New Predictive Equations Improve Monitoring of Kidney Function in Patients with Diabetes

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Running title: new renal predictive equations in diabetes

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Abbreviations: CG, Cockroft-Gault formula • CKD, chronic kidney disease • CysC, Cystatin C • Cys-eGFR, glomerular filtration rate estimated via cystatin formula • GFR, glomerular filtration rate • iGFR, isotopic measurement of glomerular filtration rate • MCQ, Mayo Clinic Quadratic equation • MDRD, Modification of Diet in Renal Disease • rMDRD, re-expressed Modification of Diet in Renal Disease
OBJECTIVE–The Cockcroft-Gault (CG) and MDRD equations poorly predict GFR decline in diabetic patients. We sought whether new equations based on serum creatinine (Mayo Clinic Quadratic -MCQ- or re-expressed MDRD -rMDRD) or 4 cystatin C–based equations (Cys-eGFR) were less biased and better predicted GFR changes.

RESEARCH DESIGN AND METHODS–In 124 diabetic patients with a large range of isotopic GFR (56.1±35.3 mL/min/1.73m², range 5-164), we compared the performances of the equations before and after categorization in GFR tertiles. Twenty patients had a second determination two years later.

RESULTS–The CG was the least precise. The MDRD was the most precise but the most biased according to the Bland & Altman procedure. By contrast with the MDRD and, to a lesser extent, MCQ, three of the four Cys-eGFR were not biased. All equations overestimated the low GFRs, whereas only the MDRD and Rule’s equation underestimated the high GFRs. For the subjects studied twice, isotopic GFR changed by -8.5±17.9 mL/min/1.73m². GFR changes estimated by the CG (-4.5±6.8) and MDRD (-5.7±6.2) did not correlate with the isotopic changes, whereas new equations-predicted changes did: MCQ: -8.7±9.4; (r=0.44, P<0.05) and all four Cys-eGFR: -6.2±7.4 to -7.3±8.4 (r =0.60 to 0.62, all P<0.005), such as 100/cystatin C (r=0.61, P<0.005).

CONCLUSIONS–The new predictive equations better estimate GFR than the CG. Although the MDRD remains the most accurate, it poorly predicts GFR decline as it overestimates low and underestimates high GFR. This bias is lesser with the MCQ and Cys-eGFR, so they better predict GFR changes.
Chronic kidney disease (CKD) is a major health problem worldwide with dramatically rising incidence and prevalence. Patients with diabetes are particularly affected by this negative development. It is necessary to stratify CKD and estimate its progression, since diabetes is the leading cause of End-Stage Renal Disease (1). The National Kidney Foundation (NKF) guidelines recommend estimating Glomerular Filtration Rate (GFR) in subjects with CKD (2). According to the NKF and the American Diabetes Association (ADA), GFR can be estimated in adults by using the Cockcroft & Gault formula (CG) or the Modification of Diet in Renal Disease equation (MDRD) (1,3). Neither of these equations based on serum creatinine is highly predictive of GFR. The CG is less accurate (4), biased by body weight (5), and less robust in patients with poor glycemic control (6). The simplified MDRD equation allows renal function to be classified with acceptable precision and requires only usual information about the patient. However, adjustment may be required in order to avoid error due to creatinine assays and calibrators (7). Moreover, the MDRD is known to underestimate high or normal GFR, leading to dramatic inaccuracy evidenced in the DCCT cohort (8). Only 70% of subjects overall may be considered well-stratified according to the K/DOQI with these equations (9). Their precision seems even worse for estimating CKD progression, leading to unacceptable inaccuracy (10). The estimated equations reflected the measured GFR decline only in the most advanced (K/DOQI stage 3) cases (11), suggesting that variable predictive performance due to GFR level may play a role in this imprecision.

New predictive equations therefore need to be developed and validated. They could be based on the results of serum creatinine (sCr) in subjects with - as in the MDRD - or without renal impairment. The Mayo Clinic Quadratic equation (MCQ) was established this way (12). Another means is to include the promising new renal marker cystatin C in formulae based solely on a serum level without requiring any clinical information (13). In 30 type 2 diabetes during a 4-yr study there was a close relationship between longitudinal trends in iothalamate clearance and trends in renal function estimated by the mean of 100/cystatinC (14), in contrast to creatinine-based estimates of GFR (GC and MDRD). It appears of particular interest therefore to study the known CysC-based equations and to compare them to recent creatinine-based formula, in order to determine whether these new predictive equations are less biased according to the GFR level, and whether they allow GFR trends to be established in diabetic subjects.

We compared the estimation of GFR by conventional (CG, MDRD) and new equations (re-expressed rMDRD (7), MCQ, and CysC-based equations) to 51Cr-EDTA measured GFR in 124 diabetic patients with a large range of renal function. The four cystatin-based equations were recently proposed in (i) the general population by Rule et al (15) and Arnal (16-17) and in (ii) diabetic patients by Tan et al (18) and MacIsaac et al (19). To focus on biases according to GFR level, we performed a Bland & Altman procedure and repeated the comparison after categorizing the subjects in tertiles of GFR levels. In 20 patients, GFR was also measured and predicted two years later to investigate whether the new equations were more efficient in predicting GFR change.

**RESEARCH DESIGN AND METHODS**

**Patients**

One hundred twenty-four adult diabetic patients attending our clinical unit (Service de Nutrition-Diabétologie, Hôpital Haut-Lévêque, Pessac, France) were studied, mainly men (n=78) with type 2 diabetes (n=88), aged 62±13 yrs (19-83), with a 27.5±4.6 kg/m² BMI (15.6-40.7) and their Albumin Excretion Rate was 575±864

*Note: The text is a continuation of the previous one.*
mg/24 hr (5-4000). No patient was dialyzed during the study.

**Analytical methods**
Serum creatinine was determined on a multiparameter analyzer (Olympus AU 640: Olympus Optical, Tokyo, Japan) using the Jaffé method with bichromatic measurements according to the manufacturer's specifications, and the analyzer was calibrated and controlled daily. The procedure remained constant throughout the study. The results were obtained in µmol/L and converted into mg/dL in order to perform the predictive equations. Serum CysC (mg/L) was determined on a nephelometric analyzer (Behring Nephelometer 2, Paris La Défense Cedex, France) by means of particle-enhanced immunonephelometry (N latex CysC, Dade Behring, Marburg, Germany) after calibration and control. Clearance of the radionuclide marker was measured after intravenous injection of 51Cr-EDTA (Cis Industries, Gif/Yvette, France). Patients were studied in the morning at 9 am after a light breakfast. After a single bolus of 100 µCi (3.7 MBq) of 51Cr-EDTA, 4 venous blood samples were drawn at 75, 105, 135 and 165 minutes, and urinary samples were collected at 90, 120, 150 and 180 minutes, as described (20). The final result was the mean of the four clearance values. If urinary flow was too weak in any period or if a clearance value was not within ±20% of the mean of the other three, the value was excluded and the mean calculated on the other three clearances. Fewer than 5% of the values were thus excluded. 51Cr-EDTA radioactivity was measured in a gamma counter (COBRA 2, model 05003, Packard Instruments, Meriden, CT).

**Estimation of renal function**
Single serum creatinine and CysC measurements were performed the day before the isotopic measurement of GFR (iGFR).

**1. Creatinine-based formula**

1a. **Cockcroft and Gault formula** (CG):
\[
CG = \frac{(140 - \text{age [yrs]}) \times \text{body weight [kg]} \times \text{serum creatinine [µmol/L]}}{K}
\]
where K is a constant: 1.23 for men and 1.04 for women (21).

1b. **Modification of Diet in Renal Disease study equation (MDRD):**
We used the simplified equation (22):
\[
\text{MDRD} = 186 \times (\text{serum creatinine [mg/dL]}^{1.154} \times (\text{[yrs]}^{−0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African-American}).
\]

1c. **Re-expressed Modification of Diet in Renal Disease study equation (rMDRD):**
Significant error being introduced when the MDRD equation is used with different creatinine assays or calibration, the simplified MDRD was recently recalculated with serum creatinine measurements calibrated to an enzymatic assay (7):
\[
\text{rMDRD} = 175 \times (\text{serum creatinine [mg/dL]}^{1.154} \times (\text{[yrs]}^{−0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African-American}).
\]

1d. **Mayo Clinic Quadratic equation (MCQ) (12):**
\[
\text{MCQ} = \exp(1.911 + 5.249/\text{SCr} − 2.114/\text{SCr}^2 − 0.006868\text{Xage (yrs)} -0.205 \text{ if female})
\]
In all formula, SCr = serum creatinine [mg/dL]

**2. Cystatin C-based formula**
Several CysC-based predictive equations for calculating GFR have been recently published and evaluated with different CysC assays; they may lead to inaccurate GFR estimates if an inappropriate formula is used (23). We chose formulae by using our own methodology to measure serum CysC (immunonephelometry, Dade Behring). As a disease-specific formula has been tested in diabetes for estimating GFR (18) using a different methodology (immunoturbidimetric method (Dako, High
Wycombe, U.K.) on a Cobas FARA analyzer (Roche Diagnostics, Lewes, U.K.), we have tested this formula but accurately comparing different methodologies is classically difficult.

2a. Cystatin-estimated GFR according to Arnal (16-17)
It was used in 208 patients aged 1-80yrs with various etiologies and having insulin determination of GFR:

\[
\text{Cys-eGFR(Arnal-Dade)} = \frac{74.835}{(\text{CysC}^{1.333})}
\]

2b. Cystatin-estimated GFR according to Rule et al (15)
This equation was derived from patients with native kidney disease (n=204) having hypertension as mean suspected etiology. iGFR was measured by iothalamate clearance.

\[
\text{Cys-eGFR(Rule)} = 66.8X(\text{CysC})^{-1.30}
\]

2c. Cystatin-estimated GFR according to MacIsaac et al (19)
In 126 diabetic patients (mainly type 2 diabetes), the iGFR was measured by clearance of \(^{99}\text{mTc-diethylene-triamine-penta-acetic acid}\) (88±2 ml/min/1.73 m\(^2\) with 78%>60 ml/min/1.73 m\(^2\)).

\[
\text{Cys-eGFR(MacIsaac)} = \frac{(84.6/(\text{CysC})-3.2}{88}\]

2d. Cystatin-estimated GFR according to Tan et al (18)
An unbiased conversion algorithm between plasma CysC and iGFR measured by iohexol clearance was used in type 1 diabetes, including a subgroup of healthy subjects.

\[
\text{Cys-eGFR(Tan)} = \frac{87.1/\text{plasma CysC}}{6.87} - 6.87
\]

In all formulae, CysC = serum cystatinC [mg/L].

The results of the CG and iGFR were adjusted to body surface area using Dubois' formula (24) before comparisons. The results of the MDRD, rMDRD, MCQ and cystatin-based formulae are directly expressed as adjusted to body surface area.

Statistical analysis
The results of the predictive equations were compared to iGFR by regression analysis, paired t tests, and Bland & Altman procedures. The regression analysis and paired t tests were repeated after categorizing the subjects in tertiles according to their measured GFR. The precision of the equations was assessed by the absolute differences between their results and the iGFR, and by the % of estimations within ±15%, ±30% and ±50% of the iGFR. The sensitivity and specificity for the diagnosis of moderate (GFR <60 ml/min/1.73 m\(^2\)) and severe (GFR<30) renal failure were assessed from non-parametric receiver operating characteristic (ROC) curves, generated by plotting sensitivity versus 1-specificity, giving the ideal test a sensitivity equal to 1 and a specificity equal to 1. Areas Under the Curve (AUC) were calculated and compared as published (25).

In the 20 subjects who were studied twice, the two measured and predicted GFR were compared by paired t tests, and the measured and predicted GFR changes were compared by regression analysis. These calculations were performed with SPSS software, version 10.0 and MedCal software. Results are presented as mean ±SD; \(P<0.05\) was considered significant.

RESULTS
Overall performances of predictive equations
Serum creatinine was 148±79 µmol/L and serum cystatin C 1.56±0.84 mg/L (0.49-5.48). Mean iGFR was 56.1±35.3 mL/min/1.73 m\(^2\) (8.5-164). The results of the eight predictive equations are presented in Table 1. The mean Cys-eGFR(Arnal-Dade) alone did not differ from the reference iGFR and was not biased. Such was also the case in a lesser extent with Cys-eGFR (MacIsaac and Tan), according to the Bland & Altman plots. The highest absolute difference with the iGFR was obtained with CG, while the lowest was obtained with the MDRD, rMDRD and Cys-eGFR(Rule).
The Area under ROC curve (Table 1) was significantly lower with the CG than the others for the diagnosis of moderate renal failure (GFR<60 mL/min/1.73m²). For the diagnosis of severe renal failure (GFR<30 mL/min/1.73m²), the best AUC was by the MDRD.

Type of diabetes
The study involved both type 1 (n=36; BMI=25.0±3.1 kg/m²) and type 2 diabetes (n=88; BMI=28.5±4.7 kg/m², P<0.001 vs type 1) having an iGFR=62.9±34.3 (range 10-145) and 53.3±35.5 ml/min/1.73m² (range 8-164), respectively. CG formula was not biased according to the Bland & Altman procedure but was characterized by the highest absolute percentage of difference with iGFR in the two types of diabetes. The MDRD and rMDRD were biased in type 1 (r=-0.57, P<0.001) and type 2 diabetes (r=-0.64, P<0.001), MCQ being biased only in type 2 (r=-0.26, P<0.01). Cys-eGFR(Rule) alone was biased only in type 2 diabetes (r=-0.28, P<0.01). The influence of lean mass in CysC equations has been demonstrated especially in patients with extreme body composition (26), the lack of systematic significant observed difference in cys-eGFR formulae suggests that CysC is unaffected by the body composition of our sub-groups of diabetics.-

Prediction of GFR according to GFR tertiles
The performances of all estimations are presented in Table 2. All the predictive equations overestimated low GFR, the MDRD, rMDRD and Cys-eGFR (Rule) also underestimated high GFR (-21%, -25% and -11.5%, respectively). In the medium GFR tertile, only the MDRD and Cys-eGFR (Arnal-Dade) did not significantly differ from iGFR. The Cys-eGFR (Arnal-Dade) gave (i) a correct estimation of GFR in both the high and medium tertiles, and (ii) one of the lowest (+25%) overestimations in the low tertile.

Prediction of CKD progression
The 20 subjects who underwent a second evaluation were mainly men (n=16) with type 2 diabetes (n=13), having an iGFR change of -8.5±17.9 ml/min/1.73m². Their mean initial age was 68±10 yrs, BMI was 25.8±4.1 kg/m². Serum creatinine and CysC significantly increased after two years (P<0.001 and 0.003, respectively; Appendix 1). The characteristics of the eight tested formulae with the mean difference in their changes are shown in Appendix 1. The relations between measured and estimated renal function changes are depicted in Figure 1 (completed in Appendix 2). The rate of iGFR change was significantly correlated with its estimations by the MCQ (r=-0.45, P<0.05, Fig 1C) and by the four Cys-eGFR (P<0.005) [r=0.60 for Cys-eGFR(Arnal-Dade) (Fig 1D); 0.61 for Cys-eGFR(MacIsaac), Cys-eGFR(Tan) (Fig 2C) and 0.62 for Cys-eGFR(Rule) (all three in Appendix 2)], whereas the correlation with the CG (r=0.35) (Fig 1A), MDRD (r=0.41) (Fig 1B) and rMDRD (r=0.41) (Appendix 2, A) did not reach significance. The iGFR changes correlated to the trend in 100/Cystatin C (r=0.61, P<0.005) (Fig 1E), whereas the correlation with the trend in 100/Creatinine did not reach significance (r=0.41).

CONCLUSIONS
While conventional GFR predictive equations are known to lack predictive power, the diabetic population represents a specific challenge. The effects of hyperglycemia (6) and BMI-related bias (5) have led most investigators to avoid using the CG in recent reports (26-27). As the CG calculates GFR proportional to body weight, this tendency is likely to increase since the mean BMI of subjects entering dialysis is increasing twice as fast as the BMI of the US general population, as recently reported (28). Because a high BMI seems an important risk factor for End Stage Renal Disease (29), this error is unacceptable. Replacing the CG by the MDRD equation is
not necessarily the solution. Although diabetic nephropathy is quite a common cause of CKD, most diabetic subjects retain normal renal function during their lifetime. High GFR may also be present at the earliest stage of diabetic nephropathy. Owing to its underestimation of normal and high GFR (14, 19), the MDRD is not adequate, so new formulae are required.

Although this work confirms that some cystatin-based equations—have a predictive potential similar to the CG and MDRD in diabetes (19), the use of complicated or expensive tools (CysC determination is nowadays 10-fold more expensive than creatinine determination) is not justified unless they demonstrate a clear advantage; however, if measuring cystatin-C proves to be a simple and accurate way of detecting CKD, its current use should lead to a significant reduction in its cost. Many studies have demonstrated the interest of CysC as a marker of renal function in diabetic patients, but fewer investigations have compared various CysC-eGFR formulae with updated creatinine-based formulae, especially to follow the trends of renal function. To our knowledge, this study is the first to incorporate a comparison of four Cys-eGFR equations with four creatinine-eGFR ones.

For our patients, all creatinine- or cystatin-based formulae were more accurate than the CG in diagnosing renal failure, as demonstrated by areas under ROC curves. Based on precision (absolute percentage variation with iGFR), the most accurate tool for estimating GFR in renal insufficient diabetics remains the MDRD (similar to rMDRD) and the Cys-eGFR (Rule) formula. The precision of MCQ and Cys-eGFR ( Arnal-Dade) were slightly lower than with the latter. Of particular interest, cystatin C-based formulae did not underestimate high GFR (except Rule’s equation), in contrast with MDRD (-21%) and rMDRD (-25%), as expected because they were not biased.

Obtaining a low bias seems crucial in determining CKD progression: a predictive formula that underestimates normal GFR by –20% (42-123 ml/min/1.73m²) and overestimates low GFR by +33% (10-76 ml/min/1.73m²), as did the MDRD, will underestimate GFR change, as recently reported (10, 14). We found no significant improvement in prediction by using the re-expressed MDRD. The better value of the MDRD at more advanced CKD stages reported elsewhere (11) was not unexpected, as MDRD performance improves when GFR declines. The absence of bias according to the GFR level is an obvious advantage for determining CKD progression with Cys-eGFR. Cys-eGFR(Arnal-Dade) was especially interesting as it gave (i) a correct estimation of GFR in both high and medium tertiles, and (ii) one of the lowest (+25%) overestimations in the low tertile. The creatinine-based MCQ gave an intermediate performance, as could be expected because it has been established from the results of a mixed population that did not only include renally insufficient subjects (12), unlike the MDRD.-

Even though the follow-up involved only 20 patients, significant results obtained in a small cohort suggest that better accuracy would be achieved in a larger one. Our results are in line with those of Perkins et al. who reported better agreement of 100/cystatin than 100/creatinine with GFR decline in 30 type 2 diabetic patients with high baseline GFR (>120 ml/min/1.73m²) (14); we extend this finding to renal insufficient diabetic patients, with mean GFR changing about -4 ml/min/1.73m² as usually reported (10-11); moreover, it appears that changes in GFR as estimated by 100/cystatin predicted changes in isotopic GFR equally as well as the cystatin prediction equations. These results obtained in 20 variable patients are not sufficient to affirm that the less biased Cys-eGFR ( Arnal-Dade) equation can estimate changes in GFR on an individual basis. However, our findings, like those of others, point to the usefulness of CysC as a marker of GFR, and should lead to larger population studies with further validation. Finally, any calibration differences between the Dade-Behring BNII
nephelemeter used in this study and other CysC assays can lead to inaccurate GFR estimates, a well-described problem with creatinine equations. Further work is needed to improve (i) cystatin C measurement by harmonization of methods and calibration as in recent work concerning standardization of creatinine (7), and (ii) the precision of cystatin C-derived formulae.

Besides estimating renal function, it would be of interest to measure serum CysC in diabetic subjects since CysC predicts increased cardiovascular risks that may be missed by measurement of kidney function using serum creatinine (30). Our work mainly shows that they are promising for evaluating CKD progression in diabetic subjects with various Cys-eGFR equations, in agreement with the point of view that specific prediction formulae could be used for particular patient groups (31). Disease-specific formulae have to be restricted to specific medical prescription owing to the frequent lack of clinical information concerning referred patient samples in laboratories (16). This study provides a kinetic basis for previous static work reporting that serum CysC is valuable in detecting early or mild diabetic nephropathy (32) for screening early impairment of renal function, at a time when active management is important. The fact that the highest and medium GFR were well estimated and that the lowest GFR were less overestimated by the Cys-eGFR(Arnal-Dade) in particular means that it is possible to obtain a global estimation of the change (high GFR becoming a low GFR) close to that measured by iGFR. If the cost of determining GFR by cystatin C is prohibitive or unavailable, then the MCQ seems a good alternative to the MDRD for the most obese and/or poorly controlled patients, whose CG would otherwise be imprecise and biased.

Acknowledgements: the authors thank Ray Cooke for the revised manuscript.
REFERENCES


Table 1: Results of predictive equations in the entire diabetic population (n=124) divided into formulae related to creatinine and cystatin. For the Bland & Altman comparison, r and P represent the correlation and its specificity between [average(tested equation+iGFR)] and (tested equation-iGFR). For the receiver-operating characteristic curves for the estimated equations, AUC= area under the ROC curves. *P<0.05 vs other AUC.
Isotopic GFR = 56.1±35.3 ml/min/1.73m² (range : 8-164).

<table>
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<tr>
<th>CREATININE-BASED FORMULA</th>
<th>CG</th>
<th>MDRD</th>
<th>rMDRD</th>
<th>MCQ</th>
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<tr>
<td>Mean±SD (ml/min/1.73m²):</td>
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<tr>
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<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<td>Median absolute %Δ with iGFR:</td>
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<td>27.7±24.6</td>
<td>26.2±21.7</td>
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<td>r</td>
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<td>Tan</td>
<td>Rule</td>
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### Difference with iGFR (non parametric):

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<th>NS</th>
<th>&lt;0.001</th>
<th>&lt;0.001</th>
<th>&lt;0.01</th>
</tr>
</thead>
</table>

### Median absolute %Δ with iGFR:

<p>| | | | | |</p>
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>31.2±33.0</td>
<td>42.9±45.4</td>
<td>38.3±41.0</td>
<td>27.1±27.4</td>
<td></td>
</tr>
</tbody>
</table>

### Bland & Altman:

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>( r )</td>
<td>-0.02</td>
<td>-0.12</td>
<td>-0.11</td>
<td>-0.18</td>
</tr>
<tr>
<td>( P )</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>2SD</td>
<td>47.8</td>
<td>40.6</td>
<td>40.6</td>
<td>41.4</td>
</tr>
</tbody>
</table>

### Accuracy (%)

<p>| | | | | |</p>
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<tr>
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</thead>
<tbody>
<tr>
<td>Within±15%</td>
<td>31</td>
<td>32</td>
<td>30</td>
<td>39</td>
</tr>
<tr>
<td>Within±30%</td>
<td>64</td>
<td>55</td>
<td>59</td>
<td>67</td>
</tr>
<tr>
<td>Within±50%</td>
<td>87</td>
<td>72</td>
<td>77</td>
<td>89</td>
</tr>
</tbody>
</table>

### AUC

<p>| | | | | |</p>
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>iGFR&lt;60ml/min/1.73m² (n=76):</td>
<td>0.95</td>
<td>0.96</td>
<td>0.96</td>
<td>0.96</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>90.8</td>
<td>92.1</td>
<td>92.1</td>
<td>92.1</td>
</tr>
<tr>
<td>Specificity</td>
<td>89.6</td>
<td>87.5</td>
<td>87.5</td>
<td>87.5</td>
</tr>
<tr>
<td>Criterion</td>
<td>≤61.9</td>
<td>≤71.8</td>
<td>≤69.5</td>
<td>≤55.7</td>
</tr>
</tbody>
</table>

### AUC

<p>| | | | | |</p>
<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>iGFR&lt;30ml/min/1.73m² (n=36):</td>
<td>0.93</td>
<td>0.94</td>
<td>0.94</td>
<td>0.94</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>88.9</td>
<td>80.6</td>
<td>80.6</td>
<td>80.6</td>
</tr>
<tr>
<td>Specificity</td>
<td>85.2</td>
<td>94.3</td>
<td>94.3</td>
<td>94.3</td>
</tr>
<tr>
<td>Criterion</td>
<td>≤35.4</td>
<td>≤42.4</td>
<td>≤40.0</td>
<td>≤29.5</td>
</tr>
</tbody>
</table>
Table 2. Performance of predictive equations. * P<0.05, **P < 0.01, *** P<0.001.

<table>
<thead>
<tr>
<th></th>
<th>Low GFR tertile</th>
<th>Medium GFR tertile</th>
<th>High GFR tertile</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>41</td>
<td>42</td>
<td>41</td>
</tr>
<tr>
<td>Isotopic GFR</td>
<td>21.4</td>
<td>49.8</td>
<td>97.2</td>
</tr>
<tr>
<td>range</td>
<td>8-34</td>
<td>34-67</td>
<td>67-164</td>
</tr>
</tbody>
</table>

**CREATININE BASED FORMULA**

|                         |               |                   |                  |
| CG                      | 35.6          | 56.1              | 98.4             |
| range                   | 16-80         | 23-102            | 37-208           |
| r                       | 0.37**        | 0.25              | 0.59***          |
| P vs iGFR               | ***           | *                 | NS               |
| MDRD                    | 28.2          | 49.0              | 77.0             |
| range                   | 10-76         | 28-81             | 42-123           |
| r                       | 0.59***       | 0.39**            | 0.65***          |
| P vs iGFR               | ***           | NS                | ***              |

**MCQ**

|                         |               |                   |                  |
| range                   | 29.9          | 57.6              | 95.4             |
| r                       | 0.60***       | 0.39**            | 0.65***          |
| P vs iGFR               | ***           | NS                | ***              |

**CYSTATIN BASED FORMULA**

**Arnal-Dade**

|                         |               |                   |                  |
| range                   | 26.7          | 49.6              | 91.1             |
| r                       | 0.62***       | 0.21              | 0.30*            |
| P vs iGFR               | ***           | NS                | NS               |

**MacIsaac**

|                         |               |                   |                  |
| range                   | 36.4          | 60.9              | 101.3            |
| r                       | 0.64***       | 0.27              | 0.42**           |
| P vs iGFR               | ***           | ***               | NS               |

**Tan**

|                         |               |                   |                  |
| range                   | 33.9          | 58.5              | 99.1             |
| r                       | 0.64***       | 0.27              | 0.42**           |
| P vs iGFR               | ***           | **                | NS               |

**Rule**

|                         |               |                   |                  |
| range                   | 25.2          | 46.1              | 86.0             |
| r                       | 0.62***       | 0.24              | 0.41**           |
| P vs iGFR               | *             | *                 | **               |
Figure 1. Correlation between measured change (two-years follow up – initial) in renal function as determined from isotopic Glomerular Filtration rate (iGFR) and five estimated formulae in 20 diabetic patients, based on creatinine: Cockcroft and Gault (CG in A), Modification of Diet in renal Disease (MDRD in B), Mayo Clinic Quadratic Equation (MCQ in C, \( P<0.05 \)) or based on Cystatin C: according to Arnal-Dade Behring (16-17) in D and according to the 100/cystatin C formula published by Perkins BA et al (14) in E. Points in the lower right quadrant of a plot represent false-positive results for renal function for the measured iGFR (iGFR=0 ml/min/1.73m²) and indicate an underestimation of renal change. Points in the upper left quadrant of a plot represent false-negative results for renal function change for the measured iGFR (iGFR<0 ml/min/1.73m²).