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Monitoring Renal Function and Limitations of Renal Function Tests

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Chronic kidney disease (CKD) is a world-wide public health problem, with adverse outcomes of kidney failure, cardiovascular disease, and premature death. The National Kidney Foundation, through its Kidney Disease Quality Outcome Initiative (K/DOQI) and other National institutions, recommend glomerular filtration rate (GFR) estimates for the definition, classification, screening, and monitoring of CKD. Prediction equations based on serum creatinine values were chosen both for adults (Cockcroft-Gault [C-G] and Modification of Diet in Renal Disease [MDRD] study equations) and for children (Schwartz and Counahan-Barratt equations). This review aims to evaluate from recent literature the clinical efficiency and relevance of these equations in terms of bias, precision, and reproducibility in different specific indications (eg, screening CKD, assessment of disease progression, or therapy efficacy) in different populations. Because these prediction equations based on serum creatinine have limitations, especially in the normal or near-normal GFR range, kidney transplant recipients, and pediatric populations, other prediction equations based on serum cystatin C value were also considered as possibly more sensitive GFR surrogate markers. Recent guidelines state that the cystatin C-based prediction equation cannot be recommended for use in clinical practice. With prediction equations based on serum creatinine, the National Kidney Disease Education Program (NKDEP) recommendations are to report a numerical estimate in round numbers only for GFR values <60 mL/min per 1.73 m^2. The MDRD equation generally outperforms the C-G equation but may still have a high level of bias, depending on creatinine assay calibration, and low precision with, at best, approximately 80% of estimated GFR in the "accuracy range" of 70-130% of the measured GFR value, even in patients with known CKD. According to Kidney Disease Improving Global Outcomes (KDIGO) recommendations, many indications remain for GFR measurements using a clearance method. In that context, it should be recalled that radiolabeled-tracer plasma or urinary clearance methods, are safe, simple, accurate and reproducible.

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The level of glomerular filtration rate (GFR) generally is accepted as the best overall index for the complex functions of the kidney in health and disease[1] based on functional, pathological, clinical, and prognostic factors. Functional coupling between GFR and tubular function is largely dependant on the "positive" glomerulotubular balance and the "negative" tubuloglomerular feedback, which ensure integrated regulation of whole nephron function. GFR is central to the National Kidney Foundation classification and staging diagnosis of chronic kidney disease (CKD). In 2002, clinical practice guidelines from the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (K/DOQI) and then, in 2004 and 2006, Kidney Disease Improving Global Outcomes (KDIGO) controversies conferences[2,3] recommended GFR estimate for the definition and classification[1] as well as for screening and monitoring of CKD.[3] CKD is a public health problem worldwide.[4] Thus, the Chronic Kidney Disease Initiative was implemented to formulate a plan of action to solve a number of issues, such as identifying, caring for, and reaching the optimal outcomes.[5] CKD is defined as a GFR <60 mL/min per 1.73 m^2 or kidney damage for at least 3 months regardless of cause.[1] Long-term adverse outcomes associated with CKD include kidney failure, complications of impaired kidney function and, more commonly, increased cardiovascular risk and death.[6-9]

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Table 1 KDOQI Recommendations[1]

Creatinine clearance estimation (mL/min)	
Cockcroft-Gault, 1976 (adults)[25]	Clcr = [(140 − age) × weight]/[Scr × 72] (× 0.85 if female)
Schwartz, 1976 (children)[28]	Clcr = (0.55 × length)/Scr
GFR estimation (mL/min/1.73 m²)	
4v-MDRD, 2005 (adults)[27]	DFG = 175* × $(Scr)^{-1.154}$ × $(age)^{-0.203}$ (× 0.742 if female)
	DFG = 175* × $(Scr)^{-1.154}$ × $(age)^{-0.203}$ (× 1.21 if Afro-American)
Counahan-Barratt, 1976 (children)[29]	DFG = (0.43 × length)/Scr

Prediction equations based on serum creatinine (Scr) recommended by the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI).[1] 4v-MDRD means 4-variable ("abbreviated") equation from the Modification Diet for Renal Disease (MDRD) Study.[26,27]

*Coefficient derived from an enzymatic assay traceable to isotopic-dilution mass spectrometric assay (reference method) being 186 in the previously published (2000) version of MDRD equation derived from an creatinine assay based on Jaffé reaction.[26]

What are the indications for GFR measurements or estimations? First, in CKD, GFR assessment is used (1) for the early detection of impaired renal function in patients with risk factors, (2) for the evaluation of disease progression and prognosis, (3) for treatment assessment, and (4) for defining the need for dialysis or transplantation. GFR measurements also are necessary for potential kidney donors, before dosing with high toxicity drugs excreted by the kidney, and for clinical research where GFR is the primary outcome.[1-3,5,10,11] Accurate measurement by clearance of exogenous filtrated markers often is considered too complex and, therefore, surrogate markers, such as serum values of endogenous markers, are recommended in routine practice. Regarding clearance methods, inulin "has long been considered as the gold standard,"[12] but this method is expensive and time-consuming because it requires constant infusion, bladder catheterization (for good reproducibility), significant blood sample volume, and the implementation of a difficult assay. Currently, its use is limited to investigational research. However, unlabeled markers (such as iodine contrast media) and radiolabeled tracers (such as ^{125}I-iothalamate, ^{51}Cr-EDTA, ^{99m}Tc-DTPA) enable accurate (low bias and high precision) and reproducible measurements of GFR. The aim of this review article is not to discuss the utility and methodological issues of such clearance methods, which are reviewed extensively in recent publications, guidelines, and a consensus report,[13-22] but to analyze the clinical relevance of surrogate markers, such as prediction formulae based on serum creatinine (Scr) and/or cystatin C (ScysC).

According to the guidelines of the NKF-K/DOQI, prediction equations taking into account serum creatinine level (Scr) and given variables for creatinine production, such as age, gender, body weight, and race, are recommended for GFR estimate in clinical practice. GFR estimates based on a Scr prediction equation are more reliable than 24-hour creatinine clearance because most patients do not collect timed urine samples accurately.[23] Creatinine clearance can vary up to 27% in routine clinical practice (day-to-day coefficient of variation).[24] Two formulae are recommended for predicting either creatinine clearance or GFR: for adult patients, the Cockcroft-Gault (C-G) equation[25] and the "abbreviated," or 4-variable, Modification of Diet in Renal Disease (4v-MDRD) study equation,[26,27] respectively, and in children, the Schwartz[28] and Counahan-Barratt[29] equations, respectively (Table 1).

Compared with the clearance method, these formulae based on serum values appear to be simpler, less costly, and easily available. However, their efficiency should be demonstrated in terms of bias (average difference between estimated and measured values), precision (scatter of estimates around the measured value), accuracy (composite of bias and precision), and reproducibility (e.g., within the same patient over time, intraassay, interlaboratory) in different specific indications (eg, screening CKD, assessment of progression and therapy effectiveness) and in different populations.

Evaluation of Prediction Formulae Based on Serum Creatinine

CKD Populations

The performance of prediction formulae based on Scr depends on the population. Therefore, the assessment should be conducted in CKD patients with a GFR range similar to the MDRD study sample (mean GFR of 40/mL/min per 1.73 m²)[30] or a creatinine clearance similar to the population studied by Cockcroft and Gault (mean creatinine clearance of 73 mL/min).[25] However, the clinical relevance should also be validated in severe CKD and renal failure, kidney transplant recipients, CKD patients with normal baseline GFR, or hyperfiltration and in longitudinal studies.

CKD Population With Decreased GFR

Four major studies evaluating these equations in CKD patients with GFR less than 60 mL/min per 1.73 m² were published in 2004-2005.[31-34] Because the 4v-MDRD equation generally outperformed the C-G equation, only the 4v-MDRD equation is shown in Table 2. In summary, in approximately 2,350 patients with a mean GFR ranging from 24 to 48 mL/min per 1.73 m² (measured by urinary clearance of four different markers of GFR), the bias was low and varied from −6.1% to +1%. However, the "accuracy within 30%" (as defined by NKF-K/DOQI,[1] corresponding to the percentage of estimated values within a range of 70-130% of the

Table 2 Validation Studies of 4v-MDRD Equation in Large Series of CKD Populations (GFR <60 mL/min/1.73 m²)

		GRF		Evaluation MDRD Equation		
	No. of Patients	Marker	Mean (range), mL/min/1.73 m²	Bias*	Precision†	P 30%‡
Rule et al[31] (2004)	320	Iothalamate	48 (5-133)	−6.2%	$r^2 = 0.79$	75%
Poggio et al[32] (2005)	579 (non-diabetes)	^{125}I-iothalamate	36 (10-81)	1%		74%
	249 (diabetes)		24 (9-52)	−4%	$r^2 = 0.81$	63%
Cirillo et al[33] (2005)	149	Inulin	<60	−3.1%	N/A	N/A
Froissart et al[34] (2005)	1051	^{51}Cr-EDTA	<60	1.3 mL/min/1.73 m²	8.5 mL/min/1.73 m²	83%

GFR were measured by urinary clearance methods using (unlabeled) iothalamate, ^{125}I-iothalamate, inulin or ^{51}Cr-EDTA.
*Bias is defined as the mean difference between estimated and measured GFR, as expressed in percentage or mL/min per 1.73 m².
†Precision is defined as either r^2 derived by linear regression or one SD of bias (mL/min per 1.73 m²).
‡P 30% is "accuracy within 30%" corresponding to the percentage of estimated values within a range of 70-130% of the measured GFR.

Figure 1 95% confidence intervals of the measured GFR values for each value of MDRD estimated GFR (solid lines). Mean measured GFR value for each value of estimated GFR (dotted line). For a 4v-MDRD estimated GFR of 60 mL/min per 1.73 m², the actual measured GFR is between 37 and 90 mL/min per 1.73 month², values corresponding to stage 1 to 3 of the CKD classification. (Adapted with permission from Froissart et al.[34])

measured GFR [mGFR]) for the general population was between 63% and 83%. In other words, one-third to one-fifth of patients have an estimated GFR (eGFR) outside this rather large "accuracy" range. As an example, Figure 1 (adapted from Froissart and coworkers[34]) shows that for a 4v-MDRD eGFR of 60 mL/min per 1.73 m² (the threshold of stage 3 CKD according to NKF-K/DOQI), the actual mGFR is between 37 and 90 mL/min per 1.73 m² (corresponding to stage 1 to 3 of the CKD classification). Subgroup analyses[33,34] showed that the degree of error is not only a function of GFR (larger at higher GFR) but also varies with gender (less in female patients for 4v-MDRD equation), age (underestimation of GFR for older patients with the C-G equation), and body mass index (underestimation of GFR at lower BMI for both equations and overestimation of GFR for higher BMI with the C-G equation).

Kidney Failure and Severe CKD

Three studies published in 2005 concluded that these prediction equations were not valid for a CKD population of patients with severely impaired renal function.[35-37] In patients with a Scr greater than 400 μmol/L, the 4v-MDRD equation underestimated GFR by 10% whereas C-G equation strongly overestimated GFR by approximately 35%.[35] In hospitalized patients with severely impaired renal function (GFR 17 ± 18 mL/min per 1.73 m²), Poggio and coworkers[36] obtained a mean GFR overestimation of 53% and 71% by the 4v-MDRD and C-G equations, respectively. Only one-third of these patients had an eGFR value in the "accuracy within 30%" range! In type-1 and -2 diabetic patients soon to be

Table 3 Validation Studies in Type-1 Diabetes Patients With Normal Baseline GFR or Hyperfiltration (GFR >140 mL/min per 1.73 m^2)

	GFR (mL/min/1.73 m^2)	C-G eGFR (mL/min/1.73 m^2)	4v-MDRD eGFR (mL/min/1.73 m^2)
Vervoort[46] (2002) (noncomplicated diabetes)	122 ± 18	119 ± 16	108 ± 18
Absolute difference (90th percentile)		23%	32%
Ibrahim[47] (2005) (DCCT cohort)*	122 ± 23	116 ± 21	110 ± 19
Bias (mL/min/1.73 m^2)		−6	−22
Accuracy			
Within 10%		39%	25%
Within 30%		88%	78%

C-G eGFR and 4v-MDRD eGFR were GFR estimated by Cockcroft-Gault[25,26] and 4 variable-MDRD equations,[26] respectively.
Bias and accuracy within 30% are defined as in Table 2. Accuracy within 10% is the percentage of estimated GFR within 90-110% of the measured GFR.
*Diabetes Control and Complications Trial (DCCT) cohort of patients with Scr <1.2 mg/dL.

referred to dialysis, Rigalleau and coworkers[37] demonstrated that using C-G and 4-v MDRD equations, 52% and 34% of these patients, respectively, would have had a delayed referral to nephrologists (GFR less than 30 mL/min per 1.73 m^2). Similarly, 60% and 45%, respectively, would have had a delayed preparation for dialysis (GFR less than 25 mL/min per 1.73 m^2).

Kidney Transplant Recipients

Although "accuracy within 30%" has been considered as appropriate in clinical practice for CKD patients by NFK-K/DOQI, in kidney transplant recipients "accuracy within 10%" is recommended to detect functional changes and enabling early treatment adaptation. In 6 recently published series,[38-43] including 1480 kidney transplant recipients, the percentages of GFR estimated by C-G and 4v-MDRD equations, in this "accuracy within 10%" interval, was very low and ranged between 24% and 44% and 10% and 36%, respectively. In these series, 4v-MDRD formulae outperformed C-G formulae. Mariat and coworkers,[41] performing 500 consecutive inulin clearances in 294 renal transplant recipients, showed that other prediction equations based-on SCr, such as Walser,[44] Jelliffe,[45] and Nankivell[46] formulae had 95% limits of agreement >40 mL/min per 1.73 m^2, apart.

CKD Patients With Normal Baseline GFR or Hyperfiltration

Patients at early stages of diabetes may have normal baseline GFR or even hyperfiltration (GFR >140 mL/min per 1.73 m^2). Two studies performed on type-1 diabetes and 4 on type-2 diabetes patients showed that prediction equations underestimated normal and high GFR values.[47-52] As shown in Table 3 (GFR 122 ± 18 mL/min per 1.73 m^2), the 2 prediction equations underestimated GFR, especially the 4v-MDRD equation in noncomplicated type-1 diabetic patients (119 ± 16 and 108 ± 18 for C-G and 4v-MDRD eGFR, respectively) and had a low accuracy as the median absolute difference at 90th percentile being 23% and 32% for C-G and 4v-MDRD equations, respectively. Poor results were also reported in the Diabetes Control and Complications Trial (DCCT) patients cohort with a normal Scr values less than 1.2 mg/dL.[48] Both prediction equations underestimated measured GFR with higher bias for 4v-MDRD equation (22 mL/min per 1.73 m^2) and a poor accuracy, especially within a 10% range recommended for efficient patient management (39% and 25% for C-G and 4v-MDRD equations, respectively). In both studies, 4v-MDRD equation offered no advantages over the C-G formula.

Longitudinal Studies

Normal Baseline GFR and Hyperfiltration: Type-2 Diabetes

Four studies assessed the mean rate of GFR decline over time in type-2 diabetes patients from normal baseline GFR or hyperfiltration levels to overt diabetic nephropathy.[49-52] Both prediction equations underestimated GFR with wide limits of agreement. Although Nielsen and coworkers[49] reported an overestimation of the rate of change in GFR using C-G equation versus ^{51}Cr-EDTA plasma clearance measurement (−2.8 ± 2.3 versus 1.5 ± 0.5 mL/min/year), 3 recent studies have reported underestimation of the rate of decline of GFR (Table 4).[50-52] In conclusion, GFR estimations based on these equations are unacceptable for monitoring kidney function in type-2 diabetes patients with incipient and overt diabetic nephropathy. In the studies of Fonstseré[51] and coworkers and Rossing[52] and coworkers, 4v-MDRD equation did not outperform C-G equation for estimating the rate of decline of GFR over time.

Reduced Baseline GFR

Depending on the issue considered, either mean slope of GFR decline over time or clinical issues, the validation of these prediction equations may be regarded as different. Two studies, both published in 2004, reported divergent conclusions with either overestimation[38] or underestimation[53] of the mean slope of GFR decline. Gaspari and coworkers[38] performed plasma iohoxol clearance in 81 renal transplant recipients at 6, 9, and 21 months after surgery (baseline GFR: 56 ± 15 mL/min per 1.73 m^2). All 12 prediction equations tested showed a tendency toward GFR overestimation.

Table 4 Longitudinal Studies of Type-2 Diabetic Patient With Normal Baseline GFR and Hyperfiltration

Study/No. of Patients (Follow-up)	Baseline GFR (mL/min/1.73 m²)			Rate of GFR Decline (mL/min/year)		
	Measured	C-G	4v-MDRD	Measured	C-G	4v-MDRD
Nielsen[48] (1999)						
n = 36 (2.7-7.5 yrs)	104 ± 18 (^{51}Cr-EDTA)	82 ± 16	–	−1.5 ± 2.5	−2.8 ± 5.3	–
Perkins[49] (2005)						
n = 30 (m = 3.8 ± 0.3 yrs)	153 ± 27 (iothalamate)	–	130 ± 32	−4.4 ± 10.3%	–	−2.8 ± 10.3%
n = 10, stable function	148 ± 18	–	137 ± 21	2.9 ± 2.0%	–	−0.7 ± 7.1 %
n = 20, declining function	156 ± 30	–	127 ± 35	−8.1 ± 10.9%	–	−4.4 ± 11.2%
Fontseré[50] (2000)						
n = 87 (over 10 yrs)	>140 (^{125}I-iothalamate)	–	–	−4.8 ± 4.7	−0.9 ± 1.4	−1.0 ± 2.5
	140-90	–	–	−3.0 ± 2.3	−1.2 ± 2.5	−0.7 ± 1.5
	30-89	–	–	−1.4 ± 1.8	−1.0 ± 0.9	−1.3 ± 1.4
Rossing[51] (2006)						
n = 156 (3-17 yrs)	117 ± 24 (^{51}Cr-EDTA)	103 ± 24	42 ± 20	−4.1 ± 4.2	−3.4 ± 3.2	−2.9 ± 2.8

C-G and 4v-MDRD are estimated GFR using Cockcroft-Gault[25] and 4 variable-MDRD[26] equations, respectively. ^{51}Cr-EDTA, ^{125}I-iothalamate (^{125}I-ioth.) and unlabeled iothalamate (ioth.) are GFR markers used in clearance methods to measure GFR. In the study from Perkins et al,[49] the measured and C-G/4v-MDRD estimated rates of GFR decline over time are expressed in percentages of the baseline values (not in mL/min/year). C-G eGFR overestimates and 4v-MDRD eGFR underestimates the rate of GFR decline over time.

Walser[44] showed that the use of 4v-MDRD equations resulted in the best performance; however, no more than 45% of estimated values were within ±10% error. The estimated rates of GFR decline also were overestimated, that is, −5.0 mL/min per 1.73 m²/year for Walser's equation and −5.9 mL/min per 1.73 m²/year for the 4v-MDRD equation, whereas the mGFR decline was −3.0 mL/min per 1.73 m²/year. The authors concluded that prediction equations do not ensure a rigorous assessment of renal function in kidney renal transplant recipients.

Lewis and coworkers[53] compared 9,742 matched pairs of ^{125}I-Iothalamate mGFR (25-65 mL/min per 1.73 m²) to eGFR by the 4v-MDRD equation in 1094 African Americans with hypertensive nephrosclerosis (African American Study of Kidney Disease and Hypertension: AASK cohort). The mean slope of GFR decline during a 4-year follow-up was significantly underestimated (−1.64 ± 0.10 versus −1.92 ± 0.11 mL/min per year). On the contrary, the accelerated decline of GFR between the early phase (3 to 24 months) and the late phase (2 to 4 years) was overestimated by the 4v-MDRD equation compared with the measured value (−1.69 ± 0.20 in early phase and −2.34 ± 0.16 in late phase for mGFR versus −1.30 ± 0.18 in early phase and −2.58 ± 0.14 during the late phase for eGFR).

Considering clinical issues, such as time-to-event composite outcome or risk factors for the progression of kidney disease, the AASK investigators demonstrated that eGFR is an efficient surrogate marker for the mGFR-based outcomes.[53,54] Thus, considering effects of the therapeutic interventions on time-to-event composite outcome (including 50% GFR decline and stage renal disease or death), the main conclusions of the trial were similar taking into account eGFR or mGFR.[53] An objective of CKD studies is to identify risk factors for disease progression, characterized by the rate of change over time or time-to-event (time until specified decline in kidney function or end stage renal disease). The relationships between 35 baseline risk factors and eGFR outcomes were compared with those of the same factors and mGFR in the AASK cohort. The effects of risk factors were similar between eGFR and mGFR based time-to-event outcomes. An agreement between eGFR and mGFR was also observed for slope-based outcomes but with a somewhat weaker concordance ($r = 0.92$ versus $r = 0.98$, respectively).

Identifying the Early Stages of CKD

The C-G and 4v-MDRD equations also should be assessed in populations with normal or near-normal Scr to select potential kidney transplant donors, to identify patients with known CKD without significant changes in Scr or in high risk patients because of cardiovascular diseases, and to screen for the early stages of CKD in the general unselected population.

Kidney Transplant Donors

In 4 recently published studies,[32,34,55,56] including a total number of 1220 kidney transplant donors, neither 4v-MDRD

nor C-G formulae were validated, and the authors did not recommend their use to select the kidney transplant donors (Table 5). Indeed, GFR was underestimated, with a mean bias ranging from −29 to −6 mL/min per 1.73 m^2 and low values of "accuracy within 30%" ranging from 54% to 86%. A possible explanation for this very large range of underestimation could be the difference in creatinine assay calibration between different laboratories, as it will be discussed later in this review.

Patients With CKD and Normal Scr or at Higher Risk

As shown in Table 6, prediction equations are not efficient to identify the early stages of known CKD in patients with normal or near-normal Scr.[57-59] In patients with a normal Scr (<1.5 mg/dL) with known CKD[57] or cardiovascular disease,[58] GFR was markedly underestimated with large bias and a poor accuracy within 30%. In patients with chronic heart failure and systolic dysfunction, GFR was still underestimated by both prediction equations (−6 and −12 mL/min per 1.73 m^2 with C-G and 4v-MDRD equations, respectively) and accuracy within 30% was approximately 75-80%. In general, prediction equations underestimated at upper values of GFR, whereas they overestimated at lower values of GFR. In these clinical circumstances, 4v-MDRD equation did not outperform the C-G equation. A similar result was obtained recently by Rule and coworkers,[22] who showed in early autosomal dominant polycystic kidney disease (GFR: 95 mL/min per 1.73 m^2, range: 79-115) a lower eGFR with 4v-MDRD equation (79 mL/min per 1.73 m^2, range 63-96) than with C-G equation (101 mL/min per 1.73 m^2, range: 82-126).

General Population

Rule and coworkers[60] compared eGFR in a general population on the basis of equations derived from different subsets of the general population. Adults (age ≥45 years) were randomly selected between 1997 and 2000 from the Olmsted County, Minnesota, population and had their Scr measured. GFR was estimated using previously reported equations[31] derived from a sample of patients with CKD, a sample of healthy persons (kidney donors) and a combined sample. Scr was measured with the same assay used to derive these equations proposed by the Mayo Clinic group. The prevalence rate of reduced eGFR (<60 mL/min per 1.73 m^2) varied markedly according to the equation (1982 subjects enrolled). Thus, the prevalence rate of stage 3 CKD was 12% (95% confidence interval [CI][16] 10-13%), with CKD patients derived equation; 0.2% (95% CI 0.1-0.5%), with kidney donors derived equation; and 5.7% (95% CI 4.8-6.8%) when using the equation derived from both CKD and healthy persons. The authors concluded that 4v-MDRD equation, established from CKD patients with a mean GFR about 40 mL/min per 1.73 m^2, cannot be used that to diagnose CKD in a general population.

Table 5 Validation Studies in Kidney Transplant Donors

		GFR		MDRD-eGFR	Evaluation MDRD eq.		
	No. of Patients	Marker	Mean ± SD (mL/min/1.73 m^2)	Mean ± SD (mL/min/1.73 m^2)	Mean Bias (mL/min/1.73 m^2)	Precision (r^2)	P 30%
Rule et al[31] (2004)	580	Cold ioth.	101 ± 17	72 ± 11	−29	0.19	54%
Lin et al[55] (2003)	117	^{125}I-ioth.	103 ± 16	95 ± 25	−18.3	0.02	65%
Poggio et al[32] (2005)	457	^{125}I-ioth.	106 ± 18	97 ± 21	−9.0*	0.13	86%
Froissart et al[34] (2005)	112	^{51}Cr-EDTA	≥90		−5.8*	N/A	N/A
	50		60-89		+0.6*	N/A	N/A

Abbreviations and definitions as in Table 2.

Table 6 Validation Studies for the Diagnosis of Early Stages of CKD in Populations With Normal or Near-normal Scr

	Population	Clearance Method	GFR (mean [range]), mL/min/1.73 m²		Bias (mL/min/1.73 m²)	Precision (r^2)	Accuracy (30%)
Bostom[57] (2002)	Known CKD and Scr	Pl.$Cl_{iohexol}$	(109 [18-205])	C-G	−26.5	0.17	59
n = 109	<1.5 mg/dL			4v-MDRD	−41.7	0.29	28
Verhave[58] (2005)	CVD risk screening and	u.$Cl_{99mTc\text{-}DTPA}$	(99 [33-201])	C-G	−21*/−5†	0.32	71*/87†
n = 850	Scr <1.5 mg/dL			4v-MDRD	−29*/−12†	0.34	51*/89†
Smilde[59] (2006)	CHF and syst.dysf.	u.$Cl^{125}_{i\text{-}ioth.}$	(73 [13-133])	C-G	−6	0.63	76
n = 234				4v-MDRD	−12	0.68	80

CVD, cardiovascular disease; CHF and syst.dysf., chronic heart failure with systolic dysfunction; Pl.Cl, plasma clearance; u.Cl, urinary clearance. Other abbreviations and definitions as in Table 2.
*Jaffé reaction assay.
†Enzymatic assay for serum creatinine measurements.

Other Populations Than White Patients

Both C-G and 4v-MDRD equations have been evaluated in other populations than the white population used to derive prediction equations.[61-64] In healthy Indians,[61] with a mean GFR of 83 mL/min (range of 61-130 mL/min), the mean bias was −14 mL/min and + 18 mL/min for C-G and 4v-MDRD eGFR, respectively. The accuracy within 30% was also low at 71% and 76% for C-G and 4v-MDRD, respectively, making these formulae suboptimal for clinical use in this population. Two studies were conducted in Chinese patients with CKD.[63,64] Both C-G and 4v-MDRD equations significantly overestimated GFR in patients with stages 4 to 5 CKD, whereas they significantly underestimated GFR in stage 1 CKD patients.[63] From 9 geographic regions of China, 684 adult patients with CKD were included in a study to adjust a modified MDRD equation to Chinese patients (4v-MDRD formula × 1.227 for Chinese patients). Using this modified formula, the percentage of eGFR that did not deviate by more than 30% from the ^{99m}Tc-DTPA plasma clearance-GFR (accuracy within 30%) reached >75%.[64] In South Asian (Pakistan) patients with CKD, the percentage of eGFR within 30% of the measured creatinine clearance values was 50% and 65% for 4v-MDRD and C-G equations, respectively.[62] Similarly, the authors suggested introducting an ethnic factor to improve the performance of GFR prediction equations.[62]

The Pediatric Population

As shown in Table 7, results obtained in children using a prediction equation, even the 2 formulae recommended by the NKF-K/DOQI (Schwartz[28] and Counahan-Barratt[29]), were worse, especially in terms of precision, than those obtained using either the C-G or 4v-MDRD formula in adults.[65-70] Although Zapitelli and coworkers[68,69] reported low bias using either Schwartz or Leger[71] formulae, all the other published series reported bias about 10-20% of relative error.[28,65,66,70] As demonstrated by Mattmann and coworkers[70] using alternative patient demographics other than length or height (like in the Schwartz and Counahan-Barratt formulae), such as weight and height (Leger and BCCH1[70] formulae) or age and gender (BCCH2[70] formula), reduced neither the mean bias, which was still about 20-25%, nor the large width of 95% limit of confidence (in average 90%, ranging from −40% to + 50%). In this study, the sensitivity to accurately identify a 30% relative decrease in GFR was about 60%, whatever the formula used.

Other Issues Regarding Prediction Formulae Based on SCR

Scr Assay Standardization

A major concern that affects both formulae is the accuracy of the creatinine assay. The lack of assay standardization is one

Table 7 Validation Studies in Pediatric Populations

Study	No. Patients (Age)	GFR Method	Formulae Tested	Bias (Mean)	95% LOA*
Pierrat[65] (2003)	198 (3-19 yrs)	Inulin	Schwartz	+20 (mL/min/1.73 m^2)	−20 to +20 (mL/min/1.73 m^2)
Filler[66] (2003)	536 (1-18 yrs)	Plasma cl DTPA	Schwartz	+11%	−37% to +58%
Schwartz[28] (1976)	27 (12-18 yrs)	Plasma cl iohexol	Schwartz	+12 (mL/min/1.73 m^2)	–
Zappitelli[68] (2006)	65 (2-21 yrs)	Urinary cl "cold" iothalamate	Schwartz	+7%	−42% to +56%
Zappitelli[69] (2007)	195 (2-21 yrs)	Urinary cl "cold" iothalamate	Schwartz	NS	−40% to +41%
			Schwartz Mod	NS	−40% to +39%
			Leger	+5.5	−37% to +48%
			Leger Mod	+1.6 (mL/min/1.73 m^2)	−39% to +42%
Mattmann[70] (2006)	86 (2-20 yrs)	Plasma cl DTPA	Schwartz	18%	−39% to +31%
			Leger	25%	−47% to +50%
			CB	20%	−43% to +32%
			BCCH1	18%	−30% to +39%
			BCHH2	23%	−43% to +55%

Schwartz Mod and Leger Mod are Schwartz[28] and Leger[71] formulae using regression-derived coefficients in place of the original coefficients. CB is Counahan-Barratt formula.[29] BCCH1 and BCCH2 are British Columbia's Children's Hospital formulae, using either weight and length (BCCH1) or age and sex (BCCH2) as parameters.[70] The 95% LOA is 95% limits of agreement. Bias is defined as in Table 2. Other abbreviations are defined in Table 2.

of the major limitations for the validation of prediction equations based-in Scr.[10,72-78] Most of auto analyzers used today measure Scr by a modified Jaffe's kinetic rate color reaction. The picric acid Jaffe's reaction overestimates Scr up to 20-30% in healthy subjects, attributable to presence of "noncreatinine chromogens," which react with picric acid (nonspecificity bias[72]). The cross-calibration of Scr assays to adjust this bias is not standardized across laboratories, leading to substantial variations.[72-74,79] These analytical flaws lead to substantial differences in GFR estimation. In 2003, the College of American Pathologists conducted a testing survey from 5624 laboratories using 50 different instrument-method combinations.[72] Gas chromatography-isotope dilution mass spectrometry (ID-MS) was considered as the golden method. Numerous routine methods of Scr analysis were biased between −0.06 and 0.31 mg/dL at a concentration of 0.90 mg/dL, generating a potential error of up to 33% in the estimation of GFR. The bias range variability was mainly related to manufacturer equipment rather than the type of method, with 63% of alkaline picric acid methods and 50% of the enzymatic methods giving significant biases. In this study,[72] Miller and coworkers concluded that if the maximal tolerable global error for calculated GFR was 15%, the maximal allowable calibration bias would be 0.034 at Scr of 1.0 mg/dL. Appling this clinical criterion, only 18% of the peer groups met the performance goal. Depending on the method used for this adjustment, Scr values will be different in the same patient and produce significant differences in eGFR, as shown in Table 8, where 4 different correction strategies for "noncreatinine chromogen" interference were considered in the same 20,108 patients.[74] Scr is different and, consequently, 4v-MDRD eGFR, ranged from 72 ± 18 to 133 ± 56 mL/min per 1.73 m^2 in females and from 76 ± 16 to 98 ± 32 in males. Enzymatic assays do not detect noncreatinine chromogens and yield lower values for Scr. Thus, in a recent study, an enzymatic assay to be traceable to the gold standard method (ID-MS) was used to refit the MDRD equation.[79] However, Lamb and coworkers[73] recently showed in a sample of 46 adults (GFR = 55 ± 17 mL/min per 1.73 m^2) that eGFR given by 4v-MDRD equation was still biased, varying by 14% according to the creatinine assay methodology (Table 9).

In conclusion, the best solution would be: (1) a worldwide standard, (2) the use of specific assays for serum creatinine, and (3) the development of a new formula. A short-term solution, which has been already recommended,[80] is to line up Scr assay to that one used by the MDRD laboratory (or

Table 8 Serum Creatinine (Scr) Values From Different Strategies[34,74-76] to Correct the Interference due to "Non-Creatinine Chromogens" and Corresponding GFR Estimated Values With the 4v-MDRD Prediction Equation in 20,108 Patients

	Van Biesen[74] (2006)	Coresh[75] (2002)	Hallan[76] (2004)	Froissart[34] (2005)
Males, Scr (mg/dL)	1.13 ± 0.28	0.93 ± 0.28	1.01 ± 0.31	1.19 ± 0.33
4v-MDRD (mL/min/1.73 m^2)	76 ± 16	98 ± 32	90 ± 30	66 ± 10
Females, Scr (mg/dL)	0.93 ± 0.25	0.73 ± 0.26	0.79 ± 0.28	0.97 ± 0.29
4v-MDRD (mL/min/1.73 m^2)	72 ± 18	133 ± 56	121 ± 50	94 ± 27

Values are mean ± SD. The mean GFR varies from 72 to 133 mL/min per 1.73 m^2.
Adapted from Van Biesen et al.[74]

Table 9 Susceptibility of 4v-MDRD eGFR to Different Creatinine Assay Methodologies

	Creatinine (μmol/L)		4v-MDRD (mL/min/1.73 m²)	
	Median	Difference (95% CI)	Mean	Difference (95% CI)
ID-MS	94.6		63.3	40.7
Enzym. (Ortho)	97.5	19.6%	59.8	35.1
Enzym. (Roche)	87.5	16.9%	68.8	46.8
Jaffe rate	95.0	35.7%	60.4	33.6

Reference method for creatinine assays was the isotopic-dilution mass spectrometry (ID-MS).
Reference method for GFR measurements was the ^{51}Cr-EDTA plasma clearance (GFR = 54.7 ± 17.0 mL/min per 1.73 m²).
This table, adapted from Lamb et al,[73] gives median values and 95% confidence intervals (95% CI) for differences (expressed in percentages) between the estimated and reference values for either creatinine assays (versus ID-MS) or 4v-MDRD estimations (versus ^{51}Cr-EDTA plasma clearance).

alternatively to apply correction factors suitable for their own creatinine assays). In view of analytical variability, the National Kidney Disease Education Program (NKDEP)[80] recommended use of the 4v-MDRD equation published in 2005 (calibration factor 175)[27] or in 2000 (calibration factor 186),[26] depending on whether a creatinine method has been calibrated to traceable ID-MS method or not.

Non-GFR Variability of Scr

A major limitation of prediction equations based-on Scr relies on the nonstraightforward relationship between Scr and GFR. A significant increase in Scr will be detected only when GFR should have decreased to approximately 60% of its normal level.[23] The influence of nonrenal parameters on Scr explains the different profiles of relationship between Scr and GFR observed in populations with and without CKD.[10,75,76,81-83] The non-GFR variability is estimated by equations supposed to model creatinine production with factors such as age, gender, race, weight, body mass index, and activity. However, ingestion of cooked meat (rapid increase in Scr), muscle/fat mass ratio in body weight, and extrarenal creatinine degradation by intestine bacteria (blocked by some antibiotics) cannot be modeled. Rule and coworkers[83] found different regression slopes of Scr versus GFR in healthy population, transplant recipients and patients with native CKD (Fig. 2). For example, healthy subjects have 15% greater GFR than patients with native kidney disease when considering the same Scr level of 1.0 mg/dL.

Another issue is the range of GFR, which differs between healthy and diseased populations. The interval of variation of GFR is larger in populations with CKD (by a factor 10 from 6 to 60 mL/min per 1.73 m²) than in healthy persons (by a factor 3 from 60 to 180 mL/min per 1.73 m²). It results a greater signal (GFR variation) to noise (non-GFR variation) ratio for Scr level in CKD versus healthy populations. Scr could eventually depend stronger on creatinine production than on GFR, with higher variability also in the bias. Among healthy people, an increase in Scr from 0.8 to 1.2 mL/dL reflects more probably changes in muscle mass or protein intake, rather than GFR impairment.[10]

Another limitation is the incorrect hypothesis that the interference of noncreatinine chromagens is constant, whatever the GFR level, allowing use of a linear recalibration equation.[75,76] In normal renal function, noncreatinine chromogens comprise approximately 14% (range 5-22%) of the total Jaffe's reaction, whereas it contributed to only 5% (range 0-15%) of the total measured level when Scr ranged from 6 to 30 mg/dL.[84] Thus, their relative effect is greater and will induce greater bias and bias variability[75] at greater GFR levels in early stages of CKD and healthy persons (about 25% at GFR = 100 mL/min per 1.73 m² and about 10% at GFR = 25 mL/min per 1.73 m²).

Evaluation of Prediction Formulae Based on Serum Cystatin C

Serum cystatin C concentration (ScysC) is argued to be a reliable surrogate marker of GFR. In a meta-analysis of 46 articles through December 2001, Dharnidharka and coworkers[85] concluded that ScysC is superior to Scr as a marker of GFR, according to correlation coefficients and receiver-operating-curve (ROC) analysis. Similarly, in a review of 24 articles from June 2000 to September 2001, Laterza and cowork-

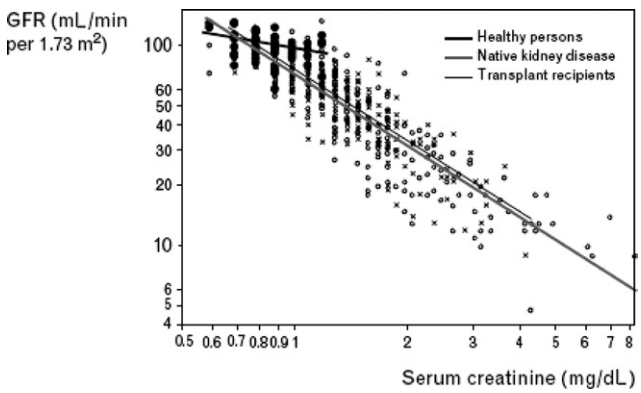

Figure 2 Relationship between serum creatinine and measured GFR (unlabeled iothalamate clearance) on a logarithmic scale in 50 healthy subjects (closed circles), 204 patients with native kidney disease (open circles) and in 206 solid organ transplant recipients. (Adapted with permission from Rule.[83])

ers[86] concluded, when examining clinical utility, that ScysC was superior to Scr in 15 studies, whereas ScysC was equivalent (but providing no advantages) than Scr in the remaining 9 studies.

Cystatin C is a 121-amino-acid, 13-kDa protein that is a member of a family of potent, noncovalent, competitive inhibitors of mammalian lysosomal cysteine proteinases. It has multiple biological functions, including control of extracellular proteolysis and modulation of the immune system. Considered as a housekeeping gene, it is produced in all nucleated cells at a "relative constant" rate. Cystatin C seems to have possible advantages over serum creatinine as a surrogate of GFR, because of its claimed "constant" rate of production and its intrarenal handling, being freely filtrated, completely reabsorbed and, then catabolized by the tubular epithelial cell.[87] Thus, Cystatin C could be a more sensitive marker for early and mild changes of GFR in the detection in renal function, with a particular interest in the pediatric population (especially in patients younger than 4 years of age) and renal transplant recipients. Unfortunately, several studies have shown that ScysC levels may be influenced by a number of factors other than GFR. Consequently, formulae should be developed in which such factors have to be included, just as is done for prediction equation-based Scr. From data collected in the Prevention of Renal and Vascular End-Stage Disease (PREVEND) cohort, older age, male gender, greater weight, greater height, current cigarette smoking, and higher serum C-reactive protein (CRP) levels were independently associated with greater ScysC, even after adjusting for creatinine clearance.[88] In this PREVEND cohort, they was no evidence that multivariate ScysC-based estimates of renal function were superior to multivariate Scr-based estimates. McDonald and coworkers[89] recently reported that in 77 patients with CKD (mean GFR 46 ± 29 mL/min per 1.73 m^2), only absolute GFR and total lean mass significantly explained the variance in ScysC. Moreover, the prediction equation when including total lean mass performed better than the equation with only ScysC, with "accuracy within 30%" being 71 versus 51%, respectively.

Cystatin C may have an antiinflammatory protective role against atherosclerosis and may reflect inflammation, which predicts cardiovascular diseases independently of GFR.[90,91] ScysC has been showed to decrease in hypothyroidism[92] and, conversely, to increase in hyperthyroidism and with the use of glycocorticoid.[93] These effects support that the generation of cystatin C may be increased in settings of increased metabolic rate, as a result of increased cell turnover.

Cystatin C production may vary, but cystatin C excretion, either renal or extrarenal, also may change over the whole GFR range of CKD. Urinary cystatin C excretion and its fractional renal excretion significantly increased in adults with decreased creatinine clearance.[94] The extrarenal excretion of cystatin C is approximately 20 mL/min per 1.73 m^2 (ie, about 15% of the total clearance) and may increase at reduced GFR.[95,96] Considering all these factors, it is not surprising that different regression slopes between measured GFR (iothalamate clearance) and ScysC were reported in healthy persons, patients with native kidney diseases and transplant recipients.[81] In conclusion, cystatin C should not be interpreted as purely a marker of GFR.

Automated immuno-assay to measure cystatin C has been developed based on either particle-enhanced turbidimetric immuno-assay (PETIA) or particle-enhanced nephelometric immuno-assay (PENIA). The PETIA method generally produces reference values that are 20-30% greater than those from PENIA methods.[86] PENIA method is generally more precise with narrower 95% confidence interval and a stronger correlation between GFR and the reciprocal of ScysC.[85,97] Regarding this very important issue, ScysC has no advantage on Scr. Another unresolved issue is the requirement of standardized calibration for ScysC measurements. Presently, different GFR prediction formulae are used for PENIA and PETIA methods (Table 10).[66,69,81,95,98-100]

An important limitation of ScysC compared with Scr is its greater intraindividual variability (75% versus 7%, respectively).[101] Indeed, the interindividual variation explains 25% whereas intraindividual variance explains 75% of biological variability. A significant ($P \leq 0.05$) difference for sequential values should be 37% for ScysC (only 14% for Scr) The authors concluded that Scr was still a better marker for detecting GFR changes over the time in individual with CKD.[101]

Table 10 Prediction Equations Based on Serum Cystatin C (ScysC) Values Determined Either by Particle-Enhanced Turbidimetric Immuno-Assay (PETIA) or Particle-Enhanced Nephelometric Immuno-Assay (PENIA) in Adults and Children

Adults		
Hoek[99] (2003)	$GFR = (80.35/ScysC) - 4.32$	PENIA
Sjöström[95] (2005)	$GFR = (124/ScysC) - 22.3$	PETIA
Grubb[100] (2005)	$GFR = 89.12/ScysC^{-1.675}$	PETIA
	$GFR = 99.19/ScysC^{-1.713} \times 0.883$ (if female)	
Rule[81] (2006)	$GFR = 66.8/ScysC^{-1.30}$	PENIA
	$GFR = 76.6/ScysC^{-1.16}$ (if transplant)	
Children		
Bökemcamp[98] (1999)	$GFR = 137/ScysC - 20.4$	PETIA
Filler and Lepage[66] (2003)	$GFR = 91.62 \times (1/cysC)^{-1.675}$	PENIA
Grubb[100] (2005)	$GFR = 84.69 \times ScysC^{-1.693} \times 1.384$ (if age <14 yrs)	PETIA
Zappitelli[68] (2006)	$GFR = 75.94/(ScysC)^{-1.17} \times 1.2$ (if transplant)	PENIA

GFR in mL/min/1.73 m^2 and ScysC in mg/L.

Potential Specific Indications

As shown in the first part of this review article, prediction equations based on Scr are not very precise or accurate in the detection of early and mild changes of GFR, especially in the pediatric population and renal transplant recipients. Consequently, looking for a potential benefit of prediction equations based-on ScysC over prediction equations based-on Scr, we will only focus on these specific indications.

Diagnosis of Early and Mild Decline in GFR

In a short series of 51 patients with impaired renal function, Coll and coworkers[102] reported a greater sensitivity (93%) for ScysC than for Scr (87%) in the detection of patients with a GFR ≤84 mL/min per 1.73 m^2, the threshold for CKD in this study. ScysC started to increase at GFR >88 mL/min per 1.73 m^2, whereas Scr did when GFR was ≥75 mL/min per 1.73 m^2. Similar results for the detection of a reduced GFR (≤80 mL/min per 1.73 m^2) were reported in 52 type-2 diabetes patients.[103] Nevertheless, in this series (mean GFR = 77 mL/min per 1.73 m^2, range 16-137), the diagnostic accuracy of ScysC and C-G eGFR were similar (90 and 85%, respectively). In 30 patients with type-2 diabetes and GFR in the range of hyperfiltration (GFR = 153 ± 27 mL/min per 1.73 m^2), 100/ScysC as been reported much more strongly correlated with GFR changes over a 4-year follow-up period ($r = 0.77$, $P < 0.001$) than with serial measurements of 100/Scr ($r = 0.32$, $P = 0.08$), C-G eGFR ($r = 0.22$, $P = 0.25$) and 4v-MDRD eGFR ($r = 0.31$, $P = 0.09$), especially when GFR was higher than 100 mL/min per 1.73 m^2.[50]

Renal Transplant Recipients

As previously reported by Keevil and coworkers[101] in healthy volunteers, ScysC had greater intraindividual variations than Scr in steady-state kidney transplant recipients.[104] This might be critical for early detection of rejection and other function impairment. In pediatric renal transplant recipients, ScysC were significantly greater in transplant recipients than in the control healthy group, although both groups did not have significantly different inulin clearance values. The prediction formula based on ScysC derived from nontransplant recipients underestimated GFR by approximately 25% in children transplant recipients with similar renal function.[98] Similarly in adult transplant recipients, Rule and coworkers reported an underestimation about 20%, when using prediction formula derived from patients with native CKD in adults.[81] Consequently, the authors proposed a specific prediction formula[81] as Zapitelli and coworkers[68] in children (Table 10). In a recent study, White and coworkers compared prediction equation-based Scr and ScysC in 198 adult renal transplant recipients.[43] Filler and Lepage,[66] Le Bricon and coworkers,[105] and Rule and coworkers[81] made comparisons using equations based on ScysC and C-G for eGFR and 4v-MDRD for Scr. Although the Filler equation outperformed 4v-MDRD and C-G equations for the classification of CKD stage (76% versus 65% and 69%, respectively), the area under the receiver-operating curve for overall stage classification was uniformly poor for all equations (0.52-0.56). All equations underestimated GFR and had a poor precision (mean standard deviation of the difference between mGFR and eGFR being 12 mL/min per 1.73 m^2). Accuracy within 10% was about 40% for Filler and Le Bricon equations, about 30% for the C-G and 4v-MDRD equations, and only 25% for the Rule equation. The authors concluded that the overall diagnosis accuracies were similar for both ScysC- and Scr-based equations and that there was currently no evidence that the adoption of these equations for classification would lead to improved recognition of CKD complications or patient care.

Pediatric Population

Analyzing 14 studies involving 782 subject samples that have compared ScysC with Scr, recent guidelines[106] concluded that is difficult to draw any definitive conclusion about the superiority of cystatin C over serum creatinine. For example, in a series of 103 patients younger than 18 years (13 ± 5 years) with a mean GFR (±SD) of 74 (±35) mL/min per 1.73 m^2 (using unlabeled iothalamate urinary clearance), Zappitelli and coworkers[68] compared eGFR from Schwartz's formula[28] to volumes obtained from a new equation and 3 previously published formulae based on ScysC.[68] As recommended to improve performance characteristics of the prediction equation, the authors redefined the coefficients by means of regression from the studied sample rather than using coefficients previously published by Bokenkamp,[98] Filler,[66] and Grubb[100] (Table 11). Although all cystatin C-based equations had low bias and a better precision than Schwartz's equation, 95% limits of agreement were large, ranging from −36 to + 36 mL/min per 1.73 m^2 (−42 to + 56 mL/min per 1.73 m^2 for Schwartz's formula). The accuracy within 30% was also improved to approximately 80% versus 65% for Schwartz's formula. However, if the cystatin C-based equations were more sensitive, they were nevertheless less specific than Schwartz's formula for screening GFR <90 mL/min per 1.73 m^2 (sensitivity: 94 versus 80%, specificity: 67% versus 81%, respectively).

As Bouvet and coworkers,[107] Zappitelli and coworkers derived a prediction formula using both ScysC and Scr to estimate GFR and reported some increase in the percentage of eGFR in the accuracy within 30% range. In conclusion, as stated in a recently published review,[96] "several important questions remain before ScysC and ScysC-based prediction equations can be recommended for use in clinical practice."

Recommendations and Conclusions

If there is no recommendation for the use of a ScysC-based prediction equation in clinical practice, what are the current recommendations for use of prediction equations based of Scr? Rather than comment on conclusions from recently published reviews and analyses,[11,77,83,108,109] I would like to summarize the main conclusions and recommendations of the KDIGO controversies conferences[2,3] and from the report of

Table 11 Comparison of Performance Characteristics of Schwartz Equation (Scr) and Bokenkamp, Filler, and Zappitelli Equations (ScysC) in a Pediatric Population

	Mean Bias (95% CI)	95% LOA	Within 30% of GFR (%)	Sensitivity (%)/Specificity (%) for mGFR <30 mL/min per 1.73 m^2	Sensitivity (%)/Specificity (%) for mGFR <90 mL/min per 1.73 m^2
Schwartz[28]	6.9 (2.3-11.6)	−42.3 to 56.1	65	74/100	80/81
Bokenkamp[98]	0.0 (−3.4 to 3.3)	−35.7 to 35.7	73	68/100	94/67
Filler[66]	−1.4 (−5.0 to 2.1)	−39.2 to 36.3	79	84/98	94/67
Zappitelli[68]	−1.2 (−4.4 to 2.3)	−36.5 to 34.3	82	90/100	94/67

mGFR is the GFR measured by urinary clearance of unlabeled iothalamate (mGFR = 74 ± 35 mL/min per 1.73 m^2) in 103 patients (13 ± 5 years old).
Schwartz[28] and cystatin C-based equations (Bokenkamp,[98] Filler,[66] Grubb,[100] and Zappitelli[68]) used coefficients derived on-site from the study sample.
Data from Grubb equation with new coefficients locally derived are not shown, as "modified" Filler and Grubb equations were almost identical (GFR in mL/min per 1.73 m^2 = 79.04 × [1/ScysC]$^{1.156}$ and 79.2 × [1/ScysC]$^{1.157}$ × 1.002 for age <14 yrs, respectively).
Mean bias and 95% limit of agreement (95% LOA) are mL/min per 1.73 m^2.
Adapted from Zappitelli et al.[68]

Table 12 When Clearance Measurements May Be Necessary to Estimate GFR

- Extremes of age (elderly, children)
- Extremes of body size (obesity, type 2 diabetes, low body mass index, ie, <18.5 kg/m^2)
- Severe malnutrition (cirrhosis, end-stage renal failure)
- Grossly abnormal muscle mass (amputation, paralysis)
- High or low intake of creatinine of creatine (vegetarian diet, dietary supplements)
- Pregnancy
- Rapidly changing kidney function
- Prior to dosing (high toxicity drugs, excreted by the kidney)
- Prior to kidney donation

Adapted from KDIGO recommendations.[2]

the laboratory working group of the National Kidney Disease Education Program (NKDEP).[80]

The main limitations to use prediction equations based on Scr, including MDRD Study equations, are as follows:

- Standardization of calibration does not correct for analytical interferences ("nonspecificity bias").
- Variability in Scr measurement makes all prediction equations substantially less accurate in normal and the slightly increased range of Scr (<1.5 mg/dL or <133 μmol/L), which is the relevant range for detecting CKD (GFR <60 mL/min per 1.73 m^2 in adults).
- Prediction equations, including the MDRD Study equation, have not been adequately tested in children, elderly >75 years, pregnant woman, patients with serious comorbid conditions, or persons with extremes of body weight, body size, muscle mass, or nutritional status. Applications to these patient groups may lead to error in eGFR.
- Adjustment of routine method calibration to traceable gas chromatography, liquid chromatography–isotope–dilution mass spectrometry (GS-IDMS) will impact clinical interpretation.

Thus, the recommendations are:

- Report eGFR values >60 mL/min per 1.73 m^2 as >60 mL/min per 1.73 m and not as a exact number. For values <60 mL/min per 1.73 m^2, the report should give the numerical estimate rounded to the nearest whole number, such as 35 mL/min per 1.73 m^2. If creatinine assay is calibrated to a traceable reference method, the numerical value could be reported till GFR ≥90 mL/min per 1.73 m^2.
- Average multiple measurements are necessary to improve the precision of eGFR because values from 45 to 59 are estimated with less precision.

The clinical circumstances in which clearance measurements may be necessary are shown in Table 12. There are situations in which eGFR may be unreliable or where a high degree of accuracy is required. Thus, GFR measurements may be necessary at extremes of age, such in elderly and

children, at extremes of body size (obesity, such as in type-2 diabetes patients, or low body mass index <18.5 kg/m^2), in severe malnutrition (such as cirrhosis, renal failure, cancer, etc) or in abnormal intake of creatinine or creatine, in the presence of grossly abnormal muscle mass, during pregnancy and when kidney function is changing rapidly. GFR may also be measured when a high accuracy is required as for example before kidney donation or dosing with anticancer drugs which have high toxicity and are excreted by the kidney. Finally, GFR should be measured by a clearance method, when renal function is the primary outcome of clinical research (KDIGO stated that urinary clearance of exogenous filtration markers was less susceptible to error than plasma clearance).

In other words, these recommendations support the use of prediction equation based-on Scr if a patient has a known CKD, with neither a very low renal function, nor a near-normal function at the opposite. These prediction equations are not currently validated for the detection of early decline of GFR in patients with risk factors (possible role of cystatin C?), the estimation of disease progression to determine prognosis or to confirm the need of dialysis of transplantation, but may be used to assess the effectiveness of therapy according to clinical outcome issues.

Other biomarkers for the prediction of renal disease progression are in evaluation, such as C-reactive protein (CRP),[110] serum and urinary interleukin-6 (IL-6),[111] asymmetrical dimethyl arginine (ADMA),[112] symmetrical dimethyl arginine (SDMA),[113] or neutrophil gelatinase-associated lipocalin (NGAL).[114] However, we should keep in mind that plasma or urinary clearance measurements with radiolabeled tracers are safe (because of the tracer dose), easy to perform with a single bolus injection, accurate with low bias and high precision, and have good reproducibility.

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