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New equations for the estimation of renal function and when to use them

Outline

Introduction to renal clearance and GFR

Why is renal clearance so important for medication dosing?

eCrCl and eGFR calculations - why do these keep changing

Why change to a more modern equation?

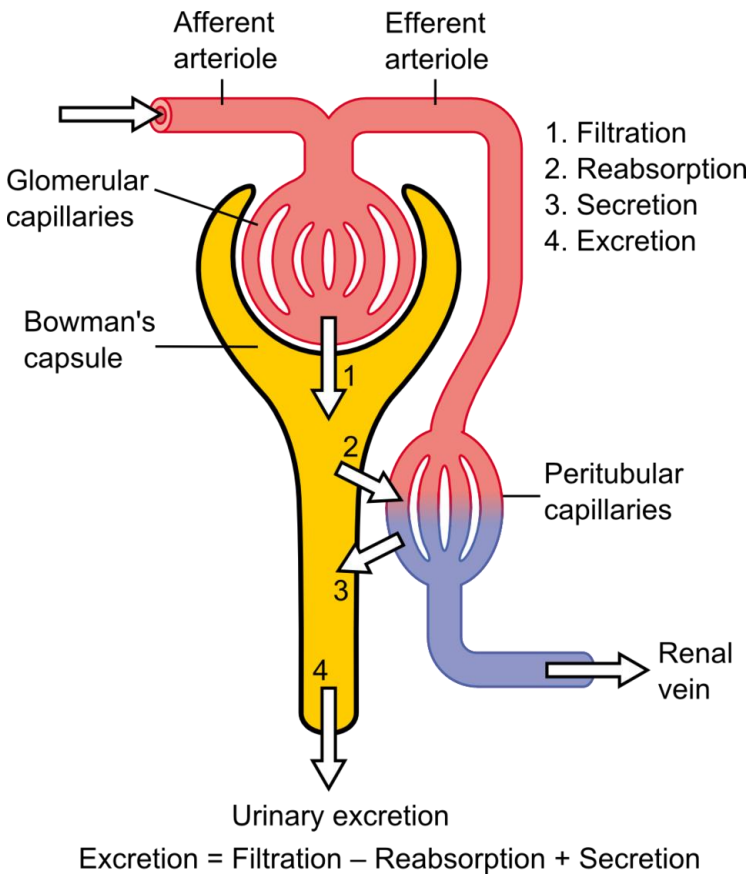
Which are the best equations to use for estimating clearance?

Summary and conclusions

Conflicts of interest

I have no conflicts to declare

Clearance of drugs and toxins



- **Clearance = volume of body fluids from which a substance is completely removed in a specific period of time**
- **First define with regard to metabolic products**

- Drugs and toxins can be cleared from the body by
  - Renal excretion
  - Non-renal excretion (liver, lungs, intestine)
  - Enzymatic or non-enzymatic degradation

- Characteristics that favor renal clearance
  - Small size (<300 Da)
  - Water solubility
  - Metabolized slowly
- Characteristics the favor non-renal excretion
  - Lipid solubility (large V_d) and protein binding
  - Volatility (anesthetics)

https://www.pharmacy180.com/article/factors-affecting-renal-excretion-or-renal-clearance-2498/

Renal Clearance (most drugs or their metabolites)

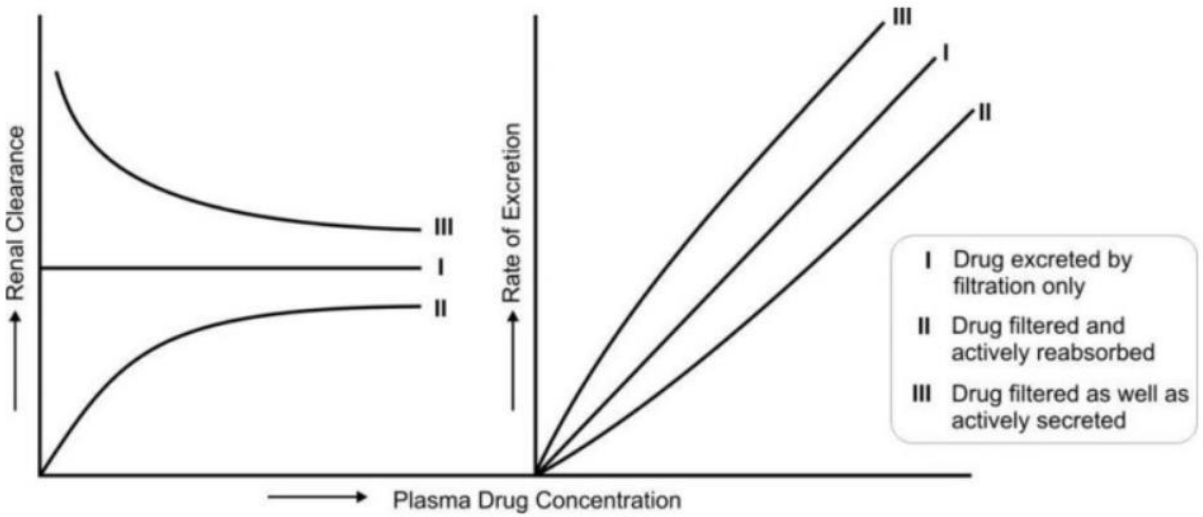


Fig. 6.3. Renal clearance and rate of excretion of a drug in relation to its plasma concentration as affected by the physiologic processes — filtration, active reabsorption and active secretion

Glomerular filtration rate

- Unidirectional filtration of small ionized/unionize compounds
- This is the primary mode of excretion for many drugs and their metabolites

Tubular Secretion

- This is a carrier mediated tubular process that adds a compound to the filtrate to increase clearance
- Important for anions (OATs) including uric acid, penicillins, salicylates, glucuronides, sulphates and others
- Important for cations (OCTs) including morphine, catecholamines, cholines, and histamines
- Can be saturated and so is more important at low plasma concentrations (e.g. loop diuretics)

Tubular Reabsorption

- Mainly for filtered nutrients (like glucose or vitamins) but might prolong half-life for some drugs
- May be active or passive (for weak acids like aspirin)
- Active transport can be saturated

https://www.pharmacy180.com/article/factors-affecting-renal-excretion-or-renal-clearance-2498/

Jennifer Le and Eva Civian Drug absorption in Merck Manual Reviewed and Revised 2024

Clearance by the kidney (metabolites, toxins, and drugs)

Generally speaking, pharmacokinetics of drugs is altered by renal disease

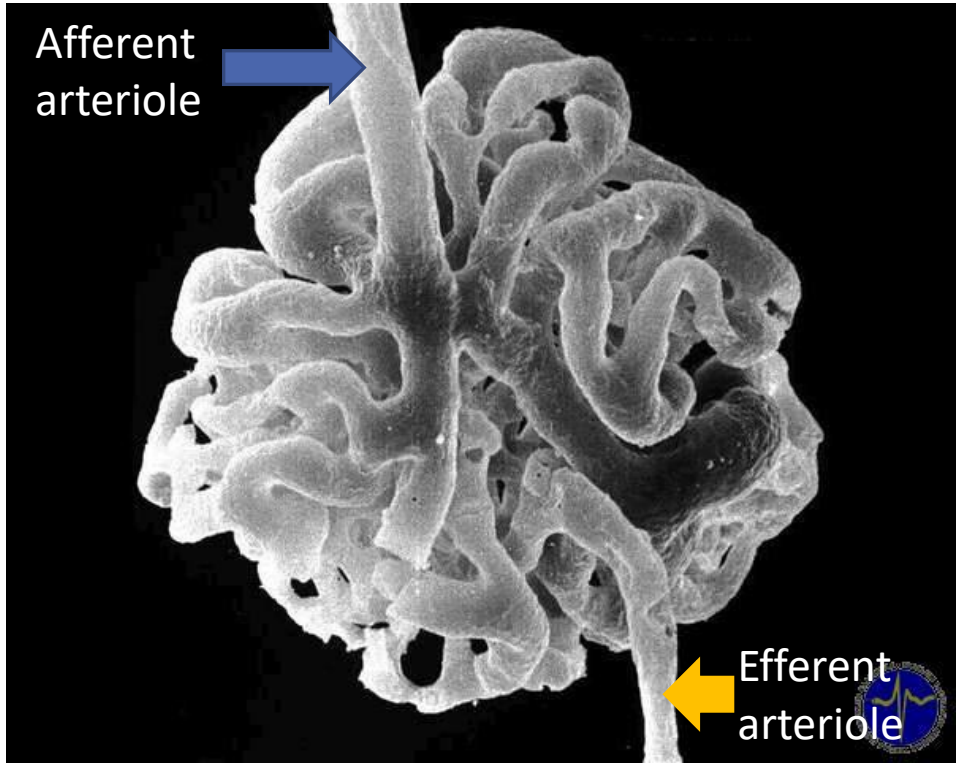
Drug dose = Renal elimination + non-renal elimination + degradation.

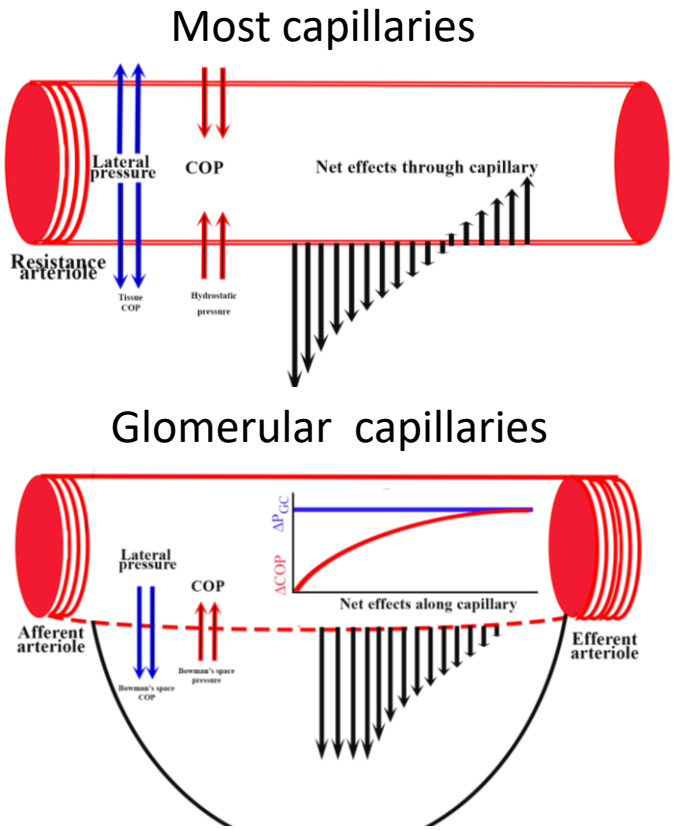
Clearance by the kidney (metabolites, toxins, and drugs)

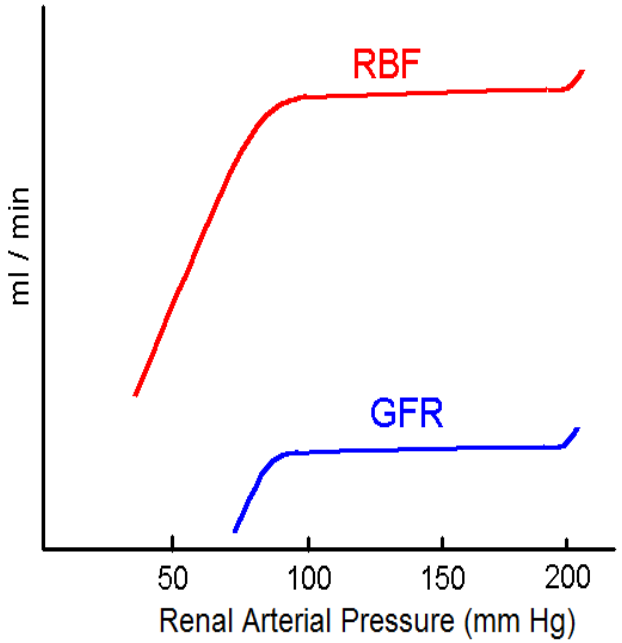
For drugs and toxins that are renally cleared

Drug dose = Normal dose x RF (% of normal)

Glomerular filtration





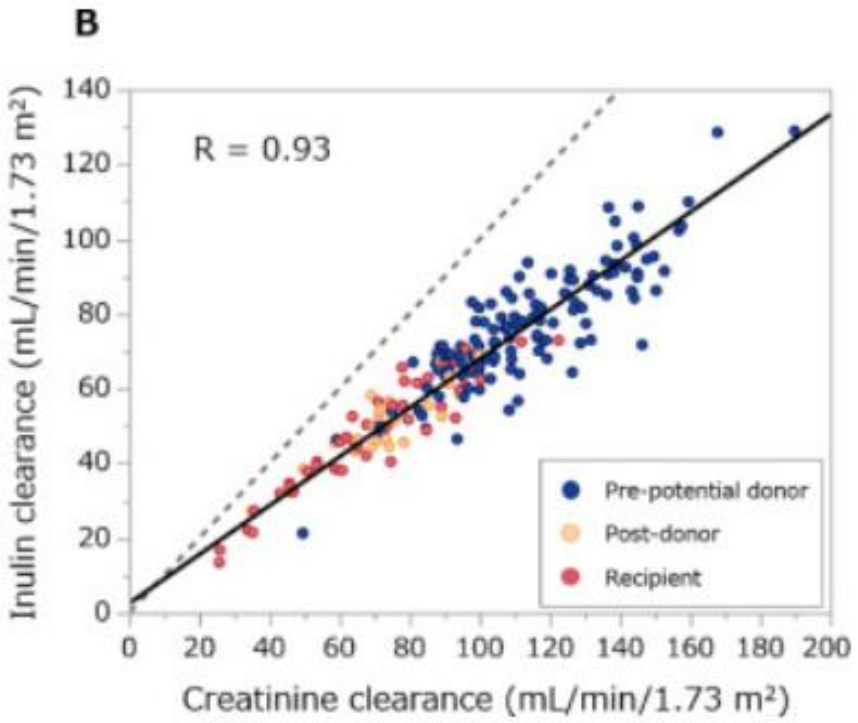


The glomerulus is a “portal” system (art-cap-art)

Frank- Starling’s law (1896) - Fluid Flux = $J_v = K_f(P_c-P_i)-(\pi_c-\pi_i)$

Measuring GFR

Clearance of a compound that is filtered but not secreted or reabsorbed



Inulin (1%; Fuji Yakuhin, Saitama, Japan) was administered intravenously using an infusion pump under fasting, medication-suspended, and hydrated conditions. The infusion rate was 300 mL/h for 0–30 min and 100 mL/h for 30–120 min. To maintain urine output during clearance measurements, participants were given 500 mL of water 30 min before the start of inulin administration and 60 mL of water at each urine collection time point. Participants urinated completely 30 minutes after the start of administration and urine was collected every 30 minutes (60, 90, and 120 minutes after the start of administration).

Clearance was calculated as follows:
Ux (mg/dL) × V (mL/min) / Px (mg/dL)

Kawamura et al Lancet 43:2022:DOI: 10.1016/j.eclinm.2021.101223

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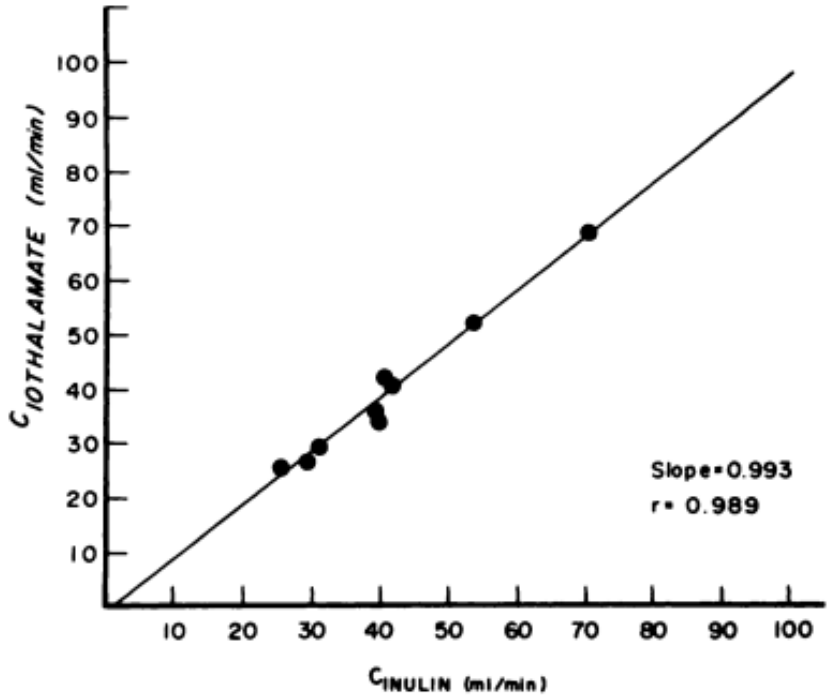
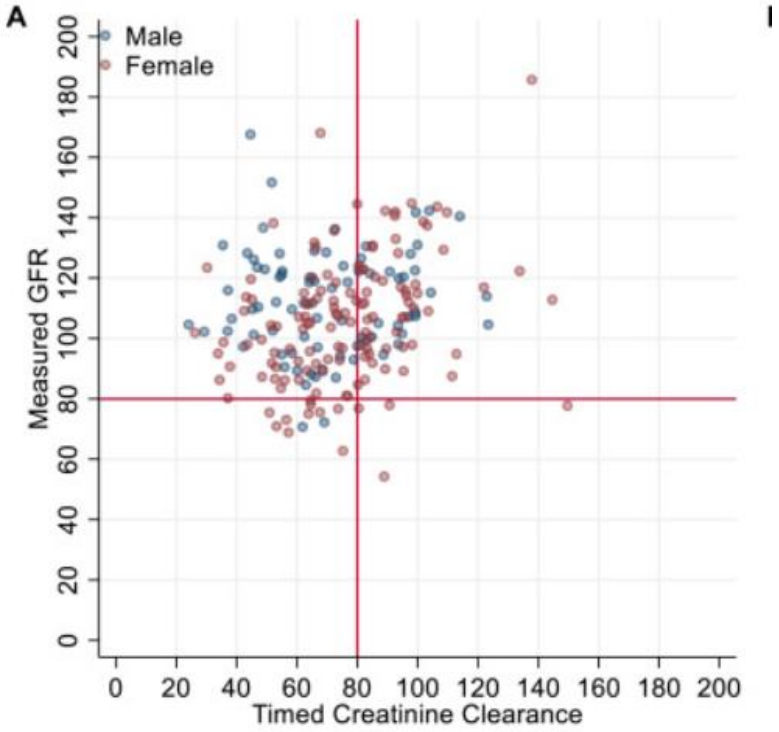


FIG. 2. Comparison of ^{125}I-iothalamate clearance with standard inulin clearance.

Subjects were admitted to the general clinical research center the morning after an overnight fast. The study visit involved evaluation of renal function after both a bolus injection and during constant infusion of iothalamate. After intravenous catheter placement and throughout the entire evaluation, subjects remained semireclined except during voiding. After oral water loading (750 ml over 45 min), each subject received a bolus injection of iothalamate 456 mg (Conray-30; Mallinkrodt, St. Louis, MO) over 2–3 minutes at approximately 9 A.M. An oral fluid regimen of approximately 250 ml/hour was maintained throughout both phases of the study. Venous blood samples (7 ml) were obtained immediately before and 5, 10, 15, 30, 45, 60, 90, 120, 150, and 180 minutes after the dose.

Barbour et al J Nucl Med. 17(4) 1976 and Dowling et al Pharmacotherapy 19(8) 1999

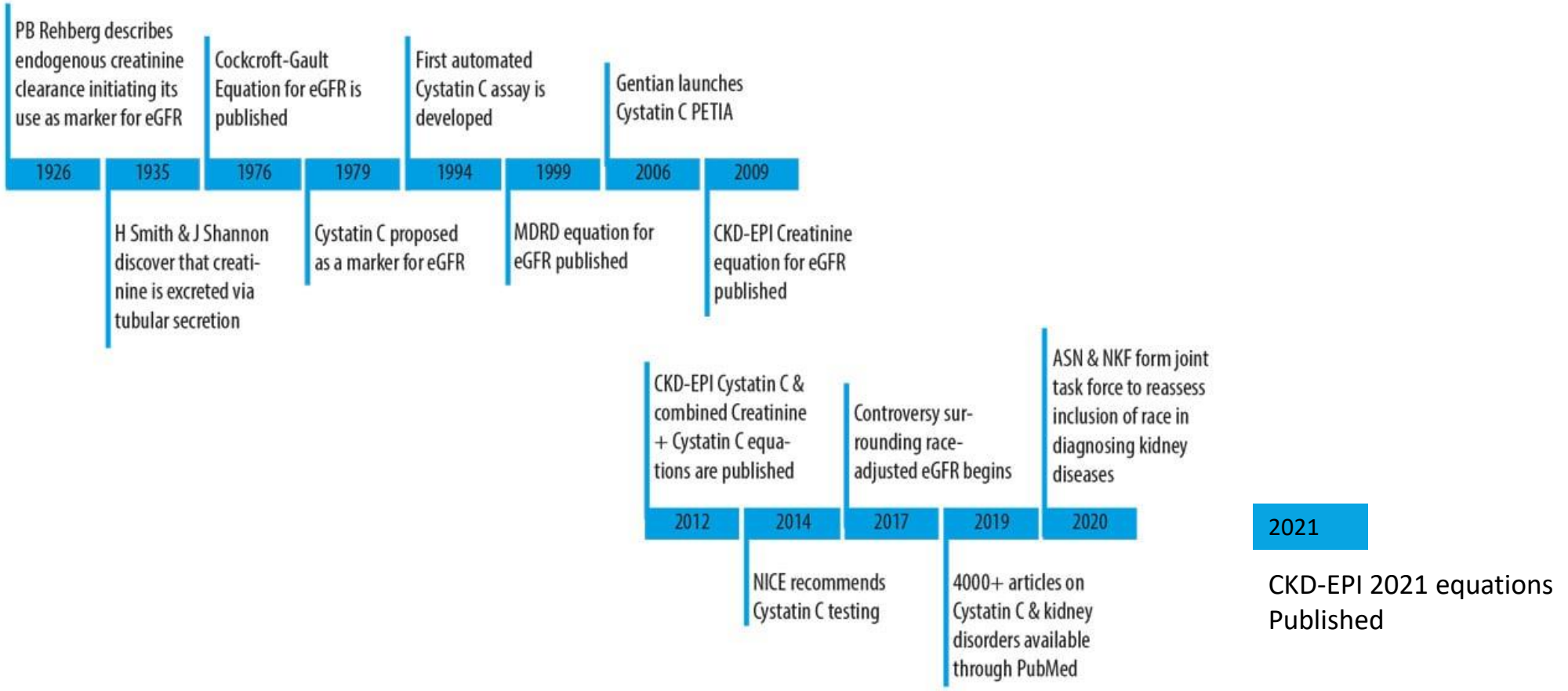
24-hour creatinine clearance



- **Collection errors are common**
  - In kidney donors measured creatinine clearance underestimated iothalamate GFR by about 40 (IQR 20.5-63.3) in males and 32 (IQR 14.2-46) ml/min
  - When done correctly, the 24-hour creatinine clearance overestimates the iothalamate GFR by about 10% because of secretion of creatinine
- Creatinine excretion is usually estimated to be 15-20 mg/kg/d in a patient at steady state (not in AKI). Collection errors occur in at least 20% of collections and this is higher in outpatients , for children, for the elderly, and those with cognitive issues
- Many studies have suggested that eGFR may be better than 24-hour creatinine collections in estimating GFR

Kestenbaum et al Population-Based Limits of Urine Creatinine Excretion Kid. Int. Reports 7(11):2022
Husain et al Timed Creatinine Clearance and Measured Glomerular Filtration Rate in Living Kidney Donors Kidney Medicine 5(1) 2023

Estimating GFR
creatinine clearance and estimating equations



https://www.gentian.com/news/cystatin-c-glomerular-filtration-rate

Estimating GFR - what is wrong with Cockroft-Gault?

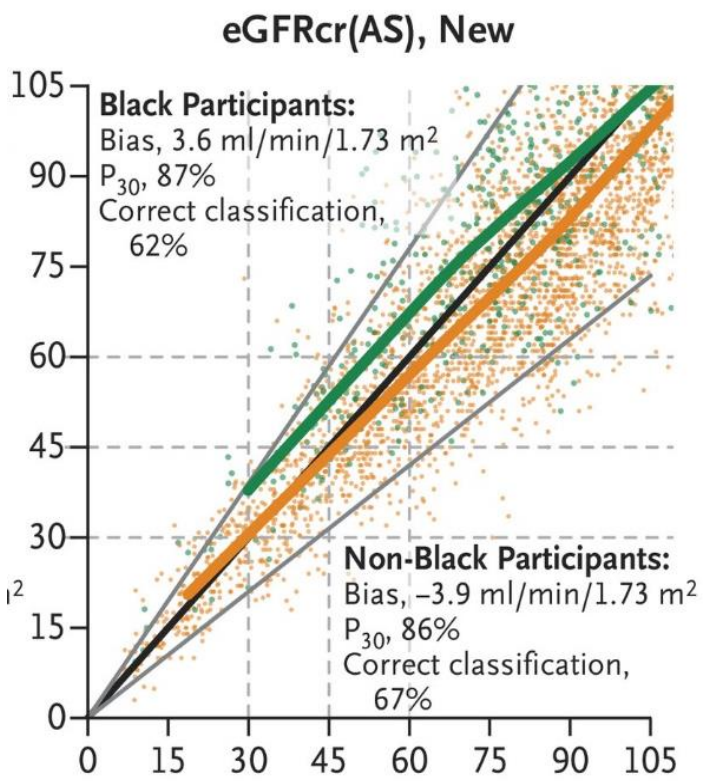
For the last 50 years, dosage adjustment recommendations and normograms used for medication cleared by the kidneys have been developed using the Cockroft-Gault equation

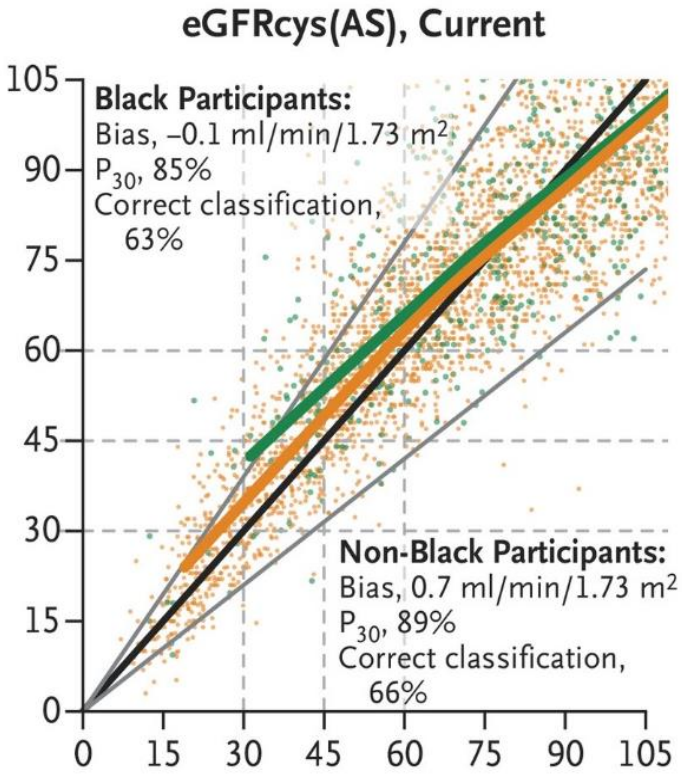
What is wrong with Cockroft-Gault?

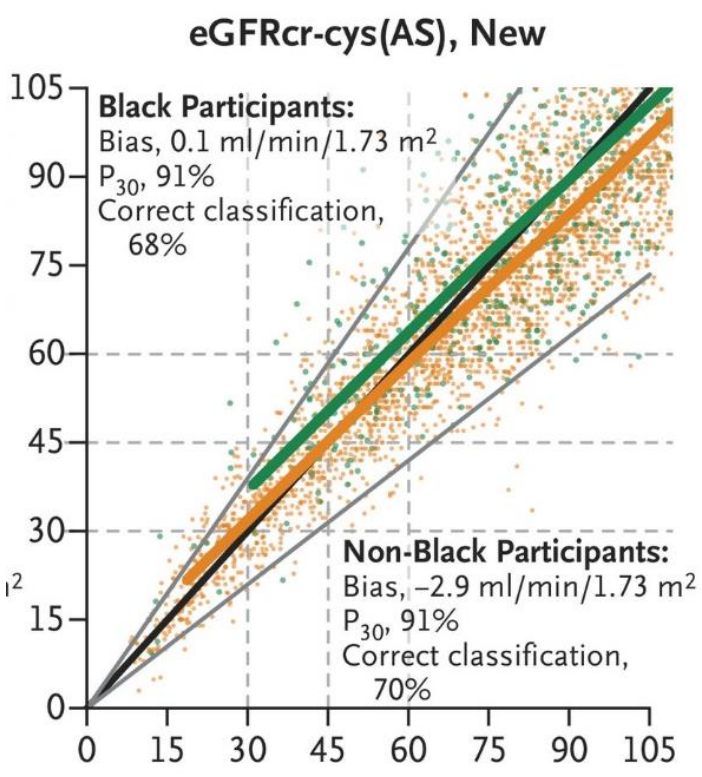
- Concerns are derived from it's historical context
- The C-G study, published in 1976 was developed in a population of 249 while males. It has never been validated in large, diverse populations
  - Adjustments for female sex (-15%) was estimated and not scientifically generated
- C-G was validated against 24-hour creatinine clearance not GFR
- Creatinine measurements were not standardized in 1976 (serum creatinine decreased by 12% after IDMS standardization in 2011)
- Weight is used to adjust the equation for body size but the weight of the US population has changed significantly since 1976
- Finally, many algorithms for adaptions for older age inflated serum creatinine by a variable amount resulting in significant C-G variability

Bzowckyj et al A call to action: Transition from Cockroft-Gault estimated creatinine clearance to race-free estimated GFR JACCP 2025
St.Peter et al Moving forward from Cockroft-Gault creatinine clearance to race-free estimated GFR to improve medication-related decision-making AJHSP 2025

Estimating GFR
CKD-EPI 2021 and the inclusion of Cystatin C





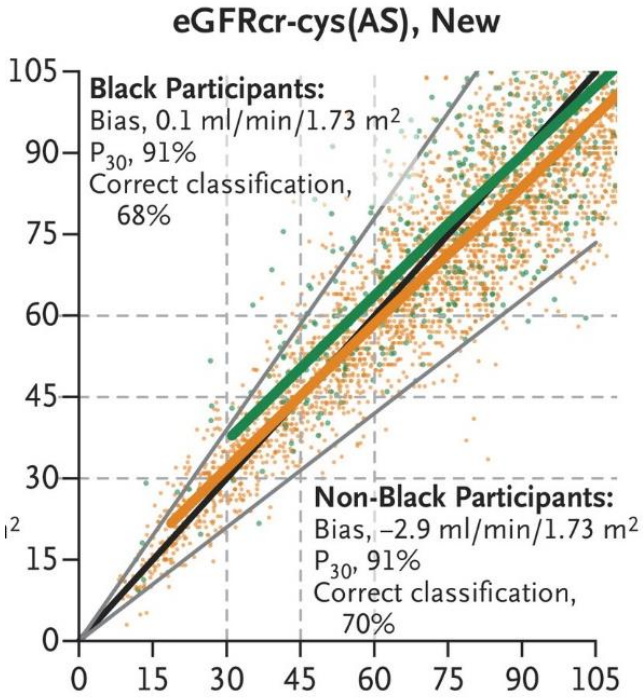


Inker et al New Creatinine- and Cystatin C0Based Equations to Estimate GFT without Race NEJM 385:2021
Guidance for Industry: Parmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing FDA CDER 2024

eCrCL > eGFR
Moving outside of the comfort zone

Many pharmacists, educators, and researchers have doubts after decades of using C-G CrCL to adjusted medication doses. Here are some of the cornerstones driving the paradigm shift to eGFR

- Modern equations are race-free (critical in evaluating GFR as the multiracial makeup of the US population changes)
- eGFR is often adjusted based on BSA (1.73 m^2) to allow for staging of CKD and comparisons between population groups. This correction can be removed for dosing calculations
- Increased awareness of the role of cystatin C to improve precision
- Critically, it must be remembered that C-G or eGFR equations provide an estimate and clinical context and monitoring are key
  - Therapeutic monitoring is still essential for drugs with small therapeutic windows
  - Most new medications are being tested using eGFR-based dosing, but more research is needed in underrepresented groups



St.Peter et al Moving forward from Cockroft-Gault creatinine clearance to race-free estimated GFR to improve medication-related decision-making AJHSP 2025
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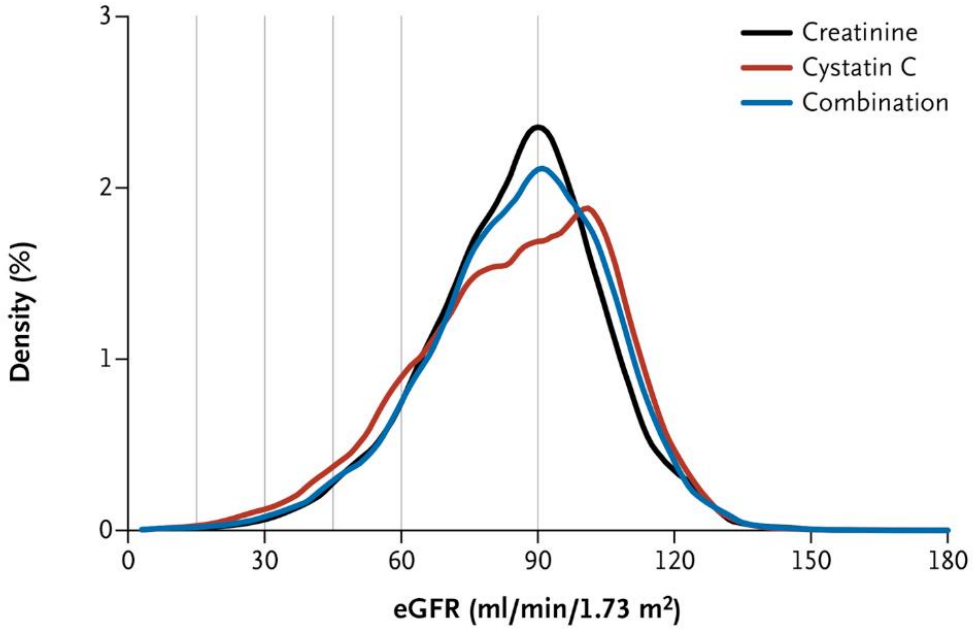
Limitation of creatinine and cystatin C

Creatinine-based eGFR (since 1976)

- Slow in AKI
- Affected by muscle mass – eating disorders, extreme sports, amputees, spinal cord injury
- Affected by creatine supplements, trimethoprim, and cimetidine

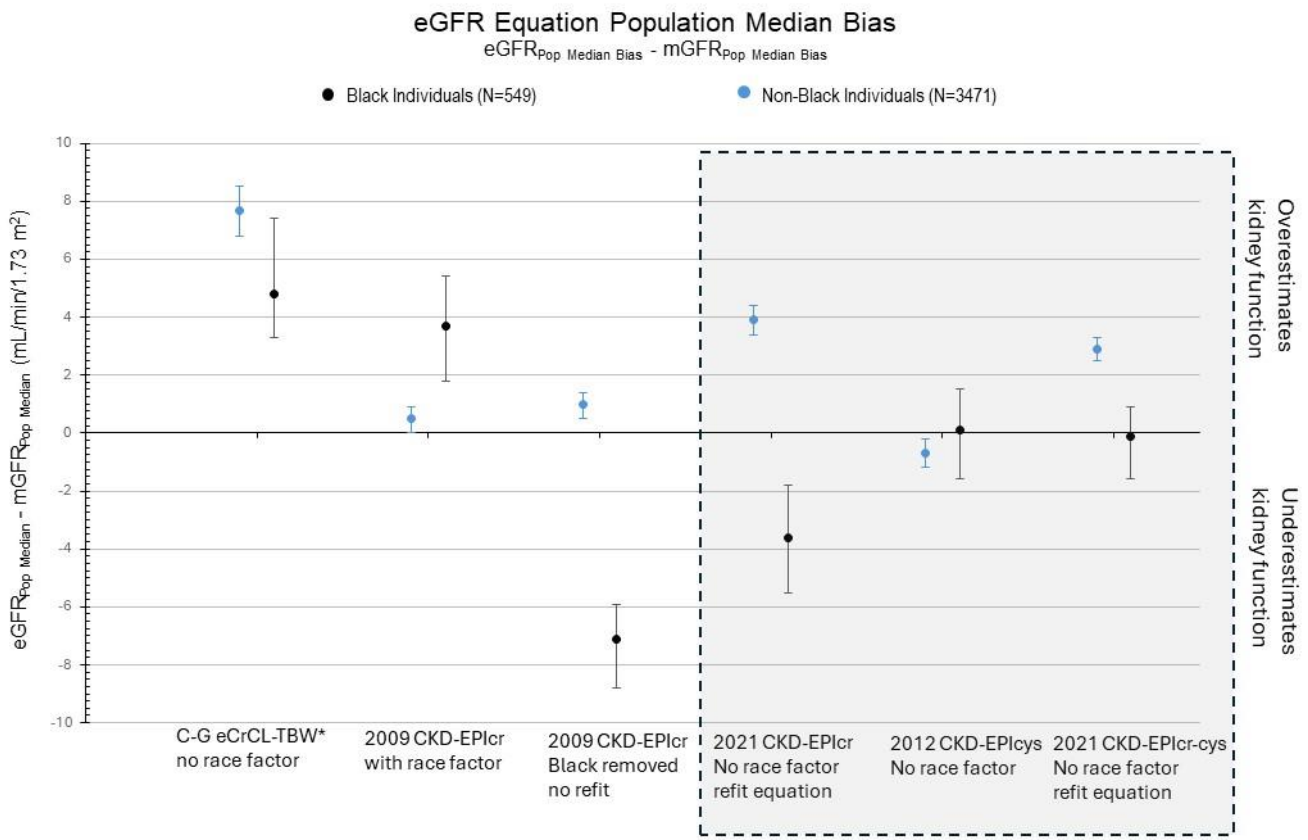
Cystatin C

- Cystatin C is a 13-kDs cysteine proteinase
- Produced by all nucleated cells and filtered by the
- Measurement is expensive (10 x Creatinine assay)
- In one study of patients with CKD3a, adding cystatin C to eGFR based on creatinine resulted in
  - 30 % of patients being reclassified as not having CKD, while
  - 25% had more advanced CKD that initially estimated
- Cystatin C also increases with inflammation and CVD
  - Leukemia and thyroid disease
  - Corticosteroid treatment
  - Atherosclerotic CVD, smoking, diabetes, and obesity
  - Active inflammation and autoimmunity
- Unpredictable in critically ill



Benoit et al Cystatin C as a biomarker of chronic kidney disease: latest developments Expert Rev Mol Diagn 2021, Shlipak et al Cystatin C versus creatinine in determining risk based on kidney function. N Engl J Med. 2013. September 5;369(10):932–43, Lertnewapan et al Cystatin C is Associated with inflammation but not Atherosclerosis in SLE Lupus 21(3) 2011, Odden et al Cystatin C Level as a Marker of Kidney Function in HIV infection – The FRAM Study Arch. Intern. Med. 2007

Performance of estimation equations vs measured GFR in the CKD-Epi 2021 dataset



Summary and conclusion
Thriving in uncertainty

1. **Kidney function is a critical determinant of drug clearance**
2. **Pharmacists, clinicians and researches have been using the Cockroft-Gault equation to estimate creatinine clearance for the last 50 years**
3. **The national kidney foundation and the FDA have recommended switching to modern eGFR equations to guide medication adjustments**
   - Have been tested in more diverse patient populations
   - Not weight dependent
   - More accurately predict GFR an pharmacokinetics
4. **It is important to realize that all modern equation have limitations with P_{30} precision measures of ~90%**
   - We should not be numerologists
   - Measure therapeutic levels and/or GFR/Creatinine clearance when dosing decisions re critical

Some quick cases to think about

You are contacted by pharmacy regarding a patient of yours with type 2 diabetes who has been doing well on metformin for the last 20 years. He is 92 years old and has a stable creatinine of 1.5 mg/dL with normal electrolyte and acid-base homeostasis. He is 145 lb and a recent cystatin C that was done in hospital was 1.0 mg/dL

1. His C-G eCRCl is 29 ml/min and he should stop the metformin and transition to insulin or glipizide
2. His eGFRcre is 43 ml/min and this is the best equation to use when adjusting his medications dose
3. The combined eGFRcre-cys is 60 ml/min and so he could continue with metformin
4. There is no good way to estimate his eGFR and we should order a 24 hr urine creatinine clearance.

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Some quick cases to think about

You are asked to evaluate a 50-year-old Veteran for compensation. He owns a boxing and bodybuilding business and tells you that he regularly uses creatine supplements to boost performance in competitions. He is 5'10" with a weight is 210 lb (BMI 30.1) with a creatinine of 1.6 mg/dL, but is maintaining normal serum electrolyte and bicarbonate levels. You check a serum cystatin C and it is 0.9 mg/dL.

1. He has CKD stage 3a because the eGFRcre is 52 ml/min/1.73m^2
2. We cannot evaluate his eGFR because he is taking creatine supplements and creatine cross reacts with creatinine in the standard IDMS assays
3. In this case, the combined eGFRcre-cys would be the best estimate of his GFR and would allow us to stage his kidney disease
4. The cystatin-based eGFR (eGFRcys) is 93 ml/min/1.73m^2 and so, he does not have kidney disease
5. We should collect a 24-hour urine for creatinine clearance and this will accurately determine the CKD stage

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Some quick cases to think about

You are asked to help adjust the dose of Vancomycin for a Veteran with MRSA septicemia and osteomyelitis. He is a 58-year-old man with tetraplegia following a diving accident in 2010. He is hypotensive in the ICU on inotropes and has a suprapubic catheter in place that has drained 400ml in the last 24 hours. The creatinine has risen from his baseline of 0.8 mg/dL to 2.5 mg/dL. The cystatin C is 4.8 mg/dL.

1. The eGFRcre is 28 ml/min and so we should load with 15-20 mg/kg and then dose every 24 hours
2. The combined eGFRcre-cys is 15ml/min and so we should load with 15-20 mg/kg and dose every 3 days
3. Creatinine and cystatin c both have issues in this patient and so we should insist on an iothalamate clearance study before starting Vancomycin
4. Vancomycin cannot be used in this patient
5. There are no good ways to estimate GFR in acute kidney injury. This patient should be loaded with 15-20 mg/kg and levels should be checked daily to guide redosing

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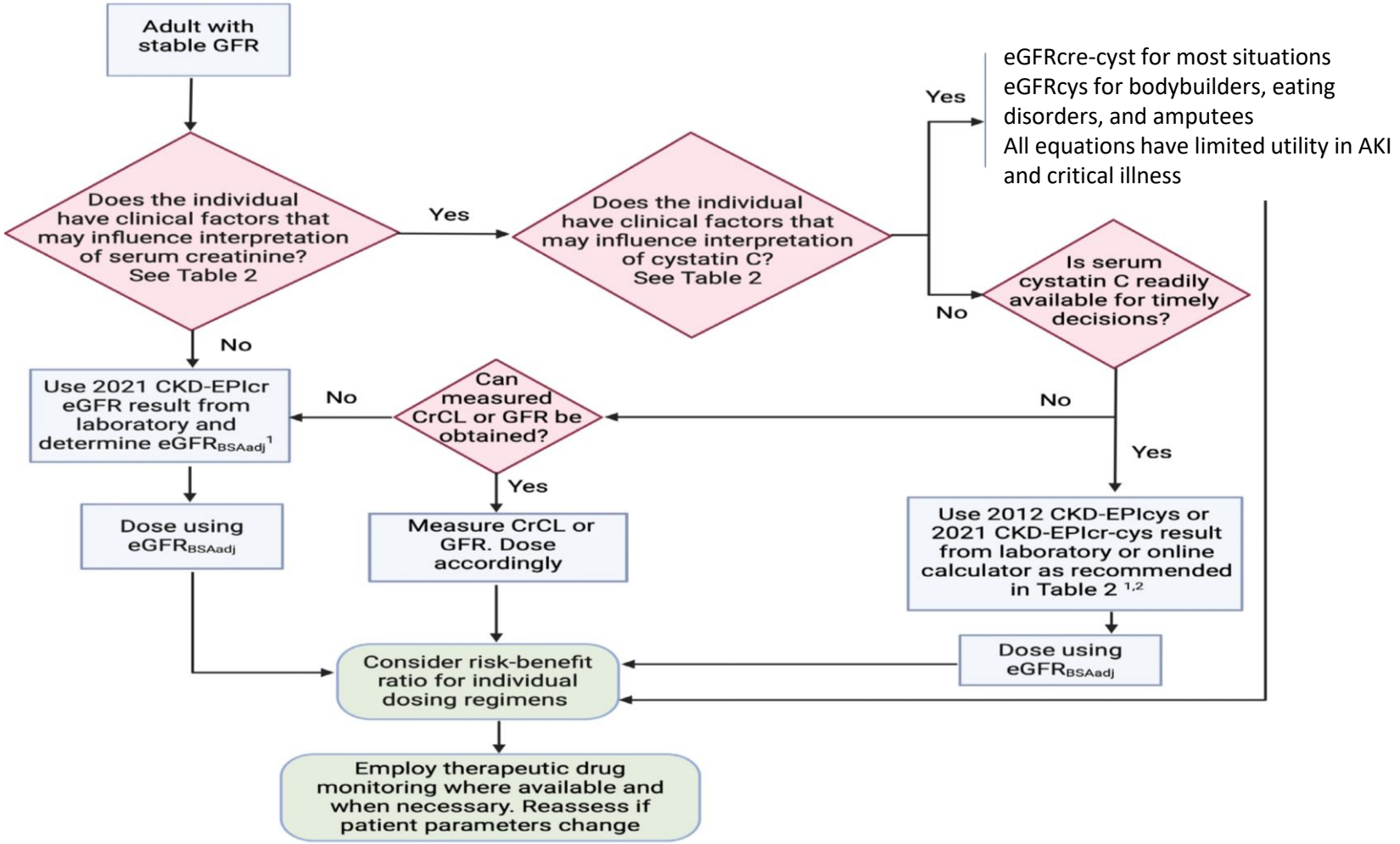
Figure 2. A pragmatic approach for using estimated glomerular filtration rate for dosing medications in adult patients ...



Am J Health Syst Pharm, Volume 82, Issue 12, 15 June 2025, Pages 644–659, https://doi.org/10.1093/ajhp/zxae317

Q & A