CYSTATIN C:

A novel biomarker for estimating *glomerular filtration rate (eGFR)* in clinical practice

Chronic Kidney Disease (CKD)

In Canada, 2.6 million people have Chronic Kidney Disease (CKD)

Only 3% of people with CKD will reach End Stage Kidney Disease (ESKD) requiring dialysis or transplant

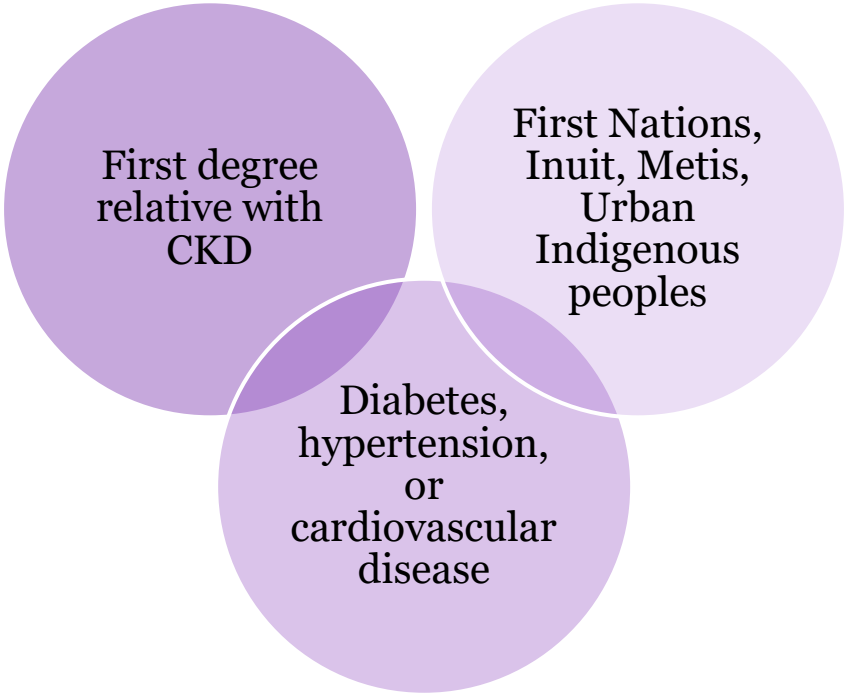
The majority of people with CKD can be managed in primary care

Importance of early detection

- CKD usually progresses silently, often reducing kidney function before symptoms develop.

- If CKD is identified early, the risk of progression of ESKD can be reduced with upstream control of risk factors.

Who to screen for CKD



How to screen for CKD

Blood test to estimate Glomerular Filtration Rate (eGFR)

Urine test for albumin-to-creatinine (ACR) ratio

Grill AK, Brimble S. Approach to the detection and management of chronic kidney disease: What primary care providers need to know. Canadian Family Physician. 2018 Oct 1;64(10):728-35.

Confirming CKD

Measure Urine ACR and eGFR

If eGFR <60 mL/min/1.73m²

repeat measurement in 3 months, or sooner if clinical concern dictates (i.e., rapid decline from previous eGFR result or unexpectedly low eGFR)

&/or

If urine ACR ≥ 3 mg/mmol

repeat measurement 1 or 2 more times over the next 3 months (at least 2 out of 3 random urine ACRs must be elevated (≥ 3) in order to be considered abnormal)

Grill S, Brimble A. Approach to the detection and management of chronic kidney disease: what primary care providers need to know. *Canadian Family Physician | Le Médecin de famille canadien*. 2018;64:728-735.

Prognosis of CKD by GFR and Albuminuria Categories

GFR categories (ml/min/1.73 m^2) Description and range				Albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-90			
	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

Levey AS, Tangri N, Stevens LA. Classification of chronic kidney disease: a step forward. Ann Intern Med. 2011 Jan 4;154(1):65-7.

Monitoring CKD

Once CKD diagnosis is confirmed after 3 months

If eGFR <30 and/or Urine ACR>60:
Patient has CKD

-Based on above parameters, consider seeking consultation from nephrology

-Work-up: urine R&M, electrolytes, CBC, calcium, phosphate, albumin

If eGFR 30-59 and/or Urine ACR 3-60:
Patient has CKD

-Monitor in Primary Care

-Work-up: urine R&M, electrolytes

-Follow eGFR & Urine ACR every 6 months

→ If eGFR remains stable for 2 years, follow eGFR and Urine ACR every 12 months

eGFR ≥ 60 and Urine ACR <3:
Patient does not have CKD

- Remeasure eGFR and Urine ACR annually for patients with DM, less frequently otherwise, unless clinical circumstances dictate more frequent measuring

*Refer to the KidneyWise Toolkit for more details on monitoring CKD in Primary Care

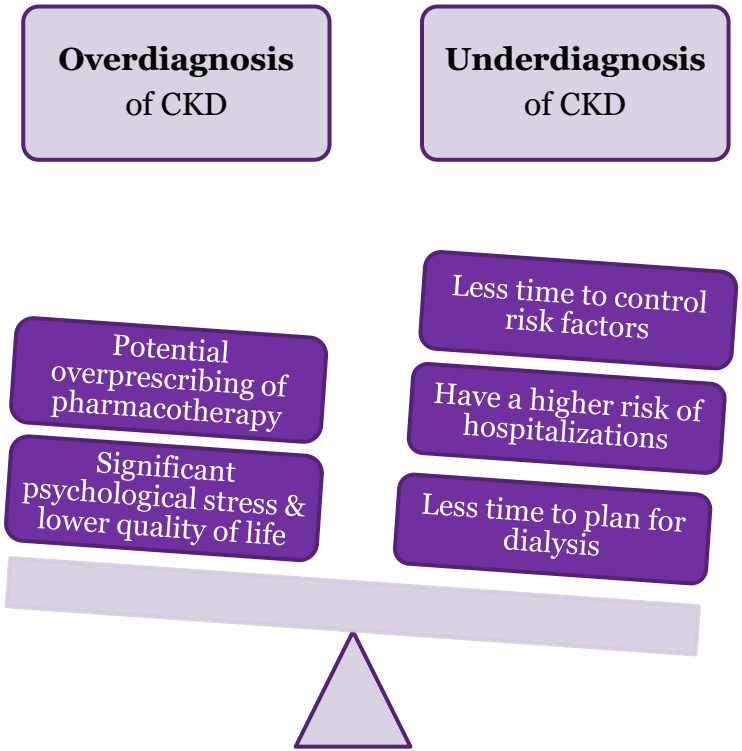
Grill S, Brimble A. Approach to the detection and management of chronic kidney disease: what primary care providers need to know. *Canadian Family Physician | Le Médecin de famille canadien*. 2018;64:728-735.

Glomerular Filtration Rate

- Serum Creatinine is the most commonly used renal marker for estimating GFR
  - It is a naturally occurring endogenous compound freely filtered at the glomerulus and has relatively minor absorption and secretion by the renal tubules.
- However, it has several inherent limitations that limit its clinical reliability.

Monitoring in CKD Stage 3A

- The majority of patients with eGFR <60 mL/min/1.73m² have Stage 3A CKD
- Signifies an inflection point in the disease course where accurate diagnosis is critical



Creatinine in Early Stages of CKD

- Serum creatinine remains in the normal range until 50% of renal function is lost, resulting in a *"creatinine blind area"* in early CKD *(including all of stage G3A, eGFR 45-59 ml/min)*, where serum creatinine is insensitive to loss of kidney function

Limitations of Serum Creatinine

Non-renal factors affecting serum creatinine

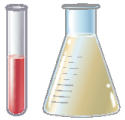
- Sex
- Ethnicity
- Dietary intake, such as diets high in protein
- Muscle mass
- Drugs that affect tubular secretion of creatinine

Cystatin C

- Cystatin C is a small 13 –kDa protein that is a member of the cysteine proteinase inhibitor family.
- It is produced at a constant rate by all nucleated cells, is freely filtered, and *(unlike creatinine)* is not secreted.
- In contrast to creatinine, there is little cystatin C in the urine because the proximal tubular cells reabsorb and catabolize it.
- Since there is no tubular secretion, Cystatin C is more sensitive to small changes in GFR in the early stages of CKD.

Using **Cystatin C** alone or with creatinine provides more **accurate estimation** of **GFR**, **earlier** detection of **CKD** and risk of **cardiovascular disease**

eGFRcr-cys provides the most accurate estimation of GFR

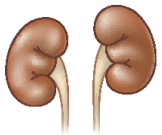


Compared to gold-standard measured GFR

✓ **eGFRcr-cys**
Greatest precision
Least bias

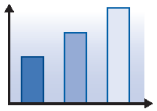
eGFR by CKD-EPI using creatinine alone (eGFRcr), cystatin C alone (eGFRcys) or creatinine + cystatin C (eGFRcr-cys). All eGFR measures in ml/min/1.73 m².

eGFRcys and eGFRcr-cys should confirm diagnosis of CKD



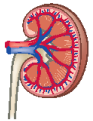
If eGFRcr 45-60 or ~~eGFRcr 60–90~~ + CV risks

Measure eGFRcys and eGFRcr-cys



Use lowest eGFR to guide management

eGFRcys predicts cardiovascular disease risk earlier than eGFRcr



Compared with reference **eGFR 90**

Doubling of cardiovascular risk:

at **eGFRcys** 60–70 (early)[5,7]

at **eGFRcr** 30–40 (later)[5,7]

ndt NEPHROLOGY DIALYSIS TRANSPLANTATION

Lees, JS and Mark, PB; NDT Digest (2020)
@NDTSocial

Nephrol Dial Transplant, Volume 36, Issue 1, January 2021, Pages 39–41, https://doi.org/10.1093/ndt/gfaa152

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cystatin C versus Creatinine in Determining Risk Based on Kidney Function

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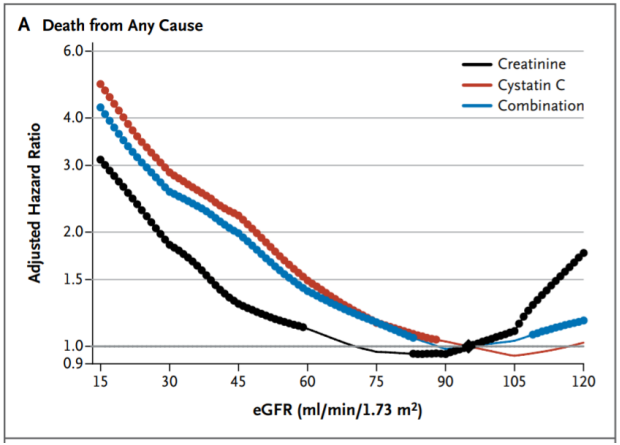
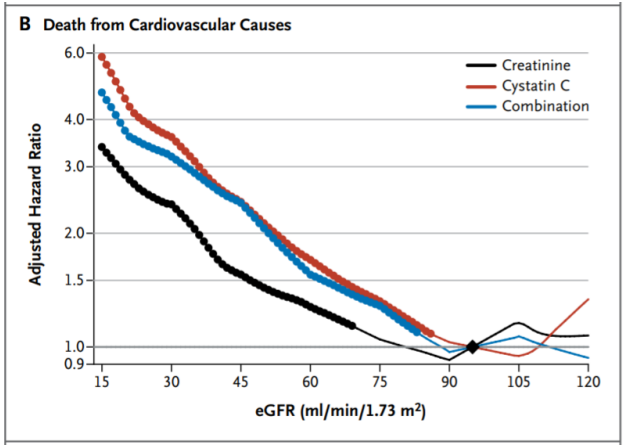
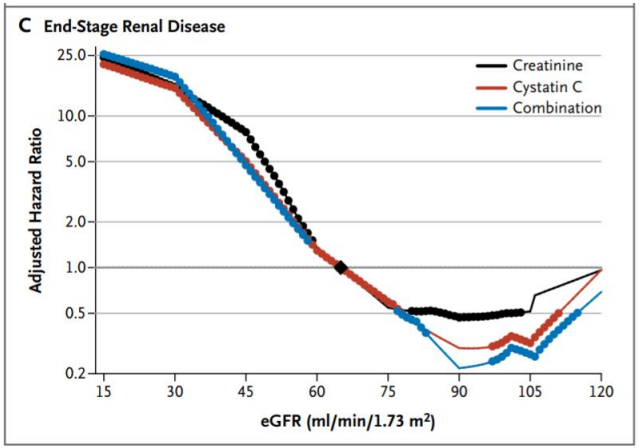
CKD Prognosis Consortium meta-analysis of 16 cohorts, 90,000 individuals: *"The use of cystatin C alone or in combination with creatinine strengthens the association between the eGFR and the risks of death and end-stage renal disease across diverse populations"*







Benefits of Cystatin C

Cystatin C is more reliable than Serum Creatinine

- Unlike creatinine, Cystatin C serum levels are unaffected by age, sex, diet, muscle mass, race and medications.

Clinical reliability

- Cystatin C is more sensitive to actual changes in GFR in the early stages of CKD than serum creatinine-based GFR estimates.

Benefits of Cystatin C

Clinical Reliability

- Has demonstrated to have a higher diagnostic accuracy than MDRD, or C-G equations in people with diabetes, enabling early detection and treatment in both Type 1 and 2 diabetes.
- Creatinine based GFR measurements are not reliable and not recommended in hepatic disease. Cystatin C has been shown to be a reliable marker of kidney function in people with cirrhosis.

Pucci L, et al. Cystatin C and estimates of renal function: searching for a better measure of kidney function in diabetic patients. Clinical chemistry. 2007 Mar 1;53(3):480-8.
Wang D, et al. Role of Cystatin C and glomerular filtration rate in diagnosis of kidney impairment in hepatic cirrhosis patients. Medicine. 2017 May;96(20).

1. Clinical Practice Point

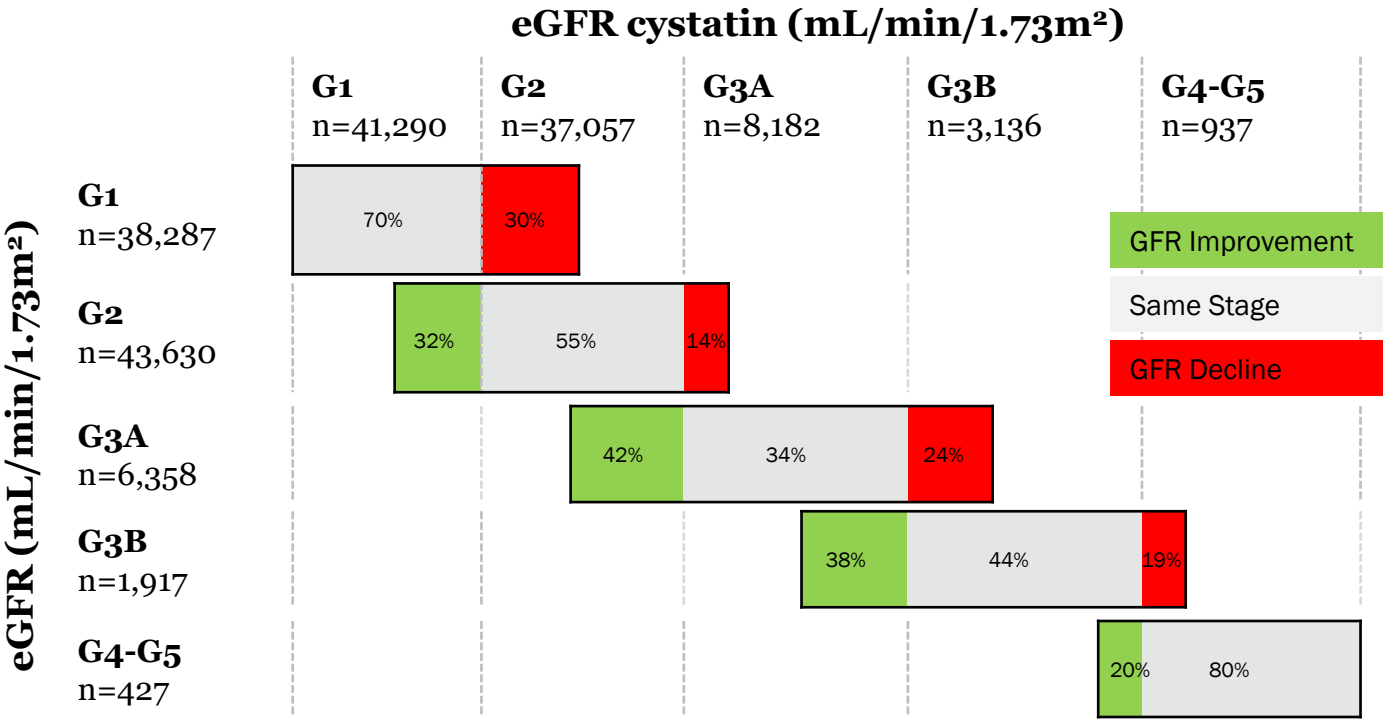
Cystatin C as a confirmatory test for CKD

A patient who presents with:

1. No albuminuria,
2. A serum creatinine eGFR of 45-60 mL/min/1.73m^2,
3. A Cystatin c eGFR > 60 mL/min/1.73m^2

→ Would be classified as **not having CKD**

2. Clinical Practice Point



Cystatin C reclassifies some individuals to either more or less advanced CKD stages, particular in people **with CKD Stage G3A, highlighting the clinical utility of Cystatin C to confirm or "unconfirm" CKD**

Adjusted for age, sex, race, smoking, systolic BP, total cholesterol, diabetes, history of CVD, BMI, and albuminuria -- **Shlipak et al., NEJM 2013**

3. Clinical Practice Point

Serum creatinine—based eGFR <u>underestimates</u> eGFR in:

- People with extreme muscle mass;
- People on high protein diets; protein supplements;
- People on medications known to decrease creatinine secretion;
- People of African descent

Serum creatinine—based eGFR <u>overestimates</u> eGFR in:

- People with poor nutritional status;
- People on low protein diets;
- People with cirrhosis

Measuring Cystatin C in these conditions provides a more accurate eGFR measurement.

Clinical Practice Point

- Cystatin C can estimate GFR independent of race/ethnicity
- Cystatin C can be very useful when creatinine based eGFRs are in the 45-60 ml/min/1.73m^2 range and there is no albuminuria
- In these scenarios, a normal cystatin C eGFR suggests the patient does not have CKD

Illustrative Case #1

- 48-year-old
- Male
- Healthy lifestyle
- Muscular, exercises regularly

- Serum creatinine: *130 umol/L*
- Serum Cystatin C: *0.98 mg/L*
- Urine ACR: 1.5 *mg/mmol*

eGFR:

- Creatinine: *56 ml/min/1.73m²*
- Cystatin C: *84 ml/min/1.73m²*

Illustrative Case #1

- Patient likely does not have CKD
- Muscle mass can affect creatinine generation and muscular persons can have a higher serum creatinine and a lower eGFR Cr
- Cystatin C is not affected by muscle mass
- Normal Urine ACR in this patient also confirms the lack of CKD

Illustrative Case #2

- 78-year-old
- Female
- Mixed race, self-identifies as black, known to have CKD

- Serum creatinine: *180 umol/L*
- Serum Cystatin C: *1.8 mg/L*
- Urine ACR: *50 mg/mmol*

eGFR:

- Cr African American: *26 ml/min/1.73m²*
- Cr Non-AA: *23 ml/min/1.73m²*
- Cystatin C: *31 ml/min/1.73m²*

Illustrative Case #2

- Race based estimates of eGFR may not be accurate in mixed race individuals, and may introduce biases in delivery of care
- Cystatin C is not affected by race/ethnicity and can be a preferred filtration marker in these individuals
- This patient would have a higher eGFR, >30 with cystatin C and may not need nephrology consultation at this point

Illustrative Case #3

- 60-year-old
- Male
- Diabetes
- Normal muscle mass, normal diet

- Serum creatinine: *130 umol/L*
- Serum Cystatin C: *1.1 mg/L*
- Urine ACR: *1.5 mg/mmol*

eGFR:

- Creatinine: *51 ml/min/1.73m²*
- Cystatin C: *69 ml/min/1.73m²*

Illustrative Case #3

- For most patients, eGFR Cr and eGFR Cys C will agree (diff < 20 %)
- On occasion, eGFR measurements using Creatinine or Cystatin C can differ by 30 % or more
- A more accurate estimate in this case is likely the average of the two measurements
- This individual can be considered to not have CKD due to the normal ACR and normal cystatin C eGFR

Final Take Home Points

- Cystatin C has fewer non-renal determinants than serum creatinine
- In patients with a serum creatinine based eGFR of 45-59 ml/min/1.73m^2 , a normal cystatin C eGFR (> 60 ml/min) can confirm the absence of CKD
- Measuring Serum Creatinine, Cystatin C and albuminuria *("triple marker" approach)* is the most informative for CKD detection and risk stratification

More Information, Questions?

Please Contact Us: cystatinc@alphalabs.ca

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