Alternatives for the Bedside Schwartz Equation to Estimate Glomerular Filtration Rate in Children

Hans Pottel, Laurence Dubourg, Karolien Goffin, and Pierre Delanaye

The bedside Schwartz equation has long been and still is the recommended equation to estimate glomerular filtration rate (GFR) in children. However, this equation is probably best suited to estimate GFR in children with chronic kidney disease (reduced GFR) but is not optimal for children with GFR >75 mL/min/1.73 m^2. Moreover, the Schwartz equation requires the height of the child, information that is usually not available in the clinical laboratory. This makes automatic reporting of estimated glomerular filtration rate (eGFR) along with serum creatinine impossible. As the majority of children (even children referred to nephrology clinics) have GFR >75 mL/min/1.73 m^2, it might be interesting to evaluate possible alternatives to the bedside Schwartz equation. The pediatric form of the Full Age Spectrum (FAS) equation offers an alternative to Schwartz, allowing automatic reporting of eGFR since height is not necessary. However, when height is involved in the FAS equation, the equation is essentially equal to the Schwartz equation for children, but there are large differences for adolescents. Combining standardized biomarkers increases the prediction performance of eGFR equations for children, reaching P10 ≈ 45% and P30 ≈ 90%. There are currently good and simple alternatives to the bedside Schwartz equation, but the more complex equations combining serum creatinine, serum cystatin C, and height show the highest accuracy and precision.

Key Words: Bedside Schwartz equation, Pediatric FAS Equation, Serum cystatin C, Serum creatinine

BACKGROUND

Estimating glomerular filtration rate (GFR) in children has a 40-year-old history, dating back to 1976 when Schwartz and colleagues[1] published his very simple bedside formula eGFR = 0.55 × L/Scr, where L is the height of the child and Scr represents serum creatinine (Scr) expressed in mg/dL. The coefficient of 0.55 has been replaced by 0.413 for children and adolescents, when isotope dilution mass spectroscopy (IDMS) standardized assays for Scr became available.[2] The height of the child serves as surrogate for muscle mass, since creatinine, which is a breakdown product of muscle mass, changes during growth of the child. The Schwartz formula has been recommended by KDIGO to estimate GFR in children. One downside of this equation is the need for the height of the child, which is commonly not available in the clinical laboratory, making automatic reporting of estimated glomerular filtration rate (eGFR) along with Scr impossible. Automatic reporting of eGFR for adults is mandatory in many countries, allowing early identification of patients with chronic kidney disease (CKD), with evidence demonstrating the benefits of early referrals.[3] Indeed, in adults, evidence-based strategies have been shown to prevent progression of CKD.[4] The rationale for automatic reporting in children is less clear, since there are multiple risk factors, such as hypertension and proteinuria, for progression of CKD in children. Moreover, the incidence of CKD in children is much lower than in the adult population. However, early reporting of decreased eGFR may allow early detection and intervention which can only be to the benefit of the child.

In a recent overview, Pottel[5] has extensively reported on the different eGFR equations for children, and therefore, in this review, we will focus on alternative equations applicable to (multiple) biomarkers for standardized assays only. We then give specific insights comparing the bedside Schwartz equation with the pediatric part of the Full Age Spectrum (FAS) equation. Next, we elaborate on the possibility to define kidney function based on the reference interval of single biomarkers or the combination of biomarkers, without using eGFR equations. Finally, we present the prediction performance of eGFR equations combining multiple (standardized) biomarkers, namely Scr and serum cystatin C (ScysC), using real measured GFR data as comparison.

REFERENCE METHOD, STANDARDIZED Scr, AND CYSTATIN C

The gold standard method to obtain measured GFR (mGFR) is kidney clearance of inulin, but several reference methods have shown acceptable accuracy with sufficient scientific evidence.[6] The mGFR data used in this article have been obtained by the gold standard inulin kidney clearance method or by iohexol or ^{51}Cr-EDTA plasma clearance, using the slope-intercept method followed by the Bröchner-Mortensen correction.[7]

Standardization of Scr assays with reference to the gold standard IDMS method has been introduced some 10–15 years ago. Most enzymatic Scr assays are nowadays equivalent to the IDMS method. The data used in this article were all obtained with IDMS traceable enzymatic Scr assays, and it should be emphasized that this is

From the Department of Public Health and Primary Care, KU Leuven Campus Kulak Kortrijk, Kortrijk, Belgium; Exploration Fonctionnelle Rénale, Groupement Hospitalier Edouard Herriot, Hospices Civils de Lyon, Lyon, France; Department of Nuclear Medicine & Molecular Imaging, University Hospital Leuven, Leuven, Belgium; and Nephrology-Dialysis-Transplantation, University of Liège, CHU Sart Tilman, Liège, Belgium.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Address correspondence to Hans Pottel, Department of Primary Care and Public Health, KU Leuven Kulak, Etienne Sabbelaan 53, 8500 Kortrijk, Belgium. E-mail: Hans.Pottel@kuleuven-kulak.be

1548-5595/$36.00

https://doi.org/10.1053/j.ackd.2017.10.002

critically important for children that have lower Scr values, requiring high accuracy and precision results.[8] Indeed, compensated Jaffe assays may give negative Scr concentrations after compensation (= subtracting a constant value) in very young children. Limits of quantitation of the assays should be as low as 0.15 mg/dL, since newborns typically have Scr values of about 0.23 mg/dL 1 month after birth.[9]

Many clinical laboratories still use the Jaffe-type Scr assays instead of enzymatic Scr assays due to the higher cost of the latter, but the gap becomes smaller and more and more laboratories switch to enzymatic assays, especially for children.

The situation is different for ScysC. In 2010, there became a certified standard available (ERM-DA471/IFCC)[10] against which ScysC-assays could be calibrated, and only very recently a candidate isotope dilution mass spectrometry method for cystatin C was presented and can potentially serve as gold standard method.[11] Part of the data in this study were obtained with the calibrated particle enhanced turbidimetric (PETIA, Tina quant®) assay of Roche, and part of the data were obtained with the calibrated particle enhanced nephelometric (PENIA) method of Siemens. Calibration of cystatin C assays is as essential as for Scr. Although there is still work to do, as the current certified material is about five times higher than the "normal" cystatin C values, and only a one-point calibration is applied, it has been shown that calibration against the certified material reduces variability and increases accuracy.[11-12]

CLINICAL SUMMARY

- The pediatric form of the Full Age Spectrum (FAS) equation offers an alternative to the bedside Schwartz equation, allowing automatic reporting of estimated glomerular filtration rate (eGFR) since height is not necessary, and mostly not available in the clinical laboratory.
- Combining standardized biomarkers increases the prediction performance of eGFR equations for children, reaching P10 ≈ 45% and P30 ≈ 90%. The bivariate Schwartz equation and the multiplicative form of the FAS equation are very similar.
- eGFR equations perform best in the population for whom they were originally designed for, with preference for FAS in healthy and mildly kidney diseased children (GFR > 60 mL/min/1.73 m^2) and with preference for Schwartz in the kidney diseased children (GFR < 60 mL/min/1.73 m^2).
- We recommend that clinical laboratories should report serum creatinine along with the height-independent FAS prediction. Clinicians would use the height-dependent FAS, and in case, the FAS eGFR is < 60 mL/min/1.73 m^2, use the Schwartz equation to obtain a second estimate of GFR.

MULTIPLE BIOMARKER EQUATIONS

To our knowledge, there are only a very limited number of combined Scr and ScysC-based eGFR equations for children available that were obtained with reference to IDMS traceable Scr and the certified standard for ScysC. Although the best performing combined Schwartz equation was based on height, Scr, ScysC, blood urea nitrogen, and gender, ScysC was not calibrated against the certified standard when this equation was derived. This complex Schwartz formula was originally published in 2009 using turbidimetric ScysC values[13] and was

$$\mathrm{eGFR} = 39.1\ (\mathrm{Ht}/\mathrm{Scr})^{0.516}\ (1.8/\mathrm{CysC})^{0.294}$$

$$(30/\mathrm{BUN})^{0.169}\ 1.099^{\mathrm{male}}\ (\mathrm{Ht}/1.4)^{0.188}$$

The equation was reevaluated using immunonephelometric ScysC values[14] and was

$$\mathrm{eGFR} = 39.8\ (\mathrm{Ht}/\mathrm{Scr})^{0.456}\ (1.8/\mathrm{CysC})^{0.418}$$

$$(30/\mathrm{BUN})^{0.079}\ 1.076^{\mathrm{male}}\ (\mathrm{Ht}/1.4)^{0.179}$$

This Chronic Kidney Disease in Children Cohort Study equation showed high accuracy and precision and minimal bias in the Chronic Kidney Disease in Children Cohort Study population, that is, this equation worked well in children with CKD in a range of GFR from 15 to 75 mL/min/1.73 m^2. Confirmation of the utility of this equation is desirable in other populations of children (healthy and diseased), but both equations suffer from the drawback that ScysC has not been calibrated against the certified standard, and since its original publication in 2009 and republication in 2012, only a limited number of external validation studies for both equations have been published.[15-21] We have used the univariate (for Scr or ScysC) and bivariate form (with both Scr and ScysC) of the above equation (without the blood urea nitrogen information) on our data to compare it with alternative equations. An overview of the equations used in this study is given in Table 1.

In the following section, we restrict ourselves to equations that were derived and are applicable to standardized biomarkers Scr and ScysC.

Recently, Pottel and colleagues[22-23] published the FAS equation to estimate GFR from Scr and/or ScysC, or from the combination of both biomarkers. The pediatric form (which is actually valid between 2 and 40 years of age) of the Scr-based FAS equation is a very simple equation:

$$\mathrm{FAS}_{\mathrm{crea}} = 107.3/[\mathrm{Scr}/\mathrm{Q}_{\mathrm{crea}}]$$

The form of this equation follows from modeling the data of Piepsz[24-25] and establishing a plateau value of 107.3 mL/min/1.73 m^2 for healthy children between 2 and 15 years of age. As Scr raises linearly with age in that age period and following the correlation between GFR and the reciprocal of creatinine, Pottel and colleagues[26] normalized Scr to make it independent of age (and sex) and established a direct relationship between

Table 1. Overview of Equations Used in This Comparison Study, With Reference to the Original Publication

Name (Reference)	Equation
$Schwartz_{bed}$[2]	0.413 Ht/Scr (Scr in mg/dL, Ht in cm)
$Schwartz_{crea}$[14]	42.3 $(Ht/Scr)^{0.780}$ (Scr in mg/dL, Ht in m)
$Schwartz_{cysC}$[14]	40.9 $(1.8/ScysC)^{0.931}$ (ScysC in mg/L)
$Schwartz_{combi}$[14]	41.6 $(Ht/Scr)^{0.443}$ $(1.8/CysC)^{0.479}$ (Scr in mg/dL, ScysC in mg/L, Ht in m)
FAS_{crea}[26-28]	107.3/[Scr/Q_{crea}] with Q_{crea} (mg/dL) function of age (Table 2) or using $Q_{crea}(Age) = 0.21 + 0.057 \times Age - 0.0075 \times Age^2 + 0.00064 \times Age^3 - 0.000016 \times Age^4$ for boys $Q_{crea}(Age) = 0.23 + 0.034 \times Age - 0.0018 \times Age^2 + 0.00017 \times Age^3 - 0.0000051 \times Age^4$ for girls
$FAS_{crea}(Ht)$[28]	107.3/[Scr/Q_{crea}] with Q_{crea} (mg/dL) function of height (Table 2) or using $Q_{crea}(height) = 3.94 - 13.4 \times Ht + 17.6 \times Ht^2 - 9.84 \times Ht^3 + 2.04 \times Ht^4$ (Ht in m)
FAS_{cysC}[23]	107.3/[ScysC/Q_{cysC}] with $Q_{cysC} = 0.82$ mg/L for children
FAS_{combi} and $FAS_{combi}(Ht)$[23]	107.3/[Scr/Q_{crea} + ScysC/Q_{cysC}]
FAS_{Mult} and $FAS_{Mult}(Ht)$ (unpublished)	$107.3/\sqrt{\frac{Scr}{Q_{crea}} x \frac{ScysC}{Q_{cysC}}}$
LM-REV[29]	LM-REV = exp[X – 0.0158 × Age + 0.438 × ln(Age)] with $X = 2.50 + 0.0121 \times (150 - Scr)$, for females and Scr <150 μmol/L $X = 2.50 - 0.926 \times \ln(Scr/150)$, for females and Scr ≥150 μmol/L: $X = 2.56 + 0.00968 \times (180 - Scr)$, for males and Scr<180 μmol/L: $X = 2.56 - 0.926 \times \ln(Scr/180)$, for males, and Scr ≥180 μmol/L Conversion: Scr (mg/dL) = Scr(μmol/L)/88.4
CAPA[30]	$130 \times ScysC^{-1.069} \times age^{-0.117} - 7$ (ScysC in mg/L)

Abbreviations: CAPA, Caucasian Asian Pediatric Adult; FAS, Full Age Spectrum; LM-REV, revised Lund-Malmö; Scr, serum creatinine.

the value of 107.3 mL/min/1.73 m^2 and the reciprocal of this normalized Scr. When a child has a Scr level equal to the Q_{crea} value, which is defined as the mean or median Scr value of the 1-year age-specific distribution of Scr of healthy children, then $Scr/Q_{crea} = 1$ and eGFR = 107.3 mL/min/1.73 m^2, the mean GFR value for healthy children. The concept of the FAS equation is that it essentially matches mean Scr levels with mean GFR levels in healthy populations. The pediatric FAS equation was first published in 2012[27] and extended by Hoste and colleagues[28] to adolescents in 2015 and is now extended to the full age spectrum.[22] It has been shown that this concept also applies for other biomarkers: Scr/Q_{crea} can be replaced by $ScysC/Q_{cysC}$ or a combination of both biomarkers, for example, the average of both normalized biomarkers: $(Scr/Q_{crea} + ScysC/Q_{cysC})/2$. In case of ScysC, the normalization factor $Q_{cysC} = 0.82$ mg/L[23] (Table 1).

Other eGFR equations have been developed for children, but none of them combines standardized Scr and ScysC in one equation for children. However, it has recently been shown that combining the Scr-based revised Lund-Malmö (LM-REV) equation[29] with the ScysC-based CAPA equation[30] also shows higher accuracy and precision than any single biomarker–based equation.[31]

The LM-REV equation and CAPA equation are also presented in Table 1.

Combining LM-REV with CAPA simply means to take the mean of both equations: (LM-REV + CAPA)/2.

Contrary to the FAS equation, which is based on the concept that mean normalized Scr matches mean GFR, the LM-REV and CAPA equations, like all other eGFR equations, have been derived from statistical modeling of measured GFR data against Scr (or ScysC) and demographic variables.

In the following sections, we focus on the popular bedside Schwartz equation and compare it to the pediatric FAS equation, find out the benefits of using combined biomarkers as such and combined biomarker equations, by comparing the combined Schwartz equation, the combined FAS equation, and the combination of Lund-Malmö and CAPA to measured GFR.

COMPARING THE SIMPLE BEDSIDE Scr-BASED SCHWARTZ WITH FAS

The normalization factor Q_{crea} in the pediatric FAS equation can be obtained in two different ways: (1) Q_{crea} can be considered as the mean Scr value of the age-specific distribution of healthy children, but (2) Q_{crea} can also be matched to the height of the child, by use of growth curves (Table 2). Table 2 should be interpreted with caution, as these values have been determined in a Belgian population of healthy children. The mean Scr values were obtained from a large hospital database[9] which was subdivided according to age/gender. For each 1-year age period, the Scr values of healthy children were selected and the mean/median (which is the same when the distribution is Gaussian) is presented as Q_{crea} in Table 2. National Belgian growth curves[32] were used to match age with mean height of the children. To estimate GFR from Scr, there are two possibilities: either the Q_{crea} corresponding to the age of the child can be considered or the Q_{crea} corresponding to the height of the child can be chosen, which are not necessarily the same for a child at a specific age with a specific height. This is especially true during adolescence, where children may be variable in height at the same age. Height is probably a better indicator for muscle mass and thus for the corresponding Scr value. This is also the reason

Table 2. Mean or Median Scr Values for Healthy Children (Q_{crea}) in mg/dL, According to Age or Height (Ht)

	Ht (cm)	Q_{crea} (mg/dL)
Age (y)		
1	75.0	0.26
2	87.0	0.29
3	95.5	0.31
4	102.5	0.34
5	110.0	0.38
6	116.7	0.41
7	123.5	0.44
8	129.5	0.46
9	135.0	0.49
10	140.0	0.51
11	146.0	0.53
12	152.5	0.57
13	159.0	0.59
14	165.0	0.61
Males		
15	172.0	0.72
16	176.0	0.78
17	178.0	0.82
18	179.0	0.85
19	180.0	0.88
20	181.5	0.90
Females		
15	164.5	0.64
16	166.0	0.67
17	166.5	0.69
18	167.0	0.69
19	167.5	0.70
20	168.0	0.70

Abbreviation: Scr, serum creatinine.

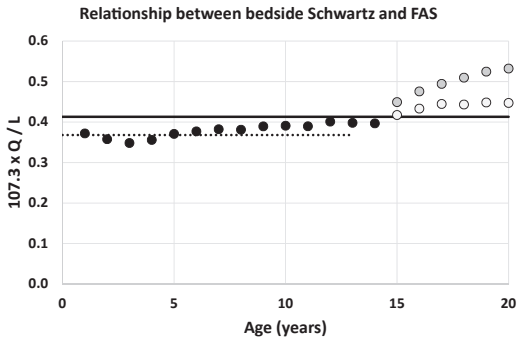

Figure 1. Plot of 107.3 × Q_{crea}/L vs age should be equal to 0.413, the constant of the Schwartz equation in case $FAS_{crea} = Schwartz_{bed}$. The solid horizontal line corresponds to 0.413, the Schwartz constant; the horizontal dotted line corresponds to 0.368, the value used in the modified Schwartz-Lyon equation for children below 13 years of age. The circles are calculated from Table 2, using the Q_{crea} values obtained from healthy Belgian children, and height (L) is obtained as the median from the Belgian national growth curves (for healthy children). Abbreviation: FAS, Full Age Spectrum.

why the FAS equation with Q_{crea}(height) gives better predictions than the FAS equation with Q_{crea}(Age).[22,33]

Hoste and colleagues[28] have modeled the Q_{crea} values against age, and Q_{crea} against height, to allow interpolation (to predict Q_{crea} for values in between the values in Table 2), resulting in 4th degree polynomials (Table 1).

Note that there are two polynomials for Q_{crea}(Age) due to the difference between adolescent males and females, that is, adolescent males gain muscle mass in a much faster way than females in this age period, starting from Q_{crea} = 0.61 mg/dL at 14 years of age, on average, and reaching the average plateau value of 0.90 mg/dL, whereas females only reach the value of 0.70 mg/dL. Q_{crea}(height) could be modeled in one 4th degree polynomial, showing that height is a better surrogate than age for gaining muscle mass, as it is independent of gender.

The pediatric part of the FAS equation can be rewritten as $FAS_{crea} = 107.3 \times Q_{crea}/Scr$. As the Schwartz equation also estimates GFR, it follows that $107.3 \times Q_{crea} = 0.413 \times L$. As both equations have been derived in a totally different way and from totally different data sets (Pottel used healthy children and Schwartz used growth-retarded kidney diseased children), the discrepancy between both equations should not be surprising. Figure 1 presents the plot of 107.3 × Q_{crea}/L vs age, with the data obtained from Table 2, which should correspond to the coefficient in the Schwartz Equation (0.413) in case the FAS equation and Schwartz equation are equal. This plot shows that for children up to 14 years of age, the results are indeed very similar, but the difference is large for adolescents. For children up to 14 years of age, small adaptations of the coefficients (of the Schwartz or FAS equation) can solve the discrepancy: for example, a perfect match between the FAS equation and the Schwartz equation would be obtained if 0.413 is replaced by 0.385 (a difference of about 7%), or, if 107.3 is replaced by 115, or combinations of modifications. Anyhow, this analysis shows that the FAS and Schwartz equations are essentially approximately the same for children up to 14 years of age, when height in the Schwartz equation is matched with the Q-value at the same age (Table 2). The FAS equation has the advantage that it can also be applied when height is not available.

For female and male adolescents, there is a clear deviation from the Schwartz coefficient of 0.413, showing that Schwartz and FAS deviate strongly for these children. Indeed, others have shown that modifications to the Schwartz equation are required. The Schwartz-Lyon equation is a modification of the original Schwartz equation derived by De Souza and colleagues.[34] She found that for girls and boys <13 years, the coefficient is 0.368 and 0.413 for boys ≥13 years. Based on this analysis, we may conclude that the Schwartz coefficient is probably a little bit too high for (healthy) younger children and needs to be optimized for adolescents, which is not surprising since the data used by Schwartz only contained children up to 16 years of age.

In Figure 2, we plotted 107.3 × Q_{crea}/L vs the height of the child, showing that the Schwartz coefficient of 0.413 (or 0.385, according to FAS) is more or less valid for children with height <165 cm, which is mostly true for girls and boys <13 years, corresponding to the Schwartz-Lyon modification. Male adolescents are clearly a much more difficult population to model in a simple eGFR equation, with more pronounced differences between Schwartz,

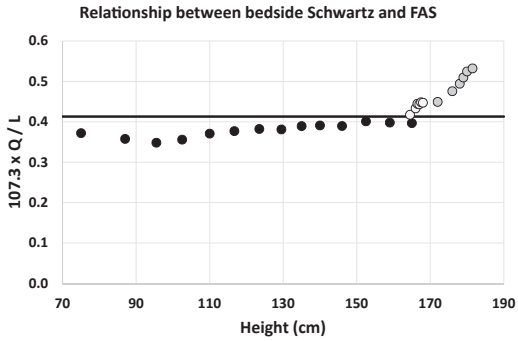

Figure 2. Plot of 107.3 × Q_{crea}/L vs height (cm). The horizontal solid line corresponds to the Schwartz coefficient of 0.413. Up to a height of 165 cm, the coefficient is approximately constant, but for adolescents with height >165 cm (mostly boys), the coefficient should be higher, according to the FAS equation. Abbreviation: FAS, Full Age Spectrum.

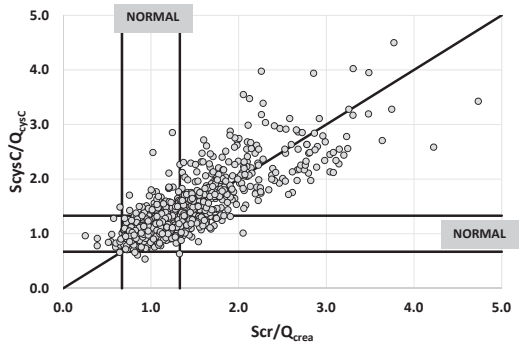

Figure 3. $ScysC/Q_{cysC}$ against Scr/Q_{crea} for $n = 845$ measurements from children between 2 and 18 years of age. The diagonal line is the identity line. The horizontal and vertical lines correspond to the reference interval (0.67–1.33) of the normalized biomarker, which may be considered as the normal region for the normalized biomarkers. Abbreviation: Scr, serum creatinine.

FAS, and Schwartz-Lyon. The advantage of the FAS equation over all other equations is that it makes the transition between children and adults, as the pediatric FAS equation is part of the more general FAS equation which is valid for all ages. Both the Schwartz equation and Schwartz-Lyon equation suffer from the drawback that they really differ from adult equations at the transition age of 18 years. For example, for a value of Scr = 0.85 mg/dL (the average value for an 18-year old adolescent male, see Table 2) and a height of 179 cm, Schwartz and Schwartz-Lyon predict an eGFR = 87 mL/min/1.73 m^2 which is very low compared to the eGFR-prediction by the CKD-EPI-equation,[35] which gives 124.3 mL/min/1.73 m^2 for the same adolescent male. The FAS equation predicts 107.3 mL/min/1.73 m^2 at the average Scr value for the average height at the age of 18 years.

COMBINING BIOMARKERS Scr AND ScysC

As the form of the FAS equation is valid for both normalized biomarkers, it is easy to understand that the same estimated GFR can only be obtained from both biomarkers, when $Scr/Q_{crea} = ScysC/Q_{cysC} = (Scr/Q_{crea} + ScysC/Q_{cysC})/2$. It also follows that the ratio of FAS_{cysC}/FAS_{crea} is equal to the (reciprocal) ratio of the normalized biomarkers: $[Scr/Q_{crea}]/[ScysC/Q_{cysC}]$. Therefore, when the estimated GFR from Scr (FAS_{crea}) differs significantly from the estimated GFR from ScysC (FAS_{cysC}), this is an immediate consequence of the difference between normalized biomarkers.[36-37]

To demonstrate the above reasoning, we plotted $ScysC/Q_{cysC}$ against Scr/Q_{crea} in Figure 3 for $n = 845$ measurements of children between 2 and 18 years of age. This data set has been previously described[36-37] and contains serial measurements of $n = 368$ children, a data set with unique measurements only, used and described before[15-16] to compare eGFR equations. It has been shown previously that both normalized and rescaled biomarkers share the same common reference interval of (0.67-1.33).[23,36-37]

A very simple approach to define or diagnose kidney disease in children would be to consider whether the normalized biomarker is within the reference interval of (0.67-1.33) (Table 3). We applied that rule to a cohort of 845 measurements on children aged between 2 and 18 years. Children with biomarker values within the reference interval have indeed mean mGFR values which are not different from 107.3 mL/min/1.73 m^2, the value predicted by the FAS equation at the mean $Scr = Q_{crea}$ or $ScysC = Q_{cysC}$ level.

Table 3 also shows that Scr/Q_{crea} is approximately equal to "1," the mean Scr value for healthy children. The deviation by 7% from "1" for $ScysC/Q_{cysC}$ might be due to the not optimal normalization factor of 0.82 mg/L that has been used or it may be due to the specific data set, as all children were from nephrology clinics with specific underlying (kidney) pathologies. We can also not rule out assay-related reasons for this deviation (calibration issues, differences between Roche and Siemens assays).

We defined the kidney function as "abnormal" when the normalized biomarker was greater than 1.33 and as "normal" when the normalized biomarker was less than or equal to 1.33. We then performed ROC analysis, using measured GFR as the confirmatory test (Table 4). This

Table 3. Overview of the Mean Measured GFR, Mean Scr, Mean ScysC (With 95% CI) for the $n = 380$ Measurements of Children With Both "Normal" Biomarker Values

n, Total	n, "normal"	Age (y)	Mean Age (y)	Scr/Q_{crea}	$ScysC/Q_{cysC}$	mGFR (mL/min/1.73 m^2)
246	135	(2-10)	6.5	0.99 (0.96–1.02)	1.07 (1.05–1.10)	107.0 (103.2–110.9)
599	245	(10-18)	14.7	0.99 (0.97–1.01)	1.07 (1.05–1.09)	104.6 (101.7–107.5)

Abbreviations: CI, confidence interval; GFR, glomerular filtration rate; mGFR, measured GFR; Scr, serum creatinine.

Table 4. ROC Analysis

Marker	Age Group	# Normal	# Abnormal	Threshold	AUC	SE	S (%)
Scr/Q_{crea}	2-10	170	76	79.0	0.937	0.016	78.9
	10-18	358	241	72.0	0.940	0.009	80.5
ScysC/Q_{cysC}	2-10	158	88	78.0	0.873	0.023	65.9
	10-18	290	309	78.0	0.910	0.012	77.0
Combined	2-10	159	87	81.0	0.931	0.016	80.4
	10-18	318	281	79.8	0.961	0.007	86.8

Abbreviations: mGFR, measured GFR; Scr, serum creatinine.
"Abnormal" is defined as marker >1.33 and "normal" as ≤1.33. mGFR is considered as the confirmatory test. The "threshold" is the value of mGFR corresponding with the most optimal sensitivity at a specificity of 90%. AUC is the area under the ROC curve (an ideal ROC curve has AUC = 1) and SE is the standard error on the AUC. S (%) is the sensitivity at the reported threshold, corresponding to a specificity of 90%; "combined" means the average of both rescaled biomarkers.

way of working is turning things around, as GFR is normally used to define kidney status. However, this ROC analysis demonstrates that children with biomarkers within the reference interval have mGFR values mostly above 80 mL/min/1.73 m^2, corresponding to a specificity of 90% and a sensitivity of more than 80% (in case of combining both biomarkers). This finding confirms the earlier report of Pottel and colleagues[38] that abnormal GFR starts below 75 mL/min/1.73 m^2 for children. The upper limit of the biomarker's reference interval (1.33) would correspond to FAS = 107.3/1.33 = 81 mL/min/1.73 m^2. According to the FAS concept, this value could be considered as the lower limit for the eGFR reference interval. We therefore compared the effect of the threshold of 60 mL/min/1.73 m^2 with 81 mL/min/1.73 m^2 on the consistency with the biomarker reference interval and found that there was about 10% more agreement ($p < 0.0001$) when the threshold of 81 mL/min/1.73 m^2 was used (Table 5). This demonstrates that, in the case of children, the reference interval of (0.67-1.33) can be used to diagnose healthy kidney status, corresponding with a GFR threshold of 81 mL/min/1.73 m^2.

PREDICTION PERFORMANCE OF COMBINED eGFR EQUATIONS

In this section, we focus on eGFR equations that use both Scr and ScysC for children. We compare the combined Schwartz equation (which has not been designed for standardized ScysC) with the combined FAS equation and with the combination of the LM-REV and CAPA equations that are based on the single biomarkers.[31]

To compare the performance of different eGFR equations, we took out all serial measurements in the previous data set, resulting in $n = 368$ children, for whom we used the first measurement only. We have published the performance results of different equations before,[22-23] but we here add the Scr-based LM-REV equation and the combination of LM-REV with the ScysC-based CAPA equation (see Table 6). We also present the results of the univariate and bivariate Schwartz equations, using Scr and ScysC in Table 7.

The performance of the FAS equation and LM-REV equation is relatively similar (see Table 6) overall, but LM-REV performed much worse than FAS in the <60 mL/min/1.73 m^2 subgroup. The univariate and bivariate Schwartz equation performed worse than the other combined equations in the ≥60 mL/min/1.73 m^2 subgroup, but much better than the other equations in the <60 mL/min/1.73 m^2 subgroup. This demonstrates that both FAS and Schwartz perform best in the subgroups for which they were originally designed for. It may also suggest that "one" equation to predict GFR in both healthy and diseased children will never be as accurate as separate equations, specifically designed for either of both groups.

To find an explanation for these differences, we plotted the univariate Scr-based equations for Scr/Q_{crea} = 1, Scr/Q_{crea} = 0.67 and 1.33, the midpoint, and lower and upper limits of the Scr/Q_{crea} reference interval (Fig. 4). We did the same for the univariate ScysC-based Schwartz, FAS equation, and the CAPA equation, again at midpoint (0.82 mg/L) and the reference interval limits (Fig. 5).

For children with mGFR <60 mL/min/1.73 m^2, LM-REV does not show good performance, as seen from Table 6, mainly because the estimated GFR is much too high (bias = 16.6 mL/min/1.73 m^2) which can also be observed

Table 5. Frequency of Patients With Normal/Abnormal Biomarkers in the Subgroups Defined by mGFR

	(Scr/Q_{crea} + ScysC/Q_{cysC})/2 ≤ 1.33					(Scr/Q_{crea} + ScysC/Q_{cysC})/2 > 1.33						% Agreement		
Age Group	mGFR < 60	mGFR ≥ 60	mGFR < 81	mGFR ≥ 81	Total	mGFR < 60	mGFR ≥ 60	mGFR < 81	mGFR ≥ 81	Total	Grand Total	Threshold of 60 mL/min/1.73 m^2	Threshold of 81 mL/min/1.73 m^2	McNemar's *P*-Value
2-10	0	159	14	145	159	28	59	67	20	87	246	76.0	86.2	0.0008
10-18	1	317	38	280	318	152	129	245	36	281	599	78.3	87.6	< 0.0001

Abbreviation: mGFR, measured GFR; Scr, serum creatinine.
% Agreement = agreement between kidney status defined as healthy or diseased, once based on the biomarker combination with threshold 1.33 and once based on the measured GFR with threshold 60 or 81 mL/min/1.73 m^2.

Table 6. Children $n = 368$ (Age ≤ 18 Years)

All ($n = 368$)	Scr-Based eGFR				ScysC-Based eGFR		Combined Scr/ScysC-Based eGFR		
mGFR = 89.2	FAS_{crea}	FAS_{crea}(Ht)	$Schwartz_{crea}$	LM-REV	FAS_{cysC}	CAPA	FAS_{combi}	FAS_{combi}(Ht)	LM-REV + CAPA
eGFR – mGFR	12.3 (7.7; 17.0)	3.8 (0.9; 6.6)	11.1 (8.1; 14.1)	2.9 (0.7; 5.0)	−5.1 (−7.2; −3.1)	0.3 (−2.0; 2.6)	0.9 (−0.9; 2.7)	−2.2 (−4.0; −0.4)	1.6 (−0.2; 3.3)
eGFR/mGFR	1.17 (1.12; 1.21)	1.06 (1.04; 1.09)	1.15 (1.12; 1.18)	1.10 (1.07; 1.10)	0.98 (0.96; 1.01)	1.03 (1.00; 1.05)	1.05 (1.03; 1.07)	1.01 (0.99; 1.03)	1.06 (1.04; 1.08)
RMSE	47.0 (27.2; 67.6)	28.3 (11.4; 39.2)	31.3 (13.9; 42.9)	21.0 (18.6; 23.2)	20.4 (17.9; 22.5)	22.3 (20.0; 24.3)	17.5 (15.1; 19.7)	17.6 (15.5; 19.7)	17.1 (15.1; 18.9)
Lin's CCC	0.43 (0.36; 0.49)	0.65 (0.59; 0.70)	0.63 (0.57; 0.68)	0.68 (0.63; 0.72)	0.73 (0.68; 0.77)	0.74 (0.68; 0.78)	0.81 (0.77; 0.84)	0.80 (0.77; 0.84)	0.80 (0.76; 0.83)
P10 (%)	32.3 (27.5; 37.1)	42.7 (37.6; 47.7)	40.5 (35.5; 45.5)	31.5 (26.8; 36.3)	40.5 (35.5; 45.5)	36.4 (31.5; 41.4)	44.6 (39.5; 49.7)	43.2 (38.1; 48.3)	45.1 (40.0; 50.2)
P30 (%)	78.3 (74.0; 82.5)	84.5 (80.8; 88.2)	79.9 (75.8; 84.0)	77.4 (73.2; 81.7)	86.1 (82.6; 89.7)	76.6 (72.3; 81.0)	90.8 (87.8; 93.7)	92.1 (89.4; 94.9)	88.6 (85.3; 91.9)
mGFR < 60 mL/min/1.73 m^2 (n = 57)									
mGFR = 45.2	FAS_{crea}	FAS_{crea}(Ht)	$Schwartz_{bed}$	LM-REV	FAS_{cysC}	CAPA	FAS_{combi}	FAS_{combi} (Ht)	LM-REV + CAPA
eGFR – mGFR	12.5 (10.0; 15.1)	5.1 (3.0; 7.2)	8.8 (6.5; 11.0)	16.6 (13.6; 19.7)	6.2 (3.1; 9.3)	3.3 (−0.4; 7.1)	8.3 (6.2; 10.5)	5.0 (2.9; 7.1)	10.0 (7.3; 12.7)
eGFR/mGFR	1.31 (1.24; 1.37)	1.14 (1.08; 1.20)	1.22 (1.16; 1.29)	1.39 (1.31; 1.48)	1.17 (1.09; 1.25)	1.10 (1.01; 1.19)	1.21 (1.15; 1.27)	1.14 (1.08; 1.20)	1.25 (1.17; 1.32)
RMSE	15.8 (12.7; 18.4)	9.4 (7.5; 10.9)	12.2 (9.7; 14.2)	20.2 (17.0; 23.0)	13.1 (9.8; 15.7)	14.3 (10.4; 17.3)	11.6 (9.4; 13.5)	9.3 (7.3; 11.0)	14.3 (11.1; 16.8)
Lin's CCC	0.44 (0.29; 0.56)	0.66 (0.50; 0.77)	0.55 (0.40; 0.68)	0.36 (0.23; 0.48)	0.48 (0.29; 0.64)	0.47 (0.28; 0.63)	0.56 (0.41; 0.69)	0.65 (0.49; 0.77)	0.50 (0.35; 0.63)
P10 (%)	10.5 (2.3; 18.7)	45.6 (32.3; 58.9)	36.8 (23.9; 49.8)	14.0 (4.7; 23.3)	24.6 (13.0; 36.1)	29.8 (17.6; 42.1)	28.1 (16.0; 40.1)	38.6 (25.6; 51.6)	26.3 (14.5; 38.1)
P30 (%)	63.2 (50.2; 76.1)	71.9 (59.9; 84.0)	71.9 (59.9; 84.0)	38.6 (25.6; 51.6)	68.4 (56.0; 80.9)	66.7 (54.0; 79.3)	71.9 (59.9; 84.0)	80.7 (70.1; 91.3)	66.7 (54.0; 79.3)
mGFR ≥ 60 mL/min/1.73 m^2 (n = 311)									
mGFR = 97.3	FAS_{crea}	FAS_{crea}(Ht)	$Schwartz_{bed}$	LM-REV	FAS_{cysC}	CAPA	FAS_{combi}	FAS_{combi} (Ht)	LM-REV + CAPA
eGFR – mGFR	12.3 (6.8; 17.8)	3.5 (0.1; 6.9)	11.5 (8.0; 15.1)	0.4 (−2.0; 2.7)	−7.2 (−9.5; −5.0)	−0.2 (−2.9; 2.4)	−0.5 (−2.5; 1.6)	−3.5 (−5.6; −1.4)	0.1 (−1.9; 2.0)
eGFR/mGFR	1.14 (1.09; 1.19)	1.05 (1.02; 1.08)	1.13 (1.10; 1.17)	1.04 (1.02; 1.06)	0.95 (0.93; 0.97)	1.02 (0.99; 1.04)	1.01 (0.99; 1.03)	0.98 (0.96; 1.00)	1.03 (1.01; 1.05)
RMSE	50.7 (10.5; 77.5)	30.5 (10.1; 42.0)	33.7 (12.7; 45.9)	21.2 (18.3; 23.7)	21.5 (18.8; 23.8)	23.5 (21.0; 25.8)	18.4 (13.5; 20.8)	18.8 (16.3; 21.0)	17.6 (15.3; 19.6)
Lin's CCC	0.29 (0.22; 0.37)	0.50 (0.41; 0.57)	0.48 (0.40; 0.55)	0.52 (0.44; 0.59)	0.59 (0.52; 0.65)	0.60 (0.52; 0.66)	0.71 (0.65; 0.76)	0.69 (0.62; 0.74)	0.68 (0.62; 0.73)
P10 (%)	36.3 (31.0; 41.7)	42.1 (36.6; 47.6)	41.2 (35.7; 46.7)	34.7 (29.4; 40.0)	43.4 (37.9; 48.9)	37.6 (32.2; 43.0)	47.6 (42.0; 53.2)	44.1 (38.5; 49.6)	48.6 (43.0; 54.1)
P30 (%)	81.0 (76.6; 85.4)	86.8 (83.0; 90.6)	81.4 (77.0; 85.7)	84.6 (80.5; 88.6)	89.4 (85.9; 92.8)	78.5 (73.9; 83.1)	94.2 (91.6; 96.8)	94.2 (91.6; 96.8)	92.6 (89.7; 95.5)

Abbreviations: CAPA, Caucasian Asian Pediatric Adult; eGFR, estimated glomerular filtration rate; FAS_{crea}, Full Age Spectrum eGFR equation, based on *Q*(Age); FAS_{crea}(Ht), FAS equation based on *Q*(height); Lin's CCC, Lin's concordance correlation coefficient; LM-REV, revised Lund-Malmö; mGFR, measured GFR; P10/P30, % within 10%/30% of mGFR; RMSE, root mean square error; Scr, serum creatinine; $Schwartz_{bed}$, updated bedside Schwartz equation for children (Scr-base = 0.413 Ht/Scr). FAScysC, full age spectrum eGFR equation based on cystatin C (Table 1); Schwartzcrea, creatinine based revised Schwartz equation (Table 1), FAScombi, combined Scr/ScysC FAS equation (Table 1); FAScombi(Ht), combined Scr/ScysC FAS(height) equation (Table 1).
All assays are standardized.

Table 7. Children $n = 368$ (Age ≤ 18 Years)

All ($n = 368$)				
mGFR = 89.2	$Schwartz_{crea}$	$Schwartz_{cysC}$	$Schwartz_{combi}$	FAS_{Mult}
eGFR – mGFR	−5.7 (−7.8; −3.5)	−21.6 (−23.7; −19.6)	−10.1 (−12.0; −8.3)	−1.5 (−3.4; 0.4)
eGFR/mGFR	0.98 (0.96; 1.00)	0.79 (0.78; 0.81)	0.92 (0.90; 0.94)	1.02 (1.00; 1.04)
RMSE	21.9 (16.3; 26.3)	29.6 (27.0; 32.1)	20.5 (18.0; 22.8)	18.5 (15.3; 21.2)
Lin's CCC	0.70 (0.64; 0.74)	0.49 (0.44; 0.54)	0.72 (0.68; 0.76)	0.79 (0.75; 0.83)
P10 (%)	45.1 (40.0; 50.2)	16.0 (12.3; 19.8)	40.5 (35.5; 45.5)	44.3 (39.2; 49.4)
P30 (%)	89.9 (86.9; 93.0)	68.8 (64.4; 73.5)	90.5 (87.5; 93.5)	91.6 (88.7; 94.4)
mGFR < 60 mL/min/1.73 m^2 (n = 57)				
mGFR = 45.2	$Schwartz_{crea}$	$Schwartz_{cysC}$	$Schwartz_{combi}$	FAS_{Mult}
eGFR – mGFR	6.7 (4.7; 8.6)	−2.4 (−5.0; 0.2)	2.4 (0.4; 4.4)	5.3 (3.2; 7.5)
eGFR/mGFR	1.19 (1.12; 1.25)	0.98 (0.91; 1.04)	1.08 (1.03; 1.14)	1.15 (1.09; 1.21)
RMSE	9.8 (7.7; 11.6)	10.0 (7.5; 12.0)	7.7 (5.8; 9.3)	9.5 (7.5; 11.2)
Lin's CCC	0.59 (0.43; 0.71)	0.55 (0.35; 0.71)	0.71 (0.55; 0.81)	0.64 (0.48; 0.76)
P10 (%)	45.6 (32.3; 58.9)	36.8 (23.9; 49.8)	50.9 (37.5; 64.3)	38.6 (25.6; 51.6)
P30 (%)	78.9 (68.0; 89.9)	86.0 (76.7; 95.3)	87.7 (78.9 96.5)	80.7 (70.1; 91.3)
mGFR ≥ 60 mL/min/1.73 m^2 (n = 311)				
mGFR = 97.3	$Schwartz_{crea}$	$Schwartz_{cysC}$	$Schwartz_{combi}$	FAS_{Mult}
eGFR – mGFR	−7.9 (−10.4; −5.5)	−25.2 (−27.4; −23.0)	−12.4 (14.5; −10.4)	−2.7 (−4.9; −0.5)
eGFR/mGFR	0.94 (0.92; 0.96)	0.76 (0.75; 0.78)	0.89 (0.88; 0.91)	0.99 (0.97; 1.01)
RMSE	23.4 (17.2; 28.3)	32.0 (29.1; 34.5)	22.1 (19.3; 24.6)	19.7 (16.1; 22.7)
Lin's CCC	0.55 (0.47; 0.62)	0.33 (0.27; 0.38)	0.57 (0.51; 0.63)	0.67 (0.60; 0.73)
P10 (%)	45.0 (39.5; 50.6)	12.2 (8.6; 15.9)	38.6 (33.1; 44.0)	45.3 (39.8; 50.9)
P30 (%)	92.0 (88.9; 95.0)	65.6 (60.3; 70.9)	91.0 (87.8; 94.2)	93.6 (90.8; 96.3)

Abbreviations: eGFR, estimated glomerular filtration rate; Lin's CCC, Lin's concordance correlation coefficient; mGFR, measured GFR; P10/P30, % within 10%/30% of mGFR; RMSE, root mean square error; Scr, serum creatinine.
$Schwartz_{crea}$ = 42.3 (Ht/Scr)$^{0.780}$; $Schwartz_{cysC}$ = 40.9 (1.8/ScysC)$^{0.931}$; $Schwartz_{combi}$ = 41.6 (Ht/Scr)$^{0.443}$ (1.8/CysC)$^{0.479}$; $FAS_{Mult} = 107.3/\sqrt{\frac{Scr}{Q_{crea}} x \frac{ScysC}{Q_{cysC}}}$.

from Figure 4, where (mostly male) children between 4 and 15 years of age with Scr close to the lower limit of the Scr reference interval have estimated GFR from LM-REV mostly higher than estimated GFR from Schwartz or FAS (note that $Scr/Q_{crea} = 1.33$ corresponds to 81 mL/min/1.73 m^2). Only 3 subjects in this cohort of $n = 368$ children had Scr >150 μmol/L (or 150/88.4 mg/dL), indicating that the switch in the LM-REV equation has only be applied in 3 occasions. As both FAS and LM-REV overestimate true mGFR when mGFR <60, LM-REV does that

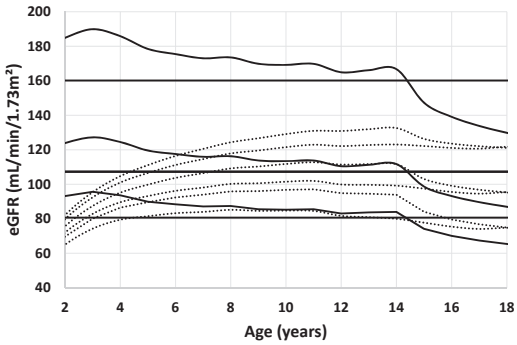

Figure 4. Serum creatinine: comparison of the bedside Schwartz equation (solid lines), the pediatric FAS (solid flat horizontal lines), and LM-REV (dotted lines, separate for males and females) for all ages, up to 18 years. The middle curves correspond to Scr = Q or Scr/Q = 1. The upper curves correspond to Scr/Q = 0.67, and the lower curves correspond to Scr/Q = 1.33. Data from Table 2 are used for the simulation. Abbreviations: eGFR, estimated glomerular filtration rate; FAS, Full Age Spectrum; LM-REV = revised Lund-Malmö; Scr, serum creatinine.

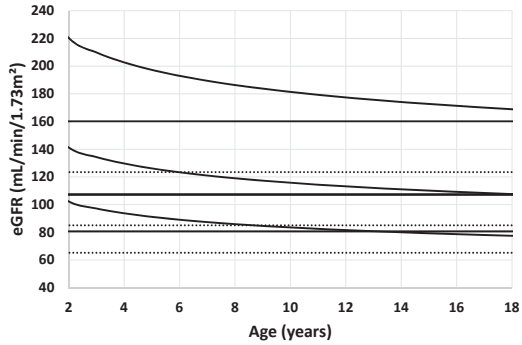

Figure 5. Cystatin C: comparison of the univariate cystatin C–based Schwartz equation (horizontal dotted lines), FAS (horizontal solid lines), and CAPA (curved solid lines) for all ages up to 18 years. The middle curves correspond to ScysC = Q or ScysC/Q = 1. The upper curves correspond to ScysC/Q = 0.67, and the lower curves correspond to ScysC/Q = 1.33. Q = 0.82 mg/L is used for ages up to 18 years. Abbreviations: CAPA, Caucasian Asian Pediatric Adult; eGFR, estimated glomerular filtration rate; FAS, Full Age Spectrum.

much more than FAS, resulting in a much higher bias. Overall, the updated simple bedside Schwartz equation performs worse than FAS, but the new univariate Scr-based Schwartz equation performs slightly better than FAS. The figure also shows that LM-REV has a much smaller variability than Schwartz or FAS, meaning that all estimated GFR results will be much closer together for LM-REV than for Schwartz or FAS. This theoretical comparison shows that there is a totally different behavior of LM-REV compared to Schwartz or FAS for children. Due to the high imprecision of all eGFR equations, this difference will probably not be so obvious when real mGFR data are used for the comparison, unless very large sample sizes are evaluated. Also for adolescents, it is clear that all equations perform differently.

For cystatin C, Schwartz and FAS are age independent, while CAPA has a built-in age dependency. The cystatin C–based Schwartz equation eGFR = 40.9 $(1.8/\text{ScysC})^{0.931}$ = $70.7/\text{ScysC}^{0.931}$ and the cystatin C–based FAS equation eGFR = 107.3/[ScysC/0.82] = 88.0/ScysC deviate from each other, mainly due to the lead coefficient (70.7 vs 88.0) explaining why FAS predictions are always greater than Schwartz predictions for the same value of cystatin C. Therefore, it may be expected that the cystatin C–based Schwartz equation is better suited for kidney diseased children and the FAS equation gives better predictions in the healthy children subgroup. The CAPA equation rather closely follows the FAS equation for ScysC = 0.82 and ScysC = 0.82 × 1.33, except for very young children (<10 years). The discrepancy between both equations is largest for low ScysC values (lower than 0.82 mg/L). Important to note is the inverse profile for CAPA vs LM-REV with age for very young children, compensating each other when both equations are combined. The CAPA equation shows an even larger variability (wider curves) than the FAS equation and much larger than the LM-REV equation for the same values of the normalized biomarkers.

The combined FAS equation has been published as 107.3 divided by the average of both normalized biomarkers. An alternative (unpublished) version of the combined FAS equation makes use of the multiplication of the biomarkers, instead of the addition, resulting in $\text{FAS}_{\text{Mult}} = 107.3/\sqrt{\frac{Scr}{Q_{crea}} x \frac{ScysC}{Q_{cysC}}}$. The results for this equation are shown in Table 7. This multiplicative form of the FAS equation is very much alike the combined Schwartz equation. Indeed, linear regression (through the origin) of the height of the child (in m) and Q_{crea} from Table 2 (for children aged ≤ 14 years) gives: $Q_{\text{crea}} = 0.3588 \times \text{L}$. Using $Q_{\text{cysC}} = 0.82$, the multiplicative form of the FAS equation becomes: $\text{FAS}_{\text{Mult}} = 58 \times \sqrt{(L/(Scr\ x\ ScysC))}$ where $58 = 107.3 \times 0.3588^{0.5} \times 0.82^{0.5}$. The combined Schwartz equation can be written as: Schwartz = 55 $[(\text{L/Scr})^{0.443} \times (1/\text{ScysC})^{0.479}]$, where $55 = 41.6 \times 1.8^{0.479}$. This shows that both equations are essentially similar, with only small differences in the coefficients (58 vs 55, and 0.5 vs 0.443 and 0.479). Predictions of both equations for the $n = 368$ children result in a linear equation of $\text{Schwartz}_{\text{combi}} = 0.823 \times \text{FAS}_{\text{Mult}} + 6.1$ with correlation coefficient of 0.98. Note, however, that correlation is not the same as agreement, as can be seen from the linear equations linking mGFR to eGFR, for FAS, we have $\text{mGFR} = 0.97 \times \text{FAS}_{\text{Mult}} + 3.4$ and for Schwartz, we find $\text{mGFR} = 1.16 \times \text{Schwartz}_{\text{combi}} - 2.7$, both equations having $R^2 = 0.72$. This shows that on the data at hand, the slope deviates much more from the ideal slope of "1" for $\text{Schwartz}_{\text{combi}}$ than for FAS_{Mult}. This proportional bias might be a consequence of the noncalibrated cystatin C results used to develop the Schwartz equation.

The combined equations reach P10 close to 45-50% and P30 close to 90-95% in the >60 mL/min/1.73 m^2 subgroup, outperforming the single biomarker equations. All equations have difficulties to accurately predict GFR when GFR <60 mL/min/1.73 m^2 (except the nonstandardized ScysC-based Schwartz equation). However, we should also realize that all children were from nephrology clinics and only 57/368 = 15% had GFR <60 mL/min/1.73 m^2, meaning that it is not very common to see children with GFR <60 mL/min/1.73 m^2.

CONCLUSIONS

The height-dependent FAS equation for children up to 14 years of age is essentially equal to the Schwartz equation, though be it with a 7% lower coefficient (0.385 vs 0.413). The difference between both equations becomes important for male adolescents. As the FAS equation allows for the transition to adults, it seems that the Schwartz equation predicts eGFR values that are too low for the (healthy) adolescent population.

eGFR equations perform best in the population for whom they were originally designed for, with preference for Schwartz in the kidney diseased children (GFR <60 mL/min/1.73 m^2) and with preference for FAS in healthy and less kidney diseased children (GFR >60 mL/min/1.73 m^2).

Biomarkers can be used as such to detect kidney disease when they are outside the reference interval, consistent with a threshold for mGFR for children of about 80 mL/min/1.73 m^2.

Finally, the combination of biomarkers shows improved prediction performance as compared to single biomarker equations. The multiplicative form of the FAS equation is very similar to the bivariate Schwartz equation.

REFERENCES

1. Schwartz GJ, Haycock GB, Edelmann CM, Spitzer M. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics.* 1976;58:259-263.
2. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BAFS. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol.* 2009;20:629-637.
3. Lunn A. Automatic reporting of creatinine-based estimated glomerular filtration rate in children: is this feasible? *EMJ Nephrol.* 2016;4:106-112.
4. Black C, Sharma P, Scotland G, et al. Early referral strategies for management of people with markers of renal disease: a systematic review of the evidence of clinical effectiveness, cost-effectiveness and economic analysis. *Health Technol Assess.* 2010;14:1-184.
5. Pottel H. Measuring and estimating glomerular filtration rate in children. *Pediatr Nephrol.* 2017;32:249-263.

6. Soveri I, Berg UB, Björk J, et al. Measuring GFR: a systematic review. *Am J Kidney Dis.* 2014;64:411-424.
7. Bröchner-Mortensen J. A Simple method for the determination of glomerular filtration rate. *Scand J Clin Lab Investig.* 1972;30:271-274.
8. Delanghe JR. How to estimate GFR in children. *Nephrol Dial Transpl.* 2009;24:714-716.
9. Pottel H, Vrydags N, Mahieu B, Vandewynckele E, Croes K, Martens F. Establishing age/sex related serum creatinine reference intervals from hospital laboratory data based on different statistical methods. *Clin Chim Acta.* 2008;396:49-55.
10. Grubb A, Blirup-Jensen S, Lindström V, et al. First certified reference material for cystatin C in human serum ERM-DA471/IFCC. *Clin Chem Lab Med.* 2010;48:1619-1621.
11. Bargnoux AS, Piéroni L, Cristol JP, et al, Société Française de Biologie Clinique (SFBC). Multicenter Evaluation of Cystatin C Measurement after Assay Standardization. *Clin Chem.* 2017;63:833-841.
12. Ebert N, Delanaye P, Shlipak M, et al. Cystatin C standardization decreases assay variation and improves assessment of glomerular filtration rate. *Clin Chim Acta.* 2016;456:115-121.
13. Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol.* 2009;20:629-637.
14. Schwartz GJ, Schneider MF, Maier PS, et al. Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. *Kidney Int.* 2012;82:445-453.
15. Chehade H, Cachat F, Jannot AS, et al. Combined serum creatinine and cystatin C schwartz formula predicts kidney function better than the combined CKD-EPI formula in children. *Am J Nephrol.* 2013;38:300-306.
16. Chehade H, Cachat F, Jannot AS, et al. New combined serum creatinine and cystatin C Quadratic formula for GFR assessment in children. *Clin J Am Soc Nephrol.* 2014;9:54-63.
17. Deng F, Finer G, Haymond S, Brooks E, Langman CB. Applicability of estimating glomerular filtration rate equations in pediatric patients: comparison with a measured glomerular filtration rate by iohexol clearance. *Translational Res.* 2015;165:437-445.
18. Siddique K, Leonard D, Borders L, Seikaly MG. Validation of the CKiD formulae to estimate GFR in children post renal transplant. *Pediatr Nephrol.* 2014;29:445-451.
19. Westland R, Abraham Y, Bökenkamp A, Stoffel-Wagner B, Schreuder MF, van Wijk JAE. Precision of estimating equations for GFR inChildren with a Solitary functioning kidney: the KIMONO study. *Clin J Am Soc Nephrol.* 2013;8:764-772.
20. Zachwiejaa K, Korohodab P, Kwinta-Rybickac J, et al. Modification of the Schwartz equations for children increases their accuracy at eGFR $>$ 60 mL/min/1.73 m^2. *Ren Fail.* 2016;38:787-798.
21. Leiona F, Hegbranta J, den Bakker E, et al. Estimating glomerular filtration rate (GFR) in children. The average between a cystatin C- and a creatinine-based equation improves estimation of GFR in both children and adults and enables diagnosing Shrunken Pore Syndrome. *Scand J Clin Lab Invest.* 2017;77:338-344.
22. Pottel H, Hoste L, Dubourg L, et al. An estimated glomerular filtration rate equation for the full age spectrum. *Nephrol Dial Transpl.* 2016;31:798-806.
23. Pottel H, Delanaye P, Schaeffner E, et al. Estimating glomerular filtration rate for the full age spectrum from serum creatinine and cystatin C. *Nephrol Dial Transpl.* 2017;32:497-507.
24. Piepsz A, Tondeur M, Ham HR. Revisiting normal (51)Cr-ethylenediaminetetraacetic acid clearance values in children. *Eur J Nucl Med Mol Imaging.* 2006;33:1477-1482.
25. Piepsz A, Tondeur M, Ham H. Escaping the correction for body surface area when calculating glomerular filtration rate in children. *Eur J Nucl Med Mol Imaging.* 2008;35:1669-1672.
26. Pottel H, Mottaghy FM, Zaman Z, Martens F. On the relationship between glomerular filtration rate and serum creatinine in children. *Pediatr Nephrol.* 2010;25:927-934.
27. Pottel H, Hoste L, Martens F. A simple height-independent equation for estimating glomerular filtration rate in children. *Pediatr Nephrol.* 2012;27:973-979.
28. Hoste L, Dubourg L, Selistre L, et al. A new equation to estimate the glomerular filtration rate in children, adolescents and young adults. *Nephrol Dial Transpl.* 2013;29:944-947.
29. Nyman U, Björk J, Lindström V, Grubb A. The Lund-Malmö creatinine-based glomerular filtration rate prediction equation for adults also performs well in children. *Scand J Clin Lab Invest.* 2008;68:568-576.
30. Grubb A, Horio M, Hansson L-O, et al. Generation of a new cystatin C-Based estimating equation for glomerular filtration rate by Use of 7 assays standardized to the International calibrator. *Clin Chem.* 2014;60:974-986.
31. Björk J, Grubb A, Larsson A, et al. Accuracy of GFR estimating equations combining standardized cystatin C and creatinine assays: a cross-sectional study in Sweden. *Clin Chem Lab Med.* 2015;53:403-414.
32. Roelants M, Hauspie R, Hoppenbrouwers K. References for growth and pubertal development from birth to 21 years in Flanders. *Belgium Ann Hum Biol.* 2009;36:680-694.
33. Schwartz GJ. Height: the missing link in estimating glomerular filtration rate in children and adolescents. *Nephrol Dial Transpl.* 2014;29:944-947.
34. de Souza VC, Rabilloud M, Cochat P, et al. Schwartz formula: is one k-coefficient Adequate for all children? *PLoS One.* 2012;7:1-7.
35. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150:604-612.
36. Pottel H, Dubourg L, Schaeffner E, et al. The diagnostic value of re-scaled renal biomarkers serum creatinine and serum cystatin C and their relation with measured glomerular filtration rate. *Clin Chim Acta.* 2017;471:164-170.
37. Pottel H, Dubourg L, Schaeffner E, et al. Data on the relation between renal biomarkers and measured glomerular filtration rate. Data in Brief, https://doi.org/10.1016/j.dib.2017.08.034
38. Pottel H, Hoste L, Delanaye P. Abnormal glomerular filtration rate in children, adolescents and young adults starts below 75 mL/min/1.73 m^2. *Pediatr Nephrol.* 2015;30:821-828.