2021 ACOI Annual Convention
And Scientific Sessions
October 27-30

Glomerular Filtration Rate and the Diverse Population

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Disclosures

- I have no financial interests or relationships to disclose


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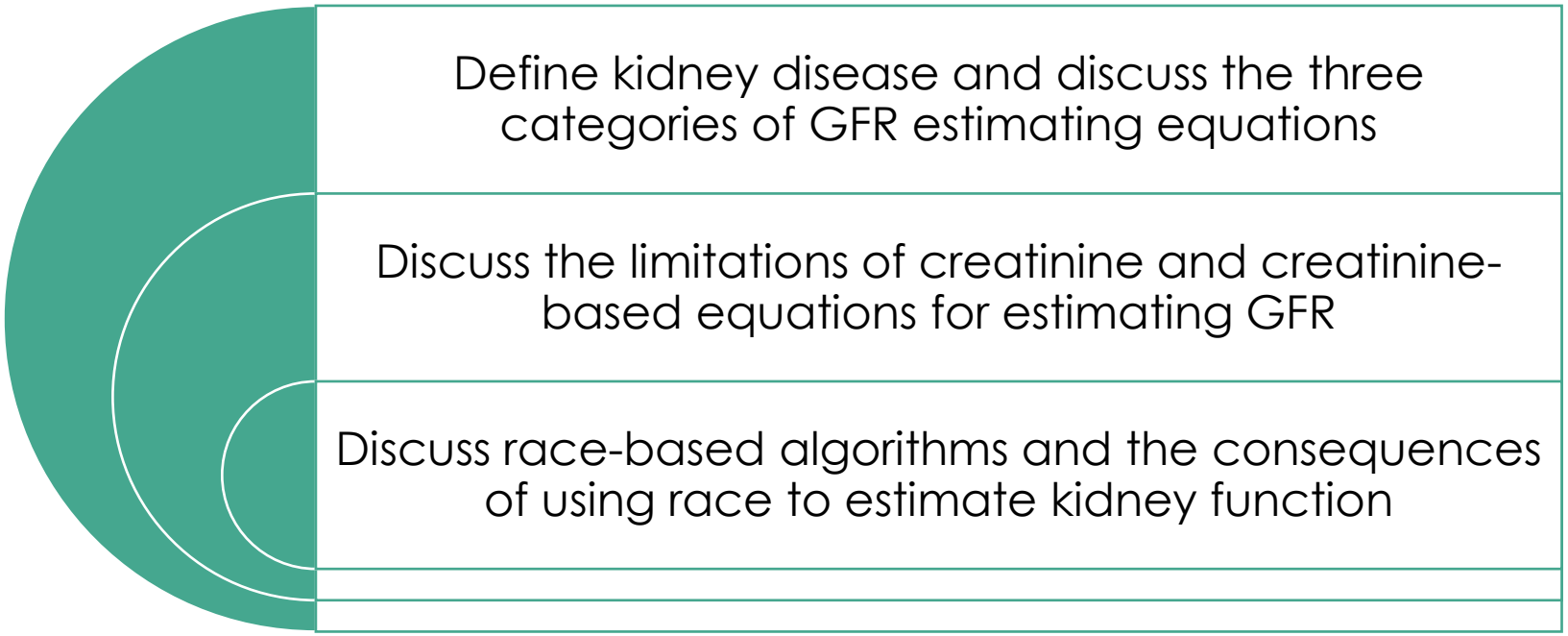
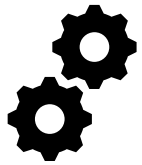
The good physician treats the disease; the great physician treats the patient who has the disease.
William Osler

Educational Objectives



Icon Legend

Know 

Think about it 

Further reading recommended 

Normal Kidney Physiology

- Maintenance of constant extracellular environment
  - Excretion of some of the waste products of metabolism
    - Urea, creatinine, uric acid
    - Excretion of water and electrolytes to match net intake and endogenous production
    - Regulate individually the excretion of water, sodium, potassium, hydrogen
      - Changed in tubular reabsorption or secretion
- Secretes hormones
  - Regulation of systemic and renal hemodynamics- Renin, prostaglandins, and bradykinin
  - Red blood cell production- erythropoietin
  - Calcium, phosphorus, and bone metabolism- 1,25-dihydroxyvitamin D3 or calcitriol

Chronic Kidney disease

- CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health AND
- CKD is classified based on cause, GFR category, and albuminuria category (CGA).

- GFR- identifies the problem
- Cause requires further evaluation- urinalysis, measurement of urine protein excretion, radiologic studies, kidney biopsy

KDIGO 2012 CKD

Chronic Kidney Disease, cont.

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1 Normal to mildly increased	A2 Moderately increased	A3 Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

KDIGO 2012 CKD

Why Test Renal Function?

TABLE 1: CLINICAL CONDITIONS WHERE ASSESSMENT OF GFR IS IMPORTANT*		
CLINICAL DECISIONS	**CURRENT LEVEL OF GFR**	**CHANGE IN LEVEL OF GFR**
Diagnosis	• Detection of CKD • Evaluation for kidney donation	• Detection of AKI • Detection of CKD progression
Prognosis	• Risk of CKD complications • Risk for CVD • Risk for mortality	• Risk for kidney failure
Treatment	• Dosage and monitoring for medications cleared by the kidney • Determine safety of diagnostic tests or procedures • Referral to nephrologists • Referral for kidney transplantation • Placement of dialysis access	• Treatment of AKI • Monitoring drug toxicity

Abbreviations: AKI: acute kidney injury; CKD: chronic kidney disease; CVD: cardiovascular disease.

*Reprinted with permission from the American Society of Nephrology via the Copyright Clearance Center. Stevens LA, Levey AS. *J Am Soc Nephrol*. 2009;20:2305-2313.

Reprinted, J Am Soc Nephrol. 2009; 20:2305-2313

Measuring vs Estimating GFR

- What is an ideal marker for GFR measurement?
  - Constant rate of production or delivered at a constant rate
  - Freely filterable at the glomerulus
  - No tubular reabsorption
  - No tubular excretion
  - No extrarenal elimination or metabolism
- Exogenous markers to measure GFR
- Marker substances:
  - Inulin (gold standard)
  - Iothalamate
- Endogenous markers to estimate GFR
  - Creatinine
  - Urea
  - Cystatin C
  - metabolism

GFR Estimation

- Clearance (C)
  - The rate at which an indicator substance is removed from plasma per unit concentration; a volume from which all of a substance is removed per unit time

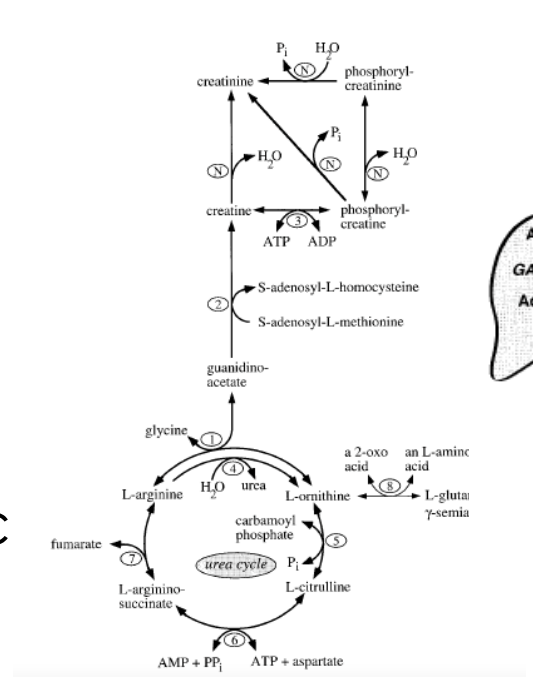
$$C_z = U_z V / P_z$$

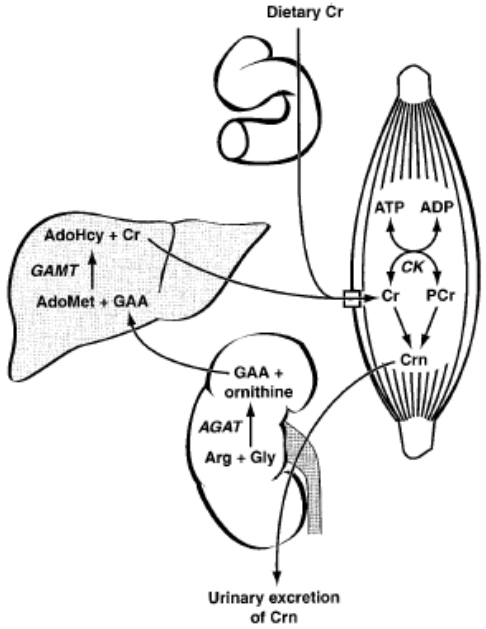
- If a substance is freely filtered and only excreted by GFR, then

$$GFR = U_z V / P_z$$

Creatinine

- Endogenous marker used to estimate GFR
- Metabolism
  - Generated in muscle by nonenzymatic conversion of creatine and phosphocreatine
  - Generation is proportional to muscle mass
  - Liver plays important role in formation of creatinine through methylation of guanidine aminoacetic acid





Physiological Reviews, Vol. 80. No 3. July 2000

AJKD, Vol 47, No 1 (January), 2006: pp 174-183

Factors Affecting sCr

- Increase sCr
  - Ketotic states, hyperglycemia (Jaffé)*
  - Cephalosporins (Jaffé)*
  - Flucytosine (enzymatic method)*
  - Cimetidine, trimethoprim (block secretion)
  - Vigorous exercise
  - Ingesting cooked meats
- Decrease sCr
  - Dietary protein restriction
  - Muscle wasting, malnutrition
  - Bilirubin (Jaffé)*
  - Renal disease
  - Advanced age
  - Female sex
  - Advanced liver disease

* These factors affect the measurement process directly

AJKD, Vol 47, No 1 (January), 2006: pp 174-183

Equations for Estimating GFR_{ADULTS}

- Creatinine-based equations
- Cystatin C-based equations
- Creatinine-cystatin C equations

- Cystatin C is an endogenous marker with less factors than sCr that affect the serum level
  - *most but not all studies show that serum cystatin C is better index of GFR than sCr alone

Equations for Estimating GFR_{ADULTS}

- Creatinine-based equations
  - Cockroft-Gault
  - Modification of Diet in Renal Disease (MDRD)
  - Chronic Kidney Disease Epidemiology (CKD-EPI)
- Cystatin C-based equations
  - CKD-EPI Cystatin C equation 2012
- Creatinine-cystatin C equations
  - CKD-EPI Creatinine-Cystatin C equation 2012

Cockroft-Gault

- Original equation paper: https://ncbi.nlm.nih.gov/pubmed/1244564 , Nephron, 1976
- C_{Cr}={((140-age) x weight)/(72xS_{Cr})} x 0.85 (if female)

- Abbreviations/ Units
  - C_{Cr} (creatinine clearance) = mL/minute
  - Age = years
  - Weight = kg
  - SCr (serum creatinine) = mg/dL

Cockroft-Gault

- This formula assumes that creatinine production decreases with advancing age and is greater in individuals with greater weight
- The equation is not adjusted for body surface area
- Equation was developed prior to the use of standardized creatinine assays
- Use with creatinine values measured by most labs in the US today will result in a 10-40% overestimate of creatinine clearance

Modification of Diet in Renal Disease (MDRD) Study Equation

- Original equation paper: https://www.ncbi.nlm.nih.gov/pubmed/10075613, Annals of IM, 1999
- $sGFR = 175 \times (S_{Cr})^{-1.154} \times (age)^{-0.203} \times 0.742$ (if female) x 1.212 (if Black)

- Abbreviations / Units
  - eGFR (estimated glomerular filtration rate) = mL/min/1.73 m^2
  - S_{cr} (standardized serum creatinine) = mg/dL
  - age = years

Modification of Diet in Renal Disease (MDRD) Study Equation

- More accurate than measured creatinine clearance from 24-hour urine collection
- MDRD study equation was derived from primarily white subjects
  - Not validated across diverse ethnic populations, in patients >60 years or <18 years, those with diabetes
- May underestimate GFR in stage 1 CKD and overestimate in stages 4 and 5 CKD

Prediction of GFR from multiple regression models derived from MDRD

- Black ethnicity was associated with a multiplication factor, indicating that the expected mean GFR is higher for black persons than for white persons when the same values are assumed for the other predictor variables

- Black coefficient of 1.21

Ann Intern Med. 1999 Mar 16;130(6):461-70

MDRD study design

- 1785 patients entered the baseline period
- 1628 patients enrolled (91%) underwent measurement of GFR (renal clearance of 125I-iothalamate)
  - 1070 randomized to the training sample, 558 in the validation sample
  - Black (n=197)
  - White (n=1304)

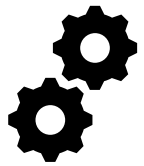
Ann Intern Med. 1999 Mar 16;130(6):461-70

Prediction of GFR from Multiple Regression Models Derived from MDRD

- Black ethnicity was an independent predictor of higher GFR
  - *Previous studies have shown that on average, black persons have greater muscle mass than white persons

Ann Intern Med. 1999 Mar 16;130(6):461-70

Prediction of GFR from Multiple Regression Models Derived from MDRD



Comparative Study

Body elemental composition: comparison between black and white adults.

S H Cohn, C Abesamis, I Zanzi, J F Aloia, S Yasumura, and K J Ellis

Published Online: 01 APR 1977 // https://doi.org/10.1152/ajpendo.1977.232.4.E419

RACIAL VARIATION IN SERUM CREATINE KINASE UNRELATED TO LEAN BODY MASS

J. G. WORRALL ✉, V. PHONGSATHORN, R. J. L. HOOPER, ELISABETH W. PAICE

Rheumatology, Volume 29, Issue 5, October 1990, Pages 371–373,
https://doi.org/10.1093/rheumatology/29.5.371
Published: 01 October 1990 **Article history** ▾

JOURNAL ARTICLE

Densitometry and Anthropometry of Black and White Children

David W. Harsha, Ralph R. Frerichs and Gerald S. Berenson

Human Biology
Vol. 50, No. 3 (September 1978), pp. 261-280
(20 pages)
Published By: Wayne State University Press

Chronic Kidney Disease-EPIdemiology (CKD-EPI)

- Original: https://www.ncbi.nlm.nih.gov/pcm/articles/PMC2763564/, Annals of IM, 2009
- Validation: https://www.ncbi.nlm.nih.gov/pubmed/?term=21107446, KI
- $eGFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] x 1.159 [if Black]

- Abbreviations / Units
  - eGFR (estimated glomerular filtration rate) = mL/min/1.73 m^2
  - S_{Cr} (standardized serum creatinine) = mg/dL
  - κ = 0.7 (females) or 0.9 (males); α = -0.329 (females) or -0.411 (males)
  - min = indicates the minimum of S_{Cr}/κ or 1; max = indicates the maximum of S_{Cr}/κ or 1
  - age = years

Chronic Kidney Disease-EPIdemiology (CKD-EPI)

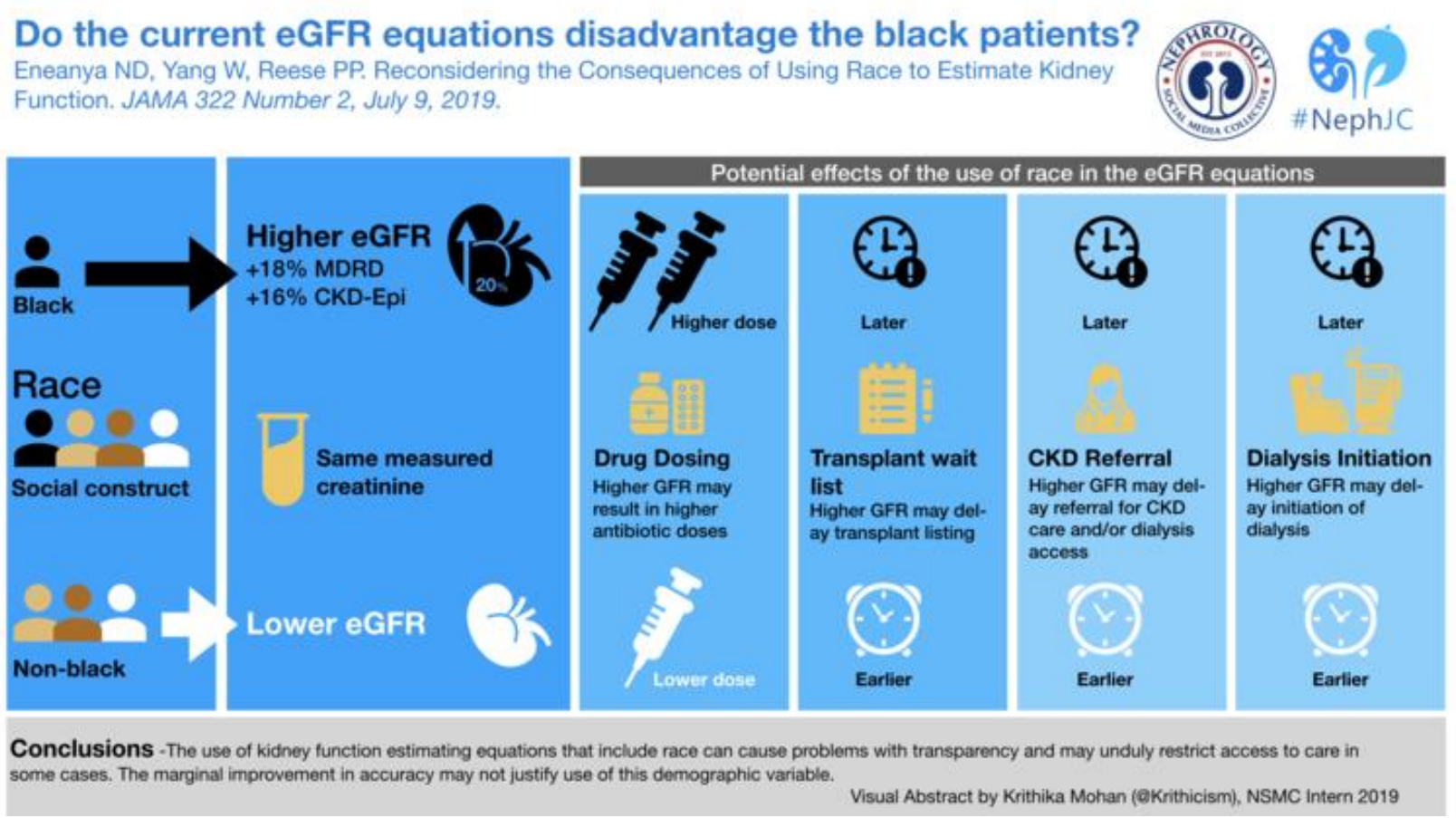
- Recommended method for estimating GFR in adults
- More accurate than the MDRD Study equation, particularly in people with higher levels of GFR

- Black coefficient of 1.16

Black coefficient

- MDRD: 1.21
- CKD-EPI: 1.16

Do Current eGFR Equations Disadvantage Black Patients?



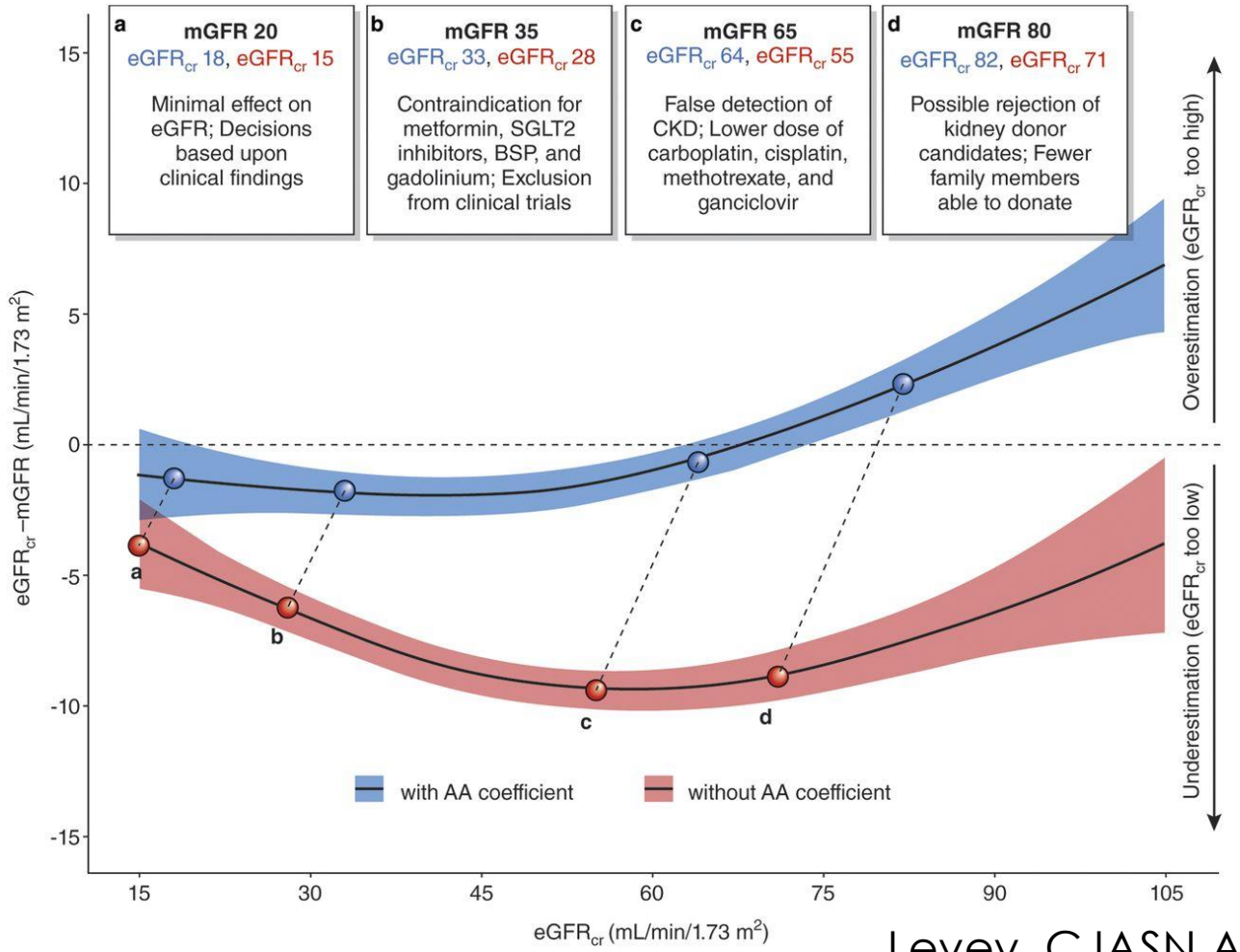
Krithika Mohan (@krithicism)

Sample Case

	White	Black
Serum creatinine µmol/l (mg/dL)	250 (2.8)	250 (2.8)
Age	55	55
Sex	F	F
Weight (kg)	80	80
Height (cm)	160	160
BSA (m^2)	1.89	1.89
Cockroft-Gault (ml/min)	28	28
MDRD (ml/min/1.73m^2)	18	22
CKD-EPI (ml/min/1.73m^2)	18	21
CKD-EPI (de-indexed) (ml/min)	20	23

http://www.nephjc.com/news/raceandegfr

Clinical Decisions Affected by Accuracy of GFR



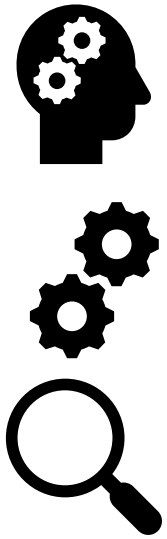
Levey. CJASN August 2020, 15 (8) 1203-1212

Examples of Race Correction in Clinical Medicine (Not just a Nephrologist's Issue)

- Cardiology- The AHA's Get with the Guidelines- Heart Failure Risk Score
- Cardiac Surgery- The Society of Thoracic Surgeons Short Term Risk Calculator
- Nephrology
  - Estimated glomerular filtration rate (eGFR) MDRD and CKD-EPI equations
  - Organ Procurement and Transplantation Network: Kidney Donor Risk Index (KDRI)
- Obstetrics- VBAC Risk Calculator
- Urology- Stone Score, UTI Calculator
- Oncology- Rectal Cancer Survival Calculator, National Cancer Institute Breast Cancer Risk Assessment Tool, Breast Cancer Surveillance Consortium Risk
- Endocrinology- Osteoporosis Risk SCORE, Fracture Risk Assessment Tool (FRAX)
- Pulmonology- PFTs

Vyas, N Engl J Med 383; 9, August 27, 2020

Use of Race in Medicine



A social rather than biologic construct

↓

Not a reliable proxy for genetic differences

↓

Diagnostic algorithms & practice guidelines adjust or "correct" outputs on the basis of race or ethnicity

↓

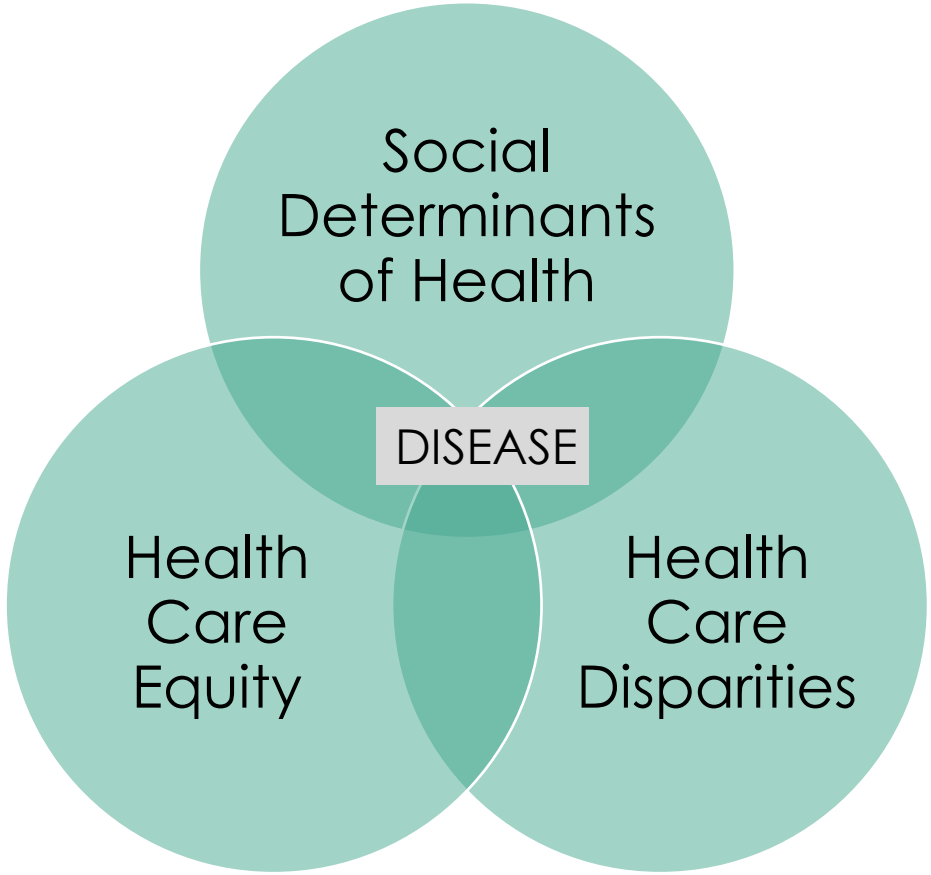
These algorithms used by physicians to individualize risk and guide clinical decisions

↓

Propagate race based medicine

Vyas, N Engl J Med 383; 9, August 27, 2020

Relationship between Inequities and Health



What is the role of the non-GFR determinants of serum creatinine?

Reassessing the Inclusion of Race in Diagnosing Kidney Diseases: An Interim Report from the NKF-ASN Task Force

Cynthia Delgado,[1] Mukta Baweja,[2] Nilka Ríos Burrows,[3] Deidra C. Crews,[4] Nwamaka D. Eneanya,[5] Crystal A. Gadegbeku,[6] Lesley A. Inker,[7] Mallika L. Mendu,[8] W. Greg Miller,[9] Marva M. Moxey-Mims,[10] Glenda V. Roberts,[11] Wendy L. St. Peter,[12] Curtis Warfield,[13] and Neil R. Powe[14]

New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race

Lesley A. Inker, M.D., Nwamaka D. Eneanya, M.D., M.P.H., Josef Coresh, M.D., Ph.D., Hocine Tighiouart, M.S., et al., for the Chronic Kidney Disease Epidemiology Collaboration*

September 23, 2021
DOI: 10.1056/NEJMoa2102953

Suggestions for GFR Estimation Now and in the Future

- Goals: Maintain and improve accuracy of GFR estimates and avoid disadvantaging any racial group
- General Suggestions:
  - Full disclosure of the use of race in GFR estimation, accommodation of those who decline, and shared decision making between patient and health care provider
  - Mindful use of endogenous filtration markers in addition to creatinine, such as cystatin C
  - Ongoing research on the causes of racial differences in the relationship of measured GFR to serum concentrations of endogenous filtration markers and clinical outcomes

Specifically…

- Briefly summarize how race impacts the results of a particular score, so clinicians can be better-informed about the score they're using.
- Make race an optional input when possible to still provide accurate information, so clinicians may opt in or out from including it, and allow them to make that informed decision (the "art" of medicine).
- Specifically draw attention to race when it exists in a calculator in the "Instructions" sections as well as our "Evidence" content to provide clearer, transparent information for our users.

https://www.mdcalc.com/race

In Your Clinic…

- Actively participate in acknowledging/addressing health care disparities
- Full disclosure of the use of race in eGFR estimating equations
- *New* The National Kidney Foundation recommends using the CKD-EPI Creatinine Equation (2021) to estimate GFR

Updated GFR Calculator

CKD-EPI Equations for Glomerular Filtration Rate (GFR) ☆

Estimates GFR based on serum creatinine, serum cystatin C, or both.

IMPORTANT

This calculator includes inputs based on race, which may or may not provide better estimates, so we have decided to make race optional. See here for more on our approach to addressing race and bias on MDCalc.

For the same creatinine value, this calculator estimates a higher GFR for Black patients.

INSTRUCTIONS

For use in patients with stable kidney function. While the combined creatinine and cystatin C equation can add accuracy, cystatin c is not available in all laboratories and the creatinine-based equation is adequate for most clinical purposes.

When to Use ^ | Pearls/Pitfalls v | Why Use v

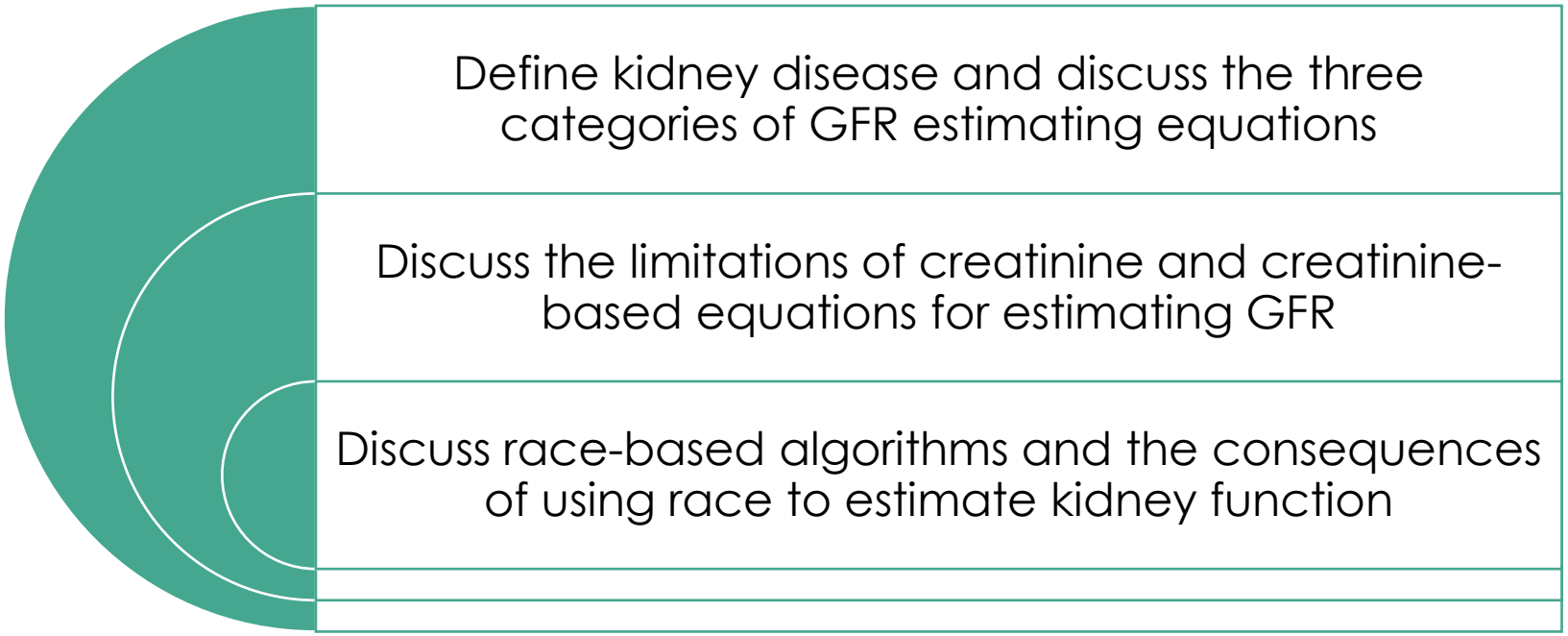
- Patients with chronic kidney disease (not acute), to measure renal function.
- CKD-EPI Creatinine is more commonly available.
- CKD-EPI Cystatin C is preferred in patients at extremes of body type (e.g. obese patients, high or low muscle mass).

Equation	CKD-EPI Creatinine / CKD-EPI Cystatin C / **CKD-EPI Creatinine–Cystatin C**
Gender	Female / Male
Age	years
Serum creatinine	Norm: 0.7 - 1.3 mg/dL ⇋
Serum cystatin C	Norm: 0.51 - 0.98 mg/L
Race Race may/may not provide better estimates of GFR; optional	Black / Non-black

https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr#use-cases

The good physician treats the disease; the great physician treats the patient who has the disease.
William Osler

Summary of Educational Objectives



QUESTIONS