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The Evolution of GFR Estimation: An update as of December 2021

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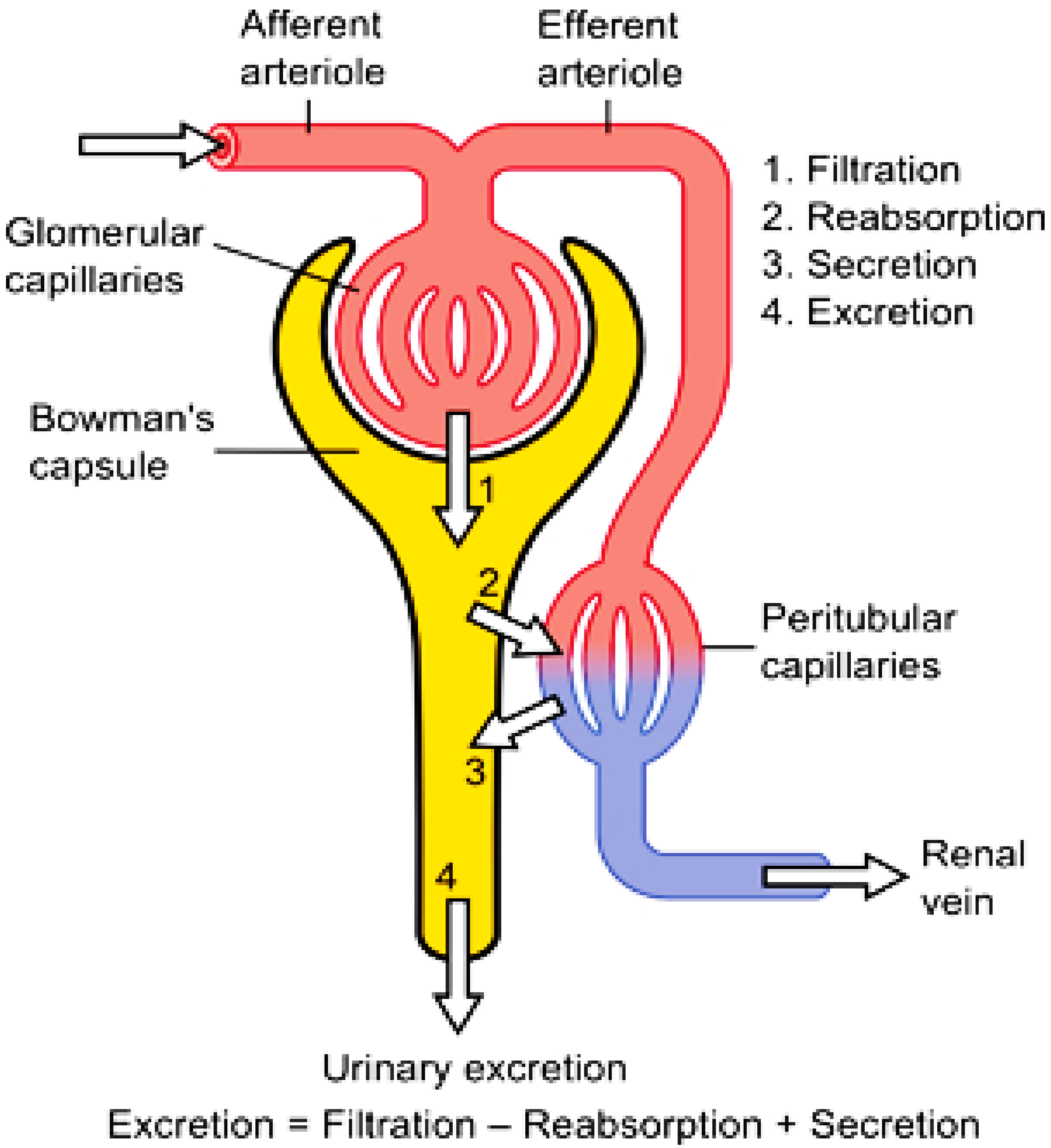
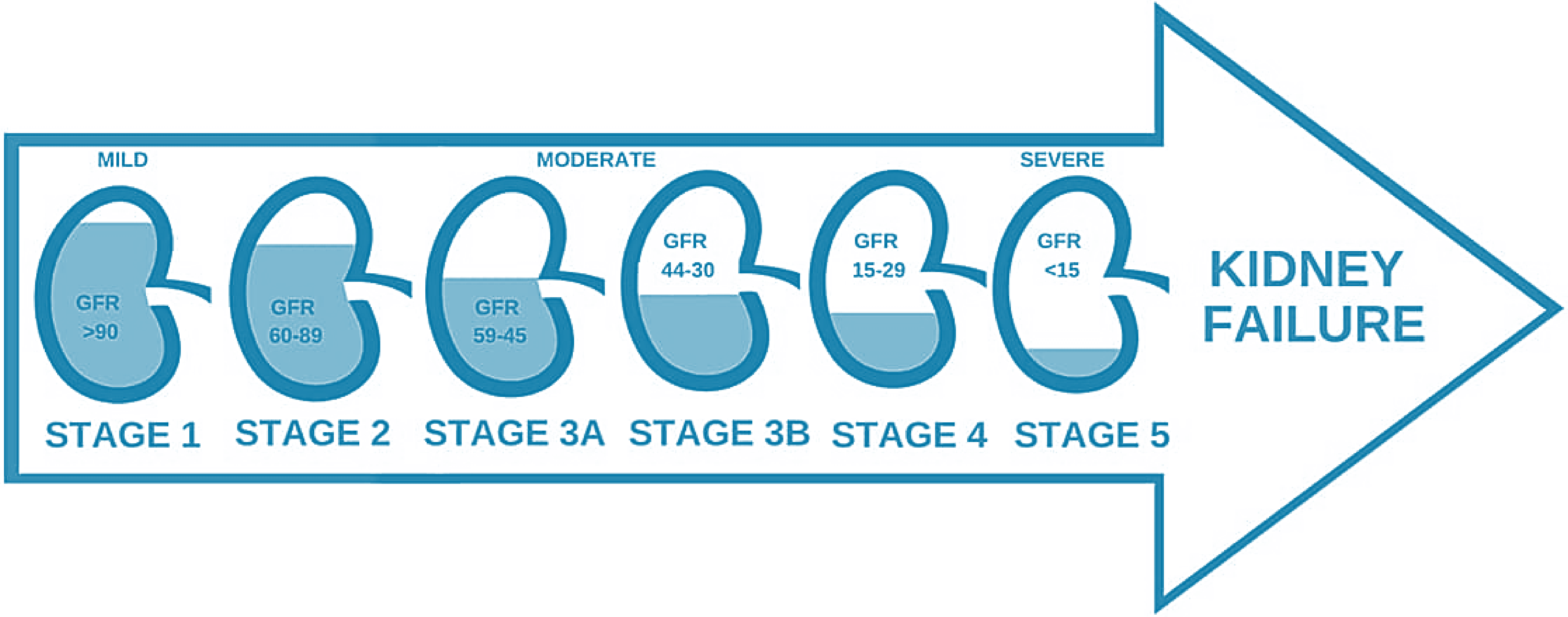
What is the Glomerular Filtration Rate (GFR) and why do we care about it?

- GFR is the volume of plasma filtered through the glomeruli per unit time
- The kidneys perform their myriad tasks on this filtrate
- Reflects the total number of functioning glomeruli and is therefore the best way to assess kidney function in health and disease



CKD, chronic kidney disease; GFR, glomerular filtration rate
Assessment of Kidney Function - UpToDate, Lesley A Inker, Ronald D Perrone: https://www.uptodate.com/contents/assessment-of-kidney-function

Stages of Kidney Disease



GFR, glomerular filtration rate

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The GFR has many uses…

- To define CKD (less than 60 ml/min for 3 months)
- To stage CKD (e.g., 59–45, 44–30, 29–15, <15 ml/min)
- To monitor rates of progression of CKD
- To dose adjust medications and make other treatment decisions
- To prognosticate outcomes in patients with CKD
- It is the primary indicator of renal function used in clinical practice guidelines (e.g. the National Kidney Foundation's Kidney Disease Quality Initiative (K/DOQI) clinical practice guidelines)

CKD, chronic kidney disease; GFR, glomerular filtration rate

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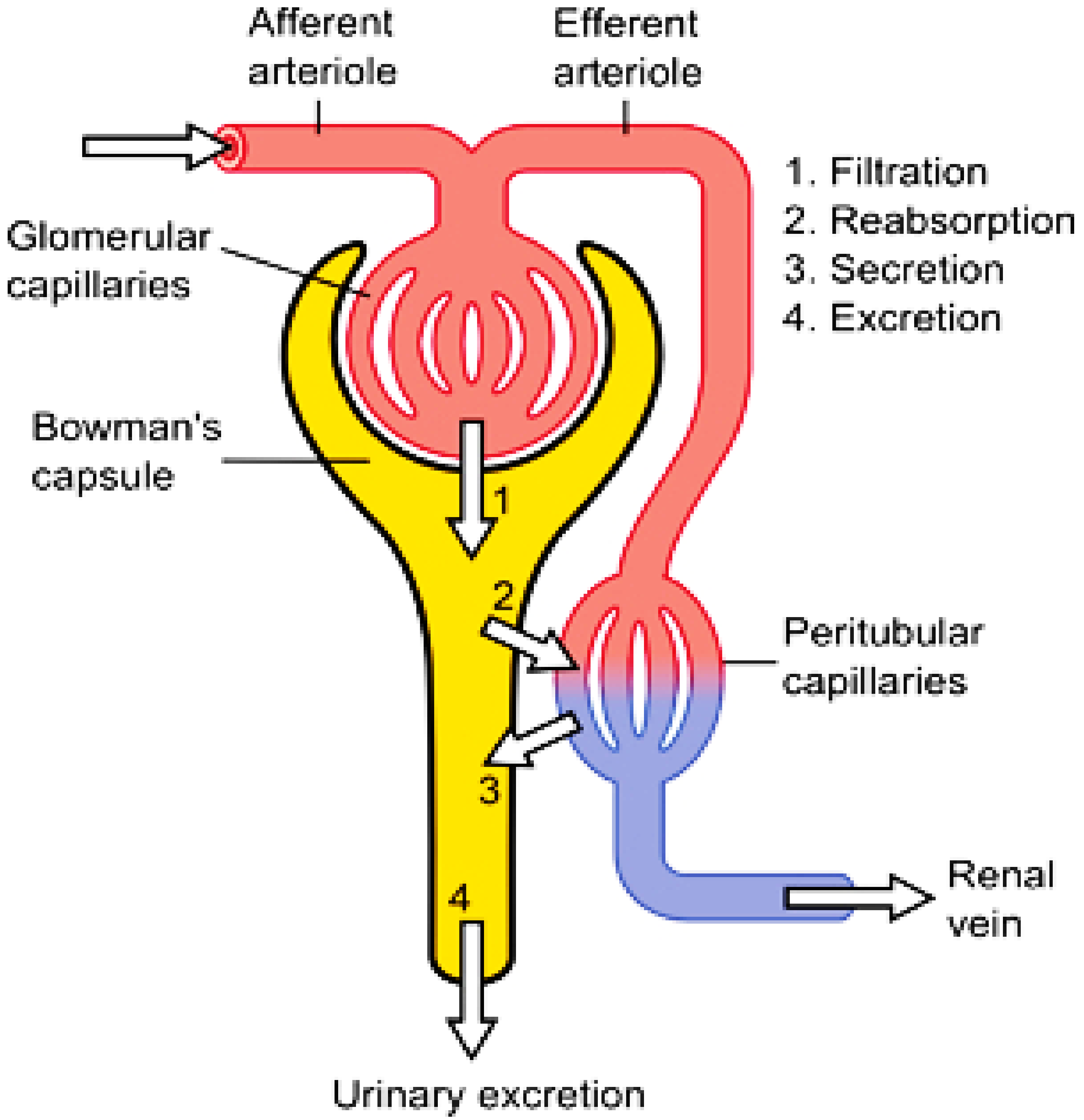
Stage of Kidney Disease NKDEP Classification

Normal	Healthy kidneys GFR > 90 mL/min per 1.73 m^2
Stage 1	Kidney damage with normal or elevated GFR GFR > 90 mL/min per 1.73 m^2
Stage 2	Kidney damage and mild decrease in GFR GFR of 60 - 89 mL/min per 1.73 m^2
Stage 3 a/b	Moderate decrease in GFR GFR of 30-44 / 45-59 mL/min per 1.73 m^2
Stage 4	Severe decrease in GFR GFR 15 - 29 mL/min per 1.73 m^2
Stage 5	Kidney failure - ESRD GFR of <15 mL/min per 1.73 m^2

ESRD, end-stage renal disease; GFR, glomerular filtration rate; NKDEP, National Kidney Disease Education Program

GFR vs solute clearance



Excretion = Filtration – Reabsorption + Secretion

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Solute Clearance

- GFR is indirectly measured by the volume of plasma that is cleared of an ideal solute by the kidneys per unit time
- Ideal solutes have a constant rate of appearance in the blood, are freely filtered by the glomerulus, and are neither reabsorbed nor secreted by the tubules
- The only ideal solutes are exogenous and administered in a research setting (e.g., inulin and 125I-iothalamate)
- Creatinine clearance is the most widely used endogenous solute clearance, but is not ideal as creatinine does not have a constant rate of appearance (e.g., reduced in muscle wasting states), and is secreted by the proximal tubule
- Cystatin represents another endogenous solute that is renally-cleared* and which has a more constant rate of appearance

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Cystatin C as a GFR Marker

- Cystatin C is a small 13 kDa protein that is a member of the cysteine proteinase inhibitor family that is produced at a constant rate by all nucleated cells
- Due to its small size & positive charge at physiological pH, it is freely filtered by the glomerulus, and is not secreted but is fully reabsorbed and catabolized in proximal renal tubules
- This means the primary determinate of blood Cystatin C levels is the rate at which it is filtered at the glomerulus making it an excellent GFR marker
- **Normal serum Cystatin C values range from 0.6 to 1.0 mg/L**

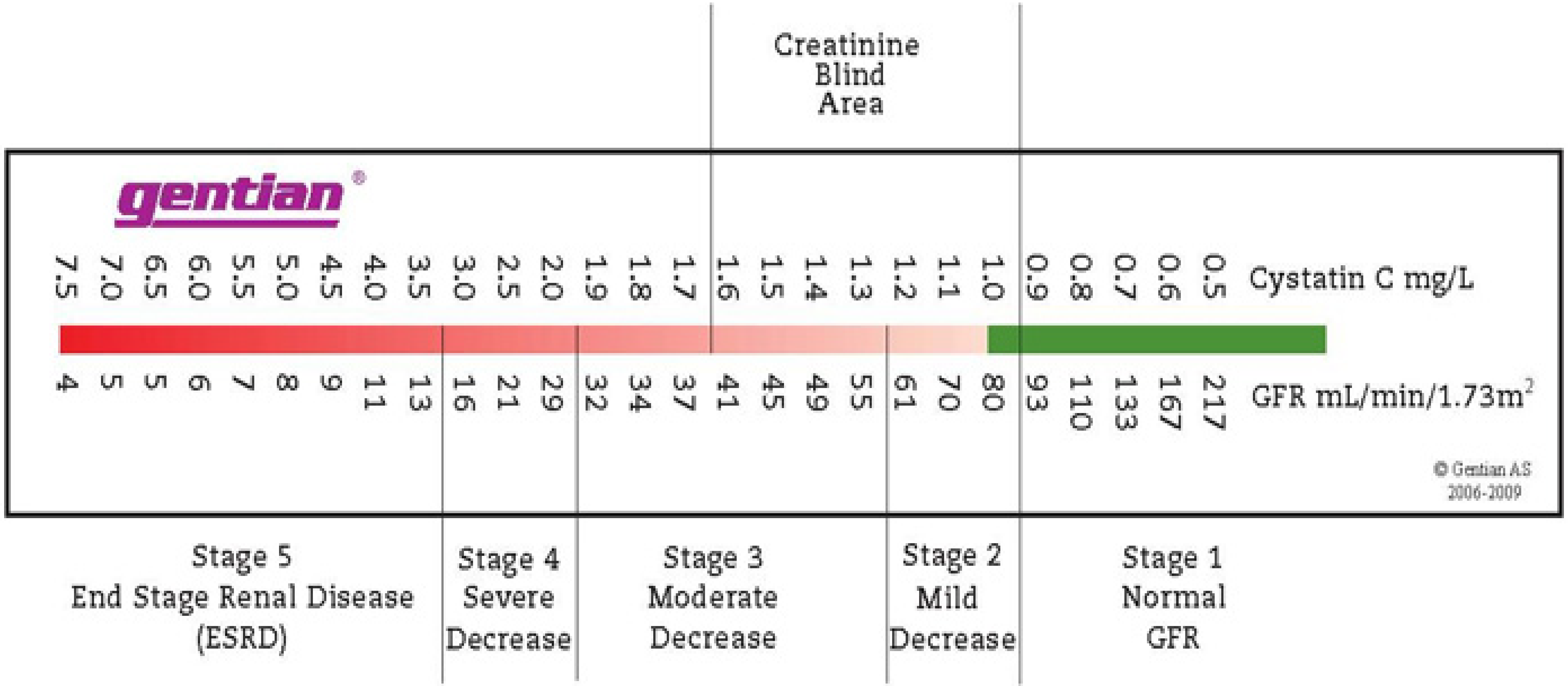
GFR, glomerular filtration rate

Cystatin C as a GFR Marker

- Unlike creatinine, Cystatin C serum levels are virtually unaffected by age (>1 yr), muscle mass, gender, and race
- A number of very simple formulas have been introduced which can be used to obtain an estimated GFR using Cystatin C
- Multiple studies have found Cystatin C to be more sensitive to actual changes in GFR in the early stages of CKD than creatinine based GFR estimates
- A significant advantage of Cystatin C based formulas, unlike creatinine-based equations, is that Cystatin C based estimated GFR formulas are not biased according to GFR and there is no GFR blind area with Cystatin C

CKD, chronic kidney disease; GFR, glomerular filtration rate

Cystatin C & Stages of CKD



CKD, chronic kidney disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate

Measured Versus Estimated GFR

Measurements of GFR are:

- Time consuming
- Cumbersome
- Expensive (especially for exogenous solute clearance assays)
- Restricted

- Estimations of GFR are designed to be:
  - Quick
  - Easy
  - Affordable
  - Widely available
- Based on serum concentrations of endogenous solutes (such as creatinine and cystatin)

GFR, glomerular filtration rate

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Challenges with GFR Estimation

- Based on endogenous solutes and their inherent limitations
- Creatinine, which is produced by muscle, varies according to race, sex, and age in GFR-independent ways
- Cystatin, which is produced by all nucleated cells, is increased in high-turnover states, use of corticosteroids, and in hyperthyroidism
- GFR estimation equations should ideally be useful across the spectrum of GFR (i.e., no inaccuracies or **blind spots** at any point in this continuum), and across all populations/demographics

GFR, glomerular filtration rate

Levy AS, Titan SM, Powe NR, Coresh J, Inker LA : Kidney Disease, Race and GFR estimation; Clin J Am Soc Nephrol 15: 1203-1212, 2020

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Key Developments in the Evolution of GFR Estimation

- Came from studies that derived equations for GFR's that predicted measured GFR's
  - Cockcroft-Gault 1976 (249 males, measured GFR used non-standardized creatinine)
  - MDRD 1999 (840 patients with CKD, measured GFR used exogeneous solute)
  - CKD-EPI creat 2009 (8,254 participants with and without CKD)
  - CKD-EPI cystatin and creat-cystatin 2012 (5,352 participants with and without CKD)
  - CKD-EPI creat, cystatin, creat-cyst 2021 (4,050 participants with and without CKD)

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease
Levy AS, Titan SM, Powe NR, Coresh J, Inker LA : Kidney Disease, Race and GFR estimation; Clin J Am Soc Nephrol 15: 1203-1212, 2020

The Cockcroft-Gault Equation

Calculation of estimated creatinine clearance (ml/min) according to the Cockcroft-Gault equation =

$$\frac{[140 - \text{age (years)}] \times \text{ideal weight (kg)}}{[\text{serum creatinine (mg/dl)}] \times 72} \quad \times 0.85 \text{ if female}$$

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41. doi:10.1159/000180580

The Modification of Diet in Renal Disease (MDRD) Equation

MDRD estimated creatinine clearance (ml/min/1.73m^2) =

175 x [serum creatinine (mg/dl)]$^{-1.154}$ x [age (years)]$^{-0.203}$ x [0.742 if female] x [1.21 if black]

Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130(6):461-470. doi:10.7326/0003-4819-130-6-199903160-00002

The CKD-EPI Consortium

"The CKD Epidemiology Collaboration (CKD-EPI) is a research group with major interests in measurement and estimation of GFR (CKD-EPI GFR)"

CKD-EPI estimated creatinine clearance ($ml/min/1.73m^2$) =

$141 \times \min[SCr\ (mg/dl)/kappa, 1]^{\alpha} \times \max[SCr\ (mg/dl)/K, 1]^{-0.209} \times 0.993^{Age} \times Sex \times Race$

For female: Sex=1.018; alpha=-0.329; kappa=0.7

For male: Sex=1; alpha=-0.411; kappa=0.9

CKD-EPI cystatin C equation ($ml/min/1.73m^2$) =

$133 \times \min[Scys/0.8, 1)^{-0.499} \times \max\ [Scys/0.8, 1)^{-1.328} \times 0.996^{Age} \times 0.932$ if female

CKD-EPI, CKD Epidemiology Collaboration; GFR, glomerular filtration rate

1. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5;150(9):604-12. doi: 10.7326/0003-4819-150-9-200905050-00006.
2. Inker LA, Eckfeldt J, Levey AS, et al. Expressing the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) cystatin C equations for estimating GFR with standardized serum cystatin C values. Am J Kidney Dis 2011;58:682-4.

CKD EPI: Creatinine + Cystatin C Equation (2012)

"Combined creatinine–cystatin C equations perform better than equations based on either of these markers alone"

CKD-EPI creatinine–cystatin C equation (ml/min/1.73m^2) =

$$135 \times \min[\text{SCr (mg/dl)}/\text{kappa}, 1]^{\alpha} \times \max[\text{SCr (mg/dl)}/\kappa, 1]^{-0.601} \times \text{Min}[\text{SCys}/0.8, 1]^{-0.375} \times \max[\text{SCys}/0.8, 1]^{-0.711} \times 0.995^{\text{Age}} \times 0.969 \text{ if female} \times 1.08 \text{ if Black}$$

For female: alpha=-0.248; kappa=0.7

For male: Sex=1; alpha=-0.207; kappa=0.09

CKD-EPI, CKD Epidemiology Collaboration; GFR, glomerular filtration rate; Scr, serum creatinine; Scys, serum cystatin C

Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C [published correction appears in N Engl J Med. 2012 Aug 16;367(7):681] [published correction appears in N Engl J Med. 2012 Nov 22;367(21):2060]. *N Engl J Med.* 2012;367(1):20-29. doi:10.1056/NEJMoa1114248

Revised CKD-EPI Creatinine + Cystatin C Equation (2021)

"New eGFR equations that incorporate creatinine and cystatin C but omit race are more accurate and lead to smaller differences between Black participants and non-Black participants than new equations without race with either creatinine or cystatin C alone"

Gender	Scr (mg/dL)	Scys (mg/L)	Equation (mL/min/1.73 m^2)
Female	≤0.7	≤0.8	$130 \times (Scr/0.7)^{-0.248} \times (Scys/0.8)^{-0.375} \times 0.995^{age}$
		>0.8	$130 \times (Scr/0.7)^{-0.248} \times (Scys/0.8)^{-0.711} \times 0.995^{age}$
	>0.7	≤0.8	$130 \times (Scr/0.7)^{-0.601} \times (Scys/0.8)^{-0.375} \times 0.995^{age}$
		>0.8	$130 \times (Scr/0.7)^{-0.601} \times (Scys/0.8)^{-0.711} \times 0.995^{age}$
Male	≤0.9	≤0.8	$135 \times (Scr/0.9)^{-0.207} \times (Scys/0.8)^{-0.375} \times 0.995^{age}$
		>0.8	$135 \times (Scr/0.9)^{-0.207} \times (Scys/0.8)^{-0.711} \times 0.995^{age}$
	>0.9	≤0.8	$135 \times (Scr/0.9)^{-0.601} \times (Scys/0.8)^{-0.375} \times 0.995^{age}$
		>0.8	$135 \times (Scr/0.9)^{-0.601} \times (Scys/0.8)^{-0.711} \times 0.995^{age}$

CKD-EPI, CKD Epidemiology Collaboration; GFR, glomerular filtration rate

Inker LA, Eneanya ND, Coresh J, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. *N Engl J Med*. 2021;385(19):1737-1749. doi:10.1056/NEJMoa2102953

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Summary Timeline

1973
Cockcroft-Gault

1999
MDRD

2009
CKD-EPI creatinine 2009

2012
CKD-EPI cystatin
CKD-EPI creatinine + cystatin

2021
Revised CKD-EPI creatinine + cystatin - race

Remaining Challenges

- Translating the latest findings into clinical practice here in Ontario
- Getting laboratories to incorporate these findings into their reports
- Educating other healthcare providers about these advances in order to streamline referral and management practices

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