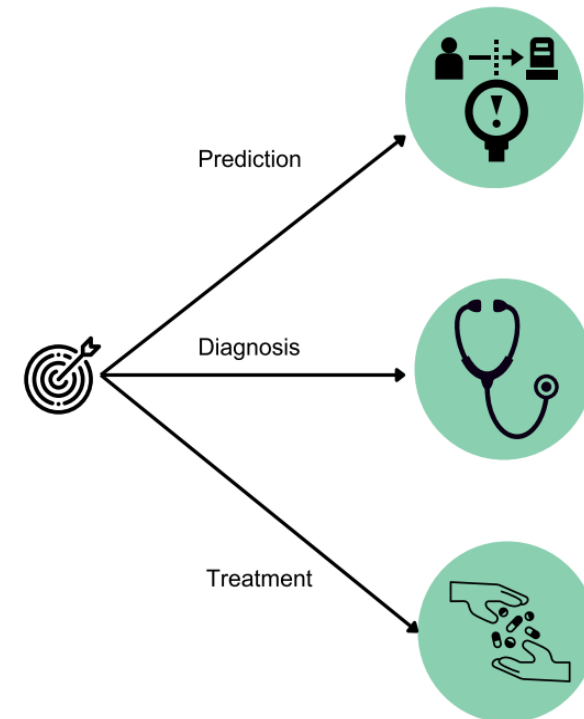|	Median eGFR (IQR)	Median difference from GFR (IQR)	Median absolute difference$^\alpha$ (IQR)	Accuracy$_{30}{}^\alpha$ N (%)	Accuracy$_{15}{}^\alpha$ N (%)
dlGFR	43.3 (28.6, 60.7)	-1.8 (-8.3, 2.9)	5.5 (2.3, 11.3)	4041 (88.3)	2572 (56.2)
CKD-EPI	43.9 (28.9, 63.6)	-1.7 (-8.2, 3.3)	5.6 (2.4, 11.6) **	3985 (87.1)	2432 (53.2)
MDRD	42.9 (28.3, 61.4)	-2.8 (-10.5, 1.9)	5.8 (2.4, 12.5)**	3876 (84.7)**	2337 (51.1)**

Wang et al. IEEE Trans Nanobioscience, 2022

Trends in difference of estimates from GFR

Wang et al. IEEE Trans Nanobioscience, 2022

De Arizon et al. Clinical Kidney Journal, 2023

Summary

- Need for study on cystatine C in CKD sarcopenic patients

- Most studies used creatinine to estimate eGFR in sarcopenic patients

- Creatinine-based eGFR through 2021 CKD-EPI as first approach

- Confirmation of eGFR through 2021 CKD-EPI creatinine-cystatin C equation

- BIS equation and cystatin C possible surprises in the short term, waiting for AI