Laboratory Testing for Chronic Kidney Disease Diagnosis and Management

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present >3 months, with implications for health.[1] Diagnostic criteria include a decreased glomerular filtration rate (GFR) or presence of 1 or more other markers of kidney damage.[1] Markers of kidney damage include a histologic abnormality, structural abnormality, history of kidney transplantation, abnormal urine sediment, tubular disorder–caused electrolyte abnormality, or an increased urinary albumin level (albuminuria).

This Test Guide discusses the use of laboratory tests that may aid in identifying CKD and monitoring and managing disease progression, comorbidities, and complications. The tests discussed include measurement and estimation of GFR as well as markers of kidney damage. A list of applicable tests is provided in the Appendix. The information is provided for informational purposes only and is not intended as medical advice. Test selection and interpretation, diagnosis, and patient management decisions should be based on the physician's education, clinical expertise, and assessment of the patient.

ESTIMATION OF GFR

Direct measurement of GFR may be problematic. The gold standard for measured GFR (mGFR) is the inulin clearance method, but this test is difficult to perform in clinical practice. Clearance measurements using iohexol, ^{125}I-iothalamate, and several chelated isotopic radiotracers provide alternatives to the inulin reference method for mGFR, but each has limitations.[2] These methods are usually reserved for specific circumstances, such as determining correct drug dosing in therapy that requires the most accurate assessment of kidney function, or when clinical decision-making is affected by having disparate results for estimated GFR (eGFR, see below).

Direct measurement of creatinine clearance and urea clearance is also an alternative to assess kidney function. Notably, the average of the 2 values is similar to GFR measured by inulin clearance (<20 mL/min/1.73 m^2) in patients not on dialysis.[3] In these patients, the overestimation due to creatinine secretion is offset by underestimation due to urea reabsorption, leading to an average value that accurately reflects GFR.[3] However, this method of calculating GFR is prone to error due to inaccurate timing of blood sampling, incomplete urine collection over 24 hours, or over collection of urine beyond 24 hours.[2,3]

Given that direct measurement of GFR may be problematic, eGFR, using either creatinine- or cystatin C–based measurements, is most commonly used to diagnose CKD in clinical practice.

Creatinine-based eGFR

GFR is typically estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[4] The CKD-EPI equation uses serum-creatinine measurements, patient age (≥18 years old), and patient sex; patient race (African versus non-African ancestry) is no longer considered.[4] Creatinine-based eGFR is recommended by the Kidney Disease Improving Global Outcomes (KDIGO) 2012 international guideline for initial assessment of GFR.[1]

Creatinine-based eGFR may be imprecise for certain individuals (see *Cystatin C–based eGFR* below). In addition, confirmation of GFR using another method may be required to avoid misclassification of some patients. Cystatin C–based eGFR provides an alternative when creatinine-based estimates are not appropriate.

Cystatin C-based eGFR

Being less influenced by diet and muscle mass, cystatin C–based eGFR testing is appropriate for patients in whom creatinine-based results may be misleading.[5] These patients include pregnant women, patients with acute illness, patients with serious comorbid conditions, people with extremes of muscle mass (eg, bodybuilders, patients with amputation, paraplegia, muscle-wasting disease, or a neuromuscular disorder), patients suffering from malnutrition, those with a vegetarian or low-meat diet, and those taking creatine dietary supplements. In addition, the KDIGO guideline recommends using cystatin C–based eGFR, or creatinine plus cystatin C–based eGFR, to confirm CKD when creatinine-based eGFR indicates a mild to moderately high risk of CKD progression (45 to 59 mL/min/1.73 m^2) in a patient without albuminuria (**Figure 1**).[1]

Figure 1. Frequency of Monitoring Chronic Kidney Disease Based on Risk of Disease Progression Assessed Using eGFR and Urine Albumin-Creatinine Ratio (Kidney Profile, test code 39165)

			Albuminuria categories and ACR ranges (mg/g creatinine)		
			Normal to mildly increased	Moderately increased	Severely increased
			<30	30-300	>300
CKD stage and eGFR range (mL/min/1.73 m^2)	1 and 2	≥60	1	1	2,R
	3A	45-59	1,C	2	3,R
	3B	30-44	2	3	3,R
	4	15-29	3,R	3,R	≥4,R
	5	<15	≥4,R	≥4,R	≥4,R

Low risk: monitor yearly if evidence of kidney damage (eg, indicated by imaging or biopsy). The NKDEP recommends that actual values above 60 mL/min/1.73m^2 be reported only as >60 due to variability near the upper limit of the reference range.[12]

Moderately high risk: monitor yearly

High risk: monitor 2 times yearly

Very high risk: monitor 3 times yearly

Very high risk: monitor ≥4 times yearly

ACR, albumin-creatinine ratio; C, confirm using eGFR based on (1) cystatin C (test code 94588) or (2) creatinine plus cystatin C; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NKDEP, National Kidney Disease Education Program; R, refer to specialist.

This figure was adapted from references 1 (with permission) and 12, is provided for informational purposes only as a guide for using laboratory tests, and is not intended as medical advice. Test selection and interpretation, diagnosis, and patient management decisions should be based on the physician's education, clinical expertise, and assessment of the patient.

A large meta-analysis has shown cystatin C–based eGFR improves risk classification for adverse outcomes (death, cardiovascular disease-related death, and end-stage renal disease) across diverse populations.[6] However, cystatin C–based eGFR may be more affected by some non-GFR determinants such as thyroid disorders, corticosteroid use, and smoking.[2] In addition, associations of elevated cystatin C levels with diabetes, obesity, and inflammation have been reported.[6,7] For these reasons, creatinine-based eGFR is recommended for patients without contraindications.

Finally, interpretation of eGFR is challenging for patients with severe obesity (BMI >40); for this group, creatinine-based eGFR may be overestimated and the utility of cystatin C–based eGFR needs to be further investigated.[8]

ALBUMINURIA AND PROTEINURIA

Albuminuria indicates increased glomerular permeability, a characteristic of CKD, and is assessed with either the urine albumin-creatinine ratio or albumin excretion rate over 24 hours. The urine albumin-creatinine ratio obtained from a random sample is more convenient and appropriate in the context of CKD. However, carefully performed 24-hour specimen collection is more accurate and appropriate in some circumstances (eg, in glomerular disease when small discrepancies between the random and 24-hour results may influence high-risk therapeutic dosing).[9]

A urine albumin-creatinine ratio result of ≥30 mg/g (albumin excretion rate ≥30 mg/24 hours) is evidence of albuminuria (30 to 300 mg/g was formerly referred to as "microalbuminuria" and >300 mg/g as "macroalbuminuria").[1]

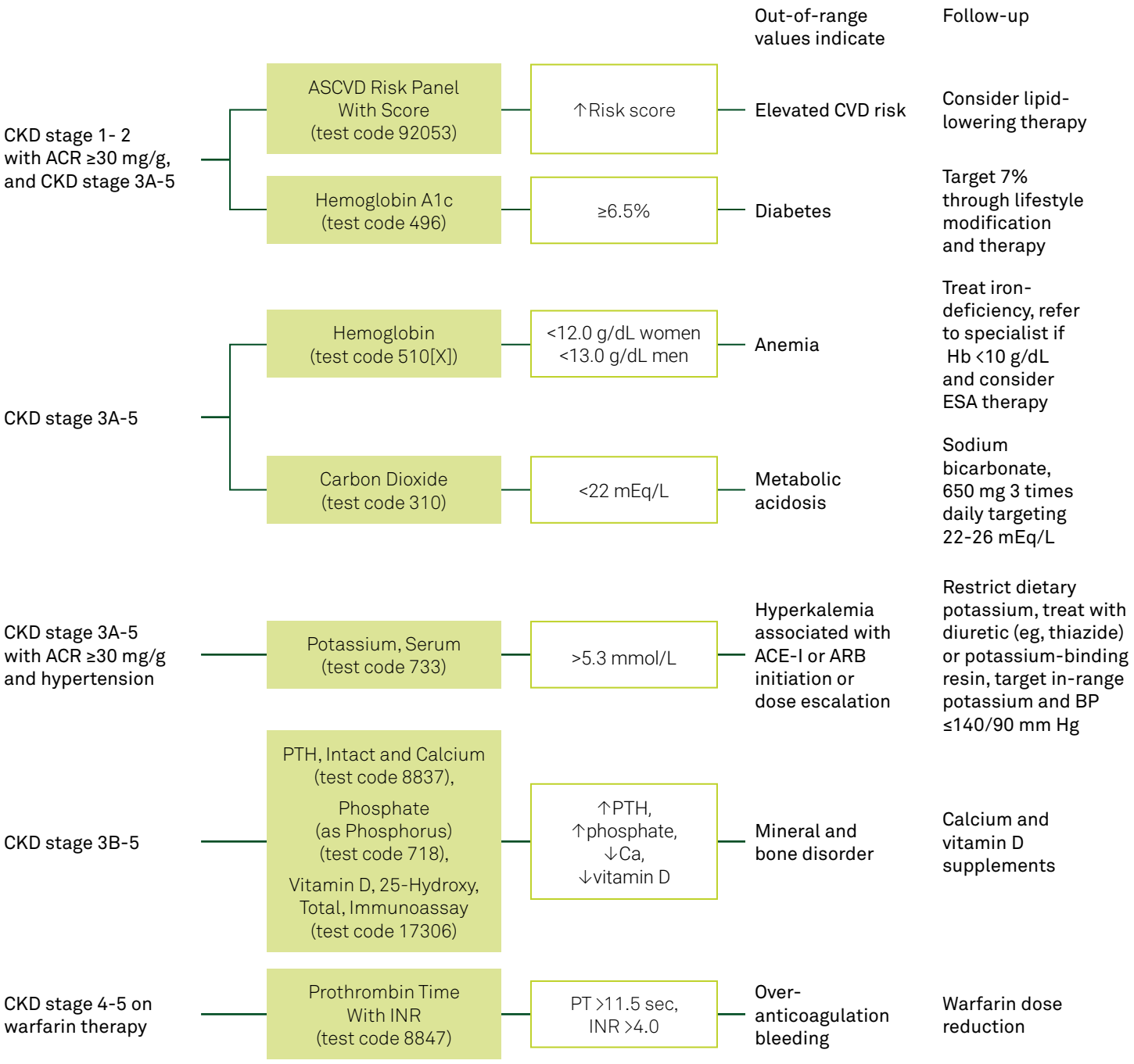
Proteinuria (urinary total protein-creatinine ratio ≥150 mg/g) may also indicate increased glomerular permeability and CKD but may have other causes that are distinguished by elevated nonalbumin proteins.[1] Examples of other causes of proteinuria include defective tubular resorption (elevated α1- and β2-microglobulin) and tubular resorption capacity being exceeded, as observed in myeloma (elevated immunoglobulin light chains).[1]

GFR, ALBUMIN-CREATININE RATIO, AND DISEASE MANAGEMENT

A GFR <60 mL/min/1.73 m^2 for >3 months and/or urine albumin-creatinine ratio ≥30 mg/g for >3 months define CKD.[1] Combined, these test results provide a "Kidney Profile" recommended by the National Kidney Foundation for diagnosing and managing CKD in at-risk patients (**Figure 1**).[1,10-12] The results are important independent risk predictors of major adverse cardiovascular events (myocardial infarction or stroke).[13]

Approaches to monitoring and managing cardiovascular risk, diabetes, and other comorbidities and complications associated with the various stages of CKD, are provided in **Figure 2**.[11]

Figure 2. Testing for Comorbidities and Complications of Chronic Kidney Disease



ACE-I, angiotensin-converting enzyme inhibitor; ACR, albumin-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESA, erythropoietin-stimulating agent; Hb, hemoglobin; INR, international normalized ratio; PT, prothrombin time; PTH, parathyroid hormone.

This figure was developed by Quest Diagnostics based on reference 11. The algorithm is provided for informational purposes and is not intended as medical advice. Test selection and interpretation, diagnosis, and patient management decisions should be based on the physician's education, clinical expertise, and assessment of the patient.

APPENDIX

Quest Diagnostics offers many tests and panels for diagnosis and management of CKD. Test offerings range from health screenings for abnormal eGFR, proteinuria, and/or albuminuria, to tests for management of CKD and its comorbidities and complications. For example, the Diabetes, Advancing Chronic Kidney Disease Management Panel (test code 91713) combines many of these tests according to the recommendations of the American Diabetes Association.[14]

APPENDIX TABLE

Tests Used in Diagnosis and Management of Chronic Kidney Disease[a,b]

Test code	Test name	Primary clinical use and differentiating factors
Screening, diagnosis, and monitoring		
6517	Albumin, Random Urine With Creatinine Includes albumin and creatinine, random urine 8459(X).	Detect albuminuria using albumin-creatinine ratio
15281	Albumin, 24-Hour Urine With Creatinine Volume measurement adds additional CPT code and charge.	Detect albuminuria using albumin excretion rate corrected for creatinine excretion
4555	Albumin, 24-Hour Urine Without Creatinine Volume measurement adds additional CPT code and charge.	Detect albuminuria using albumin excretion rate
10165	Basic Metabolic Panel Includes BUN/creatinine ratio (296), calcium (303), carbon dioxide (310), chloride (330), glucose (483), potassium (733), serum creatinine (375) with eGFR (calculated), and sodium (836).	Screen for acute and CKD Assess blood glucose, calcium, and electrolyte balance
296	BUN/Creatinine Ratio Includes BUN (294) and serum creatinine with eGFR and calculated BUN/creatinine ratio.	Screen for acute and CKD
10231	Comprehensive Metabolic Panel Includes albumin (223), albumin/globulin ratio (calculated), alkaline phosphatase (234), ALT (823), AST (822), BUN/creatinine ratio (296), calcium (303), carbon dioxide (310), chloride (330), globulin (calculated), glucose (483), potassium (733), creatinine (375) with eGFR (calculated), sodium (836), total bilirubin (287), and total protein (754).	Screen for acute and CKD and liver dysfunction Assess blood glucose, calcium, and electrolyte balance
375	Creatinine Includes serum creatinine and eGFR calculation.	Screen for CKD[c] Monitor CKD therapy and/or progression in adults
7943	Creatinine Clearance Includes creatinine, 24-hour urine (381), serum creatinine (375) with eGFR (calculated), and creatinine clearance calculated. Volume measurement adds additional CPT code and charge.	Screen for CKD[c,d] Confirm CKD using 24-hour creatinine measurement
94588	Cystatin C With Glomerular Filtration Rate, Estimated (eGFR)	Screen for CKD[e] Confirm a diagnosis of CKD Monitor CKD therapy and/or progression in adults

(Continued)

APPENDIX TABLE *(Continued)*

Tests Used in Diagnosis and Management of Chronic Kidney Disease[a,b]

Test code	Test name	Primary clinical use and differentiating factors
91713	Diabetes, Advancing Chronic Kidney Disease Management Panel Includes electrolyte panel (34392) (includes sodium [836], potassium [733], chloride [330], carbon dioxide [310]), hemoglobin (510[X]), intact PTH and calcium (8837), phosphate (phosphorus [718]), total 25-hydroxyvitamin D by immunoassay (17306), serum creatinine (375) with eGFR (calculated); and albumin, random urine with creatinine (6517) (includes albumin and creatinine, random urine (8459[X] and albumin/creatinine ratio [calculated]).	Screen for CKD in patients with diabetic nephropathy Monitor CKD therapy in patients with diabetes mellitus
91712	Diabetes, Newly Diagnosed and Monitoring Panel Includes glucose (483); HbA1c (496); hepatic function panel (10256) (includes total protein [754], albumin [223], globulin [calculated], albumin/globulin ratio [calculated], total [287], direct [285], and indirect [calculated] bilirubin, alkaline phosphatase [234], AST [822], and ALT [823]); lipid panel, standard (7600[X]) (total [334], HDL [608], and LDL [calculated] cholesterol; triglycerides [896] with reflex to direct LDL [8293] if triglycerides >400 mg/dL; cholesterol/HDL ratio [calculated]; and non-HDL [calculated]); serum creatinine (375) with eGFR(calculated); and albumin, random urine with creatinine (6517).	Screen for CKD in patients recently diagnosed with diabetes mellitus Establish baseline measurements for patients recently diagnosed with diabetes mellitus Monitor patients with diabetes mellitus
39165	Kidney Profile Includes albumin, random urine with creatinine (6517) and serum creatinine (375) with calculated eGFR.	Screen for CKD[c] Detect albuminuria Monitor CKD therapy and/or progression in adults
1715	Protein, Total, Random Urine With Creatinine	Detect proteinuria
10314	Renal Function Panel Includes albumin (223), BUN/creatinine ratio (296), calcium (303), carbon dioxide (310), chloride (330), glucose (483), phosphate (as phosphorous) (718), potassium (733), serum creatinine (375) with eGFR (calculated), and sodium (836).	Screen for acute and CKD Detect albuminuria Assess blood glucose, calcium, phosphorus, and electrolyte balance
7329(X)	Urea Clearance Includes BUN (294); urea nitrogen, 24-hour urine without creatinine (973[X]); and calculated urea clearance. Volume measurement adds additional CPT code and charge.	Screen for CKD[c,d]
Other tests for screening, diagnosis, and monitoring		
NA	Dipstick test	Rapidly check for out-of-range urine acidity, protein, glucose, bilirubin, as well as WBC, blood in the urine

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APPENDIX TABLE *(Continued)*

Tests Used in Diagnosis and Management of Chronic Kidney Disease[a,b]

Test code	Test name	Primary clinical use and differentiating factors
NA	Measured GFR	Confirm a diagnosis of CKD Determine correct drug dosing for individuals with abnormal kidney function and GFR resulting in altered pharmacokinetic or pharmacodynamic relationships
Tests for monitoring comorbidities and complications[11]		
92053	ASCVD Risk Panel With Score Includes total (334), HDL (608), and LDL (calculated) cholesterol; triglycerides (896); cholesterol/HDL ratio (calculated); non-HDL (calculated); 10-year and lifetime atherosclerotic cardiovascular risk scores (calculated); and reflex to direct LDL (8293).	Assess risk for ASCVD in patients with CKD stage 1- 2 with ACR ≥30 mg/g or CKD stage 3A-5
310	Carbon Dioxide	Monitor metabolic acidosis in patients with CKD stage 3A-5
510(X)	Hemoglobin	Monitor anemia in patients with CKD stage 3A-5
496	Hemoglobin A1c	Monitor diabetes in patients with CKD stage 1- 2 with ACR ≥30 mg/g or CKD stage 3A-5
718	Phosphate (as Phosphorus)	Monitor mineral and bone disorder in patients with CKD stage 3B-5
733	Potassium, Serum	Monitor hyperkalemia associated with ACE-I or ARB initiation or dose escalation in patients with hypertension and CKD stage 3A-5, ACR ≥30 mg/g
8847	Prothrombin Time With INR	Monitor overanticoagulation bleeding in patients on warfarin therapy with CKD stage 4-5
8837	PTH, Intact and Calcium	Monitor mineral and bone disorder in patients with CKD stage 3B-5
17306	Vitamin D, 25-Hydroxy, Total, Immunoassay	Monitor mineral and bone disorder in patients with CKD stage 3B-5

ACE-I, angiotensin-converting enzyme inhibitor; ACR, albumin-creatinine ratio; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; INR, international normalized ratio; LDL, low-density lipoprotein; NA, not available through Quest Diagnostics; PTH, parathyroid hormone; WBC, white blood cell.

[a] Panel components may be ordered separately.

[b] Reflex tests are performed at an additional charge and are associated with additional CPT codes.

[c] In at-risk adults (>18 years old) including those who have diabetes, cardiovascular disease, hypertension, previous kidney damage, systemic disease with potential kidney involvement (eg, systemic lupus erythematosus), or a family history of CKD, as wells as individuals who are moderately obese or ≥65 years old.

[d] Average of creatinine clearance and urea clearance can be used to estimate GFR in patients not on dialysis (see text).[3]

[e] In patients for whom creatinine-based results may lead to an incorrect diagnosis.

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