Modification of the Schwartz equations for children increases their accuracy at eGFR > 60 mL/min/1.73 m²

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ABSTRACT
Aim: Estimation of eGFR in children with normal kidney function using the Schwartz equations results in underestimating real GFR. Materials and methods: We propose modification of three Schwartz equations – two based on creatinine concentration (eGFRScrBS bedside) and (eGFRScr) and one 3-marker based on creatinine, urea and cystatin C concentrations (eGFRS3M). The iohexol test (reference method) was performed 417 times in 353 children >2 years with mean GFR: 98 ± 31.6 ml/min/1.73m². The assessment included also the Filler and Zappitelli equations. The modification was performed using methods: (1) based on equation, T = a [eGFRScrBS + T] + T, where T = 50, if eGFR > T, and a equals for: eGFRScrBS 1.4043, for eGFRScr 2.0048, for eGFRS3M 1.2951, and (2) based on correction of all coefficients of the original equation. Results: For comparison of all the results and for children with GFR < 60, 60-90, 90-135 and > 135 ml/min/1.73m² the correlation coefficient, relative error (RE) and root mean square relative error (RMSRE) were employed and revealed improvement of RE from 25.9 to 6.8 and 3.9% (depending on the correction method) for eGFRScr; from 19 to 8.1 and 3.9% for eGFRScrBS and: from 11.6% to 2.0 and 2.3% for eGFRS3M (respectively). The RMSRE values changed from 30 to 21.3 and 19.8% for eGFRScr, from 25.1 to 21.6 and 19.8% for eGFRScrBS and from 19.1 to 15.8 and 15.3 % for eGFRS3M. Conclusions: Modifications of Schwartz equations at GFR > 60 ml/min/1.73m² significantly improves the accuracy of calculating eGFR. The 3-markers equation is more accurate and should be employed frequently.

Introduction
Calculating a reliable GFR employing a noninvasive method poses a problem to nephrologists, what is illustrated by an increasing number of eGFR equations. In addition to creatinine concentration, cystatin C have become increasingly more common and is supposed to be a better marker of kidney function, although contrary opinions have been also expressed. Also multi-marker formulas have become well known as they are believed more accurate. Examples of such equations can be found for adult patients, such as MDRD, and CKD-EPI and Donadio’s et al. formulas. In 2009, Schwartz et al. published the tri-marker equation for children, corrected in 2012 following verification of cystatin C determination by the nephelometric method. The equation, developed in chronic kidney disease (CKD) patients with mean eGFR value of approximately 43 ml/min/1.73 m² is characterized by a very good compatibility with the iohexol method at GFR from 15 to 75 ml/min/1.73 m². In 2006, Zappitelli and Bouvet proposed the bi-marker equations for children. All the above equations (except Bouvet equation) have been developed in CKD children. Validating these equations in children with normal kidney function is considered necessary. The 2009 shortened equation of Schwartz has been evaluated in children with high GFR values, but only isolated papers estimated the accuracy of the tri-marker equation. Chehade et al. noted a high conformity of that tri-marker equation as compared to inulin clearance at the mean GFR value of 87 mL/min/1.73 m². Contrary tendencies were observed by Gao et al.

The objective of this study is to compare the eGFR values calculated by the selected equations for children to GFR results from the iohexol method and to present own modifications of the Schwartz equations for GFR > 60 ml/min/1.73m².
Material and methods

The study group consisted of 353 pediatric patients of the Department of Nephrology, University Children’s Hospital of Cracow. Detailed anthropometric data are presented in Table 1.

The height and weight of all the patients were routinely taken at the hospital by qualified nurses (using the accurate hospital weight and stadiometer – SECA 213, produced by Seca GmbH & Co with appropriate certification).

In the study group, only 31 children (7.5%) did have the Z-score for height <2 (calculated relative to data for the European population according to the 4C study: www.4c-study.org).31,32 Only 15 children (3.6%) from the entire group had the Z-score for BMI <2. The body surface area was calculated using the Haycock formula.33 The detailed description of iohexol serum clearance test (reference method) was precisely described in the recent publication34 and is included in Appendix.

Serum creatinine levels were determined by the enzymatic method (VITROS FS Ortho Clinical Diagnostics). Until 1 March 2010, the method was validated relative to HPLC. From March 2014, it was validated according to isotope dilution mass spectroscopy (IDMS). The detailed explanation may be found in previous publication.34 The total imprecision for low creatinine serum concentration (99 µmol/L) was 3.5% and, for high creatinine serum concentration (478 µmol/L), 2.6%.

Concentrations of cystatin C were determined using the nephelometric method (a Siemens N-Latex diagnostic set was used). The total imprecision of cystatin C determination for low cystatin concentration (1.0 mg/L) was 2.6%, and 2.9% for high cystatin C concentration (8.4 mg/L). Serum urea concentration was determined by the enzymatic method (VITROS FS Ortho Clinical Diagnostics). The implementation of the study and iohexol test was approved by the Bioethical Committee, Jagiellonian University Medical College.

Based on the GFRv, the children were divided into four groups.

- **Group I:** with GFR ≥135 mL/min/1.73 m²
- **Group II:** with GFR 90–135 mL/min/1.73 m², corresponding to CKD stage 1
- **Group III:** with GFR 60–90 mL/min/1.73 m², corresponding to CKD stage 2
- **Group IV:** with GFR ≤60 mL/min/1.73 m², corresponding to CKD stage 3, 4 and 5

An analysis of the anthropometric data and the values of kidney function indices in the children in every group are presented in Tables 1 and 2.

The inclusion criteria for the study were: (1) Indications for assessment of kidney function (the list of diagnosis is presented in Table 3); (2) The parents’ and the child’s consent to the iohexol test; (3) A stable, good clinical status of the patient.

The exclusion criteria were: (1) Proteinuria >1.5 g/day; (2) Serum albumin concentration <36 g/L; (3) Steroid treatment at >1 mg/kg/day; (4) Lack of the approval for the test.

Children on steroid treatment with maintenance doses (see above) were included into the study, similarly as patients on cyclosporine A and/or mycophenolate mofetil and on nephroprotective treatment, which treatment has no significant effect on cystatin C values.17,35 Since the study was performed in the same group of children as the subjects described in the study from 2014,34 Tables 1–3 are similar as in the quoted report.

**Proposal of equations modification and employed modification methods**

When GFR increased, the equations yielded clearly underestimated GFR values as compared to the real value. This is why the authors proposed a modification taking the form of the equation below for higher (normal) GFR values.

![Table 1](image)
\[
eGFR_{cor} = a \times [eGFR - T] + T \quad \text{if} \quad eGFR > T
\]
\[
eGFR_{cor} = eGFR \quad \text{otherwise}
\]

where: \( T \) – GFR threshold value, \( a \) – coefficient correcting values above the threshold value, \( eGFR \) – the analyzed original equation, \( eGFR_{cor} \) – the equation following correction.

The following equations were selected to be modified:

1. The Schwartz equations:
   a. the 2012 tri-marker equation – \( eGFR_{S3M,20} \)
   b. the 2012 equation based solely on creatinine concentration – \( eGFR_{Scr,20} \)
   c. the 2009 simplest equation based on creatinine concentration – \( eGFR_{ScrBS,2} \) employed as the bedside formula.

The differences between the (b) and (c) equations result from the correction described by Schwartz in 2012,\(^{20}\) but they trigger a significant change in the result and have been included to preserve the methodological order.

The authors took into consideration also Filler and Lepage equation – \( eGFR_F \),\(^6\) since it is a well-known pediatric formula, based on cystatin C concentration, while its employment overestimates the value of GFR as compared to the reference method.

\[
eGFR_F = 91.622 \times \left( \frac{1}{CC} \right)^{1.123}
\]  

where: \( CC \) – serum cystatin C concentration in mg/L.

The bi-marker equation developed by Zappitelli – \( eGFR_Z \)\(^5\)

\[
eGFR_Z = 507.76 \times \left( \frac{e^{0.003 \times H}}{CC^{0.835} \times Ccr^{0.547}} \right)
\]

where: \( H \) – height in cm, \( Ccr \) – plasma creatinine concentration in \( \mu \text{mol/L} \), while \( e \approx 2.7183 \).

The forms of the Schwartz equations are given in the section “Results”; Table 4 collectively presents all the formulas.
In this study, the GFR threshold value was assumed to be $T = 50 \text{mL/min/1.73 m}^2$. This was inferred from the observation that recalculation needed to be done from the equation toward the reference value and not the other way. The value of $T = 50$ was arbitrarily determined based on a series of preliminary tests.

Dispersion of the calculated eGFR values relative to the reference method increases with an increasing GFR value.$^{29,34}$ This is why the relative error (RE) expressed as a percentage value was chosen as the basic method of comparing to GFR, and to values originating from the analyzed equation:

$$\text{RE}(n) = 100\% \times \left( \frac{\text{eGFR}_x(n) - \text{eGFR}_r(n)}{\text{eGFR}_r(n)} \right)$$  \hspace{1cm} (4)

where: $n$ – number of patients, $\text{eGFR}_x$ – investigated value, while $\text{eGFR}_r$ – reference value.

The study presents a proposal of modifying GFR$_{S3M}$, GFR$_{Scr}$ and GFR$_{ScrBS}$ employing two modes.

Mode 1: According to the relation described by Eq. (1), where each time, solely the $a$ coefficient was determined. The thus modified equations were marked as $\text{eGFR}_{S3M_T}$, $\text{eGFR}_{Scr_T}$, $\text{eGFR}_{ScrBS_T}$, respectively.

Mode 2: For each of the investigated equations, its general form was maintained, with all numerical coefficients being determined anew. The thus modified equations were marked as $\text{eGFR}_{S3M_C}$, $\text{eGFR}_{Scr_C}$, $\text{eGFR}_{ScrBS_C}$, respectively.

In both modes of modification, the value of RMSRE (root mean square relative error) was minimized.

$$\text{RMSRE} = 100\% \times \sqrt{\frac{1}{N} \times \sum_{n=1}^{N} \left( \frac{\text{eGFR}_x(n) - \text{eGFR}_r(n)}{\text{eGFR}_r(n)} \right)^2}$$  \hspace{1cm} (5)

where: $N$ – number of patients.

The value of RMSE (root mean square error) for a given variable confronted with the reference variable was associated with the standard deviation SD (weighted equation) of the error comparing the same variables in keeping with the following formula:

$$\text{RMSE}^2 = \text{SD}^2 + MV^2$$  \hspace{1cm} (6)

where MV (mean value) denotes the mean value of the same error. Thus, RMSE is a measure of deviations relative to the reference value that also takes into account the error MV deviation from zero. For the zero value of the error MV, the values of error SD and RMSE are equal. In this study, the role of the error is fulfilled by the relative error.

The comparison of GFR values was performed using: eGFRx correlation graphs depending on GFR$_{Rx}$ (Figure 1a and Figure 2a), RE graphs in the eGFR$_{x}$ function (Figure 1b and Figure 2b).

The 9-field tables illustrating the effectiveness of classifying the patients to three categories based on two eGFR threshold values that is 60 and 90 mL/min/1.73 m$^2$ (Tables 5–14).

The 9-field tables were developed in such a way as to present in the form of group size such data that were at the same time illustrated by the graphs. In this way, it was possible to assess the inter-marker differences even in case of highly similar graphs. The tables constitute an extension of the concept of classic 4-field. The 9-field tables are based on a division into three categories, both in the case of the reference equation and tested equation. In this way, the authors arrived at the contingency tables (cross tables), which, nevertheless, have fields with a zero value. This fact rules out the possibility of a reliable determination of statistical significance of the congruence of the two markers employing the chi-square test; however, in case of all the presented tables, the

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### Table 4. The employed formulas description.

| Abbreviation | Marker | Author, year | Formula |
|--------------|--------|--------------|---------|
| GFR$_{p}$    | Cystatin C | Filler, 2003 | $\text{GFR}_p = 10^{0.962 + 1.123 \times \log_{10}(T)}$ |
| GFR$_{S3M}$  | Creatinine | Schwartz, 2012 | $\text{GFR}_{S3M} = 42.3 \times \left( \frac{H/100}{\text{Ccr}/88.4} \right)^{0.79}$ |
| GFR$_{Scr BS}$ | Creatinine | Schwartz, 2009 | $\text{GFR}_{ScrBS} = 0.413 \times (H/100)/\text{Ccr}/88.4$ |

$\text{CC}$, Concentration of Cystatin C in Serum in [mg/L]; $\text{Ccr}$, Concentration of Creatinine in Serum in [mmol/L]; $H$, Body Height in [cm]; $G$, for Male $G = 1$, for Female $G = 0$.
significance was sufficiently obvious that it did not require testing. In order to parameterize the contents of the employed tables, the CA (classification accuracy) parameter was proposed; its value, expressed as a per cent, gives the arithmetic mean probability of a correct classification when all the three categories are taken into account. The CA parameter takes into consideration solely correct results of a classification.

\[
CA = \left( \frac{Na(Na_{\text{ref}})}{N_{\text{ref}}} + \frac{Nb(Nb_{\text{ref}})}{N_{\text{ref}}} + \frac{Nc(Nc_{\text{ref}})}{N_{\text{ref}}} \right) \times \frac{100\%}{3} \tag{7}
\]
where \( Na (Na_{ref}) \) – the number of patients ascribed to a category based on the tested equation selected from among all the patients that were ascribed to the same category based on the reference value of GFR_{ref} (Na_{ref}). For the remaining two categories (b and c), the mechanism is the same.

Additionally, the above analyses were performed for the GFR result in all the same as above subgroups of the patients.

The statistical analysis was performed with the Matlab and Statistica v.10 software. The comparison of the eGFR results was based on the Wilcoxon nonparametric test, the Mann–Whitney’s U test and the parametric Student’s t-test. The conformity of a given result to normal distribution was assessed with the Kolmogorov–Smirnov test. ANOVA was also used. The statistical significance of differences was at \( p < 0.05 \).

**Results**

The results of a detailed analysis of the studied group of children as depending on CKD stage are shown in Table 1.

In 67.1% of the children, GFR_I amounted to \( > 90 \text{ mL/min/1.73 m}^2 \), while in 10%, it was \( > 135 \text{ mL/min/1.73 m}^2 \). Table 1 demonstrates that the Z-score for height for the children with high values of GFR_I \( > 135 \) and GFR_I \( 90–135 \text{ mL/min/1.73 m}^2 \) (Group I and II) was significantly lower as compared to the children with GFR_I \( < 60 \) and GFR_I \( 60–90 \) (Group IV and III). Similarly, the group I and II had a higher body mass as compared to the III and IV group, but the differences in the Z-score for BMI reached statistical significance only between the children with GFR_I \( < 60 \) and those with GFR_I \( \geq 135 \text{ mL/min/1.73 m}^2 \). No statistical difference was noted between the ages of the children in particular groups.

Below, the proposals of equation modification are given:

**Equation modification in keeping with Mode 1:**

for the Eq. (1) \( eGFR_{r 	ext{cor}} = a \times [eGFR - T] + T \)

where \( a \) = the coefficient in the Table 19. The determined coefficients are listed in Table 19.

Assumed \( T = 50 \text{ mL/min/1.73 m}^2 \).

**Equation modification in keeping with Mode 2**

The tri-marker Schwartz equation of 2012:\(^{20}\)

\[
eGFR_{SM} = B \times \left( \frac{H/100}{Ccr/88.4} \right)^p \times \sqrt[3]{\left( \frac{30}{Cu \times 2.8} \right)} \times G^g \times \left( \frac{H}{140} \right)^h
\]

(8)

where: \( G \) denotes sex (0 – Female, 1 – Male), \( Cu \) – plasma urea concentration in mmol/L.

The Schwartz equation of 2012:\(^{20}\)

\[
eGFR_{Scr} = C \times \left( \frac{H/100}{Ccr/88.4} \right)^p
\]

(9)

The Schwartz bed-side formula of 2009,\(^{2}\)

\[
eGFR_{ScrBS} = B \times \left( \frac{H/100}{Ccr/88.4} \right)
\]

(10)

The proposal of corrected coefficient are listed in Tables 20–22.

Figure 1a presents the correlation graphs, while Figure 1b shows the RE graphs for the analyzed original equations relative to the iohexol method. Similarly, Figures 2a and 2b illustrate the relationships for the proposed equations following their modification.

Tables 15–18 and 23 present the values of eGFR by analyzed original and corrected equations along with the RE, RE centiles, RMSE, R (correlation coefficient) and accuracy values at 10 and 30% relative to the reference method. The 9-field tables are presented in Tables 5–14.

**Discussion**

Multi-marker equations for calculating GFR are more sensitive and accurate than uni-marker.\(^3,5,22\) Due to their mathematical complexity, they cannot be used as bedside formulas. Employing such programs as, for example Excel or online calculators allows for quick eGFR calculation. The use of multi-marker equations is significantly less expensive as compared to direct methods of GFR assessment. Indications for precise and repeated GFR calculation are indisputable in a selected group of children. A separate group consists of children with body deformities and malnutrition, in whom determination of creatinine concentration by itself may be inaccurate and insufficient.\(^36\) As other authors, we suggest an additional cystatin C determination in this group. It should be remembered that multi-marker equations take into account the height of the patient, what in case of children with body disproportions may affect the error of the result in an identical manner as in case of uni-marker equations.

This study is a continuation of the report of 2014.\(^34\) The proposal of the given modification of the original equations at high GFR are shown in results section; according to Mode 1—the coefficients are given in Table 19, according to Mode 2 in Tables 20–22 or all Schwartz equations.

The most important idea of the study is the fact that modification of the Schwartz equations for
Table 5. GFR_{Scr} versus GFR_{I} (corresponding to Figure 1a).

| a_{ref} | b_{ref} | c_{ref} | a_{ref} + b_{ref} + c_{ref} |
|---------|---------|---------|-----------------------------|
| a (GFR_{Scr} < 60) | 52 | 33 | 12 | 97 |
| b (GFR_{Scr} 60–90) | 0 | 50 | 239 | 289 |
| c (GFR_{Scr} ≥ 90) | 0 | 2 | 29 | 31 |
| a + b + c | 52 | 85 | 280 | 417 |

Table 6. GFR_{ScrT} versus GFR_{I} (corresponding to Figure 2a).

| a_{ref} | b_{ref} | c_{ref} | a_{ref} + b_{ref} + c_{ref} |
|---------|---------|---------|-----------------------------|
| a (GFR_{ScrT} < 60) | 52 | 19 | 2 | 73 |
| b (GFR_{ScrT} 60–90) | 0 | 46 | 67 | 113 |
| c (GFR_{ScrT} ≥ 90) | 0 | 20 | 211 | 231 |
| a + b + c | 52 | 85 | 280 | 417 |

Table 7. GFR_{ScrC} versus GFR_{I} (corresponding to Figure 2a).

| a_{ref} | b_{ref} | c_{ref} | a_{ref} + b_{ref} + c_{ref} |
|---------|---------|---------|-----------------------------|
| a (GFR_{ScrC} < 60) | 46 | 11 | 0 | 57 |
| b (GFR_{ScrC} 60–90) | 6 | 44 | 58 | 108 |
| c (GFR_{ScrC} ≥ 90) | 0 | 30 | 222 | 252 |
| a + b + c | 52 | 85 | 280 | 417 |

Table 8. GFR_{ScrBS} versus GFR_{I} (corresponding to Figure 1a).

| a_{ref} | b_{ref} | c_{ref} | a_{ref} + b_{ref} + c_{ref} |
|---------|---------|---------|-----------------------------|
| a (GFR_{ScrBS} < 60) | 52 | 21 | 5 | 78 |
| b (GFR_{ScrBS} 60–90) | 0 | 58 | 169 | 227 |
| c (GFR_{ScrBS} ≥ 90) | 0 | 6 | 106 | 112 |
| a + b + c | 52 | 85 | 280 | 417 |

Table 9. GFR_{ScrBS}T versus GFR_{I} (corresponding to Figure 2a).

| a_{ref} | b_{ref} | c_{ref} | a_{ref} + b_{ref} + c_{ref} |
|---------|---------|---------|-----------------------------|
| a (GFR_{ScrBS}T < 60) | 50 | 19 | 1 | 70 |
| b (GFR_{ScrBS}T 60–90) | 2 | 47 | 71 | 120 |
| c (GFR_{ScrBS}T ≥ 90) | 0 | 19 | 208 | 227 |
| a + b + c | 52 | 85 | 280 | 417 |

Table 10. GFR_{ScrBSC} versus GFR_{I} (corresponding to Figure 2a).

| a_{ref} | b_{ref} | c_{ref} | a_{ref} + b_{ref} + c_{ref} |
|---------|---------|---------|-----------------------------|
| a (GFR_{ScrBSC} < 60) | 46 | 10 | 0 | 56 |
| b (GFR_{ScrBSC} 60–90) | 6 | 46 | 58 | 110 |
| c (GFR_{ScrBSC} ≥ 90) | 0 | 29 | 222 | 251 |
| a + b + c | 52 | 85 | 280 | 417 |

Table 11. GFR_{S3M} versus GFR_{I} (corresponding to Figure 1a).

| a_{ref} | b_{ref} | c_{ref} | a_{ref} + b_{ref} + c_{ref} |
|---------|---------|---------|-----------------------------|
| a (GFR_{S3M} < 60) | 49 | 9 | 0 | 58 |
| b (GFR_{S3M} 60–90) | 3 | 67 | 91 | 161 |
| c (GFR_{S3M} ≥ 90) | 0 | 9 | 189 | 198 |
| a + b + c | 52 | 85 | 280 | 417 |

Table 12. GFR_{S3M}T versus GFR_{I} (corresponding to Figure 2a).

| a_{ref} | b_{ref} | c_{ref} | a_{ref} + b_{ref} + c_{ref} |
|---------|---------|---------|-----------------------------|
| a (GFR_{S3M}T < 60) | 48 | 7 | 0 | 55 |
| b (GFR_{S3M}T 60–90) | 4 | 52 | 28 | 84 |
| c (GFR_{S3M}T ≥ 90) | 0 | 26 | 252 | 278 |
| a + b + c | 52 | 85 | 280 | 417 |

Table 13. GFR_{S3MC} versus GFR_{I} (corresponding to Figure 2a).

| a_{ref} | b_{ref} | c_{ref} | a_{ref} + b_{ref} + c_{ref} |
|---------|---------|---------|-----------------------------|
| a (GFR_{S3MC} < 60) | 46 | 4 | 0 | 50 |
| b (GFR_{S3MC} 60–90) | 6 | 57 | 35 | 98 |
| c (GFR_{S3MC} ≥ 90) | 0 | 24 | 245 | 269 |
| a + b + c | 52 | 85 | 280 | 417 |

Table 14. The classification accuracy (CA) coefficients calculated according to Eq. (7) for 9-field tables.

| X | Scr (%) | Scr_{BS} (%) | S_{3M} (%) |
|---|---------|--------------|------------|
| eGFR_{I} | 56 | 69 | 80 |
| eGFR_{T} | 76 | 75 | 81 |
| eGFR_{C} | 73 | 73 | 81 |

The 9-field tables:
The 9-fields tables for three Schwartz equations:
a. Original: GFR_{Scr} – Table 5, GFR_{ScrBS} – 7a and GFR_{S3M} – 8a
b. Corrected by method 1 – GFR_{Scr} – Table 9, GFR_{ScrBS} – 8b and GFR_{S3M} – 9b
c. Corrected by method 2 – GFR_{ScrC} – Table 7c, GFR_{ScrBS}C – 8c and GFR_{S3M}C – 9c
All are compared to GFR_{I}.
The 9-field tables:
The interpretation of the 9-field tables:
The number given in dedicated table place for example second line and third column—33 means that in such number of cases GFR calculations results according to GFR_{Scr} was < 60, in contrast such result according to iohexol method was higher: 60–90. Reading the third column: 85 results obtained by iohexol method were between 60–90, employing GFR_{Scr} 50 results were correct, 35 results were below the “reference values” (< 60) and two results overestimated GFR value (were > 90).

GFR > 60 mL/min/1.73 m² decreases the error of eGFR calculation. The employment of the correction for the bed-side formula – eGFR_{ScrBS} – decreases the RMSRE from 37.1 to 28.9 or 27.3% (depending on the mode of correction: Mode 1, Mode 2, respectively) at GFR > 135 and from 24.7 to 19.3 and 16.7% in the group of children with GFR 60–90. Similarly, corrections for the tri-marker equation eGFR_{S3M} reduce the RE (relative error) from 30.4 to 21.6 and 21.1% at GFR > 135 and from 18.1 to 13.1% at GFR 90–135 mL/min/1.73 m². For the 2012 Schwartz equation – eGFR_{Scr} – the reduction in the error value approximates that noted in the case of the eGFR_{ScrBS} formula (Tables 17 and 18).

The biggest error of the result leading to underestimation of the GFR value relatively to the reference method is shown for Schwartz equation of 2012 – GFR_{Scr} (which is not a bed-side formula!!!). The highest
Table 15. The eGFR value, RE value, RE centiles, RMSRE, R (with p value) and 10 and 30% of accuracy to GFRI in patients with GFRI < 60 mL/min/1.73 m² (N = 52).

| Equation | eGFR (mean ± SD) [mL/min/1.73 m²] | RE average value [%] | Relative error centiles (5,50,95) [%] | RMSRE [%] | R | p values (R) | Accuracy 10% | Accuracy 30% |
|----------|------------------------------------|----------------------|---------------------------------------|-----------|---|---------------|--------------|--------------|
| GFRI     | 35.5 ± 14.1                        | -0.6                 | -33.3, -9.3, 37.7                     | 21.1      | 0.872 | 0.000         | 78.8    | 34.6        |
| eGFRScr  | 33.8 ± 12.5                        | 0.1                  | -33.3, -8.6, 40.9                     | 21.4      | 0.864 | 0.000         | 78.8    | 30.8        |
| eGFRScrT | 34.1 ± 13.1                        | 8.6                  | -32.2, 9.7, 40.7                      | 25.3      | 0.869 | 0.000         | 71.2    | 30.8        |
| eGFRScrC | 38.3 ± 17.1                        | -10.1                | -44.5, -9.1, 16.9                     | 22.4      | 0.869 | 0.000         | 82.7    | 36.5        |
| eGFRScrBST | 32.0 ± 14.9                       | -9.6                 | -44.5, -9.1, 16.9                     | 22.6      | 0.863 | 0.000         | 82.7    | 34.6        |
| eGFRScrT | 37.7 ± 17.2                        | 6.8                  | -34.1, 8.0, 38.8                      | 24.6      | 0.869 | 0.000         | 71.2    | 36.5        |
| eGFRScrC | 46.1 ± 19.7                        | 33.4                 | -8.5, 34.5, 94.6                      | 43.9      | 0.897 | 0.000         | 48.1    | 17.3        |
| eGFRScrBST | 33.0 ± 15.9                       | -7.8                 | -41.3, -6.2, 17.7                     | 20.0      | 0.901 | 0.000         | 86.5    | 32.7        |
| eGFRScrBS | 36.5 ± 14.0                        | 6.2                  | -24.6, 5.4, 37.4                      | 19.4      | 0.914 | 0.000         | 84.6    | 38.5        |
| eGFRScrBS | 36.9 ± 14.7                        | 7.0                  | -24.6, 6.9, 37.4                      | 19.9      | 0.908 | 0.000         | 84.6    | 36.5        |
| eGFRScrBS | 36.4 ± 15.8                        | 3.3                  | -29.8, 5.2, 30.0                      | 17.6      | 0.911 | 0.000         | 88.5    | 38.5        |

Table 16. The eGFR value, RE value, RE centiles, RMSRE, R (p value) and 10 and 30% of accuracy to GFRI for original and corrected equations for GFRI < 60–90 mL/min/1.73 m² (N = 85).

| Equation | eGFR (mean ± SD) [mL/min/1.73 m²] | RE average value [%] | Relative error centiles (5,50,95) [%] | RMSRE [%] | R | p values (R) | Accuracy 10% | Accuracy 30% |
|----------|------------------------------------|----------------------|---------------------------------------|-----------|---|---------------|--------------|--------------|
| GFRI     | 77.9 ± 8.7                         | -18.8                | -37.1, -20.5, 6.2                     | 17.4      | 0.575 | 0.000         | 89.4    | 16.5        |
| eGFRScr  | 63.2 ± 11.0                        | -1.6                 | -33.9, -4.7, 40.6                     | 17.5      | 0.569 | 0.000         | 83.5    | 38.8        |
| eGFRScrT | 77.0 ± 21.0                        | 5.1                  | -23.5, 7.2, 43.2                      | 15.1      | 0.569 | 0.000         | 88.2    | 57.6        |
| eGFRScrC | 61.9 ± 15.2                        | -11.6                | -36.0, -13.7, 20.9                    | 15.3      | 0.569 | 0.000         | 88.2    | 38.2        |
| eGFRScrBST | 76.9 ± 20.9                       | -1.8                 | -34.2, -5.1, 40.1                     | 17.4      | 0.566 | 0.000         | 83.5    | 40.0        |
| eGFRScrC | 81.9 ± 18.1                        | 5.0                  | -23.9, 2.5, 43.6                      | 15.4      | 0.569 | 0.000         | 87.1    | 57.6        |
| eGFR     | 108.1 ± 25.9                       | 39.4                 | -8.8, 41.5, 101.5                     | 38.7      | 0.340 | 0.001         | 40.0    | 14.1        |
| eGFRScr  | 80.7 ± 12.6                        | 3.7                  | -28.2, 28.4, 44.2                     | 16.4      | 0.492 | 0.000         | 83.5    | 37.6        |
| eGFRScrBST | 74.2 ± 12.6                       | -4.5                 | -23.3, -4.3, 17.6                     | 10.5      | 0.588 | 0.000         | 96.5    | 51.8        |
| eGFRScrC | 81.4 ± 15.7                        | 4.5                  | -19.3, 3.3, 31.3                      | 13.1      | 0.588 | 0.000         | 91.6    | 43.5        |
| eGFRScrBST | 81.0 ± 15.3                       | 4.1                  | -22.8, 38.9, 29.3                     | 12.7      | 0.593 | 0.000         | 95.3    | 47.1        |

compatibility has been found for the modified tri-marker Schwartz equation (Table 23). A detailed analysis of Tables 17 and 18 for high GFR > 90 mL/min/1.73 m² indicates a significant error and underestimation of the result (>20%) in case of all the analyzed original equations except the Filler and Zappitelli equation, what confirms other opinions.37

The Filler equation has been found to significantly overestimate the value of real GFR by the mean percentage of 7.8–39%, what has been pointed out.29,37,38 The bi-marker equation of Zappitelli shows a slight mean error of 18.5% and its accuracy mildly decreases only at high values of GFR > 135 mL/min/1.73 m².

Importantly at GFR > 135 mL/min/1.73 m², none of the equations, with the exception of the modified tri-marker Schwartz formula (GFRI), shows a significant correlation with the reference method. At GFR < 60 mL/min/1.73 m², the agreement of all equations is comparable, with the exception of the Filler formula, which has the highest error (mean relative error ~ 33.4%).

The findings of this study unambiguously indicate (Tables 15–18 and 23 and Figures 1 and 2, 9-field tables) that multi-marker equations are more accurate than uni-marker formulas, which confirms others opinions.24,36,38

The greatest advantage of this study is the assessment of the real GFR based on iohexol method in a large group of children with normal kidney function and the own proposal of modifying the Schwartz equations. This seems to be a more practical solution than introducing new forms of the equations. Such an approach has been already presented, for example Inker made the value of coefficients in the equation dependent on creatinine and cystatin concentrations (the combined CKD-EPI equation).22 In the case of children, Souza, as well as Pottel proposed a correction of the bedside Schwartz equation depending on age.4,39 Pottel presented another concept of calculating eGFR at a known mean population creatinine concentration value for a given age.11 It does not require knowing the averaged creatinine concentration value.40 Nevertheless, following the analysis of the Pottel equation form, its use was abandoned since the results would be even lower (by approximately 9%) than the results by the Schwartz bedside formula (eGFRScrBS). This explains the form of the Pottel equation, which – following transformation –
Table 17. The eGFR value, RE, RE centiles, RMSRE, R (p value) and 10 and 30% of accuracy to GFR↓ in for GFR↓ 90–135 mL/min/1.73 m² (N = 238).

| Equation | eGFR↓ (mean ± SD) [mL/min/1.73 m²] | RE average value (%) | Relative error centiles (5,50,95) (%) | RMSRE [%] | R | p values (R) | Accuracy 10% | Accuracy 30% |
|----------|-----------------------------------|----------------------|----------------------------------------|------------|---|---------------|---------------|---------------|
| GFRI     | 110.7 ± 11.8                      | -30.9                | -46.1, -31.4, -13.4                    | 32.3       | 0.303 | 0.000         | 41.6           | 2.9           |
| eGFRI    | 76.0 ± 9.8                        | -36.6                | -49.7, -34.3, -14.1                    | 35.3       | 0.270 | 0.000         | 47.1           | 3.2           |
| eGFRI↓T  | 102.4 ± 10.2                      | -40.9                | -49.7, -35.4, -15.5                    | 36.7       | 0.240 | 0.000         | 50.2           | 3.6           |
| eGFRI↓C  | 93.6 ± 11.5                       | -41.4                | -49.7, -36.4, -15.4                    | 37.7       | 0.237 | 0.000         | 52.2           | 3.8           |

Table 18. The eGFR value, RE, RE centiles, RMSRE, R (p value) and 10 and 30% of accuracy to GFR↓ for GFR↓ ≥135 mL/min/1.73 m² (N = 42).

| Equation | eGFR↓ (mean ± SD) [mL/min/1.73 m²] | RE average value (%) | Relative error centiles (5,50,95) (%) | RMSRE [%] | R | p values (R) | Accuracy 10% | Accuracy 30% |
|----------|-----------------------------------|----------------------|----------------------------------------|------------|---|---------------|---------------|---------------|
| GFRI     | 143.8 ± 6.1                       | -44.0                | -57.4, -45.0, -30.0                    | 44.8       | 0.140 | 0.377         | 4.8            | 0.0           |
| eGFRI    | 80.5 ± 12.7                       | -42.2                | -50.0, -38.5, -24.5                    | 42.1       | 0.140 | 0.377         | 65.7           | 16.7          |
| eGFRI↓T  | 111.2 ± 25.4                      | -41.1                | -50.0, -38.5, -24.5                    | 42.1       | 0.140 | 0.377         | 66.6           | 16.7          |
| eGFRI↓C  | 93.7 ± 18.8                       | -34.8                | -53.7, -36.6, -14.0                    | 37.3       | 0.138 | 0.384         | 28.6           | 0.0           |
| eGFRI↓BS | 111.3 ± 26.5                      | -31.1                | -50.0, -38.5, -24.5                    | 42.1       | 0.140 | 0.377         | 66.7           | 16.7          |
| eGFRI↓BS2| 111.3 ± 22.4                      | -22.6                | -45.1, -24.6, -2.2                     | 27.3       | 0.138 | 0.384         | 66.7           | 16.7          |
| eGFRI↓C  | 154.7 ± 30.0                      | -33.8                | -53.7, -36.6, -14.0                    | 37.3       | 0.138 | 0.384         | 28.6           | 0.0           |
| eGFRIFS  | 115.2 ± 19.1                      | -30.0                | -50.0, -38.5, -24.5                    | 42.1       | 0.140 | 0.377         | 66.7           | 16.7          |
| eGFRI↓SM | 101.8 ± 12.6                      | -30.0                | -50.0, -38.5, -24.5                    | 42.1       | 0.140 | 0.377         | 66.7           | 16.7          |
| eGFRI↓SM2| 117.0 ± 16.3                      | -18.6                | -33.8, -19.5, 1.6                      | 21.6       | 0.191 | 0.226         | 83.3           | 23.8          |
| eGFRI↓SM3| 118.4 ± 17.6                      | -17.6                | -35.5, -18.4, 5.3                      | 21.1       | 0.269 | 0.085         | 83.3           | 23.8          |

Table 19. Determined coefficients a.

| Original equation | a       |
|-------------------|---------|
| eGFRI↓SM          | 1.2951  |
| eGFRI↓FS          | 2.0048  |
| eGFRI↓BS          | 1.4043  |

Table 20. Original and corrected [C] coefficients for the Schwartz equation of 2012.

| Equation | b | d | e | f | g | h |
|----------|---|---|---|---|---|---|
| GFRI↓SM  | 39.8 0.456 0.418 0.079 1.076 1.019 | 0.384 |
| GFRI↓SM2 | 38.9 0.516 0.473 0.111 1.115 1.034 | 0.384 |

Table 21. Original and corrected [C] coefficients for the Schwartz equation of 2012.

| Equation | C | p |
|----------|---|---|
| eGFRI↓FS | 42.3 | 0.79 |
| eGFRI↓FS2| 49.6 | 0.98 |

Table 22. Original and corrected [C] coefficients for the Schwartz bed-side formula of 2009.

| Equation | B |
|----------|---|
| eGFRI↓BS | 41.3 |
| eGFRI↓BS2| 49.0 |

has a mathematically identical formula as the Schwartz equation (the averaged equation of Pottel et al. eGFR = 0.376 H/Scr, where H – height, Scr – creatinine concentration in mg %). Possibly, the effect of a large group of the examined children has obliterated such relations.

In this report, the authors have not presented the analysis of results depending on sex, but such comparisons have been performed and no significant effect of sex on the accuracy of the employed equations has been noted, contrary to the others opinion. Possibly, what is most obvious for the 2012 Schwartz equation (GFR↓SM) – (Tables 5 and 14). The proposed
**Table 23.** The eGFR value (mean ± SD), average relative error (RE), the 5, 50, 95 centiles of RE (50% centile equals median value), RMSRE, correlation coefficient (R) to iohexol method (p value) and 10% and 30% accuracy in all patients (N = 417).

| Equation | eGFR (mean ± SD) [mL/min/1.73 m²] | RE average value [%] | Relative error centiles (5,50,95) [%] | RMSRE [%] | R | p values (R) | Accuracy 10% | Accuracy 30% |
|----------|----------------------------------|----------------------|---------------------------------------|-----------|---|-------------|--------------|-------------|
| GFR      | 98 ± 31.6                        |                      |                                       |           |   |             |              |             |
| eGFR<sub>Scr</sub> | 68.6 ± 17.8                      | -25.9                | -47.2, -28.4, 8.1                     | 30.9      | 0.807 | 0.000 | 52.3 | 9.4 |
| eGFR<sub>ScrT</sub> | 89.4 ± 30.8                      | -6.8                 | -36.0, -7.8, 29.9                    | 21.3      | 0.780 | 0.000 | 83.5 | 35.5 |
| eGFR<sub>ScrC</sub> | 91.3 ± 28.1                      | -3.9                 | -32.7, -5.4, 30.9                    | 19.8      | 0.796 | 0.000 | 86.8 | 43.2 |
| eGFR<sub>ScrBSC</sub> | 77.1 ± 24.0                      | -19.1                | -43.9, -20.4, 10.7                   | 25.1      | 0.795 | 0.000 | 74.8 | 18.9 |
| eGFR<sub>ScrBST</sub> | 89.0 ± 31.5                      | -8.1                 | -38.1, -9.2, 27.2                    | 21.6      | 0.781 | 0.000 | 83.2 | 35.7 |
| eGFR<sub>ScrBST</sub> | 91.5 ± 28.5                      | -3.9                 | -33.4, -5.4, 31.5                    | 19.8      | 0.795 | 0.000 | 86.3 | 43.0 |
| eGFR<sub>Cr</sub> | 124.3 ± 42.2                     | 29.5                 | -14.2, 28.3, 79.1                    | 40.6      | 0.774 | 0.000 | 53.0 | 17.3 |
| eGFR<sub>Cr</sub> | 92.6 ± 30.4                      | -4.4                 | -34.4, -4.5, 24.6                    | 18.5      | 0.825 | 0.000 | 89.0 | 41.7 |
| eGFR<sub>CrM</sub> | 83.3 ± 22.8                      | -11.6                | -34.6, -12.8, 17.6                   | 19.1      | 0.873 | 0.000 | 89.0 | 32.1 |
| eGFR<sub>CrM</sub> | 93.7 ± 28.2                      | -2.0                 | -27.2, -3.2, 26.5                    | 15.8      | 0.870 | 0.000 | 93.0 | 48.0 |
| eGFR<sub>CrM</sub> | 93.9 ± 28.7                      | -2.3                 | -26.6, -4.0, 23.7                    | 15.3      | 0.874 | 0.000 | 94.5 | 48.2 |

Tables 15–18 show eGFR values and all calculated indices for particular intervals of eGFR by GFRI.

Corrections decrease the error, and the classification accuracy coefficient is improved for all the Schwartz equations, reaching the highest values (81%) for the corrected tri-marker equation (Table 14), and the lowest for the 2012 Schwartz formula (eGFR<sub>Scr</sub>). One might ask to what degree the accuracy of GFR calculation at its high values is of a clinical importance. Being aware of some physiological individual fluctuations of GFR over time, the authors believe it is worthwhile to have in nephrology centers a precise tool for GFR calculation for selected groups of children, especially with glomerular hyperfiltration.

The limitations of the study result from too small a number of younger children and a single-center character of the study. A potential error of creatinine determinations should be explained by the employed standardization of the method that was described in the previous study (see the section on Material and methods).

**Summary**

In our opinion, in pediatric practice we should increasingly employ multiple-marker equations for GFR assessment in clinical situations that require a precise GFR estimation. While calculating eGFR according to the Schwartz equations in children with the anticipated GFR value > 60 mL/min/1.73 m², one may decrease the error by using our corrections.

**Conclusions**

1. At higher values of GFR > 60, and especially > 90 mL/min/1.73 m², the authors propose to employ new coefficients for the three Schwartz equations (the bed-side formula of 2009, the shortened equation of 2012 and the tri-marker equation). The use of the new coefficients significantly improves the accuracy of calculating GFR.

2. Multi-marker equations are characterized by a higher accuracy in eGFR calculation as compared to the uni-marker equations and should be more frequently employed.

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**References**

1. Gao A, Cachat F, Faouzi M, et al. Comparison of the glomerular filtration rate in children by the new revised Schwartz formula and a new generalized formula. *Kidney Int.* 2013;83:524–530.
2. 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.
3. Bouvet Y, Bouissou F, Coulais Y, et al. GFR is better estimated to the uni-marker equations and should be more accurately. *J Am Soc Nephrol.* 2009;20:629–637.
4. De Souza VC, Rabilloud M, Cochot P, et al. Schwartz formula: Is one k-coefficient adequate for all children? *PLoS One.* 2012;7:e53439.
5. Zappitelli M, Parvex P, Joseph L, et al. Derivation and validation of cystatin C-based prediction equations for GFR in children. *Am J Kidney Dis.* 2006;48:221–230.
6. Filler G, Lepage N. Should the Schwartz formula for estimation of GFR be replaced by cystatin C formula? *Pediatr Nephrol.* 2003;18:981–985.
7. Grubb A, Nyman U, Bjork J, et al. Simple cystatin C-based prediction equations for glomerular filtration rate compared with the modification of diet in renal disease prediction equation for adults and the Schwartz and
the Counahan-Barratt prediction equations for children. Clin Chem. 2005;51:1420–1431.

8. Hari P, Biswas B, Pandey R, Kalaivani M, Kumar R, Bagga A. Updated height- and creatinine-based equation and its validation for estimation of glomerular filtration rate in children from developing countries. Clin Exp Nephrol. 2012;16:697–705.

9. Filler G, Yasin A, Medeiros M. Methods of assessing renal function. Pediatr Nephrol. 2014;29:183–192.

10. Bokenkamp A, Domanetzki M, Zinck R, Schumann G, Byrd D, Brodell J. Cystatin C: a new marker of glomerular filtration rate in children independent of age and height. Pediatrics. 1998;101:875–881.

11. Pottel H, Hoste L, Martens F. A simple height-independent equation for estimating glomerular filtration rate in children. Pediatr Nephrol. 2012;27:973–979.

12. Blufpand HN, Westland R, Van Wijk JAE, Roelandse-Koop EA, Kaspers GJL, Bovenkamp A. Height-independent estimation of GFR in children: An alternative for the Schwartz equation. Pediatr Nephrol. 2013;28:1360.

13. Filler G. How to measure renal function in children – What is the role of cystatin C? Curr Pediatr Rev. 2006;2:225–231.

14. Filler G, Bokenkamp A, Hofmann W, Le Bricon T, Martinez-Bru C, Grubb A. Cystatin C as a marker of GFR: history, indications, and future research. Clin Biochem. 2005;38:1–8.

15. Roos JF, Doust J, Tett SE, Kirkpatrick CMJ. Diagnostic accuracy of cystatin C compared to serum creatinine for the estimation of renal dysfunction in adults and children – A meta-analysis. Clin Biochem. 2007;40:383–391.

16. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: A meta-analysis. Am J Kidney Dis. 2002;40:221–226.

17. Andersen TB, Eskild-Jensen A, Frokiaer J, Brochner-Mortensen J. Measuring glomerular filtration rate in children; can cystatin C replace established methods? A review. Pediatr Nephrol. 2009;24:929–941.

18. Martini S, Prevot A, Mosig D, Werner D, van Melle G, Guignard JP. Glomerular filtration rate: Measure creatinine and height rather than cystatin C. Acta Paediatr. 2003;92:1052–1057.

19. Donadio C, Kanaki A, Caprio F, Donadio E, Tognotti D, Olivieri L. Prediction of glomerular filtration rate from serum concentration of cystatin C: Comparison of two analytical methods. Nephrol Dial Transplant. 2012;27:2826–2838.

20. 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.

21. Zappitelli M, Zhang X, Foster BJ. Estimating glomerular filtration rate in children at serial follow-up when height is unknown. Clin J Am Soc Nephrol. 2010;5:1763–1769.

22. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012;367:20–29.

23. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of diet in renal disease study group. Ann Intern Med. 1999;130:461–470.

24. Harman WE. Glomerular filtration rate in children with chronic kidney disease. Clin Chem. 2009;55:400–401.

25. Fadrowski JJ, Neu AM, Schwartz GJ, Furth SL. Pediatric GFR estimating equations applied to adolescents in the general population. Clin J Am Soc Nephrol. 2011;6:1427–1435.

26. Staples A, Leblond R, Watkins S, Wong C, Brandt J. Validation of the revised Schwartz estimating equation in a predominantly non-CKD population. Pediatr Nephrol. 2010;25:2321–2326.

27. Selistre L, De Souza V, Cochat P, et al. GFR estimation in adolescents and young adults. J Am Soc Nephrol. 2012;23:989–996.

28. Bachetta J, Cochat P, Rognant N, Ranchin B, Hadj-Aissa A, Dubourg L. Which creatinine and cystatin C equations can be reliably used in children? Clin J Am Soc Nephrol. 2011;6:552–560.

29. Sharma AP, Yasin A, Garg AX, Filler G. Diagnostic accuracy of cystatin C-based eGFR equations at different GFR levels in children. Clin J Am Soc Nephrol. 2011;6:1599–1608.

30. 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.

31. Furth SL, Cole SR, Moxey-Mims M, et al. Design and methods of the chronic kidney disease in children (CKID) prospective cohort study. Clin J Am Soc Nephrol. 2006;1:1006–1015.

32. Querfeld U, Anarat A, Bayazit AK. 4C Study Group, et al. The cardiovascular comorbidity in children with chronic kidney disease (4C) study: Objectives, design, and methodology. Clin J Am Soc Nephrol. 2010;5:1642–1648.

33. Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: A height-weight formula validated in infants, children, and adults. J Pediatr. 1978;93:62–66.

34. Zachwieja K, Korohoda P, Kwinta-Rybicka J, et al. Which equations should and which should not be employed in calculating eGFR in children? Adv Med Sci. 2015;60:31–40.

35. Foster J, Reisman W, Lepage N, Filler G. Influence of commonly used drugs on the accuracy of cystatin C-derived glomerular filtration rate. Pediatr Nephrol. 2006;21:235–238.

36. Filler G, Huang S-S, Yasin A. The usefulness of cystatin C and related formulae in pediatrics. Clin Chem Lab Med. 2012;50:2081–2091.

37. Deng F, Finer G, Hayden S, Brooks E, Langman CB. Applicability of estimating glomerular filtration rate equations in pediatric patients: Comparison with a measured glomerular filtration rate by ioheal clearance. Transl. Res. 2015;165:437–445.

38. Zachwieja K, Korohoda P, Kwinta-Rybicka M, et al. A comparison of various methods of GFR estimation in children; the experience of a single center. Nefrol Dial Pol. 2009;13:234–240.

39. 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.

40. 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 Transplant*. 2014;29:1082–1091.

**Appendix**

Methodology of determining plasma iohexol by HPLC.

HPLC determinations were performed using a WATERS kit and Millennium 32 software. The distribution was performed using an Xterra column (C18 3.5 μm, 3.0 x 150 mm) at 30°C employing isocratic elution with the mobile phase composed of acetonitrile and water at the ratio of 4: 96, at a flow of 0.36 mL/minute. The analysis time was 15 minutes; iohexol was detected at the wavelength of 254 nm. The standard mixture was Omnipaque 300 mg/L/mL (647 mg iohexol/mL). The internal standard was iohexol Compound B manufactured by LGC Promoche.

After iohexol application to healthy patients, serum iohexol recovery was calculated in the blood samples. The following values were obtained:

- For 10.0 μg – 109.2%
- 65.0 μg – 96.6%
- 300.0 μg – 93.7%
- 647.0 μg – 96.8%

For each series of determinations, residual control serum was employed with mean iohexol value of 159.89, SD = 6.48. The extra-series coefficient of variation CV was 4.05%. The intra-series coefficient of variation equaled CV = 0.69.