AMPATHCHAT no. 18 Version 2

DIAGNOSIS OF CHRONIC KIDNEY DISEASE

Dr Marita du Plesiss

April 2026

INTRODUCTION

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for longer than 3 months, with implications for health.

The most recent Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines (2024) recommend testing people at risk for and with chronic kidney disease (CKD) using both urine albumin-to-creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR). Following incidental detection of elevated ACR, haematuria, or low eGFR, repeat testing should be done to exclude a recent acute kidney injury (AKI) event or acute kidney disease (AKD).

In adults at risk for CKD, creatinine-based estimated glomerular filtration rate (eGFRcr) should be used for initial assessment.

The highest priority conditions for CKD screening are hypertension, diabetes and cardiovascular disease (CVD) including heart failure. For diabetes, the American Diabetes Association (ADA) and KDIGO recommend annual screening of people with diabetes for CKD, starting at the diagnosis of type 2 diabetes and 5 years after the onset of type 1 diabetes. It is also important to do follow up testing on patients with recent AKI or AKD. Other high-risk people may be identified through genetic risk factors or by varying exposure to environmental pollution, pesticides, and nephrotoxic medications including significant analgesic use and herbal medication.

Criteria for CKD

Either of the following present for more than **3 months**:

1. **Decreased GFR** (< 60 ml/min/1.73m^2) (GFR categories G3a - G5)
2. Markers of **kidney damage** (one or more) may be used to diagnose CKD but urine albumin-testing is still required to estimate stage and determine risk of progression:
   - a **Albuminuria**: Albumin excretion rate (AER) ≥ 30 mg/day or albumin-to-creatinine ratio (ACR) ≥ 3 mg/mmol.
   - b Urine sediment abnormalities (e.g. persistent haematuria, red cell / white cell / granular casts, etc).
   - c Electrolyte and other abnormalities due to tubular disorders.
   - d Abnormalities detected by histology, including fibrosis and atrophy.
   - e Structural abnormalities detected by imaging (e.g. reduced kidney size and reduction in cortical thickness).
   - f History of kidney transplantation.

CLASSIFICATION OF CKD USING THE CGA SYSTEM

CKD should be classified using the CGA staging system. This includes the Cause, Glomerular filtration rate (GFR) category and Albuminuria category, as the combination of these factors relates to risk of adverse outcomes.
CKD is not a disease in itself, and staging, assignment of cause and subsequent estimation of the risk of progression and complications are important to guide treatment decisions.

1. ASSIGNMENT OF THE CAUSE OF CKD

The cause of CKD is assigned based on the presence or absence of systemic disease and the location of observed or assumed pathology within the kidney. In developed countries, hypertension and diabetes are the most frequent causes of CKD. Examples of risk factors are supplied in table 1 and diseases and pathology affecting the kidney in table 2.
Establish the cause of CKD using clinical context, personal and family history, social and environmental factors, medications, physical examination, laboratory measures, imaging, and genetic and pathologic diagnosis.

TABLE 1: RISK FACTORS FOR CHRONIC KIDNEY DISEASE AND ITS OUTCOMES

Risk factor	Definition	Examples
Susceptibility factors	Increase susceptibility to kidney damage	Older age, family history of CKD, reduction in kidney mass, low birthweight, low income or education
Initiation factors	Directly initiate kidney damage	Diabetes, high blood pressure, autoimmune diseases, systemic infections, urinary tract infections, urinary stones, lower urinary tract obstruction, drug toxicity
Progression factors	Cause worsening kidney damage and faster decline in kidney function after initiation of kidney damage	Higher level of proteinuria, higher blood pressure, poor glycaemic control in diabetes, smoking
End-stage factors	Increase morbidity and mortality in kidney failure	Lower dialysis dose (Kt/V), temporary vascular access, anaemia, low serum albumin level, late referral.

Kidney International 2005; 67: 2089-2100

TABLE 2: CLASSIFICATION OF CKD BASED ON SYSTEMIC DISEASE AND LOCATION OF PATHOLOGY WITHIN KIDNEY

	Examples of systemic diseases affecting the kidney	Examples of primary kidney diseases (absence of systemic diseases)
Glomerular diseases	Diabetes Mellitus, systemic autoimmune diseases, systemic infections, drugs, neoplasia (including amyloidosis)	Diffuse, focal or concentric proliferative glomerulonephritis, focal and segmental glomerulosclerosis, membranous nephropathy, minimal change disease
Tubulointerstitial diseases	Systemic infections, autoimmune, sarcoidosis, drugs, urate, environmental toxins (lead, aristolochic acid found in Chinese herbal medicine), neoplasia (myeloma)	Urinary tract infections, stones, obstruction
Vascular diseases	Atherosclerosis, hypertension, ischaemia, cholesterol emboli, systemic vasculitis, thrombotic microangiopathy, systemic sclerosis	ANCA-associated renal limited vasculitis, fibromuscular dysplasia
Cystic and congenital diseases	Polycystic kidney disease, Alport syndrome, Fabry disease	Renal dysplasia, medullary cystic disease, podocytopathies

ANCA: Antineutrophil cytoplasmic antibody

Kidney International Supplements 2013: 3:19-62

2. RECOMMENDATIONS REGARDING GFR ESTIMATION

- Use **serum creatinine (SCr)** and an estimating equation for **initial assessment of GFR (eGFRcr)** and **cystatin C** and calculation of GFR using both creatinine and cystatin (**eGFRcr-cys**) or cystatin only (eGFRcys) in clinical situations **where eGFRcr is less accurate** and GFR affects clinical decision-making.
- Since November 2014 Ampath has been using the **2009 CKD - EPI creatinine equation** for calculation of the GFR in **adult patients** (18 years and above), without applying a race correction factor. This is in keeping with recommendations by the European Renal Association, which advised against implementation of the more recently published CKD-EPI 2021 equation, until locally validated.
- Understand the **limitations**, variability and **factors that influence SCr**, including:
  - Recent dietary intake of meat or fish meals (maximal effect after 2 - 4 hours)
  - Muscle mass
  - Other clinical conditions (refer to table 3)
  - Factors causing analytical interference, including bilirubin, some drugs (e.g. cephalosporins, acetaminophen, aspirin and ascorbic acid), glucose, and ketones.
- **CYSTATIN C** measurement is recommended in clinical situations where eGFRcr is less accurate (refer to table 3).
- Calculation of the eGFR using a combination of creatinine and cystatin C **(eGFRcr-cys)** is **usually more accurate** than using either parameter alone, except in cases where SCr is suspected to be affected by non-GFR determinants, where eGFR using cystatin only (eGFRcys) should be used.
- Cystatin C measurement can be added on the serum collected already, within 7 days post collection. A value of less than 60 ml/min/1.73m^2 confirms the diagnosis of CKD.
- **Clinical settings in which eGFRcys and eGFRcr-cys are less accurate**
  - Hypo- or hyperthyroidism
  - Glucocorticoid excess, including exogenous administration
  - Conditions associated with chronic inflammation
  - Cancer
  - Diabetes, obesity
- When a more accurate assessment of GFR is required for management decisions, or when using medications with a narrow therapeutic index or high toxicity, consider a **timed urine collection** to determine the creatinine clearance. A **measured GFR (mGFR)** using plasma or urinary clearance of an exogenous filtration marker is the gold standard but is unfortunately not routinely available.
- The **calculated GFR (eGFR) can be corrected for body surface area** on request (test mnemonic: CRC), when the patient's height and weight are provided. The main indication for using a corrected eGFR is by oncologists for adjustment of cytotoxic drug dosages (e.g. carboplatin).
- For patients with CKD, a **change in eGFR of more than 25 %** or **decline of more than 5 ml/min/1.73m^2** on a follow up test is greater than the expected variability, and warrants further evaluation, after exclusion of changes in diet or muscle mass (if using eGFRcr).
- Among people with **CKD who initiate haemodialysis**, **GFR reductions of > 30 %** on subsequent testing exceeds the expected variability and warrant further evaluation.
- A creatinine based calculated GFR is available on request in **children** using the updated **Schwartz equation (EGFRS)**, requiring the patient's height.
  - The adult CKD staging system can be used in children over 2 years of age, however eGFR values < 90 ml/min/1.73m^2 should be regarded as abnormal (low).
  - In children younger than 2 years of age, eGFR is categorised as normal, moderately reduced (between 1 and 2 SD of the mean of the reference range) and severely reduced (more than 2 SD below the mean). Drug dosing adjustments are recommended with moderately reduced eGFR and indicated with severely reduced eGFR.

TABLE 3: CLINICAL CONDITIONS AFFECTING SERUM CREATININE AND CYSTATIN C

Clinical conditions	Cause of inaccuracy of $eGFR_{cr}$	Recommended test
Body habitus and changes in muscle mass • Eating disorders • Extreme sport/exercise/ body builder • Above-knee amputation • Spinal cord injury with paraplegia/ paraparesis or quadriplegia/ quadriparesis	Non-GFR determinants of SCr in all conditions, except for obesity.	eGFRcys may be appropriate if no comorbid illness. Suggest eGFRcr-cys in those with comorbid illness.
• Class III obesity	Non-GFR determinants of SCr and SCys.	eGFRcr-cys demonstrated to be most accurate.
Lifestyle • Smoking	Non-GFR determinants of SCys	eGFRcr if no changes to non-GFR determinants of SCr or comorbid illness.
Diet • Low-protein diet • Keto diet • Vegetarian • High-protein diets and creatine supplements	Non-GFR determinants of SCr	Minimal data, suggest eGFRcr may be appropriate if no changes to non-GFR determinants of SCr or no comorbid illness.
Medication effects • Steroids (anabolic, hormone)	Non-GFR determinants of SCr. Effect on SCys not known.	Physiological effect on SCys unknown, suggest eGFRcr-cys.
• Decreases in tubular secretion, e.g. trimethoprim, cimetidine, fenofibrate.	Non-GFR determinants of SCr	eGFRcys may be appropriate if medication affects only creatinine and no comorbid illness. Suggest using mGFR for treatment decisions based on the level of GFR.
• Broad spectrum antibiotics that decrease extrarenal elimination	Non-GFR determinants of SCr	
Malnutrition	Chronic illness, presumed impact on non-GFR determinants of SCr and SCys	eGFRcr-cys may be less accurate because of coexistence of malnutrition and inflammation. Suggest using mGFR for treatment decisions based on the level of GFR.
Cancer	Chronic illness, presumed impact on non-GFR determinants of SCr and SCys	eGFRcr-cys demonstrated to be most accurate in populations studied but likelihood of lesser accuracy in more frail people or in cancers with high cell turnover. Suggest using mGFR for treatment decisions based on the level of GFR.
Heart failure Cirrhosis	Chronic illness, presumed impact on non-GFR determinants of SCr and SCys	Suggest using eGFRcr-cys or eGFRcys for routine GFR evaluation. Suggest using mGFR for treatment decisions based on the level of GFR.
Catabolic consuming diseases Muscle wasting diseases	Chronic illness, presumed impact on non-GFR determinants of SCr and SCys	Suggest using eGFRcr-cys for routine GFR evaluation. Suggest using mGFR for treatment decisions based on the level of GFR.

Kidney International Supplements 2024; 4: S117–S314

GFR categories in CKD

- Since 2012 stage 3 has been subdivided into stage 3a and 3b, based on data supporting different risks and outcomes.
- In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.
- Although **eGFR from 60 to 89 is mildly decreased** and not regarded as CKD unless present for longer than 3 months in the presence of moderate albuminuria (> 3.0 mg/mmol), efforts should be directed at especially younger people in this category with higher risk estimations, to prevent the onset of CKD or further reductions in GFR.
- Associated risk factors for cardiovascular disease, including hypertension, dyslipidaemia, smoking and other lifestyle factors, should be addressed.
- The following additional investigations are recommended:
  - Creatinine: repeat within 14 days for confirmation (after 12 hrs of no meat consumption), and then annually.
  - Annual urine albumin-to-creatinine ratio.

- In **older persons**, in the absence of albuminuria, **GFR category 3A (eGFR of 45 – 59** ml/min/1.73 m^2) is common and is seldom progressive.
  - An eGFR based on CYSC(eGFRcys) should be calculated in older patients in this category to confirm the eGFR Stage.
  - Identification and treatment of any comorbid conditions is important, including diabetes, hypercholesterolaemia and cardiovascular conditions (e.g. HT, heart failure and atherosclerosis).
  - Follow up Creatinine (eGFR) is recommended after 6 - 12 months - if eGFR declines by more than 25 % or 5 ml/min/1.73m^2 over a year, further evaluation may be warranted.

TABLE 4: CLASSIFICATION OF CKD BASED ON SYSTEMIC DISEASE AND LOCATION OF PATHOLOGY WITHIN KIDNEY

GFR category	GFR (ml/min/1.73m2)	Terms
G1	≥ 90	Normal or high
G2	60 - 89	Mildly decreased (relative to young adult)
G3a	45 - 59	Mildly to moderately decreased
G3b	30 - 44	Moderately to severely decreased
G4	15 - 29	Severely decreased
G5	< 15	Kidney failure

Kidney International Supplements 2024; 4: S117-S314

3. ALBUMINURIA AS A MARKER OF KIDNEY DAMAGE

- **Albuminuria** is the preferred marker for assessment of kidney damage, and should be used in preference to proteinuria, as it is the earliest marker of **glomerular disease**.
- There is a **graded increase in risk** for all-cause and cardiovascular mortality, kidney failure, acute kidney injury (AKI) and CKD progression for higher albuminuria categories across all GFR categories.
- For **screening** purposes an early morning midstream urine sample (first void) for determination of the **albumin-to-creatinine ratio (ACR)** is preferred.
- The term microalbuminuria for an ACR of 3 - 30 mg/mmol (category A2) has been replaced by the term "**moderately increased**" **albuminuria**.
- An abnormal screening test should be **confirmed** by an ACR on an early morning urine sample or an albumin excretion rate (AER) in a timed urine collection.
- The use of **reagent test strips is discouraged** due to poor sensitivity at lower concentrations and because the values are not adjusted for urinary concentration.
- If non-albuminuric proteinuria is suspected, use assays for **specific proteins**, e.g. determination of Bence Jones proteins in myeloma patients.
- Patients with ACR > 3 mg/mmol (A2 - A3 categories) have increased risk for all outcomes, and current guidelines recommend a **lower systolic blood pressure target of 120 mm Hg**.
- For albuminuria monitoring of patients with CKD, a **doubling of the ACR** on a subsequent test exceeds laboratory variability and warrants evaluation.
- **Consider the following factors** when evaluating urine albumin results:
  - Haematuria, menstruation, exercise and infection cause an increase in urinary albumin/protein.
  - Female sex or lower body weight results in lower urine creatinine and falsely higher ACR or PCR values.
  - Male sex or higher body weight results in higher urine creatinine and falsely lower ACR or PCR values.
  - Urinary creatinine excretion is lower following AKI or a low protein diet and higher with high protein intake or exercise.

TABLE 5: ALBUMINURIA CATEGORIES IN CKD AND RELATIONSHIP WITH PROTEINURIA

	Categories		
Measure	**Normal (A1)**	**Moderately Increated (A2)**	**Severely Increased (A3)**
Albumin-to-creatinine ratio (ACR) (mg/mmol)	< 3	3 - 30	> 30
Albumin excretion rate (AER) (mg/24h)	< 30	30 - 300	> 300
Protein-to-creatinine ratio (PCR) (mg/mmol)	< 15	15 - 50	> 50
Protein excretion rate (PER) (mg/24h)	< 150	150 - 500	> 500
Protein reagent strip	Negative to trace	Trace to +	+ or greater

Kidney International Supplements 2024; 4: S117–S314

Nephrotic syndrome: ACR > 220 mg/mmol, AER > 2200 mg/24h, PCR > 350 mg/mmol, PER > 3500 mg/24h

Risk prediction in CKD

- Associations of all complications of CKD are incrementally increased with worsened categories of eGFR and ACR.
- The **KDIGO 2012 clinical practice guidelines** presented the combined associations of eGFR and ACR categories as "heatmaps", which are color-coded depictions of the relative risk, on a population level, for outcomes of all-cause mortality, kidney failure, AKI, and cardiovascular mortality.
- The **KDIGO 2024 clinical practice guidelines** have increased the number of outcomes to 10, including 6 that are cardiovascular related, 2 that are kidney specific (kidney failure and AKI), and 2 general outcomes (all-cause mortality and all-cause hospitaliasation). Additional analyses have been conducted using the 2021 CKD-EPI combined eGFR equation that incorporates both creatinine and cystatin C. These heatmaps depicting **relative risk** for the specific outcomes are available on their website www.kidney-international.org

- Use of an externally validated **risk equation** is recommended to estimate the **absolute risk of kidney failure** in individuals with **CKD G3 – G5 to guide treatment decisions**. The calculated absolute risk should be used in combination with eGFR-based criteria and other clinical considerations as proposed below:
  - To indicate the need for nephrology referral with 5-year kidney failure risk of 3 % – 5 %.
  - To determine the timing of multidisciplinary care (Nephrologist, dietician, nurse, pharmacist) with 2-year kidney failure risk of > 10 %.
  - To determine the modality education, timing of preparation for kidney replacement therapy (KRT) including vascular access planning, or referral for transplantation for 2-year kidney failure risk threshold of > 40 %.
- The **Kidney Failure Risk Equation (KFRE)** is an example of an equation for **CKD G3 - G5**, which can be accessed online at https://www.kidneyfailurerisk.com. It requires information on 4 variables (age, sex, eGFR and ACR) or 8 variables (first 4 + calcium, phosphate, bicarbonate and albumin) for better accuracy.
- Please note that risk prediction equations developed for use in people with CKD G3 – G5, may not be valid for use in those with **CKD G1 – G2**. To calculate the 5 year probability of an eGFR < 60 in the latter, use the following online calculator: https://ckdpcrisk.org/ckdrisk.
- For **cardiovascular risk prediction** to guide preventative therapies in people with CKD, use externally validated models that are either developed within CKD populations or that incorporate eGFR and albuminuria, e.g. QRISK calculator that was developed in the UK: https://www.qrisk.org.

CRITERIA FOR REFERRAL TO A NEPHROLOGIST (IN LINE WITH KDIGO GUIDELINES)

- > 3 % five-year risk of kidney failure requiring dialysis or transplant as estimated by a validated risk equation (e.g. Kidney failure risk equation [KFRE])
  Low or relatively rapid decline in eGFR:
  - eGFR < 30 mL/min/1.73 m^2
  - Single kidney with eGFR < 60 mL/min/1.73 m^2
  - Reduction in eGFR > 5 mL/min/1.73 m^2 or decline > 25 % per year - confirm with repeat lab testing within one to two months to rule out physiological variability.
- Consistent findings of elevated urinary protein:
  - For patients without haematuria, UACR > 70 mg/mmol or ≥ 2-fold increase in albuminuria to UACR > 60 mg/mmol
  - For patients with haematuria, UACR ≥ 30 mg/mmol; approximately equivalent to UPCR > 50 mg/mmol
- Abnormal urine microscopy (cellular casts, non-urologic haematuria, sterile pyuria)
- History of systemic autoimmune disease, multiple myeloma, or monoclonal gammopathy
- Large cystic kidneys by kidney imaging or examination
- Inability to identify a presumed cause of CKD, especially in younger patients
- Biochemical abnormalities that are difficult to manage such as hyperkalaemia, metabolic acidosis, anaemia requiring erythropoietin therapy, hyperphosphataemia, or hypocalcaemia
- Resistant hypertension
- Recurrent or extensive nephrolithiasis
- Pregnancy
- Confirmed or presumed hereditary kidney disease, such as polycystic kidney disease, Alport syndrome, or autosomal dominant interstitial kidney disease
- Difficult to manage complications of various medications, such as chemotherapeutic agents that may cause kidney injury or increase proteinuria.

REFERENCES

1. Levey AS, Eckardt K, et al. Definition and classification of Chronic Kidney Disease: a position statement from Kidney Disease Improving Global Outcomes (KDIGO). Kidney International 2005; 67: 2089-2100.
2. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. 2012. Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International, Supplement 2013; 3: 1-150. Available online at https://kdigo.org/home/guidelines/ckd-evaluation-management.
3. Kidney Disease: Improving Global Outcomes (KDIGO) 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International, Supplement 2024; 105 (Suppl 4S): S117-S314. Available online at https://kdigo.org/guidelines/ckd-evaluation-and-management.
4. Fatehi P, Hsu C. Chronic kidney disease (newly identified): Clinical presentation and diagnostic approach in adults. In: UpToDate, Taylor EN. UpToDate, Waltham, MA. (Accessed on March 20, 2025).
5. Delanaye P et al. Opinion paper. An age-calibrated definition of chronic kidney disease: Rationale and benefits. Clin Biochem Rev 2016; 37(1): 17-26.