Clinical context of patients commonly referred for renal clearance:

A nephrologist's perspective

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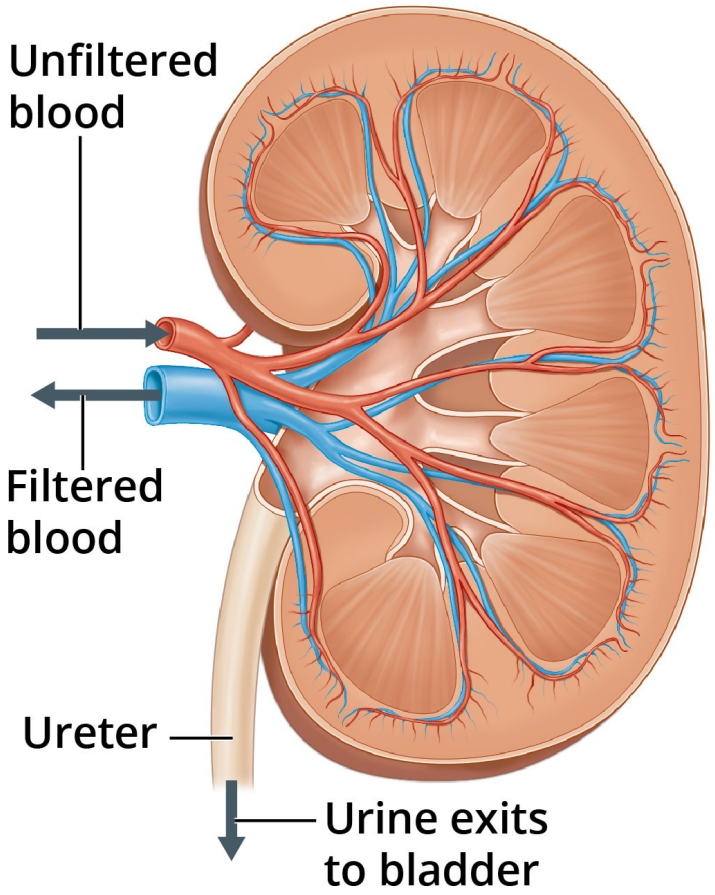
What are Nephrons

- The **nephron** is the functional unit of the kidney.
- Each kidney contains about 1,000,000 to 1,300,000 nephrons.
- The nephron is composed of **glomerulus** and **renal tubules**.
- The nephron performs its homeostatic function by ultra filtration at glomerulus and **secretion** and **reabsorption** at renal tubules.

What are the kidney functions ?

- Regulation of the following :
  - water and electrolyte balance.
  - acid base balance.
  - arterial blood pressure.
- Excretion of metabolic waste products and foreign chemicals.
- Hormonal Functions :
  - Secretion of erythropoietin
  - Activation of vitamin D
  - Activation of angiotensinogen by renin .
- Metabolic Function :
  - site for gluconeogenesis .

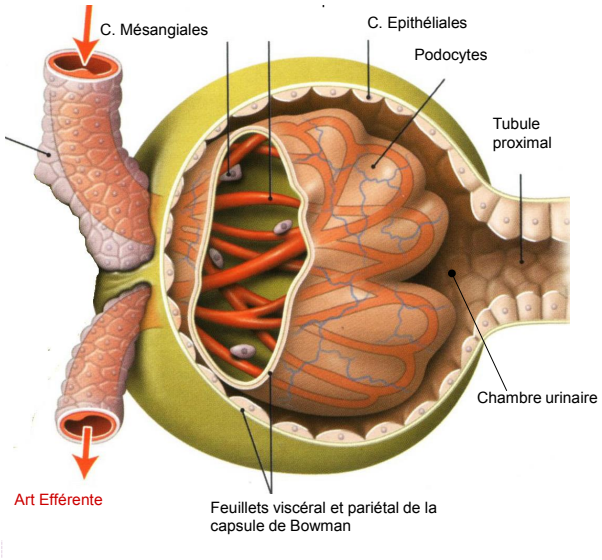


From « *kidney functions* » to « GFR »…

- In 1951, **Homer Smith** declared that the best way to test kidney function is…

…« *to measure the glomerular filtration rate (GFR) by inulin clearance* »

- Since, we have never left this « glomerulocentric » functional approach…



Today « GFR » is still considered as the « **best » overall measure of the kidney's ability to carry out these various functions »**

What is a « normal » GFR ?

- The glomerular filtration rate (GFR) is equal to the sum of the filtration rates in all of the functioning nephrons.
  - Approximately 180 liters per day (125 mL/min) of plasma are filtred

- The normal value for GFR is approximately 90 to 120 mL/min/1.73 m2 with important variation even among healthy individuals
  - Age, sex…

- Significance of a declining GFR in patients with kidney disease
  - A fall in glomerular filtration rate (GFR) implies either progression of the underlying disease (CKD) or the development of a superimposed and often reversible problem (AKI)

Limitations of GFR

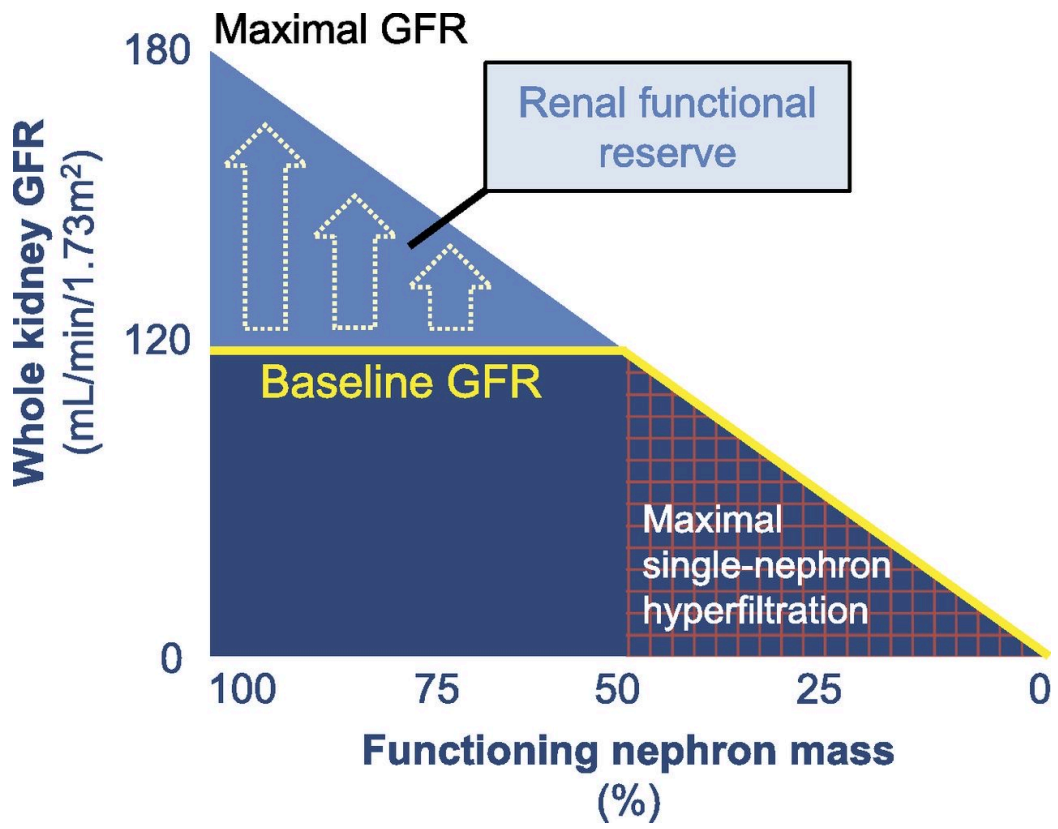
- No information on the **cause** of the kidney disease
- No evaluation of albuminuria or hematuria, morphology …
- GFR do not permit an evaluation of all the « **specific** » functions of the kidneys

Glomerular Filtration: Relevant for smaller nonprotein-bound substances

Tubular secretion and reabsorption is relevant for protein-bound substances

Limitations of GFR

- There is **not an exact correlation** between the loss of **kidney mass** (ie, nephron loss) and the loss of **GFR**.
  - The kidney adapts to the loss of some nephrons by compensatory **hyperfiltration** in the remaining, normal nephrons.
  - Thus, an individual who has lost one-half of total kidney mass will not necessarily have one-half the normal amount of GFR.
- **These concepts have important consequences:**
  - A stable GFR does not necessarily imply stable disease.
  - An increase in GFR may indicate improvement in the kidney disease or may imply a counter productive increase in filtration (hyperfiltration) due to hemodynamic factors
  - Some patients who have true underlying kidney disease may go unrecognized because they have a normal GFR.



How to « measure » GFR → « *mGFR* »

- The **true glomerular filtration rate (GFR) cannot be measured directly** in humans…
  - GFR is measured using clearance of an **« *ideal* »** substance and is defined as the volume cleared of that substance per time.
  - An ideal filtration marker should be excreted by the kidneys, not be protein-bound, and not be secreted or reabsorbed in the tubules.

- The **gold standard** method is urinary or plasma clearance of an **exogenous filtration marker**.
  - Urinary clearance of **inulin** was described by Homer Smith in 1935, and it is still the gold standard for GFR measurement.
  - Many other **exogenous markers** have been used such as
    - Technetium-99m diethylene- triaminepentaacetic acid (**99mTc-DTPA**)
    - **Iothalamate**,
    - Chromium-51 ethylenediaminetetraacetic acid (**51Cr-EDTA**)
    - Iohexol

How to « estimate » GFR → « *eGFR* »

- Methods to measure GFR are laborious, expensive, and not broadly available, and are therefore not appropriate as first-line diagnostic tools.
- In most clinical settings, blood levels of **endogenous filtration markers** are used to estimate GFR

*« To date, despite **ambitious research** to identify a **perfect endogenous filtration marker** that fulfils all criteria, namely being freely filtered and neither secreted nor reabsorbed by the kidney, being inexpensive and measurable by a standardized automated assay and not significantly influenced by other patient characteristics, has been **disappointing** so far »*

→ **Creatinine** is still the most commonly used endogenous marker

- Widely available, freely filtered by the glomerulus…
- … But subject to extrarenal elimination (gastrointestinal tract), secreted by the renal tubules, generated from muscle mass or diet (cooked meat)

How to « estimate » GFR → « *eGFR* »

- **Cystatin C** is an alternative endogenous filtration marker
  - It is freely filtered at the glomerulus, is catabolized in the tubules with reabsorption of its metabolites, and undergoes extrarenal elimination to some extent.
  - Cystatin C is not excreted in the urine
  - It is less influenced by non-GFR determinants than creatinine
    - non-GFR determinants of cystatin C include inflammation, smoking, thyroid abnormalities, and fat mass

How to « estimate » GFR → « *eGFR* »

- **Equations** that estimate GFR are most commonly used in daily practice.
  - Based on plasma creatinine (+/- cystatin C)

Advantages:

- Inexpensive
- Results are immediately available.

Disadvantages:

- Rely on endogenous biomarkers, which are confounded by non-GFR determinants:
  - Age, sex, muscle mass, drugs, diet…

How to « estimate » GFR → « *eGFR* »

Age	Marker	Reference Method	Standardized Assay	Derivation Study Characteristics	Equation	Comment
Creatinine ($eGFR_{cr}$)						
Adult	Cockcroft-Gault (1976)[a]	mCL_{cr}	No	249 men; 0% Black participants (presumed)	(140 − age × weight)/(72 × Scr) × 0.85 if female	Underestimates mCL_{cr} in older age, obesity, and edematous states
Adult	MDRD Study (2006)[b]	Urinary iothalamate	Yes	983 men/645 women; mGFR 40 mL/min/1.73 m^2; age 50.6 y; 12% Black participants	$175 \times Scr^{-1.154} \times age^{-0.203} \times 0.745$ if female × 1.212 if Black	Underestimates mGFR in high-normal GFR values
Adult	CKD-EPI $eGFR_{cr}$ (2009)[c]	Urinary iothalamate, other mGFR	Yes	4,648 men/3,606 women; mGFR 68 mL/min/1.73 m^2; age 47 y; 30% Black participants	$141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{age}$ × 1.018 if female × 1.159 if Black | α = −0.329 (female); −0.411 (male); κ = 0.7 (female); κ = 0.9 (male)	Unbiased across range of GFR; recommended in adults
Pediatric	CKiD Schwartz "bedside" (2009)[d]	Plasma clearance of iohexol	Yes	213 boys/136 girls; mGFR 41 mL/min/1.73 m^2; age 10.8 y; 15% Black participants	0.413 × (height in cm/Scr)	Iohexol measurements have since been recalibrated
Pediatric and young adult (age 18-26 y)	Average of CKiD (2009) and CKD-EPI (2009)[e]	Per CKiD 2009 and CKD-EPI 2009 equations			–	Improves eGFR accuracy in young adults; iohexol measurements have since been recalibrated
Pediatric and young adult	CKiD $eGFR_{cr}$ U25 (2021)[f]	Plasma clearance of iohexol	Yes	387 boys/231 girls; mGFR 48 mL/min/1.73 m^2; age 13 y; 7% Black participants	K × height/Scr | K for males 1-11 y, $39 \times 1.008^{(age-12)}$; 12-17 y, $39 \times 1.045^{(age-12)}$; 18-25 y, 50.8; K for females: 1-11 y, $36.1 \times 1.008^{(age-12)}$; 12-17 y, $39 \times 1.023^{(age-12)}$; 18-25 y, 41.4	Improves performance vs CKiD "bedside," especially for age <5 and >18 y
Cystatin C ($eGFR_{cys}$)						
Adult	CKD-EPI $eGFR_{cys}$ (2012)[g]	Urinary iothalamate	Yes	3,107 men/2,245 women; mGFR 68 mL/min/1.73 m^2; age 47 y; 33% Black participants	$133 \times \min(Scys/0.8, 1)^{-0.499} \times \max(Scys/0.8, 1)^{-1.328} \times 0.996^{age}$ × 0.932 if female	Similar performance to CKD-EPI $eGFR_{cr}$ but decreased impact of age, sex, and race
Pediatric	CKiD Cys (Schwartz "bedside" cystatin C; 2012)[h]	Plasma clearance of iohexol	No	389 boys/254 girls; mGFR 43 mL/min/1.73 m^2	$70.69 \times S_{cys}^{0.931}$	Iohexol measurements have since been recalibrated; cystatin C assay not standardized
Pediatric and young adult	CKiD $eGFR_{cys}$ U25 (2021)[f]	Plasma clearance of iohexol	Yes	387 boys/231 girls; mGFR 48 mL/min/1.73 m^2; age 13 y; 7% Black participants	K × 1/Scys | K for males 1-14 y, $87.2 \times 1.011^{(age-15)}$; 15-17 y, $87.2 \times 0.960^{(age-15)}$; 18-25 y, 77.1; K for females: 1-11 y, 79.9 $\times 1.004^{(age-12)}$; 12-17 y, 79.9 $\times 0.974^{(age-12)}$; 18-25 y, 68.3	Improves performance vs CKiD "bedside," especially for age <5 and >18 y

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How to « estimate » GFR → « *eGFR* »

Table 3 (Cont'd). Equations Estimating mGFR from Endogenous Filtration Markers With Large Representation of North Americans

Age	Marker	Reference Method	Standardized Assay	Derivation Study Characteristics	Equation	Comment
Creatinine and cystatin C ($eGFR_{cr\text{-}cys}$)						
Adult	CKD-EPI $eGFR_{cr\text{-}cys}$ (2012)[g]	Urinary iothalamate	Yes	3,107 men/2,245 women; mGFR 68 mL/min/1.73 m^2; age 47 y; 33% Black participants	$135 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-0.601} \times \min(Scys/0.8, 1)^{-0.375} \times \max(Scys/0.8, 1)^{-0.711} \times 0.995^{age} \times 0.969$ if female $\times 1.08$ if Black | $\alpha = -0.248$ (female); -0.207 (male); $\kappa = 0.7$ (female); $\kappa = 0.9$ (male)	Improved precision and accuracy vs CKD-EPI $eGFR_{cr}$ and $eGFR_{cys}$; recommended in adults as confirmatory test
Pediatric	CKiD $eGFR_{cr\text{-}cys}$ (2012)[h]	Plasma clearance of iohexol	No	389 boys/254 girls; mGFR 43 mL/min/1.73 m^2	$39.8 \times (height/Scr)^{0.456} \times (1.8/Scys)^{0.418} \times (30/SUN)^{0.079} \times (1.076^{male}) \times (height\ in\ m/1.4)^{0.179}$	Iohexol measurements have since been recalibrated; cystatin C assay not standardized

Table S1 displays equations developed by other research groups. Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CKiD, Chronic Kidney Disease in Children; eGFR, estimated glomerular filtration rate; $eGFR_{cr}$, eGFR from creatinine; $eGFR_{cr\text{-}cys}$, eGFR from a combination of creatinine and cystatin C; $eGFR_{cys}$, eGFR from cystatin C; mCL_{cr}, measured creatinine clearance; MDRD, Modification of Diet in Renal Disease; mGFR, measured glomerular filtration rate; Scr, serum creatinine (in mg/dL); Scys, serum cystatin C (in mg/L); SUN, serum urea nitrogen.

[a]Cockcroft and Gault, 1976 (*Nephron*. https://doi.org/10.1159/000180580).
[b]Levey et al, 2006 (*Ann Intern Med*. https://doi.org/10.7326/0003-4819-145-4-200608150-00004).
[c]Levey et al, 2009 (*Ann Intern Med*. https://doi.org/10.7326/0003-4819-150-9-200905050-00006); published correction appears at https://doi.org/10.7326/0003-4819-155-6-201109200-00024.
[d]Schwartz et al, 2009 (*J Am Soc Nephrol*. https://doi.org/10.1681/asn.2008030287).
[e]Ng et al, 2018 (*Kidney Int*. https://doi.org/10.1016/j.kint.2018.01.034).
[f]Pierce et al, 2021 (*Kidney Int*. https://doi.org/10.1016/j.kint.2020.10.047).
[g]Inker et al, 2012 (*N Engl J Med*. https://doi.org/10.1056/nejmoa1114248).
[h]Schwartz et al, 2012 (*Kidney Int*. https://doi.org/10.1038/ki.2012.169).

However all these equations estimating GFR are based on population with a large representation of North Americans

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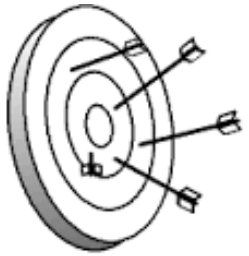
Relative performance of *eGFR* vs *mGFR*

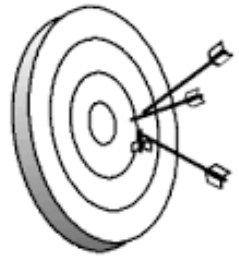
- The accuracy of GFR estimating equations is expressed as P30 , the percentage of eGFR values within 30% of the measured GFR

Estimating equation	Measured GFR reference methods	P_{30} (95% CI) (%)
MDRD[16]	Iothalamate	80.6 (79.5–82.0)
CKD-EPI creatinine[16]	Iothalamate	84.1 (83.0–85.3)
CKD-EPI cystatin C[17]	Iothalamate, iohexol, EDTA	84.2 (82.0–86.2)
CKD-EPI creatinine + cystatin C[17]	Iothalamate, iohexol, EDTA	91.9 (90.2–93.4)
Targeted metabolite panel estimated GFR[18]	Iothalamate, iohexol	96.3 (development) 98.1 (validation)



- Within-subject biological variation:
  - Similar in mGFR and eGFR
  - → no disadvantage to the use of simple estimates of GFR when monitoring patients over time

GFR measure or estimate	Within-subject biological variation (95% CI) (%)
Iohexol	6.7 (5.6–8.2)
MDRD	5.0 (4.3–6.1)
CKD-EPI creatinine	5.3 (4.5–6.4)
CKD-EPI cystatin C	5.3 (4.5–6.5)
CKD-EPI creatinine + cystatin C	5.0 (4.3–6.2)



Malyszko Kidney int 2020

When to prefer « mGFR » instead of « eGFR »?

- **In clinical scenarios and conditions where the use of creatinine-based estimating equations may not be valid…**
  - Regardless of the specific equation, the accuracy of eGFRcr or eGFRcys are limited by variation in GFR determinants of serum creatinine or cystatin that are not captured by the demographic and clinical variables.
- **To guide critical clinical decisions….**
  - Drugs with narrow therapeutic index
  - Kidney donation…

The ***Kidney Disease Improving Global Outcomes*** (**KDIGO**) guidelines suggest measuring the glomerular filtration rate (GFR) using an exogenous filtration marker 'under circumstances in which **more accurate** ascertainment of GFR will impact **treatment decisions**

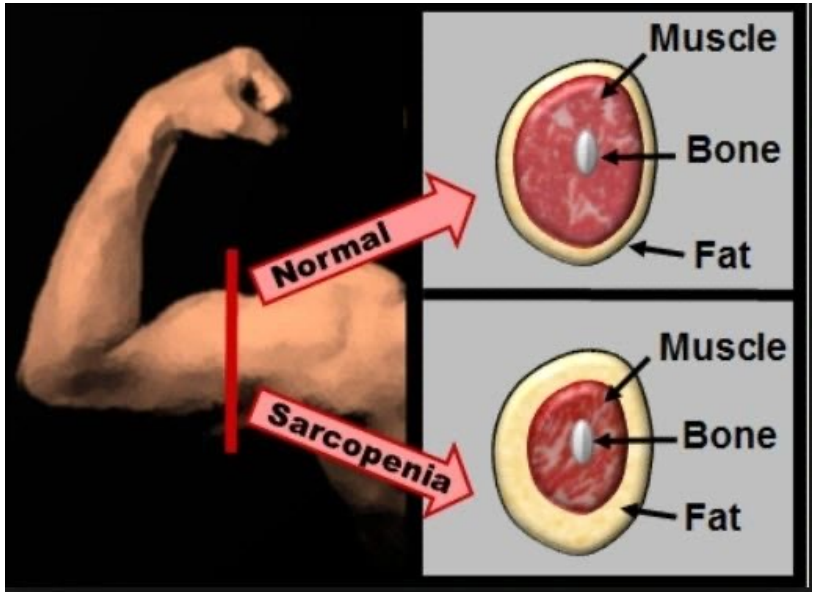
The ***European Medicines Agency*** (EMA) recommend that a method that accurately measures GFR using an exogenous marker should be used in **pharmacokinetic studies** in subjects with decreased kidney function.

Effect of body compostition

- eGFR equations were developed and validated in individuals with predominantly « ***normal*** **» body composition**.

→ Therefore eGFR equations are « not validated » in many special circumstances…
  - Extreme body composition
    - Reduction in muscle mass
    - Obesity

Reduction in muscle mass



- Creatinine originates from muscle metabolism
  - Sarcopaenia
  - Anorexia nervosa
  - Muscle dystrophy
  - Limb amputation
  - Neuromuscular disease
  - Paraplegia
  - Spina bifida
  - Cachexia
  - Malignancy
  - Chronic inflammatory disease

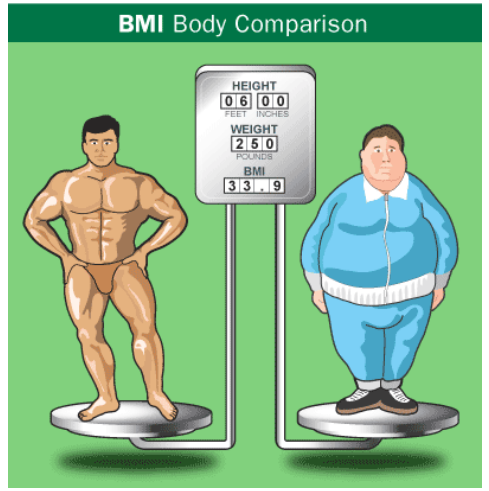
→ serum creatinine concentrations are lower

→ eGFR falsely elevated (when based on serum creatinine)

- Cystatin C has been shown to have greater accuracy in these conditions but is still inferior to mGFR

Obesity

- Obesity prevalence is increasing worldwide
- $eGFR_{cr}$ equations may overestimate GFR
  - Reduced muscle mass
- $eGFR_{cys}$ equation underestimates GFR
  - Positive association between cys C and greater fat mass.
  - Indexation to body surface area (BSA) instead of 1.73m2 may provide more accurate estimation of GFR ?
- Due to the discordant bias of both equations, the combined eGFRcre+cysC CKD-EPI equation yielded the least bias and was suggested as the most suitable equation in this setting



- **Almost all eGFR equations report GFR results indexed to the 'average' BSA of 1.73m2, which can lead to further systematic incorrectness**

→Use mGFR when critical decisions have to be made regarding treatment in advanced CKD:

dosing of potentially nephrotoxic drugs/ with a narrow therapeutic index and critical renal elimination.

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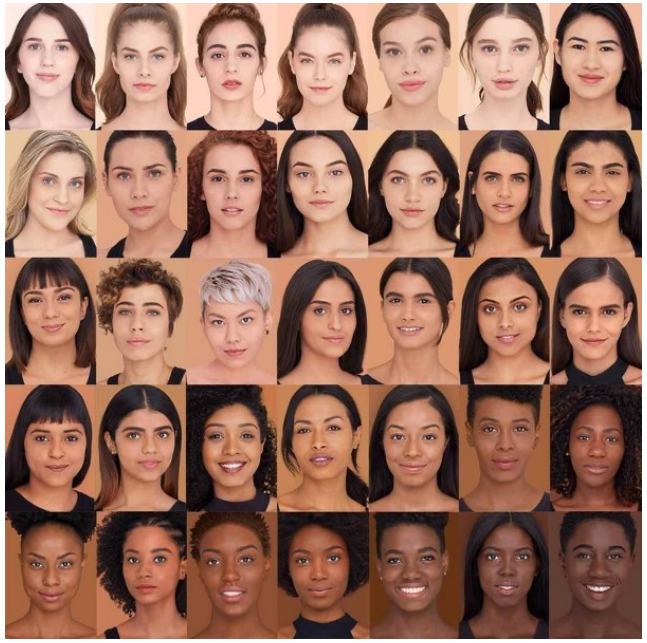
« *Race* »

- The CKD-EPI equations offer a version (2009 ><2012) where « race » is integrated as a coefficient for *African Americans*.
  - Applying the CKD- EPI race equation leads to ‘corrected’, (higher GFR) values in Black
  - Blacks had a systematically 16-20% higher serum creatinine compared with white patients at a similar mGFR (MDRD and CKD-EPI datasets)
  - Finding was thought to reflect biological differences related to non-GFR determinants of serum creatinine
    - Greater muscle mass in Blacks ? Probably not only…
    - The cause of the higher serum creatinine in the Black individuals is not well understood
      - Tubular secretion or creatinine generation.

?

« *Race* »

- However, the construct of « race » is problematic for several reasons…
  - There is no biological ground for race
  - The « race coefficient » ignores the substantial variability among Black patients… There is no « African American prototype »



- In a pair-matched analysis of 604 African Europeans and White Europeans from the Nephro Test cohort, serum creatinine in African Europeans was only 8% higher as compared with White patients at a similar mGFR
- The CKD-EPI race equation does not perform well in black living ouside the USA (Congo and Ivory Coast)
- There are also questions whether coefficients for eGFRcr for race or *ethnic groups* other than Black people are required.
  - Asian ?
  - In Japan, a modified CKD-EPI creatinine equation is used that applies a correction factor of 0.813

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« Race »

Should we eliminate the term for « Black race » when using eGFR equations ?

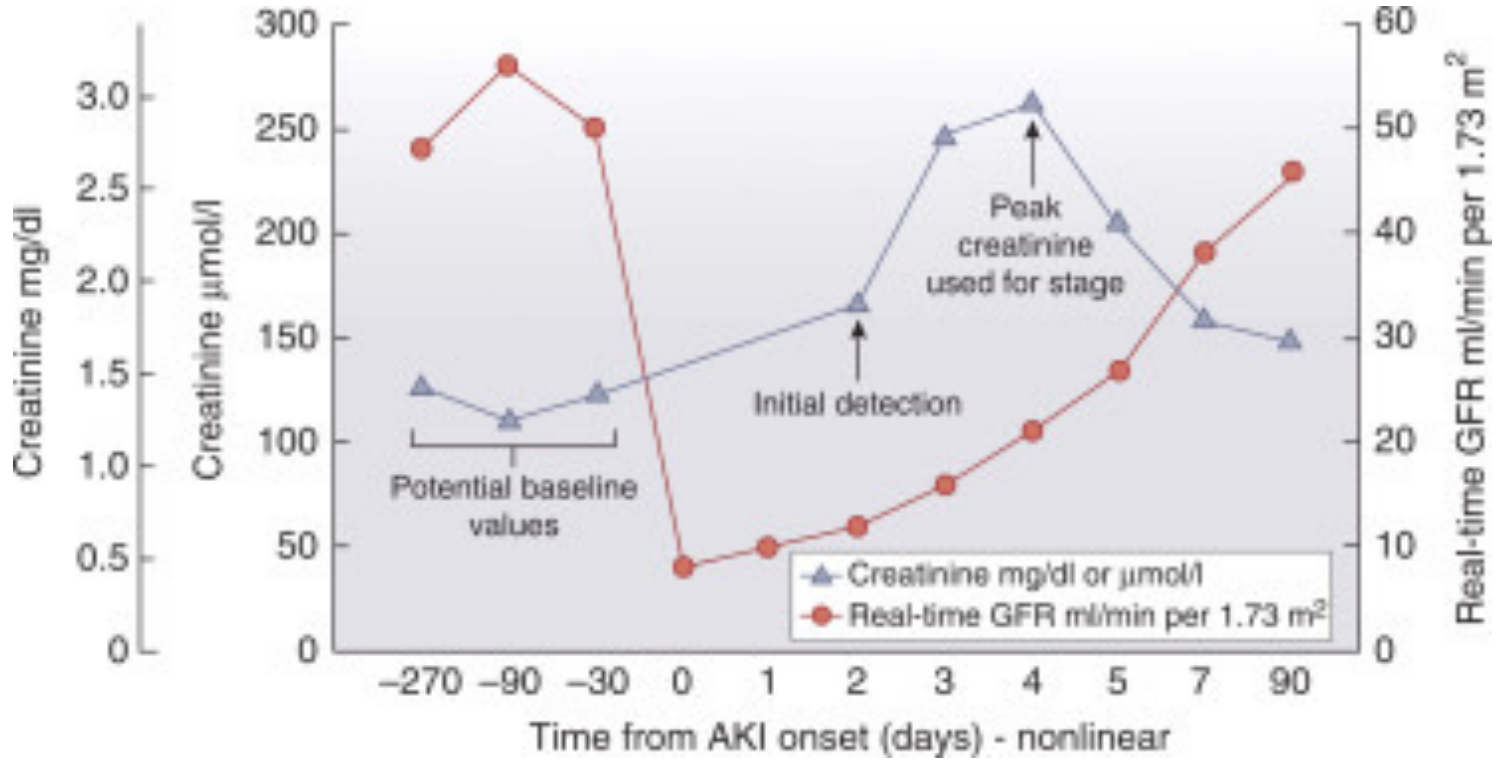
- *Its removal would lead to lower eGFR in some patients who self-identify as Black…*
- For example, if a 60-year-old man had a creatinine level of 1.0 mg/dL, he would have a eGFRcr of 94 mL/min/1.73 m2 if he self-identified as Black and a eGFRcr of 81 mL/min/ 1.73 m2 if he self-identified as White.

- Advantages of « lower eGFR »
  - Earlier care for CKD
  - Earlier kidney transplant evaluations.
- Disadvantages
  - Decrease the use of some medications ie chemotherapy
  - Insurance more expensive
  - Decrease acceptance of kidney donor candidates

→ **Better methods are needed to improve the accuracy of GFR assessment without requiring specification of race (mGFR)**

AKI

- An acute change in GFR would cause any serum levels of endogenous filtration markers to be in nonsteady state, with a **lag** until the serum levels increase to match the change in GFR. The converse is true for recovery from AKI.



Liver cirrhosis

- The inaccuracy of MDRD or CKD-EPI equations in cirrhosis is well described
- Significant overestimation of the GFR
- Due to the presence of non-GFR determinants that affect serum creatinine concentration
  - Decreased muscle mass
  - Malnutrition
  - Hepatic dysfunction
  - Bilirubin → interference with creatinine assay

- Better GFR estimation using cystatin C ?
  - Potential liver transplant recipients
  - Urinary inulin clearance as the gold-standard mGFR
  - CKD-EPI$_{cys}$ equation underestimated the mGFR by 4 mL/min/1.73 m2
  - CKD-EPI$_{cr}$ equation overestimated the mGFR by 18.4mL/min/ 1.73m2.
  - 83 % of CKD-EPI$_{cys}$ estimates were within 30% of the inulin mGFR versus only 56% of CKD-EPI$_{cr}$ estimates
- Other studies have not demonstrated the superiority of CKD-EPI$_{cys}$ in cirrhotic patients

→ Clinical indications for mGFR measurement in cirrhosis include :
medication dosing
the assessment of potential combined liver–kidney transplantation.

Cystatin C–based equations may be considered as a reasonable alternative.

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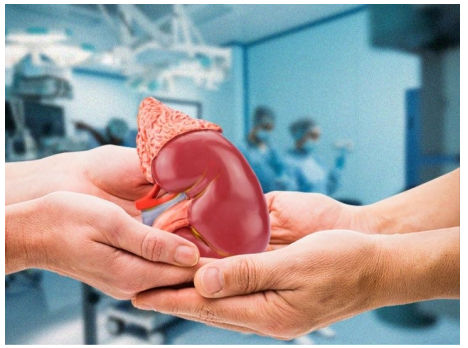
Evaluation of living kidney donor



- Evaluation of GFR is a cornerstone in the management of living kidney donors
  - Before and after Tx (follow-up after donation)
- GFR assessment must provide robust results to authorize donation safely
  - Guidelines recognize mGFR as the gold standard (however not mandatory…)
- The question of whether to use eGFR or mGFR significantly impacts the decision to authorize donation
  - In a cohort of 2733 potential living kidney donors in France, creatinine-based eGFR and mGFR were discordant in 26% of the candidates at the threshold of 90mL/min/ 1.73 m2.
  - Poor performance in older donor, lower GFR, obese donor
  - → higher risk of subsequent end-stage kidney disease
- **mGFR** should be encouraged in the evaluation of living kidney donor

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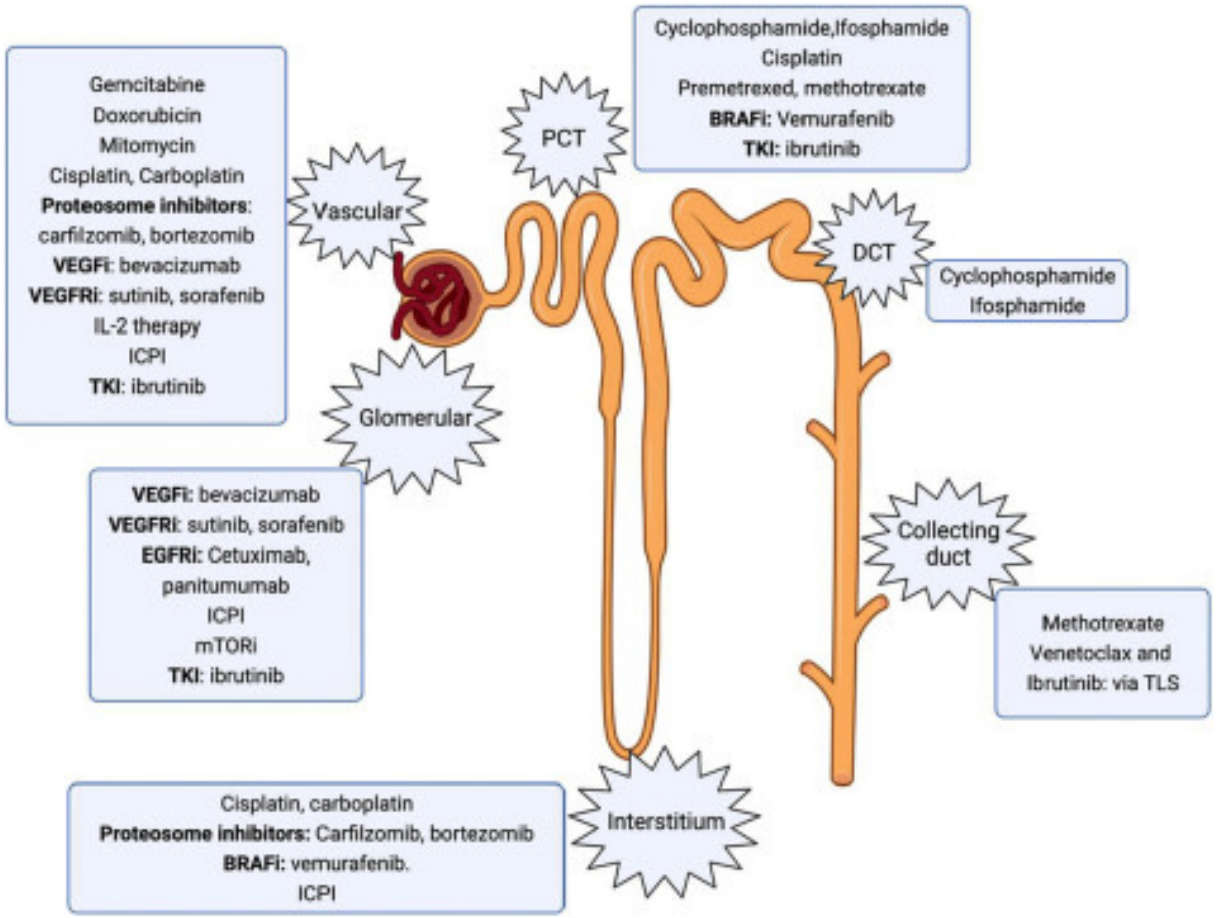
Patients with cancer

- Cachectics/ sarcopenics
- Older patients
- Unstable body weight
- Liver disease
- At high risk of AKI
- Treated with chemotherapeutic agents with a narrow therapeutic index
  - Excreted by the kidney
  - Overdosing with secondary effects (AKI or other…)
  - Underdosing with an ineffective treatment with therapeutic failure and relapse

→ **Thus, in this specific population, a precise assessment of GFR is particularly important**



Take home messages

- Glomerular filtration is only one of the many functions of the kidney.
- No « strict » correlation between GFR and renal mass
  - Hyperfiltration and AKI due to functional cause (hypoperfusion)
- Creatinine and cystatine C are the most widely marker used to estimate GFR
  - These markers have many pitfalls and are imprecise
  - It is not possible to estimate GFR during AKI with creatinine
- Situation when it is important to estimate **accurately** renal function are limited
  - To guide critical clinical decisions where eGFR equation perform poorly
    - Drugs with narrow therapeutic index (chemotherapy)
    - Kidney donor evaluation
  - Research purpose
  - When there is discrepency between clinic and eGFR (CKD-EPI)

- Creatinine + cystatine C (CKD-EPI$_{cys\text{-}Cr}$) based equations should be encouraged