An 80-year-old man with type 2 diabetes and hypertension was referred to the nephrology clinic for assessment of persistent hyperkalemia despite discontinuation of his angiotensin-converting enzyme inhibitor. The patient was frail, sedentary, and had a body mass index of 37. Select blood testing results are shown in Table 1. His estimated glomerular filtration rate (eGFR) was calculated using 3 equations that incorporated creatinine (eGFRcr), cystatin C (eGFRcys), and both creatinine and cystatin C (eGFRcr-cys), as shown in Table 2.

### Table 1. Patient’s Laboratory Testing Results

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Patient’s value</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium, mEq/L</td>
<td>5.9</td>
<td>3.3-4.8</td>
</tr>
<tr>
<td>Bicarbonate, mEq/L</td>
<td>22</td>
<td>24-32</td>
</tr>
<tr>
<td>Creatinine, mg/L</td>
<td>1.15</td>
<td>0.6-1.3</td>
</tr>
<tr>
<td>Cystatin C, mg/L</td>
<td>1.84</td>
<td>&lt;1.23</td>
</tr>
<tr>
<td>Urinary albumin-creatinine ratio, mg/g</td>
<td>504</td>
<td>&lt;30</td>
</tr>
</tbody>
</table>

SI conversion factors: To convert potassium and bicarbonate to mmol/L, multiply by 1.0; creatinine to μmol/L, multiply by 76.25.

### Table 2. Patient’s Estimated Glomerular Filtration Rate (eGFR) Values and Chronic Kidney Disease (CKD) Stage

<table>
<thead>
<tr>
<th>eGFR equation</th>
<th>eGFR, mL/min/1.73 m²</th>
<th>CKD stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using creatinine (eGFRcr)</td>
<td>64</td>
<td>G2A3</td>
</tr>
<tr>
<td>Using cystatin C (eGFRcys)</td>
<td>32</td>
<td>G3bA3</td>
</tr>
<tr>
<td>Using creatinine and cystatin C (eGFRcr-cys)</td>
<td>44</td>
<td>G3bA3</td>
</tr>
</tbody>
</table>

* eGFR was calculated using CKD Epidemiology Collaboration equations without race.1

**Answer**

A. The estimated glomerular filtration rate calculated using creatinine (eGFRcr) may be inaccurate because the patient is frail and sedentary.

**Test Characteristics**

Chronic kidney disease (CKD) is typically defined as GFR less than 60 mL/min/1.73 m² or urinary albumin-creatinine ratio (ACR) greater than or equal to 30 mg/g that is present for 3 months or more.2 Accurate assessment of GFR and albuminuria is important to determine the presence, stage, and prognosis of CKD and to inform important treatment decisions, such as when to initiate hemodialysis or consider kidney transplant. In 2021, the National Kidney Foundation and American Society of Nephrology Task Force encouraged all US clinical laboratories to adopt the CKD Epidemiology Collaboration 2021 eGFR equations without race,2 which were developed and validated using large, diverse populations.3,4

eGFRcr is the most commonly used equation to estimate GFR. Creatinine is a nonprotein nitrogenous metabolic product of creatine phosphate, derived from skeletal muscle and dietary intake of cooked meat. Creatinine is useful for estimating GFR because it is released into the bloodstream at a relatively constant rate and is filtered by the kidneys. However, serum creatinine can be influenced by factors other than kidney function. Low muscle mass, low activity levels, vegetarian diet, and conditions such as frailty, lower extremity amputation, advanced heart failure, or liver failure are associated with lower serum creatinine levels and cause eGFRcr to be higher than the actual GFR.5 Conversely, serum creatinine levels may be higher in very muscular individuals, resulting in an eGFRcr that is lower than the actual GFR.3 Recent ingestion of cooked meat and use of medications that inhibit proximal tubule secretion of creatinine (such as trimethoprim, dromedarone, cimetidine, and tyrosine kinase inhibitors) can elevate serum creatinine, leading to a reduction in eGFRcr that is not due to a true decrease in kidney filtration function.5

Use of serum cystatin C is recommended by the 2021 National Kidney Foundation and American Society of Nephrology Task Force to estimate GFR in adults with or at risk for CKD.3,4 Serum cystatin C is a low-molecular-weight protein found in all tissues in the body. It is filtered at the glomerulus and not secreted into the renal tubules or reabsorbed into the bloodstream. Although not affected by muscle mass or diet, determinants of cystatin C levels are less well-understood. However, obesity, hypothyroidism, cigarette smoking, and use of systemic corticosteroids are associated with higher cystatin C values and cause eGFRcys to be lower than actual GFR.1,5

Quiz at jamacmelookup.com
The equation eGFRc-r-cys, using both creatinine and cystatin C, typically provides the most accurate estimate of GFR for most patients in ambulatory settings. The 2021 Medicare reimbursements were $5.12 for creatinine, $18.52 for cystatin, and $10.96 for urine ACR.

### Application of Test Result to the Patient

For this patient, frailty, low muscle mass, and inactivity are likely to have lowered the creatinine value and resulted in an eGFRc that was substantially higher than his actual GFR. Because eGFRc-r-cys is not affected by muscle mass, it likely more accurately represents his actual GFR. However, the body mass index of 37 may have increased his serum cystatin C, causing the eGFRc-r-cys to be lower than his actual GFR. Therefore, the eGFRc-r-cys equation was used to guide treatment. With an eGFRc-r-cys value of 44 mL/min/1.73 m², the patient had CKD stage G3bA3, and his risk of progression to kidney failure within 5 years was 4.7% based on the Kidney Failure Risk Equation.

### What Are Alternative Diagnostic Testing Approaches?

The criterion-standard method of determining GFR is measurement of the clearance of an exogenous filtration marker, such as urinary clearance of iothalamate. A more widely available but less accurate alternative is the creatinine clearance test, which typically requires collection of urine over a 24-hour period.

**Patient Outcome**

For treatment of reduced kidney function and type 2 diabetes, the patient was prescribed a sodium-glucose cotransporter 2 inhibitor, empagliflozin, which was titrated to 25 mg orally daily. Over the next 11 months, his potassium ranged from 4.1 to 5.0 mEq/L and urinary ACR decreased from 504 mg/g to 195 mg/g. At 11 months after the initial presentation, his eGFRc-r-cys was 40 mL/min/1.73 m² and his 5-year risk of progression to kidney failure remained at 4.7%.

### Clinical Bottom Line

1. eGFRc-r-cys is the initial equation recommended for estimation of GFR, although its accuracy may be affected by muscle mass, diet, frailty, advanced heart failure or liver failure, and certain medications, such as trimethoprim, dronedarone, and tyrosine kinase inhibitors.
2. Serum cystatin C should be measured in adults with or at risk for CKD.
3. eGFRc-r-cys may underestimate actual GFR in people who smoke cigarettes, with obesity, with hypothyroidism, or who take systemic corticosteroids. In these individuals, eGFRc-r-cys typically provides the most accurate estimate of GFR.

**REFERENCES**