Renal Dosing: Part 1 - General Description

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To treat or prevent a disease, medication must reach a certain concentration at its target site. In general, the effect of the medication is proportional to its concentration at the target site. The higher the concentration, the higher the effect. If the pharmacodynamic properties (eg, the receptors, their density, and downstream machineries) of the subjects are identical, the same concentration at the target site will elicit the same response. If the pharmacokinetic properties of the subjects are also identical, the same dose will produce the identical concentration at the target site and the same effect. Unfortunately, people are different. They have different weight, height, age, gender, and genetic makeup. The same dose in different people have different responses. So, medication therapies need to be individualized and the optimal dose for a specific person should be identified in order to achieve optimal outcomes. Many medications are eliminated through the kidney. Renal function impairment reduces the elimination of those medications. Renal dosing means adjusting drug dose according to renal function, reducing drug doses in renal disease in proportion to the predicted reduction in clearance of the active drug moiety. For renally excreted medications, if the doses are not adjusted renally, the drugs would accumulate in the body and increase the risks of adverse drug reactions. Therefore, renal dosing is a very important way to individualize medication therapies for optimal outcomes.

To make renal dosing work, an accurate renal function assessment is required. Renal function is usually assessed by the glomerular filtration rate (GFR), the rate in milliliters per minute (mL/min) at which substances in plasma are filtered through the glomerulus even though renal function includes both the glomerular function determined by GFR and the tubular function which includes reabsorption and secretion. The tubular function is usually correlated with GFR. To assess GFR, a marker is needed. The characteristics of the ideal marker are as follows: 1) appear endogenously in the plasma at a constant rate; 2) freely filtered at the glomerulus; 3) neither reabsorbed nor secreted by the renal tubule; and 4) no extrarenal elimination. As no such endogenous marker currently exists, exogenous markers of GFR are used. Assessment of GFR using inulin, a polysaccharide, is considered the reference method for the estimation of GFR. It involves the infusion of inulin and then the measurement of blood levels after a specified period to determine the

rate of clearance of inulin. Other exogenous markers used include radioisotopes such as chromium-^{51}ethylene-diamine-tetra-acetic acid (^{51}Cr-EDTA), and technetium-^{99}-labeled diethylene-triamine-pentaacetate (^{99}Tc-DTPA). The most promising exogenous marker is the non-radioactive contrast agent, iohexol, especially in children. Unfortunately, the use of the above mentioned exogenous markers is not available at Northern Navajo Medical Center (NNMC). The availability and cost associated with the use of exogenous markers have encouraged the use of endogenous markers.

The most commonly used endogenous marker for the assessment of glomerular function is creatinine. The calculated clearance of creatinine is used to provide an indicator of GFR. This involves the collection of urine over a 24-hour period or preferably over an accurately timed period of 5 to 8 hours since 24-hour collections are notoriously unreliable. Creatinine clearance is then calculated using the equation: C = (U x V) / P, where C = clearance, U = urinary concentration, V = urinary flow rate (volume/time i.e. mL/min), and P = plasma concentration. For assessing the degree of renal impairment, creatinine clearance should be corrected for body surface area. However, for renal dosing, patient factors to be considered include both the degree of renal impairment and patient size. So, creatinine clearance does not need to be corrected for body surface area for drug dosing. Due to tubular secretion, theoretically, creatinine overestimates GFR by around 10% to 20%.

Creatinine is the by-product of creatine phosphate in muscle, and it is produced at a constant rate by the body. For the most part, creatinine is cleared from the blood entirely by the kidney. Decreased clearance by the kidney results in increased blood creatinine. The amount of creatinine produced per day depends on muscle bulk. Thus, there is a difference in creatinine ranges between males and females with lower creatinine values in females, children and those with decreased muscle bulk. Diet also influences creatinine values. Creatinine can change as much as 30% after the ingestion of red meat. As GFR increases in pregnancy, lower creatinine values are found in pregnancy. Additionally, serum creatinine is a later indicator of renal impairment - renal function is decreased by 50% before a rise in serum creatinine is observed.

Currently, serum creatinine is the backbone for all the GFR estimating equations although most of those equations (all newer equations) were derived based on exogenous markers as the reference. Newer endogenous markers, such as Cystatin C, offer little advantages and have availability problems (Cystatin C is not available at

NNMC). So, the equations associated with the newer markers will not be discussed in this article.

The equations

All of the following equations are only applied to the patients with stable renal function.

Cockcroft-Gault Equation - 1976

Creatinine clearance (CrCl, mL/min) = (140-age) x Weight/(72 x Scr) x 0.85 if female

Where Scr = Serum creatinine in mg/dL; age is expressed in years; weight is expressed in kilograms;

The Cockcroft-Gault (CG) equation was derived from a population of 249 Caucasian men aged 18 to 92 who were mainly on medical wards (Cockcroft 1976). No women were included in the development population. Among the 535 patients reviewed, only 21 were females. Based on previous studies (Jelliffe 1971, Jelliffe 1973, Edwards 1959), an arbitrary 15% reduction of predicted CrCl for females is used to compensate for females having less muscle mass and more fat. The equation is developed against measured urinary creatinine clearance.

Scr concentrations can be altered by patient specific factors including age, sex, weight, muscle mass, disease state, diet, and certain drug therapies, thus limiting the generalizability of the CG equation. For example, patients with hepatic impairment not only experience altered drug metabolism, but also have secondarily reduced creatinine production. In cirrhotic patients, utilization of Scr based methods overestimated true renal function by about 50% (Scappaticci 2017).

The CG equation was developed before creatinine measurement standardization. Now, to use the CG equation, a correction (Ortho-Clinical Diagnostics 2008) should be made as the following:

CrCl (mL/min) = (140-age) x Weight/(72 x (Scr x 1.065 + 0.067)) x 0.85 if female.

Because of its simplicity, the only equation that can be calculated using a simple calculator or by hand, the CG equation is widely used for drug dosing. Many drug trials have used the CG equation for renal function determination. Somehow, creatinine clearance mentioned in many publications and references is specifically referred to the result obtained from the CG equation. After more than 40 years since its creation, the CG

equation is still the major equation used for renal dosing. However, the accuracy and precision of the CG equation are not desirable. The pursuits for a better equation have continued for the past 2 decades.

MDRD Study Equation - 1999

The Modification of Diet in Renal Disease (MDRD) Study equation was derived from a study population of 1,628 men and women with chronic kidney disease (CKD), aged 18 to 70, predominantly Caucasian, nondiabetic, and who were non-kidney-transplant recipients (Levey 1999) . Besides serum creatinine, age, gender, and race, the initial MDRD equations also include serum and urine urea nitrogen or serum urea nitrogen and albumin information. However, the most used MDRD equation is the 4 parameter equation as the following:

Estimated GFR (eGFR, mL/min/1.73 m^2) = 186 x (Scr) $^{-1.154}$ x (age) $^{-0.203}$ x (0.742 if female) x (1.212 if African American)

The MDRD Study equation has been re-expressed for use with standardized serum creatinine values (Levey 2007)

eGFR (mL/min/1.73 m^2) = 175 x (Standardized Scr) $^{-1.154}$ x (age) $^{-0.203}$ x (0.742 if female) x (1.212 if African American)

The MDRD equation was only studied in patients with renal dysfunction (GFR < 60 mL/min/1.73 m^2), and therefore it should not be used in patients with normal renal function. For this reason, the MDRD equation has become deprecated in favor of the CKD-EPI equation, which was developed similarly to the MDRD equation, but is able to accurately describe GFR in patients without renal dysfunction. However, confirmed by calculating eGFR using different equations against the reported eGFR value, the MDRD equation is found to be the equation used to report eGFR value by the laboratories associated with NNMC.

Mayo Quadratic equation - 2004

Derived from 320 patients with chronic kidney disease and 580 healthy persons (Rule 2004). The equation is as the following:

eGFR(mL/min/1.73m^2) = exp (1.911 + 5.249 /Scr - 2.114 /Scr^2 - 0.00686* Age -0.205 (if female)) If Scr < 0.8 mg/dL, use 0.8 for Scr.

This equation may significantly overestimate GFR and has no utility.

CKD-EPI Equation - 2009

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was derived from a study population of 8,254 men and women. The study population included Caucasian, Black, Hispanic, and Asian individuals with and without CKD, diabetes, and kidney transplant (Levey 2009)

The CKD-EPI equation is more accurate for values > 60 mL/min/1.73 m^2 than the MDRD Study equation (Levey 2009) . A laboratory that reports eGFR numeric values > 60 mL/min/1.73 m^2 should use the CKD-EPI equation. However, the influence of imprecision of creatinine assays on the uncertainty of an eGFR value is greater at higher eGFR values and should be considered when assessing eGFR values > 60 mL/min/1.73 m^2. The CKD-EPI equation is better than the CG equation because it is more compatible with the results of 24-hour urine creatinine clearance (Ina 2014).

The byproduct of the CKD equation development is the creatinine measurement standardization. So, the CKD-EPI equation was developed for use with isotope dilution mass spectrometry (IDMS) traceable creatinine methods, which is now the method for all laboratories.

CKD-EPI Equation:

$$GFR\ (mL/min/1.73\ m2) = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}]$$

where:
Scr is serum creatinine in mg/dL,
κ is 0.7 for females and 0.9 for males,
α is -0.329 for females and -0.411 for males,
min indicates the minimum of Scr /κ or 1, and
max indicates the maximum of Scr /κ or 1.

CKD-EPI equation study population includes few elderly people; and so it may not be reliable for elderly. At lower Scr value (eg, <1.5 mg/mL), CKD-EPI equation may overestimate eGFR for elderly. Still, the 6 years' data of 278 patients from the Rugao longevity cohort (97±2 years with median follow-up of 2.6 years) showed that the CKD-EPI equation is more accurate estimation of kidney function in the elderly with

respect to GFR distribution and predictability of mortality risk than the MDRD and BIS1 equations (Wang 2020).

Revised Lund-Malmö (LM) - 2011

Swedish Caucasians (n = 850, women =376 ; median age 60, range 18-95 years) referred for GFR measurement (plasma iohexol-clearance: median 55, range 5-173 mL/min/1.73 m^2) constituted the Lund-Malmö Study cohort. LM Revised overall performed better than LM Original without LBM due to increased accuracy at measured GFR ≥90 mL/min/1.73 m^2. Comparisons with the CKD-EPI and MDRD equations suggest that the LM equations are superior for the present Swedish population, due to markedly higher accuracy of the LM equations at measured GFR <30 mL/min/1.73 $m^{2.}$ (Björk 2011). Later, a larger study with 2,847 adult Swedish patients confirmed that the revised LM equation is superior to the CKD-EPI and MDRD equations due to its higher accuracy and more stable performance across GFR, age and BMI intervals (Nyman 2014). A French study with 2,247 elderly participants (mean age 71.5 years) showed that the revised LM equation has better precision and accuracy than the CKD-EPI equation although the difference is not clinically significant (da Silva Selistre 2019). The study with 198 patients (61 years [18-93]) and 566 measured amikacin plasma concentrations revealed that the Revised LM and CKD-EPI showed the superior predictive performance of amikacin drug elimination compared to all the alternative metrics evaluated (Sáez Fernández 2019). The revised LM equation is the following:

$$\text{eGFR (mL/min/1.73m}^2\text{)} = e^{[X - 0.0158 \times \text{age} + 0.438 \times \ln(\text{age})]}$$

where:
For female Scr < 150 µmol/L (1.6968 mg/dL): X = 2.50 + 0.0121 × (150 – Scr).
For female Scr ≥ 150 µmol/L: X = 2.50–0.926 × ln(Scr/150).
For male Scr < 180 µmol/L (2.0362 mg/dL): X = 2.56 + 0.00968 × (180 – Scr).
For Male Scr ≥ 180 µmol/L: X = 2.56–0.926 × ln(Scr/180).
Scr in mg/dL can be converted to micromolar by dividing 0.011312.

Berlin Initiative Study 1 - 2012

Two estimates of GFR were developed and validated in the Berlin Initiative Study (BIS) population of adults aged 70 years or older (n= 610; mean age = 78.5 years) : 1 based on creatinine only (BIS1) and 1 based on both creatinine and cystatin C measurements (BIS2). Both showed excellent agreement with directly measured GFR (Schaeffner 2012).

BIS1: eGFR (mL/min/1.73m2) = $3736 \times \text{Creatinine}^{-0.87} \times \text{age}^{-0.95} \times 0.82$ (if female).

BIS1 is only good for elderly population (aged 70 years or older); and does not appear to be desirable even for the elderly (Wang 2020).

Full Age Spectrum (FAS)- 2016

The new FAS equation is based on normalized serum creatinine (Scr/Q), where Q is the median Scr from healthy populations to account for age and sex. Coefficients for the equation are mathematically obtained by requiring continuity during the pediatric–adult and adult–elderly transition. Research studies containing a total of 6,870 healthy and kidney diseased white individuals, including 735 children, <18 years of age, 4,371 adults, between 18 and 70 years of age, and 1,764 older adults, ≥70 years of age with measured GFR (inulin, iohexol and iothalamate clearance) and isotope dilution mass spectrometry–equivalent Scr, were used for the validation (Pottel 2016)

For 2 <= Age < 40 years:

$\text{GFR (mL/min/1.73m}^2) = 107.3 \times (\text{Scr/Q})$

For Age ≥40 years:

$\text{GFR (mL/min/1.73m}^2) = 107.3 \times (\text{Scr/Q}) \times 0.988^{(\text{Age-40})}$

The FAS equation has improved validity and continuity across the full age-spectrum and overcomes the problem of implausible eGFR changes in patients which would otherwise occur when switching between more age-specific equations. The equation reflects the fact that renal functions do not decline until 30s to 40s years old (The equation chooses 40 years old). The first equation to do so.

The FAS equation needs Q value for the calculation. The Q-values can be obtained based on either age or height. In this article, the Q value is based on age. The table for Q-values (Pottel 2016) is listed below:

Table 1. *Q*-values [=median serum creatinine in µmol/L (mg/dL)] for the FAS equation, according to age or height (from refs [4, 5, 10])

Age, years	Height[a], cm	Q^b, µmol/L (mg/dL)
Boys and girls		
1	75.0	23 (0.26)
2	87.0	26 (0.29)
3	95.5	27 (0.31)
4	102.5	30 (0.34)
5	110.0	34 (0.38)
6	116.7	36 (0.41)
7	123.5	39 (0.44)
8	129.5	41 (0.46)
9	135.0	43 (0.49)
10	140.0	45 (0.51)
11	146.0	47 (0.53)
12	152.5	50 (0.57)
13	159.0	52 (0.59)
14	165.0	54 (0.61)
Male adolescents		
15	172.0	64 (0.72)
16	176.0	69 (0.78)
17	178.0	72 (0.82)
18	179.0	75 (0.85)
19	180.0	78 (0.88)
Male adults		
≥20	≥181.5	80 (0.90)
Female adolescents		
15	164.5	57 (0.64)
16	166.0	59 (0.67)
17	166.5	61 (0.69)
18	167.0	61 (0.69)
19	167.5	62 (0.70)
Female adults		
≥20	≥168.0	62 (0.70)

[a]Height is the median height of a child or adolescent at the specified age (Belgian growth curves).

[b]Mathematical expressions for the *Q*-age and *Q*-height relationship for children, adolescents and young adults can be obtained from Hoste *et al.* [5].

Simulation and comparisons of the equations

Age and equations

It has been reported that the CG equation underestimates eCrCl for elderly people (Törner 2008) and at lower Scr value, such as 1.5 mg/dL or lower, the CKD-EPI equation may overestimate eGFR for elderly. So, how age affects the equation is worth investigating.

Laboratories associated with NNMC have a reference range of 0.5 to 1.3 mg/dL for Scr measurement. Scr values of 0.5 (lower normal limit), 0.9 (median of normal), 1.3 (upper normal limit), 1.5, 2, 3, and 5 are used for simulation. For the CG equation, weight 72 kg is used to remove or reduce the weight impact on the equation. The equations are simulated against age with age up to 101 years old at x-axis and eGFR at y-axis.

The simulations show that the Mayo Quadratic equation may significantly overestimate eGFR; and therefore it should not be used. The simulations also show that, for patients at very advanced age, the MDRD equation has a higher eGFR than the CKD-EPI equation. Considering that the CKD-EPI equation may overestimate eGFR for the elderly, the MDRD may not be suitable for the elderly population.

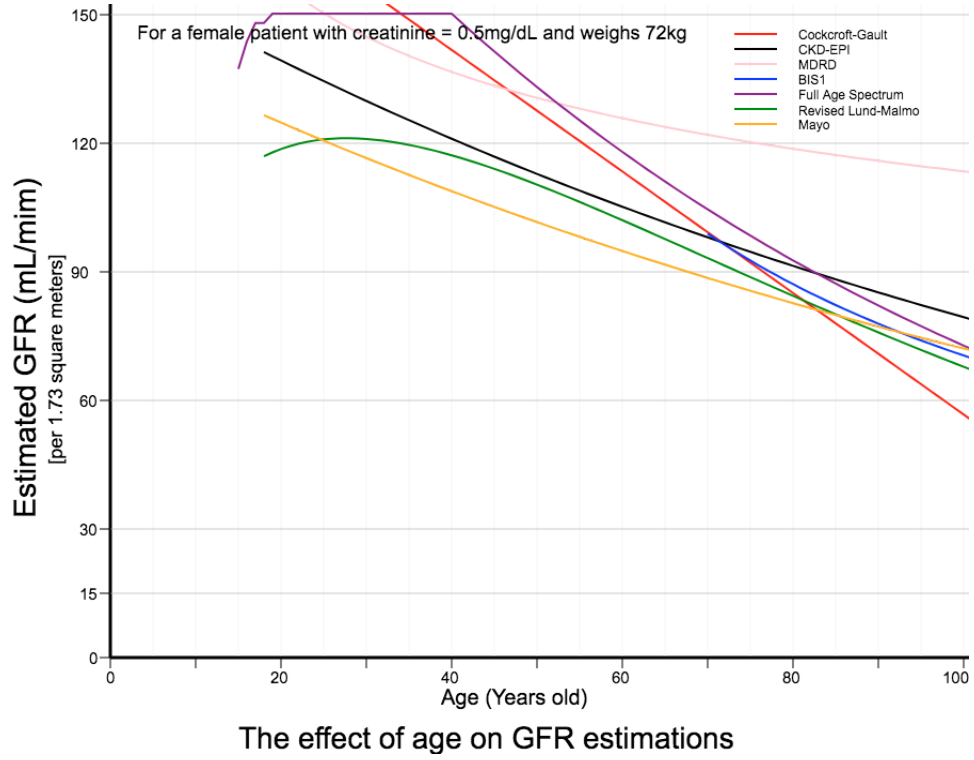
The simulations show that, for people aged 70 or older, the Revised LM and the FAS equations have the values between the CG equation and the CKD-EPI equation. For those elderly population, the CG equation systematically underestimates and the CKD-EPI equation may overestimate. Therefore, the values between the CG and CKD-EPI equation may mean better estimations. The Revised LM and the FAS equations both have a good representation of the elderly population; and may be suitable for the elderly. Compared to the CKD-EPI equation, the values from the BIS1 equation vary. Sometimes, it is lower; but other times it is higher. The BIS1 equation does not appear to be good for the elderly even though it is developed specifically from the elderly population.

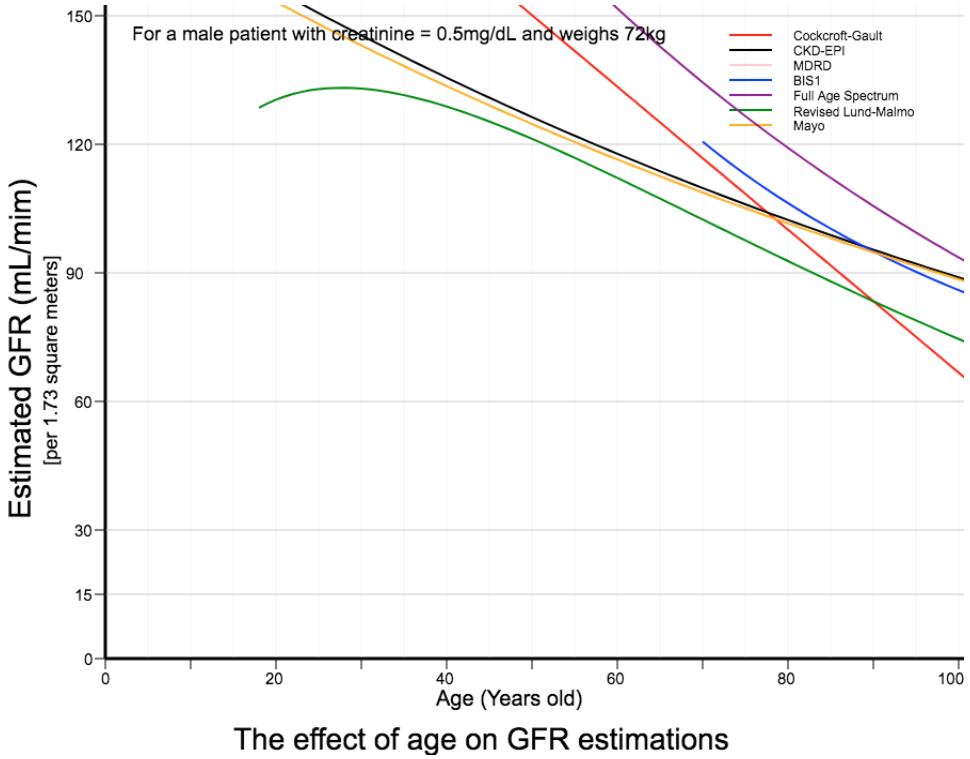
The simulations show that the CG equation has a steeper slope against age. Even though it tends to underestimate eCrCl for the elderly population, it likely overestimates eCrCl for young people, which is clearly demonstrated in the simulations.

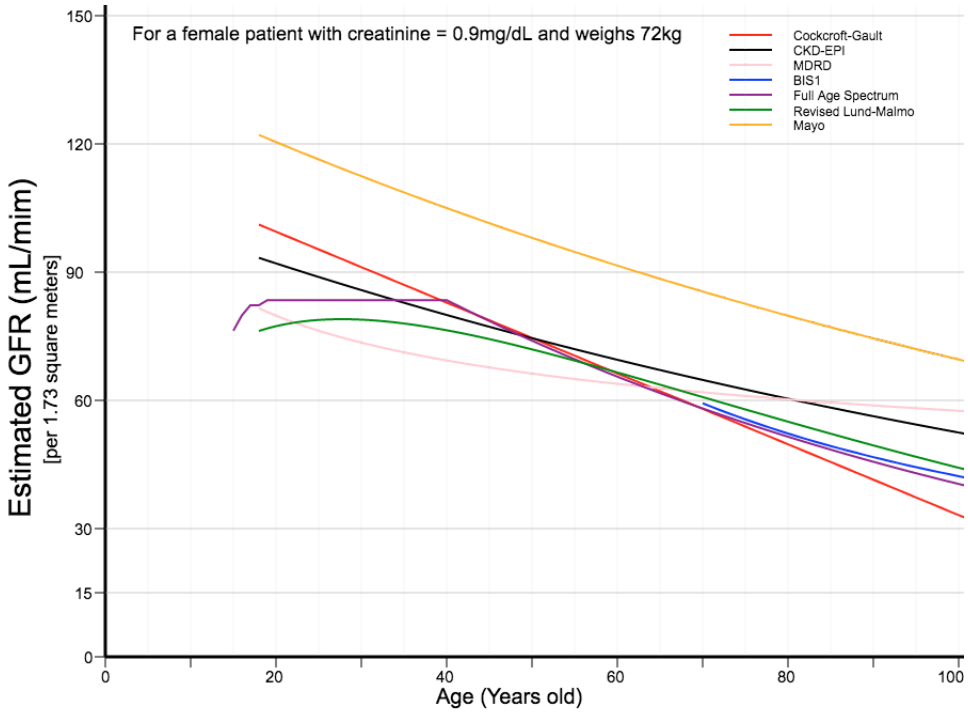
The Revised LM equation has smooth curves and appears falling at right positions. The curves are much flatter between 20 to 40 years old. So, like the FAS equation, it actually also reflects that renal function does not decline until 40 years old. Based on the

simulation results, the Revised LM equation is the equation of choice for renal function assessment.

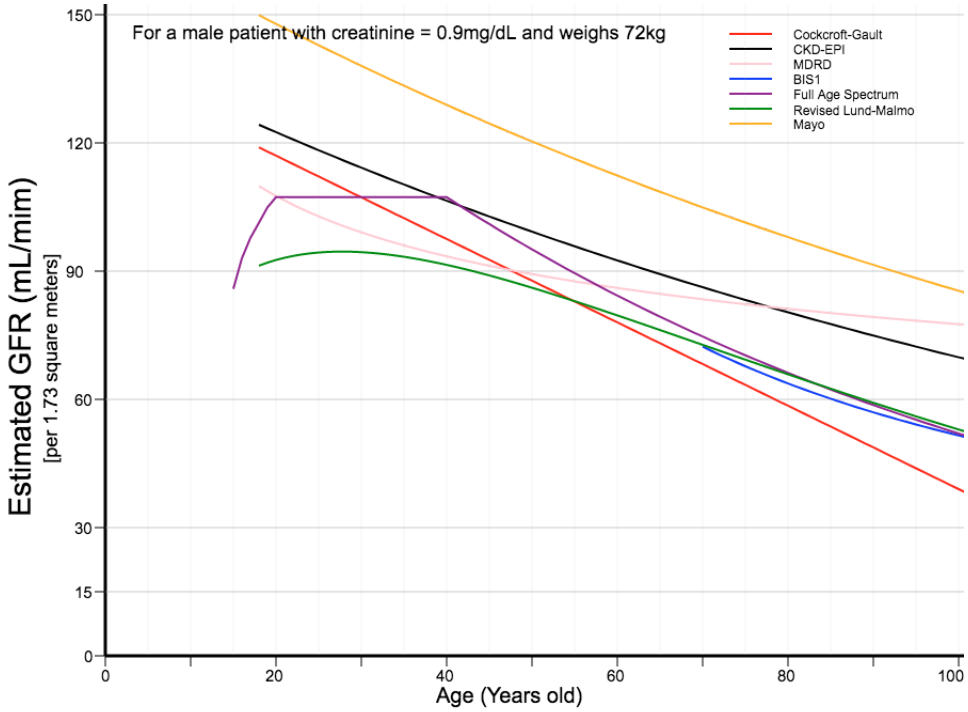
Figure 1. Simulations of the effect of age on GFR estimations







The effect of age on GFR estimations



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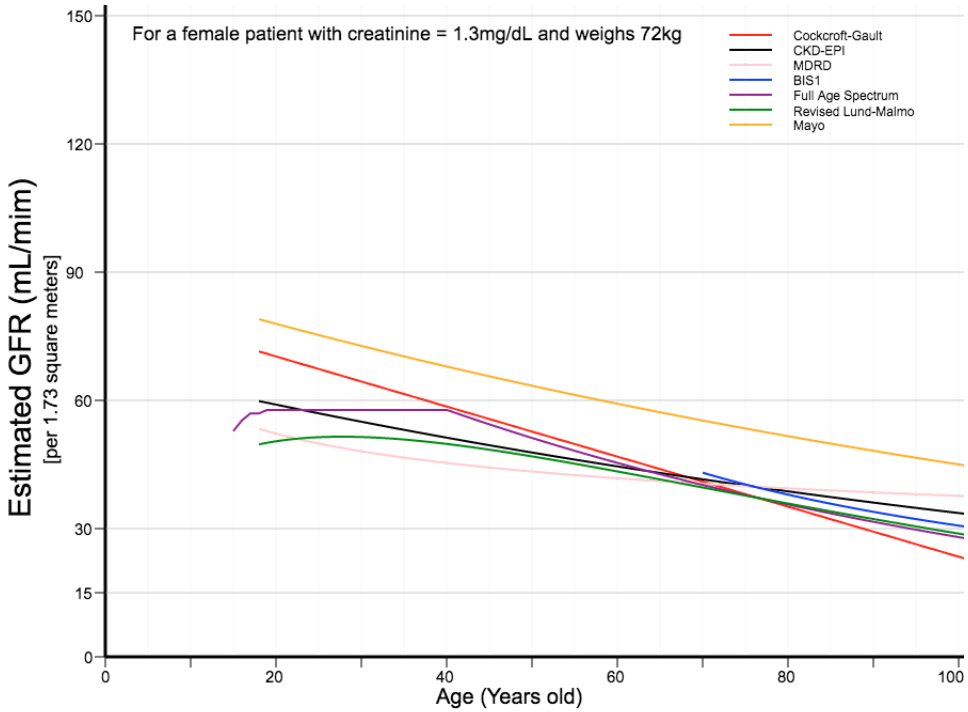

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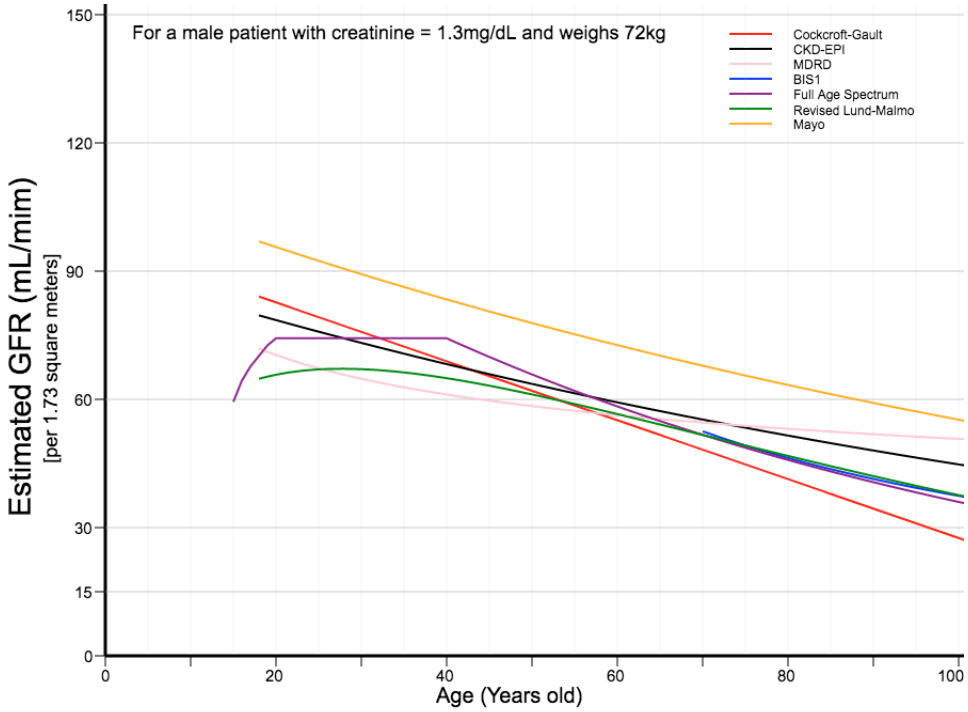

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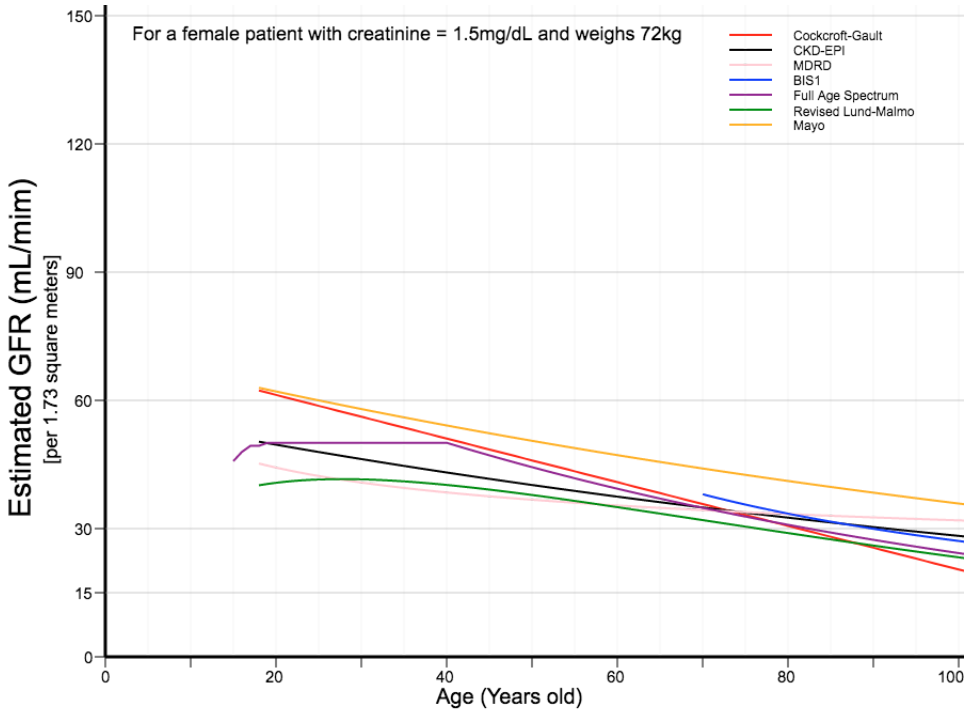

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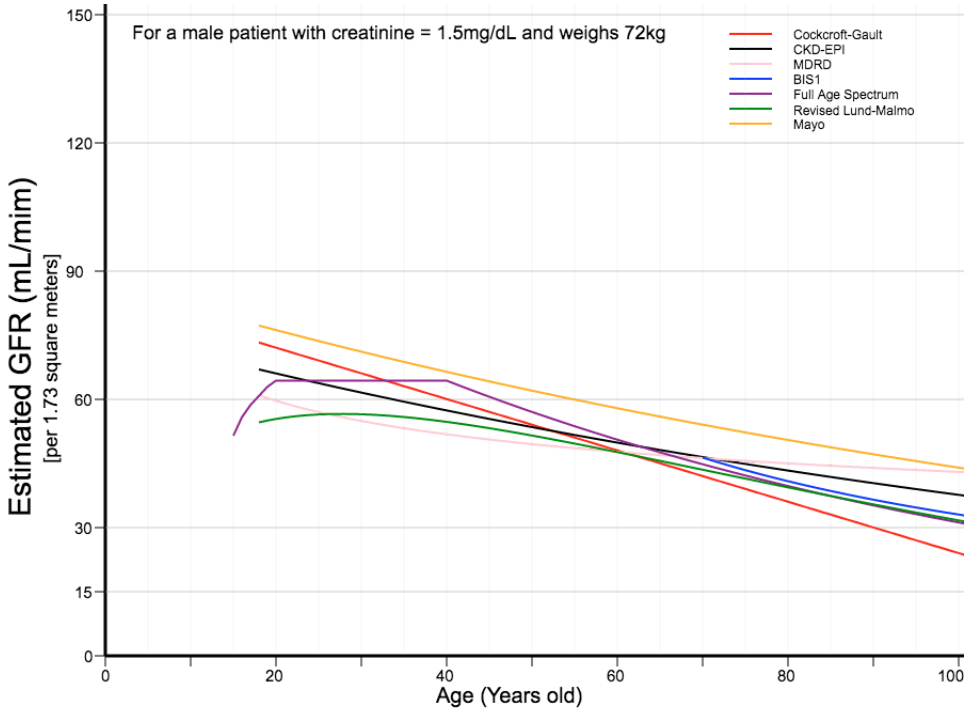

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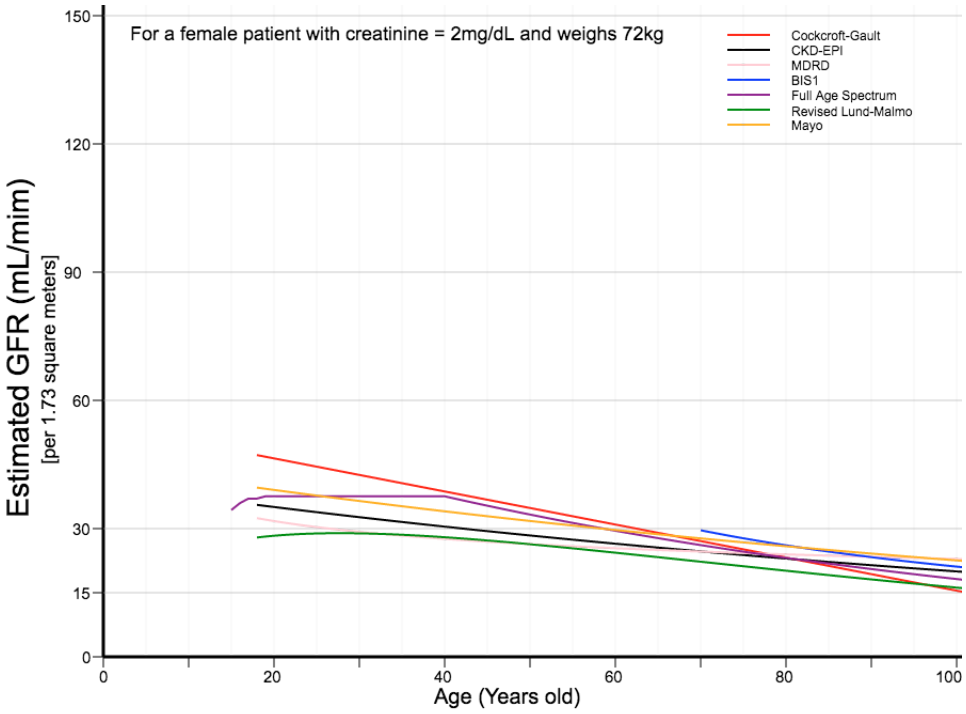

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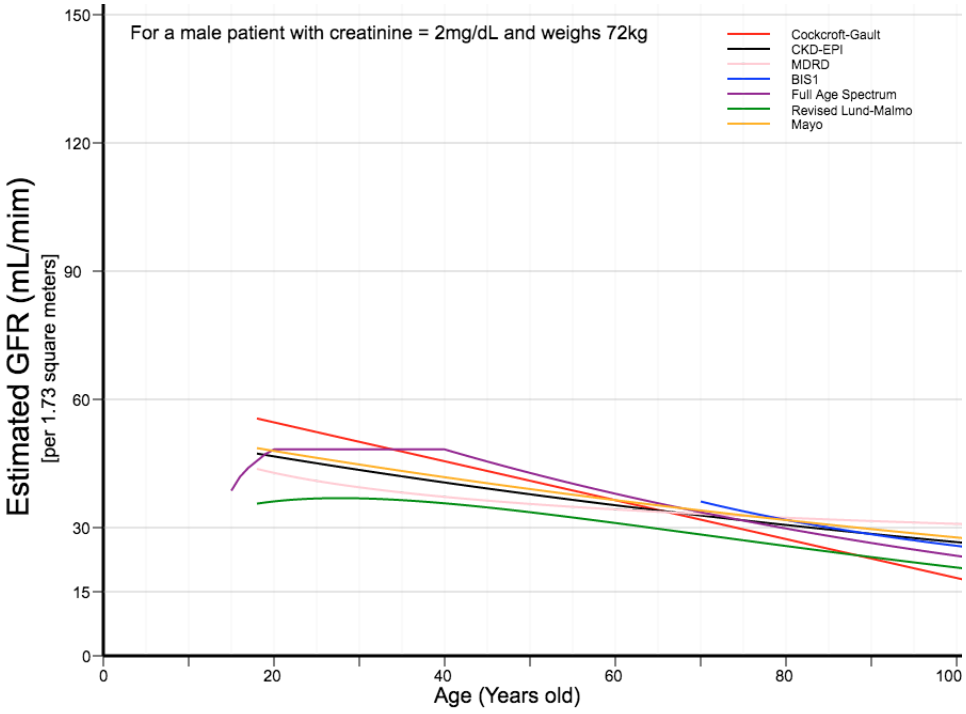

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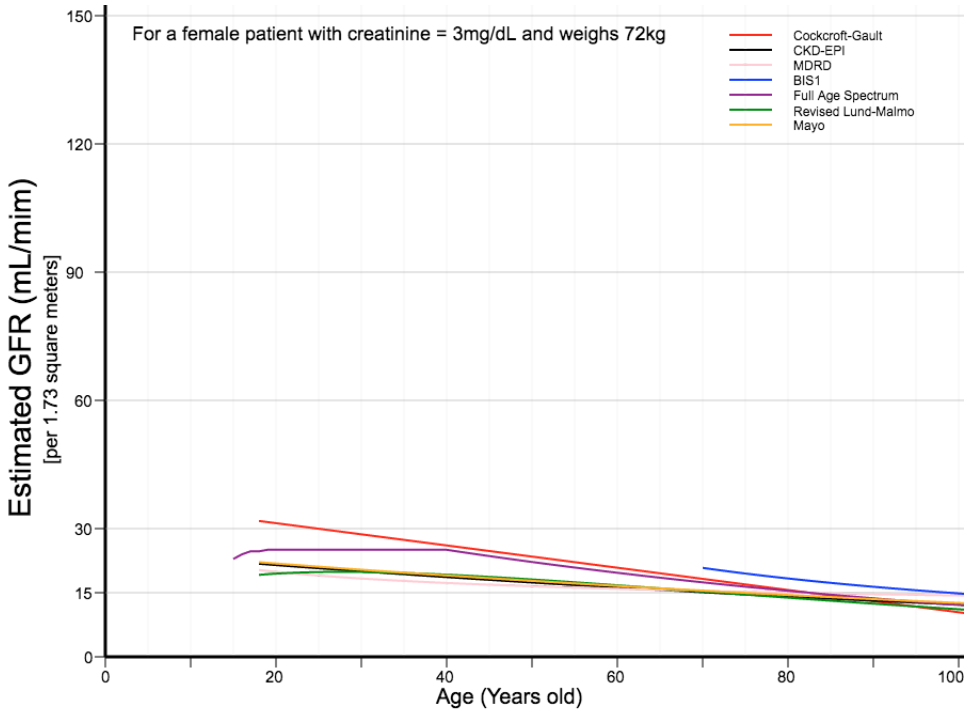

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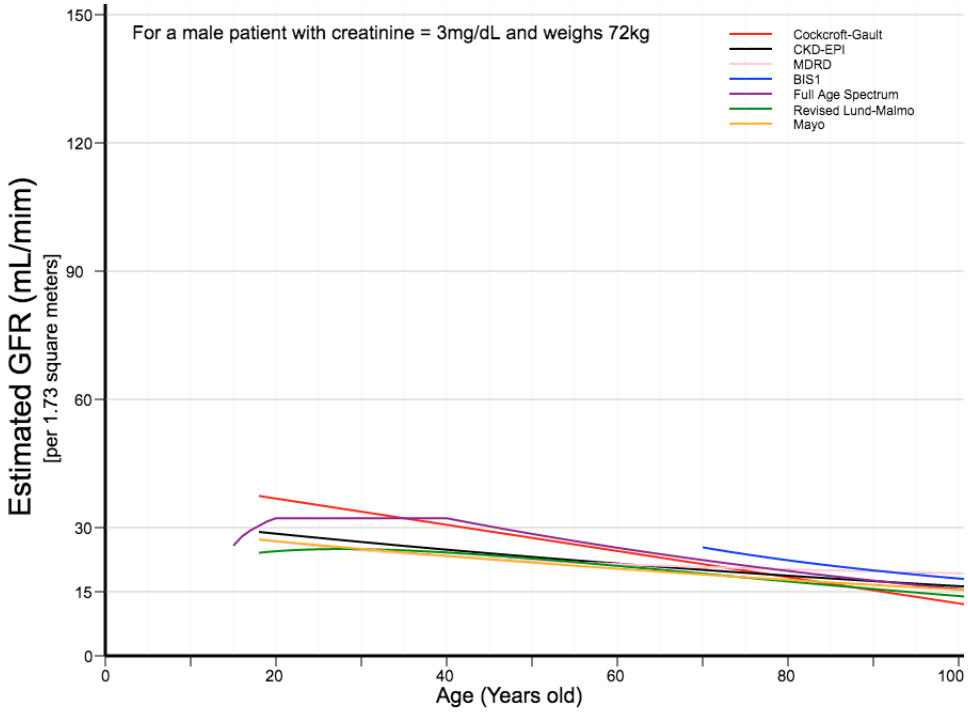

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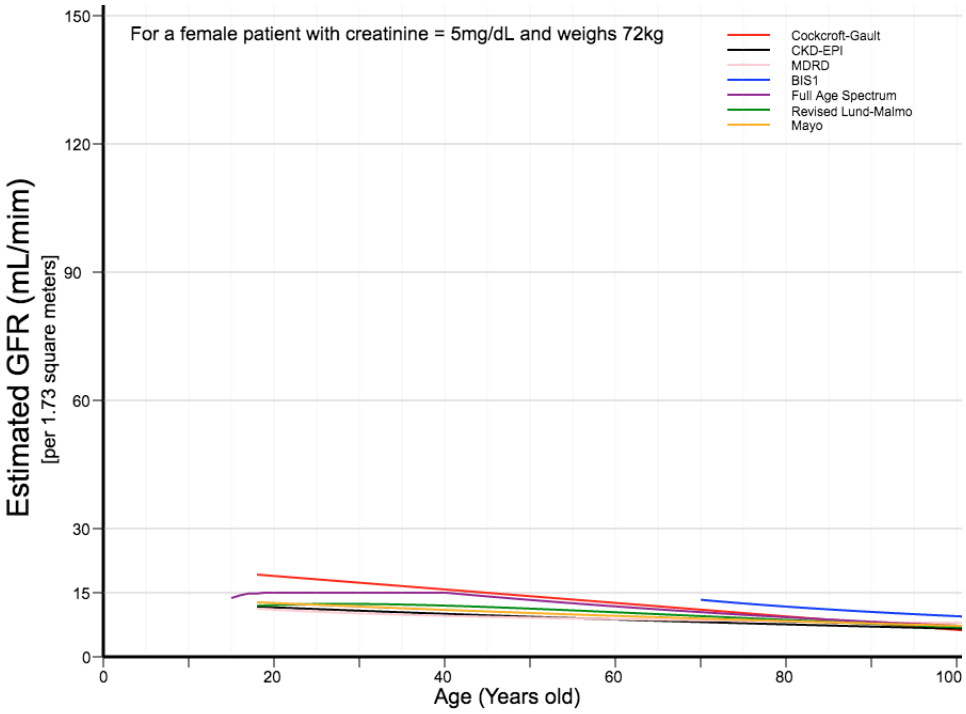

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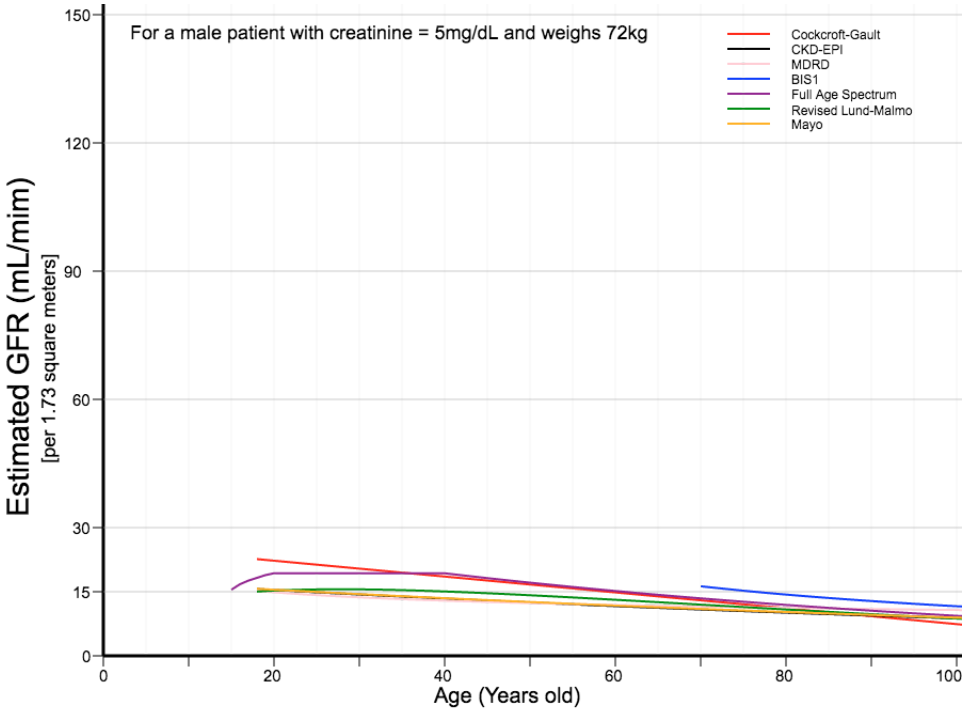


The effect of age on GFR estimations

Weight and equations

The value derived from the CG equation is called estimated creatinine clearance (eCrCl), which is weight dependent and expressed as mL/min. It reflects both the degree of renal impairment and body size; and is used for renal dosing. The value obtained from other newer equations is called estimated glomerular filtration (eGFR), which is weight independent and expressed as mL/min/1.73 m^2 . It reflects the degree of renal impairment and is used to categorize the impairment. To use for renal dosing, eGFR needs to be converted to eCrCl by multiplying the body surface area divided by 1.73.

The original CG equation uses actual body weight for calculation. But for obese patient, it was found that the actual boty weight significantly overestimated eCrCl. To solve the problem, a few methods of adjusting weight against height have been proposed. Among them are Ideal body weight (IBW) and adjusted body weight (ABW). Actual body weight is also called Total body weight (TBW). IBW was defined as the weight associated with the greatest life expectancy at each height. Although it may not be the best IBW equation (Peterson 2016), the Devine equation listed below is the IBW equation currently used for renal dosing (Pai 2000).

IBW(kg) = 50.0 + 2.3 x (Height - 60 inches) for men

IBW (kg) = 45.5 + 2.3 x (Height - 60 inches) for women

For height that is shorter than 60 inches, the IBW from Devine equation is too low to be used. There are a few solutions. Among them is the BMI methods. The simple one is IBW(kg) = 22 (kg/m2) x (height in meters) for both men and women (Moreault 2017). The one we use has lower IBW values and is as the following:

IBW(kg) = 21.53 (kg/m2) x (height in meters) for men

IBW(kg) = 19.59 (kg/m2) x (height in meters) for women

The most used ABW is as the following (McEneny-King 2017), which is also the one used for renal dosing.

ABW (kg) = IBW + 0.4 x (TBW - IBW)

The reported most accurate CrCl estimations use the following weight parameters: for TBW less than IBW, use TBW; for TBW equal to or greater than IBW but less than 120% IBW, use IBW; for TBW greater than or equal to 120% IBW, use ABW (Winter 2012).

The eCrCl derived from eGFR may also overestimate eCrCl for an obese patient. To solve the potential problem, the weight for the BSA calculation will be the same as the one used for the CG equation.

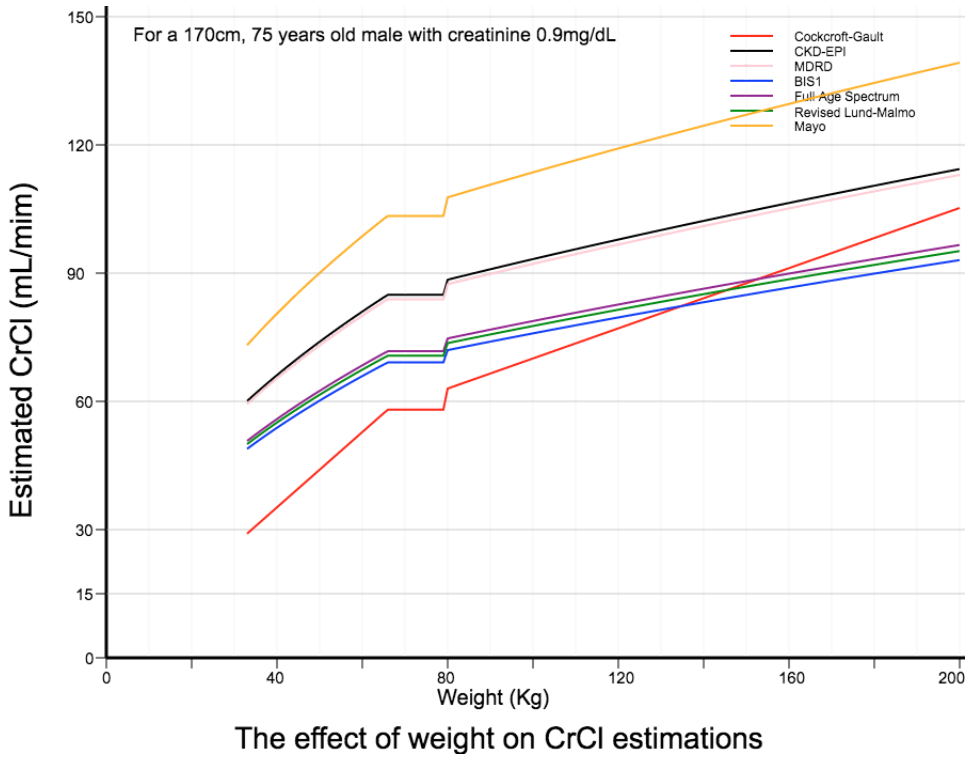
A 170 cm, 75 years old with a Scr of 0.9 mg/dL is used for simulation. The equations are simulated against weight with weight up to 200 kg at x-axis and eCrCl at y-axis. It is apparent that using TBW for TBW < IBW, IBW for TBW < 120% IBW and ABW for TBW >/= 120% IBW result in unsmooth curves. It does not make sense that when TBW is between 100% and 119% IBW, the CrCl estimations stayed the same and when TBW increased from 119% IBW to 120% IBW, the CrCl estimation jumps to almost 20% higher. The simulations are reperformed using TBW for TBW < IBW and using ABW for TBW >/= IBW. Now, the curves become much smoother. Still the slopes for TBW < IBW and TBW >/= IBW are different. The slopes are much deeper for TBW < IBW. The simulations are performed again using ABW throughout. This time, the curves become straight lines. Theoretically, these are likely the correct equations. However, studies about the patients who are underweight and CrCl are sparse. The impact of being underweight on CrCl estimation is unclear. Compared to the equations using TBW for TBW < IBW, the equations using ABW throughout will have much higher CrCl estimation for the extremely underweight patients and may cause safety concerns. Before a study clarified the impact of being underweight on CrCl estimation, TBW will be used for TBW < IBW. For more simulations, use TBW for TBW < IBW and ABW for TBW >/= IBW.

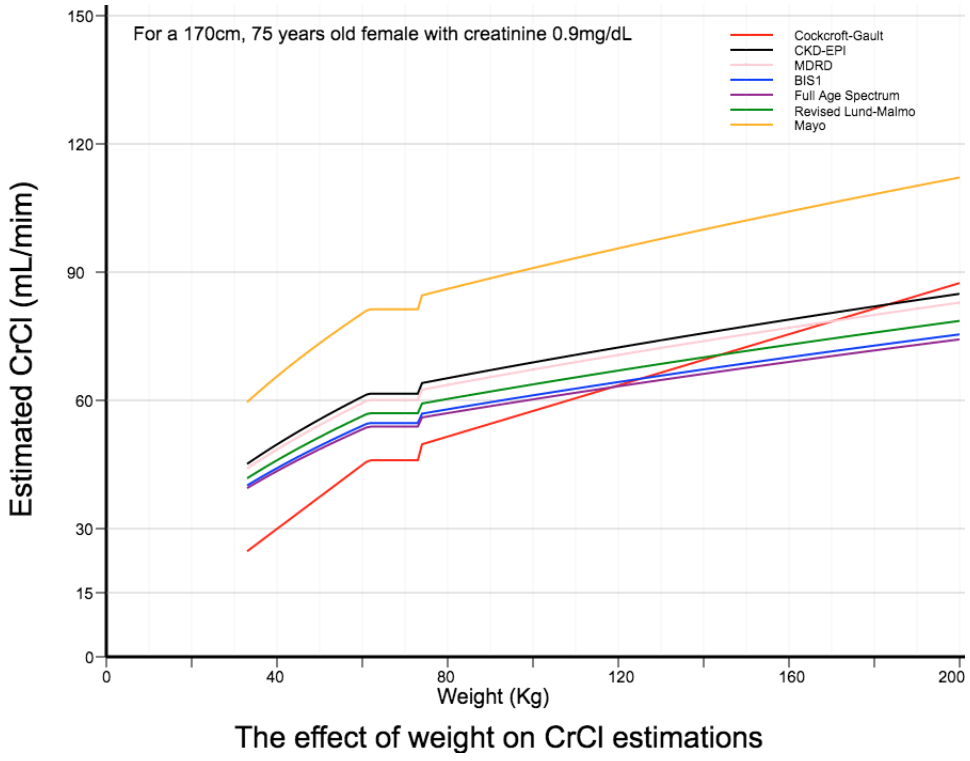
The equations using 150 cm and Scr of 1.5 mg/dL are simulated against weight for 20, 40, and 75 years old. The equations using 190 cm and Scr of 1.5 mg/dL are also simulated against weight for 20, 40, and 75 years old.

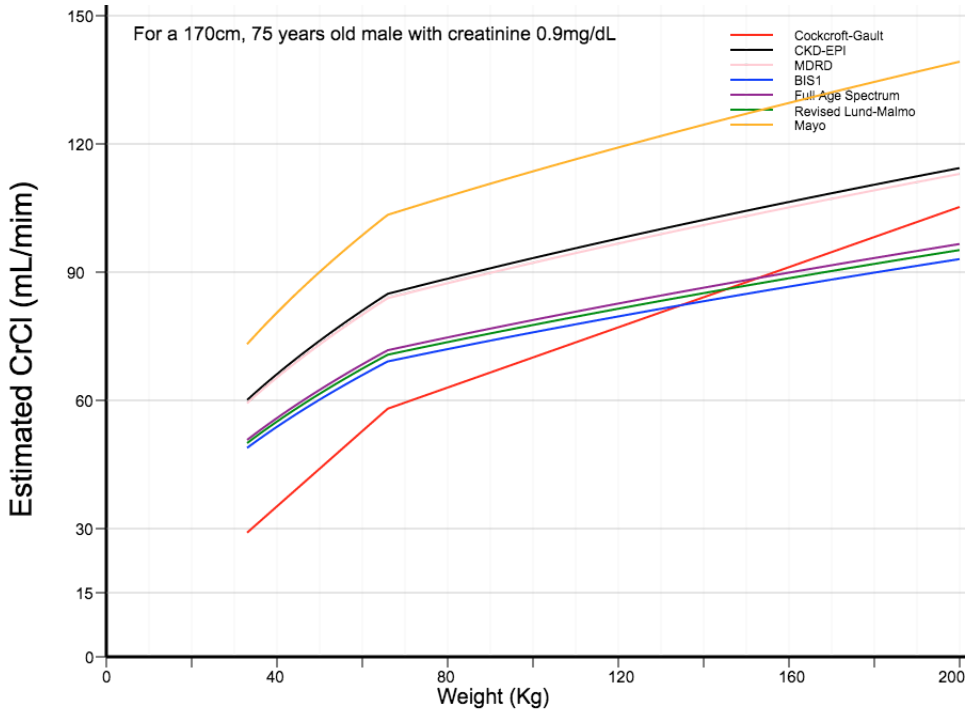
The simulations clearly show that the CG equation has the steepest slope against weight. It is likely that the CG equation overestimates CrCl for the extremely obese patient; and at the same time, it underestimates CrCl for the extremely underweight patients. The BIS1 equation significantly overestimates CrCl for patients 20 and 40 years old because it can not be used for patients younger than 70 years old. Analysis of the simulations show that the Revised LM equation has relatively conservative CrCl estimations, supporting that the Revised LM equation is the equation of choice.

The CG equation is directly correlated with weight. Strictly speaking, other equations are correlated with body surface area (BSA). BSA is used to obtain human dosing from animal studies. Similar to the finding from the simulations, the BSA-based dosing is higher for patients with very low body weight than the weight-based dosing; and lower for the very obese patients (Pai 2012).

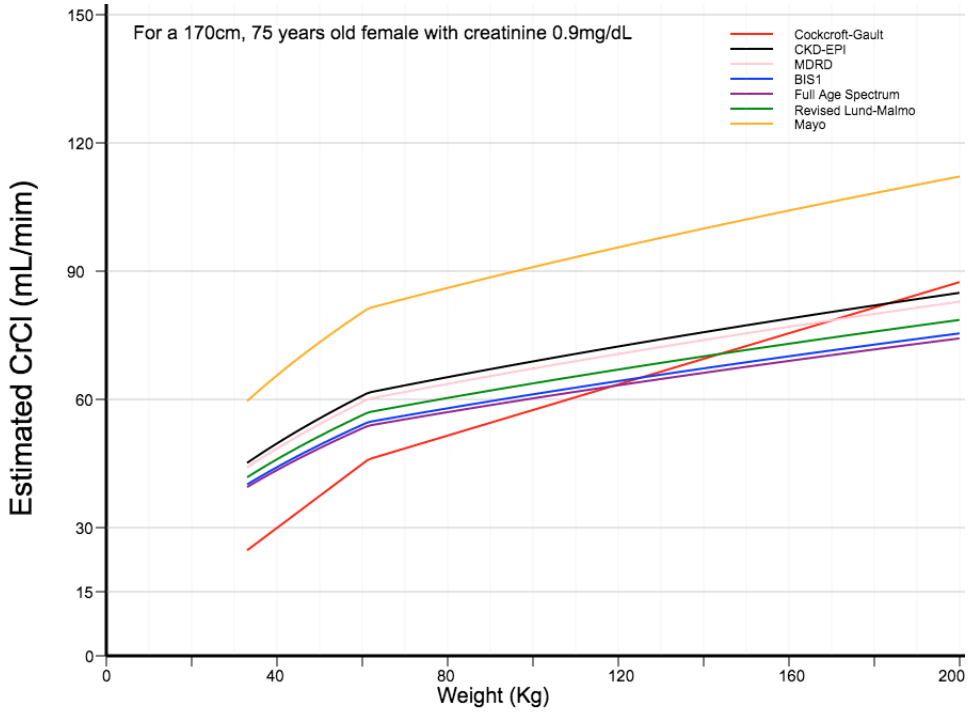
Figure 2. Simulations of the effect of weight on CrCl estimations.







The effect of weight on CrCl estimations



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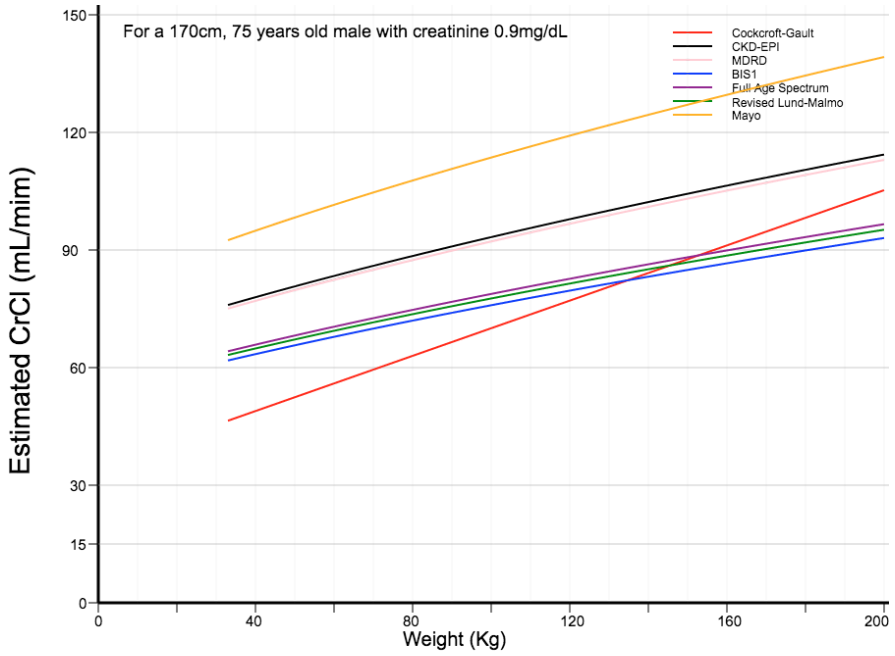

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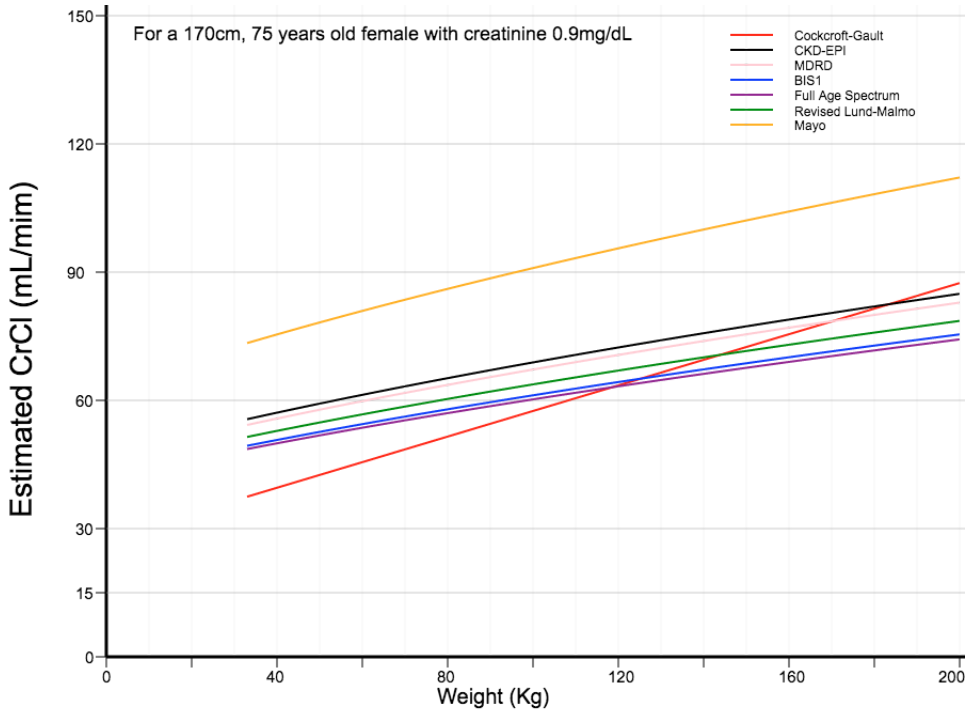

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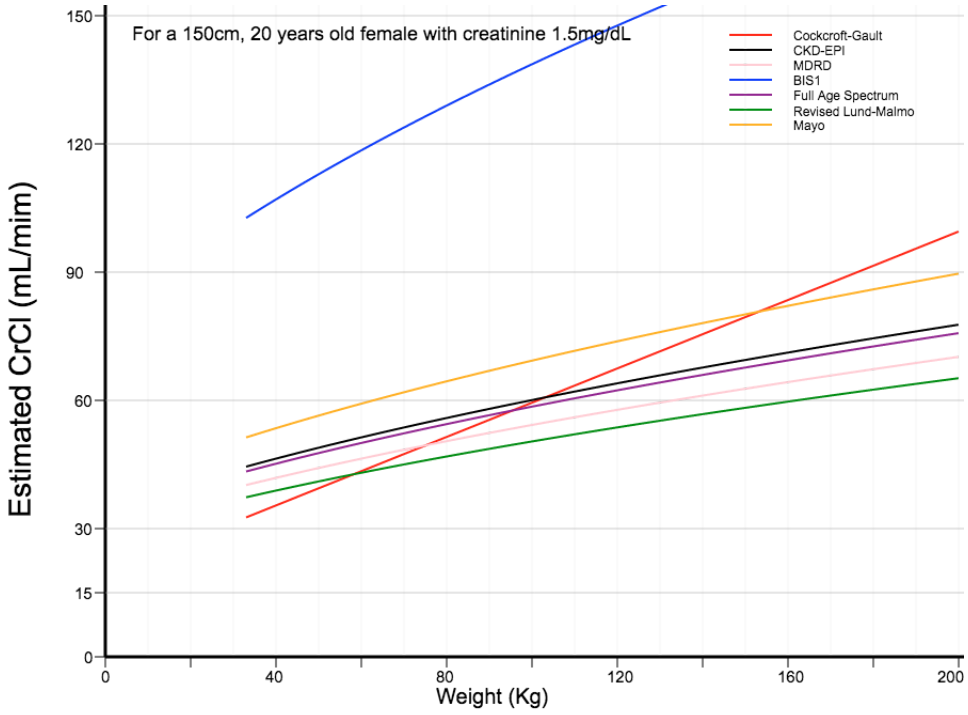

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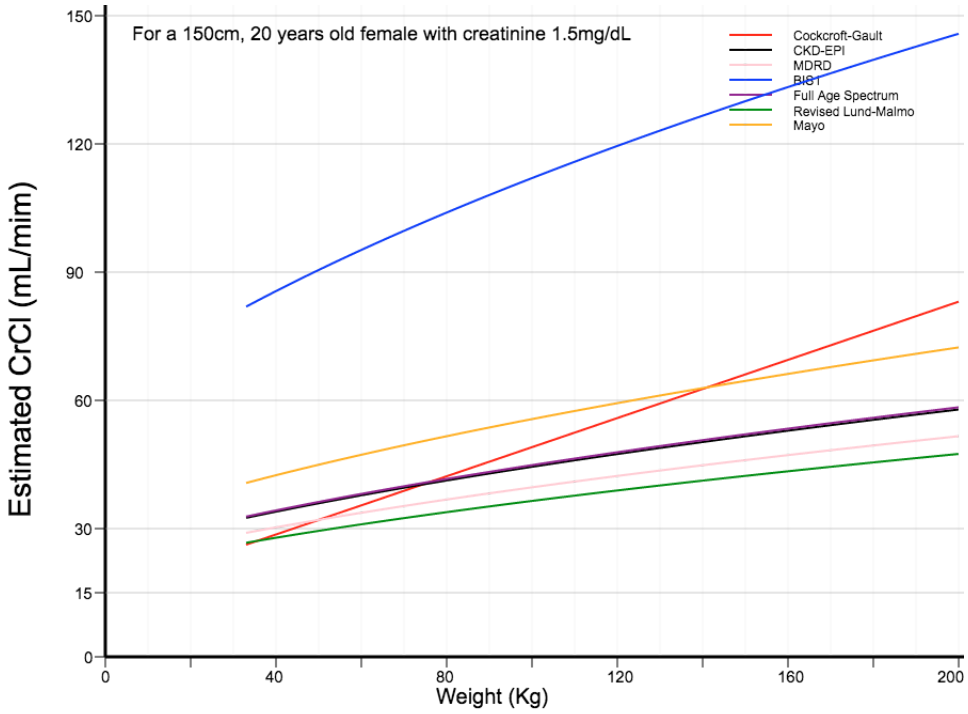

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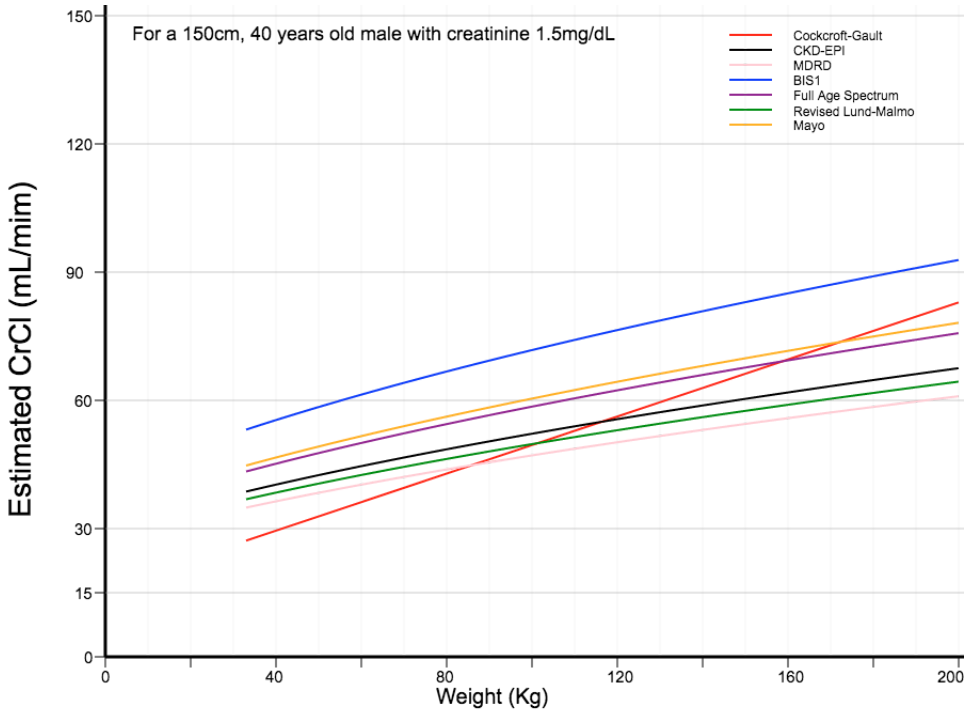

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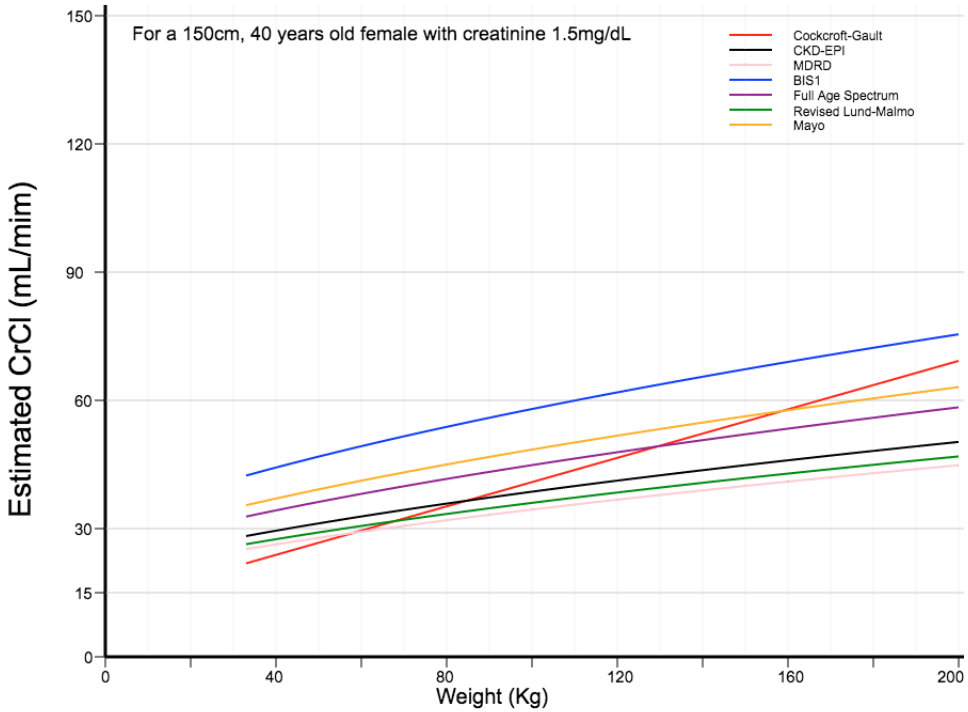

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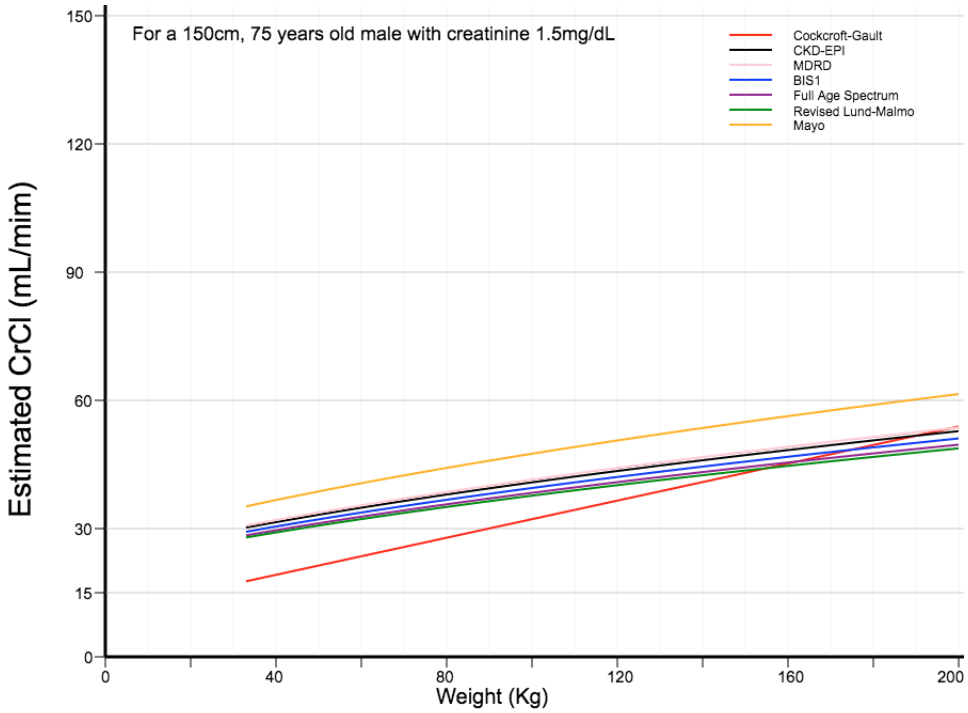

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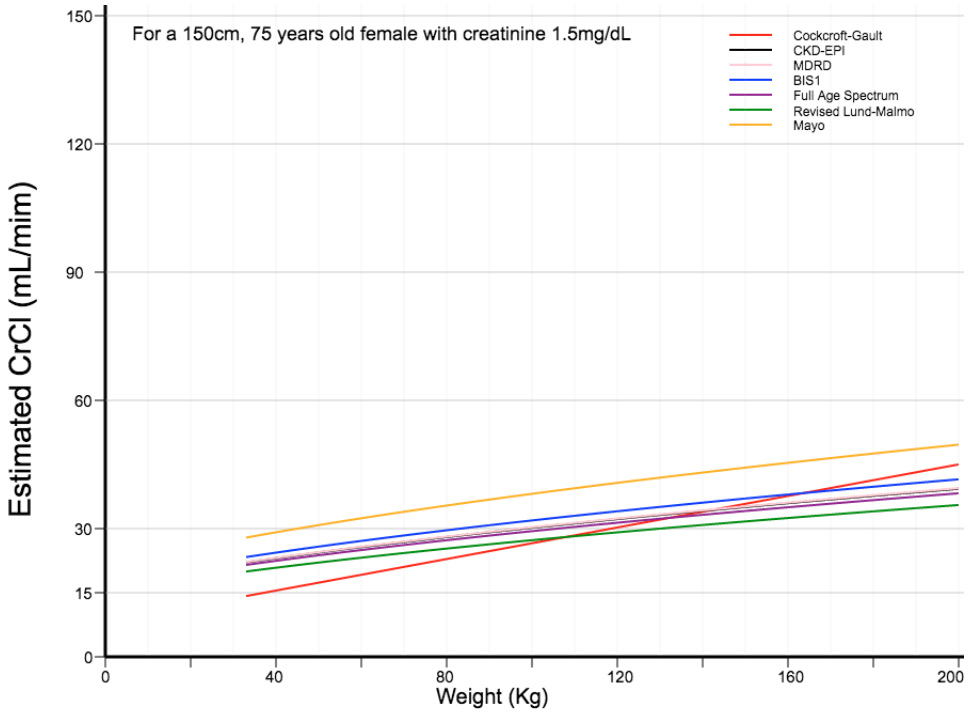

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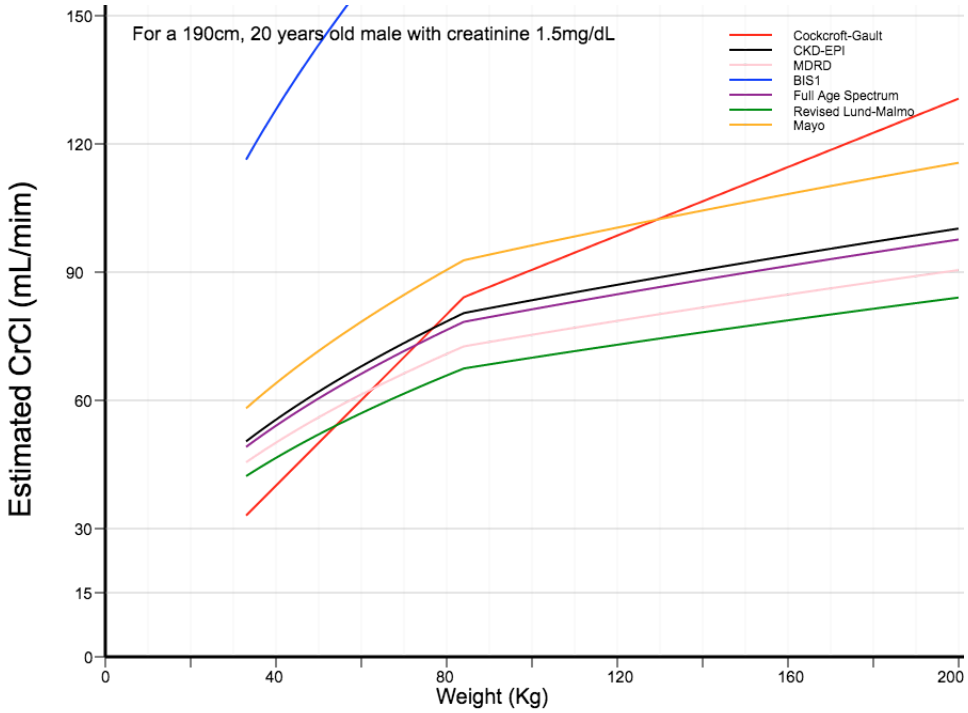

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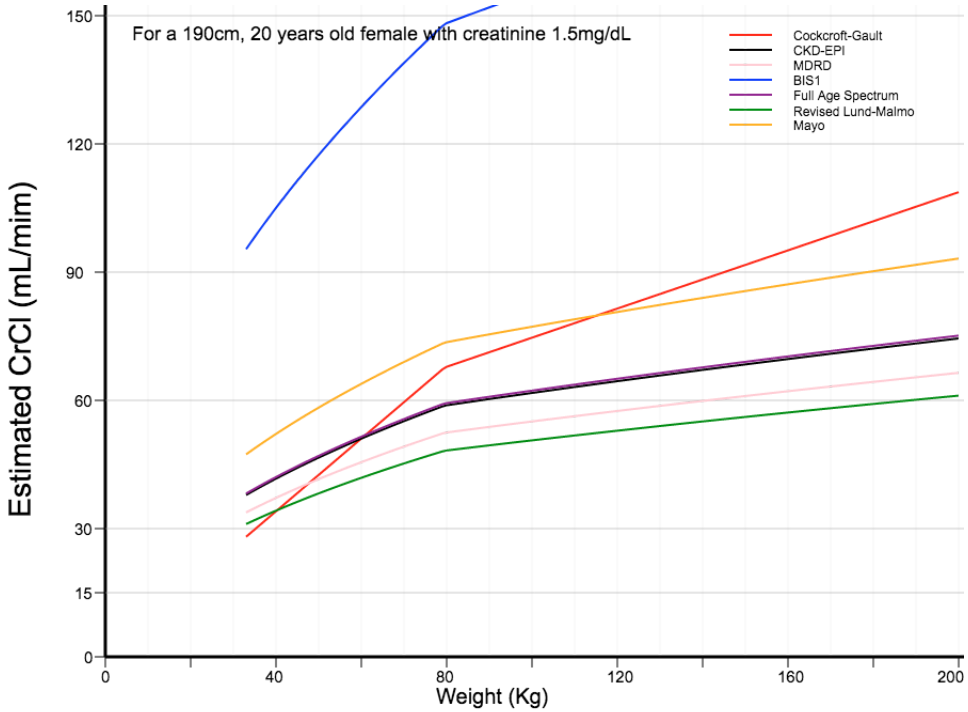
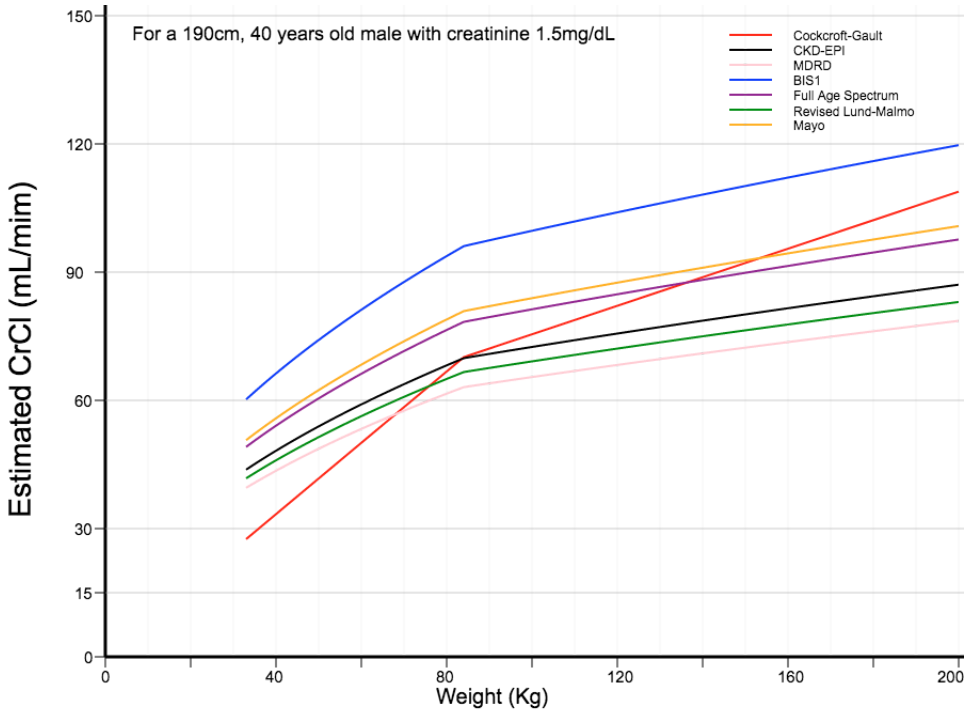


The effect of weight on CrCl estimations



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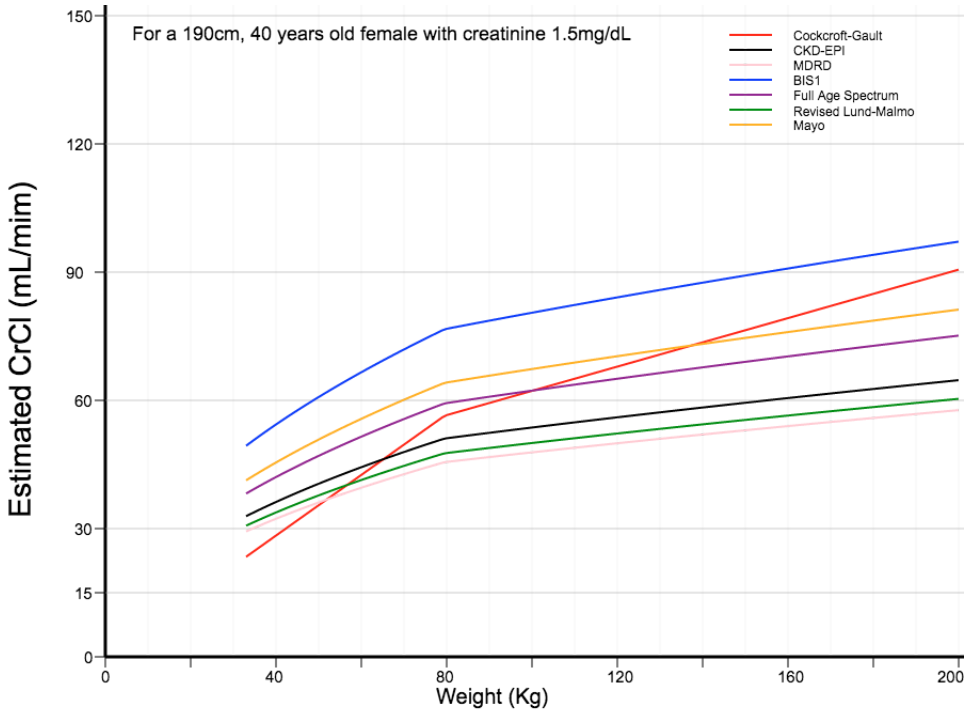

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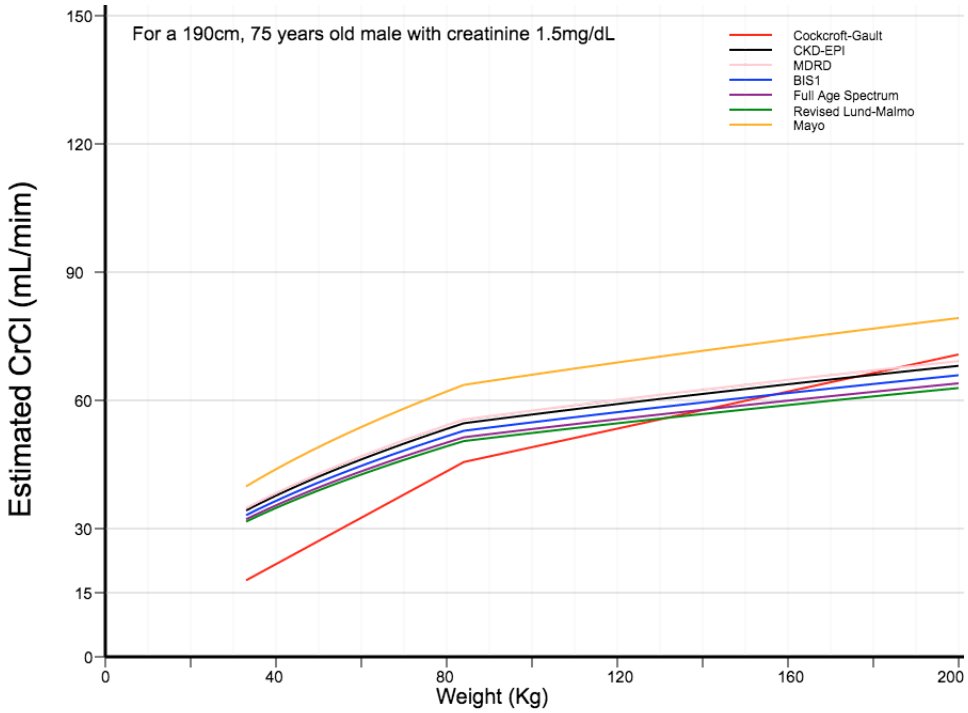

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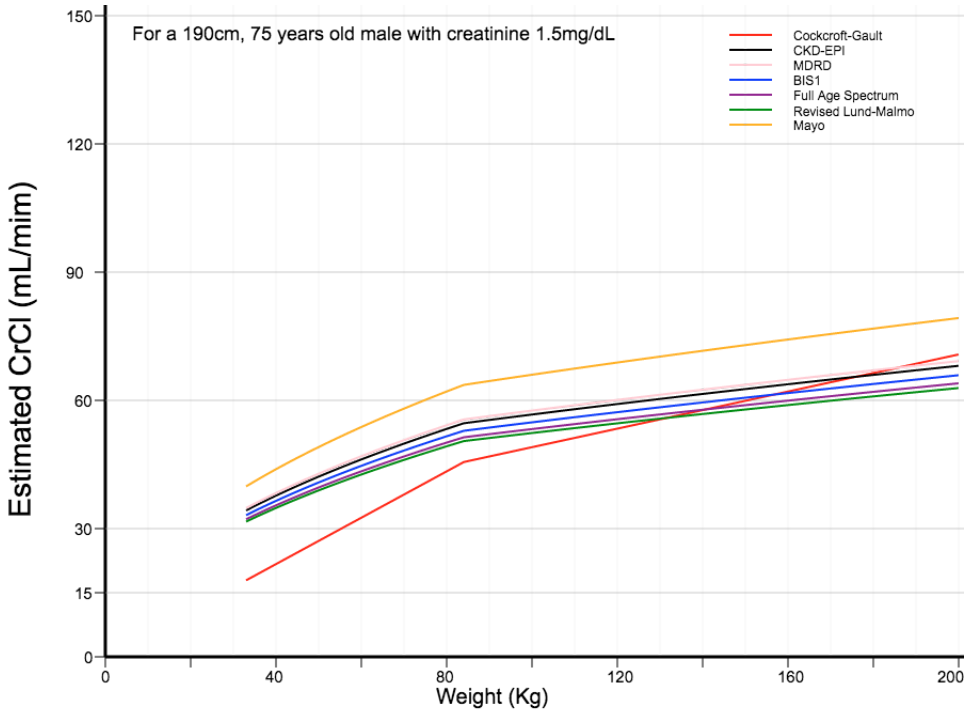


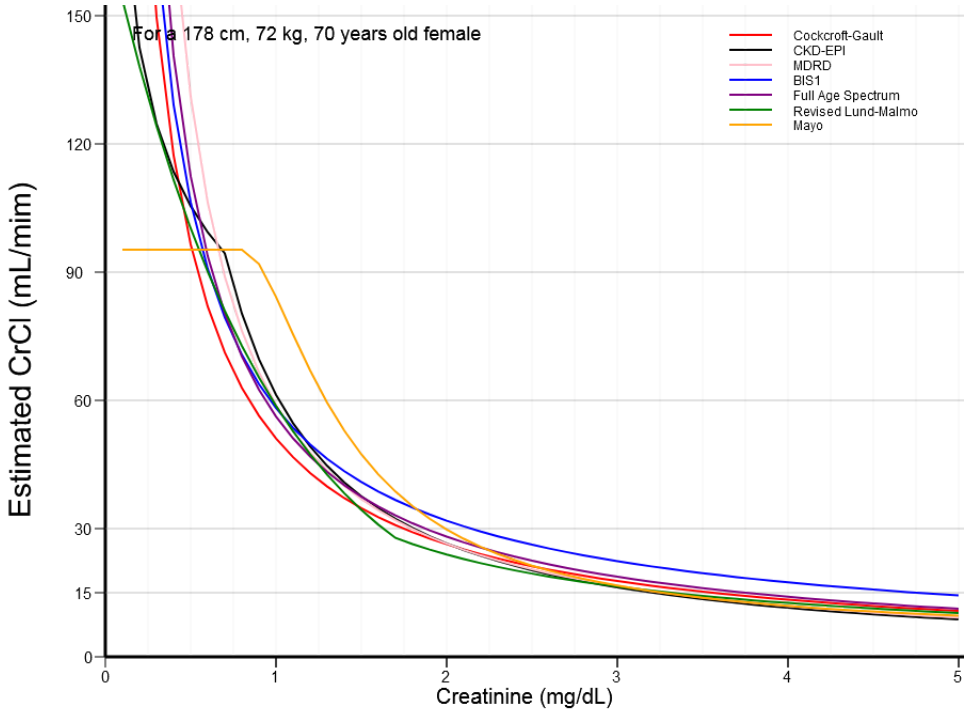
The effect of weight on CrCl estimations

Creatinine and equations

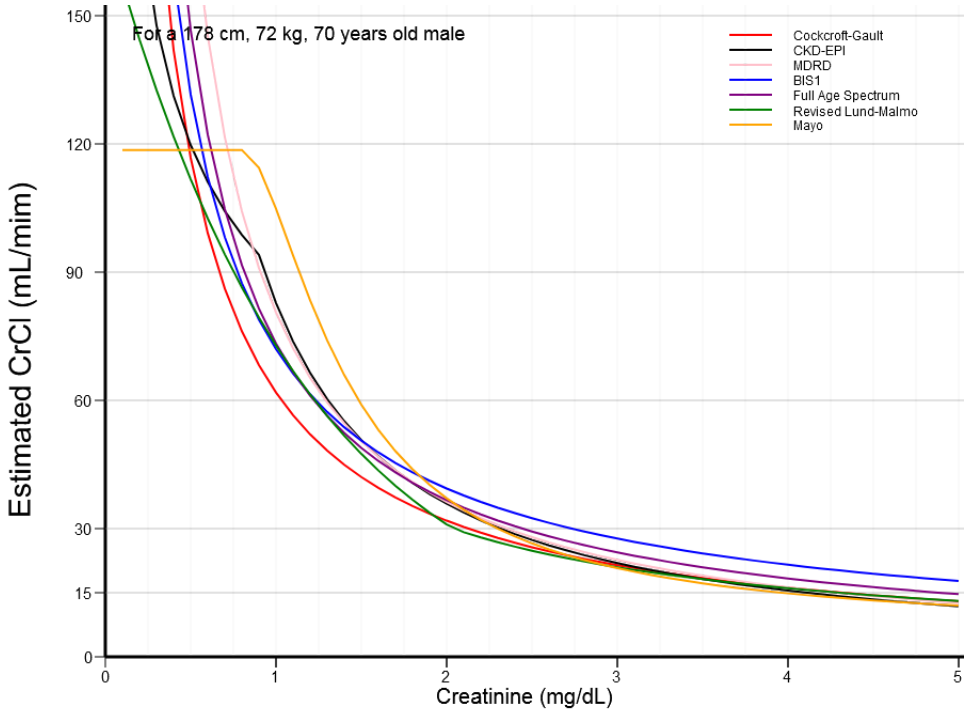
Simulations are performed using 178 cm, 72 kg, and 70 years old against creatinine with creatinine up to 5 mg/dL on the x-axis and eCrCl on the y-axis. It appears that at high creatinine concentrations, eCrCl is lower for the CKD-EPI and the revised LM equations than for the CG equation; and is significantly higher for the BIS1 equation, which does not support the use of the BIS1 equation. At the normal Scr concentration, the simulations show that the eCrCl is the lowest for the CG equation, reflecting the fact that the CG equation underestimates CrCl for the elderly.

At the lower than normal Scr concentration (< 0.5 mg/dL), eCrCl is significantly higher for the CG equation than for the CKD-EPI and the revised LM equations. Likely, the CG equation overestimates CrCl at the low Scr concentrations. Attempts have been made to correct such overestimation. One of the attempts is to round the Scr value up, for example, rounding up to 60 micromolar or 0.67872 mg/mL (Dooley 2004). However, the patient with Scr of 0.1 mg/ml and the patient with Scr of 0.6 mg/mL should have different CrCl values if other conditions are the same. Indeed, rounding Scr value up has been demonstrated to be a bad practice (Chaverri-Fernández 2016). For patients with low Scr concentration, the CKD-EPI and the revised LM equations can be used to estimate CrCl.

Figure 3. Simulations of the effect of creatinine on CrCl estimation



The Effect of Creatinine on CrCl Estimations



The Effect of Creatinine on CrCl Estimations

A few things to note

For renal dosing, specific eCrCl or eGFR values are used for the cutoff points of renal dosing. For example, eCrCl 30 mL/min is usually used as a cutoff point. The drug can be used if eCrCl is 30 or higher; otherwise, its use should be avoided. Such cutoff points make the pharmacist's job much easier. Unfortunately, renal function decline in renal impairment is a continuous process. eCrCl of 29 mL/min and eCrCl of 30 mL/min do not have much difference. P30 means the estimated value is within 30% of the true value ; and is the parameter used to assess the precision and accuracy of the equations for renal function assessment. The value is usually around 90% or lower. According to most studies, the CG equation is reported to have lower P30 values than that of the CKD-EPI, the Revised Lund-Malmö , and the Full Age Spectrum equations. Based on the P30 concept, for most patients, eCrCl of 30 mL/min actually means 21 to 39 mL/min; and eCrCl of 29 mL/min means 20.3 to 37.7 mL/min. So, there is a chance, the patient with eCrCl of 29 mL/min may have a higher true CrCl value than the patient with eCrCl of 30 mL/min. Due to this reason, estimates of renal function are useful to guide dosing of renally cleared drugs with medium therapeutic indices, but are not precise enough to guide dosing of drugs with narrow therapeutic indices. For those drugs with narrow therapeutic indices, the dosing should be guided by the drugs' effects, adverse reactions, and the blood concentration. For example, warfarin dosing is guided by INR. What should we do when the eCrCl values calculated with different equations are on the different sides of the cutoff point? If safety is a major concern and the drug is really needed (have no alternative at the moment), one solution is to reduce the dose by half. In this case, if the true CrCl is really below the cutoff point, the drug concentration from the reduced dosing of such patient will be equal or lower compared to that from the patient with true CrCl just above the cutoff point and with the dose not reduced.

Serum creatinine is affected by muscle mass and diet. So is the eCrCl and eGFR. The attempt has been made to correct the muscle mass difference by adding sex and race in the equations. However, for the same sex and race, the mass can differ very significantly. For example, one is a marathon runner and runs 5K every day; and the other is quadriplegic and has stayed in bed for a long time. To compensate for such differences, we need an activity index (the opposite of a frailty index). For normal people, the index is

1; and that is applied to the most outpatient patients. For the marathon runner, the index may be 1.2 to 1.3; for the quadriplegic, the index may be 0.6 to 0.8. On average, the CG equation underestimates CrCl for the elderly. But, it can still overestimate CrCl for that population. One possible scenario is the quaripegic patient mentioned above. The eCrCl or eGFR needs to be corrected by multiplying the activity index before being used for renal dosing. Currently, there is no easy way to define the activity index. And so the adjustment is mostly rested on the pharmacist's clinical judgement. The elderly are the most diverse population. For most elderly, the renal function declines with age. But not all the people behave like that. There is a significant portion of the elderly whose renal function does not decline with age, according to the Baltimore Longitudinal Study of Aging followed between 1958 and 1981 (Linderman 1985). None of the current equations for renal function estimation can reflect that. Extra information is needed. Such information may include the activity index.

Overestimation of eCrCl causes drug overdosing and the increased risk of adverse events. Underestimation of eCrCl causes drug underdosing and reduced drug effects. Both the overestimation and the underestimation are undesirable; and may have adverse outcomes. One purpose of this article is to increase the chance of corrected renal function estimations. But overestimation and underestimation will always happen. What should we do when the eCrCl calculated from different equations are different? Here, I propose a few principles to handle the situation. Principle 1: Use the correct eCrCl. The Revised LM equation appears to be the equation of choice. However, it is very often that we don't know which one is correct. Principle 2: Use the method associated with the drug trial if the situation has a good representation in the drug trial. Be cautious that not all the situations have a good representation in the drug trials. For example, the CG equation underestimates CrCl for underweight elderly patients. The trial may include elderly population but not the underweight elderly population. Most often, we don't know whether our case has a good representation in the drug trial. Principle 3: Use risk- benefit assessments. Following sub-principles can be used to choose one from the valid eCrCl values. Principle 3A: Use lowest eCrCl when the purpose of the medication is for symptom control, such as gabapentin. Principle 3B: Use lowest eCrCl when the purpose of the medication is for prevention, such as rivaroxaban for prevention of stroke and systemic embolism. Principle 3C: Use the highest eCrCl for antibiotic therapies especially for beta lactams, which are usually quite safe, for example Cephalexin. Infection undertreatment may cause infection spread; and may be lethal in the case of sepsis.

Based on this article, two online renal function calculators are developed. They use different input methods. One is similar to other online calculators; and uses the manually input method. The web address for this calculator is https://www.drugtnt.com/include/GFR.php. The other uses the copy and paste method; and is specifically developed for the IHS EHR system. It uses an EHR template to extract the needed information; and then copies the information from EHR and pastes it to the calculator. This calculator is able to not use the whole number for age; and the eCrCl/eGFR is more current; and may be slightly lower because the age may be bigger. The web address is https://www.drugtnt.com/include/gfr2.php.

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