Tina-quant® Cystatin C

Supporting the early detection of chronic kidney disease

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Flexible and intelligent solutions

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cobas 8000 modular analyzer series
Large volume

38 configurations

<c 502> *<e 602>* *<c 701>* *<c 702>*

cobas 6000 analyzer series
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cobas 4000 analyzer series
Low volume

3 configurations

<c 311> *<e 411>*

Chronic kidney disease

Cystatin C is a novel serum marker for the diagnosis of chronic kidney disease (CKD), which is particularly useful for detection in the early stages. It is a small protein that can be used for estimating glomerular filtration rate (GFR), the best indicator of kidney function, due to its continuous production in most cells of the body and the fact that it is freely filtered and absorbed by the kidney. Any change in GFR, however small, is reflected by a change in the serum cystatin C level, and, for this reason, increases in cystatin C are detectable much earlier in the course of CKD when levels of creatinine are still in the normal range.[11] This enables more timely diagnosis and initiation of treatment, allowing the optimal benefits of therapy for the patient to be realized. In addition, as cystatin C levels of the disease are independent of gender, muscle mass or other chronic illness, unlike creatinine levels, evidence suggests that cystatin C is a better marker for the early detection of impaired renal function; working together with creatinine for the detection of CKD across the disease continuum.

A common and increasing major health concern

Chronic kidney disease (CKD) affects around 600 million people worldwide, or approximately one in 10 people,[1] and the prevalence is rising. In some regions, such as the USA, the prevalence is estimated to be as high as 14% of the population.[2]

One reason for the increasing prevalence is the aging population: age is a risk factor for CKD and 30% of the elderly population are thought to have kidney disease in some form. In addition, along with increasing age, diabetes, cardiovascular disease (CVD) and hypertension are also associated with an increased risk of CKD. These diseases are all health issues associated with urbanized societies where unhealthy diet, increased body fat and sedentary lifestyle are common.[3]

Indeed, development of CVD is known to be a major outcome of CKD, and patients with kidney disease are three times more likely to develop CVD than a healthy population. Furthermore, there are millions of premature deaths from CVD related to CKD.[1]

The greatest challenge in managing kidney disease is that over half of all individuals are unaware that they have the condition until significant damage has developed.[4] Lack of symptoms in the early stages of the disease mean that, without monitoring, CKD can easily go undetected, leading to progressive damage and loss of kidney function. Ultimately, dialysis or kidney transplantation is required, which increases the risk to patients and puts a substantial burden on healthcare budgets. As such, early detection of CKD would be of huge benefit both in terms of patient outcome and healthcare cost savings.

A significant burden on healthcare systems

Late detection of kidney disease is known to increase the risk of progression to end-stage renal disease (ESRD) and/or development of CVD.[4] Treating ESRD with dialysis or kidney transplantation is very costly, and development of comorbidities such as CVD increase the financial burden still further[2,5] (Figure 1). In the USA, the annual cost of CKD is estimated to be $52–122 billion,[5] 70% of which is due to the presence of comorbidities. Furthermore, the later CKD is diagnosed, the more chance there is of missing the critical early window for therapeutic intervention that can delay, or even prevent, further damage.

The importance of early detection

Early intervention in patients with CKD has the potential to delay, or even prevent, the development of ESRD and complications,[4] leading to a marked impact on life expectancy, quality of life and social burden. In the USA, early intervention has been shown to reduce treatment costs by as much as 70%[5] (Figure 1), and cost savings have also been shown in the UK and Germany.[6,7]

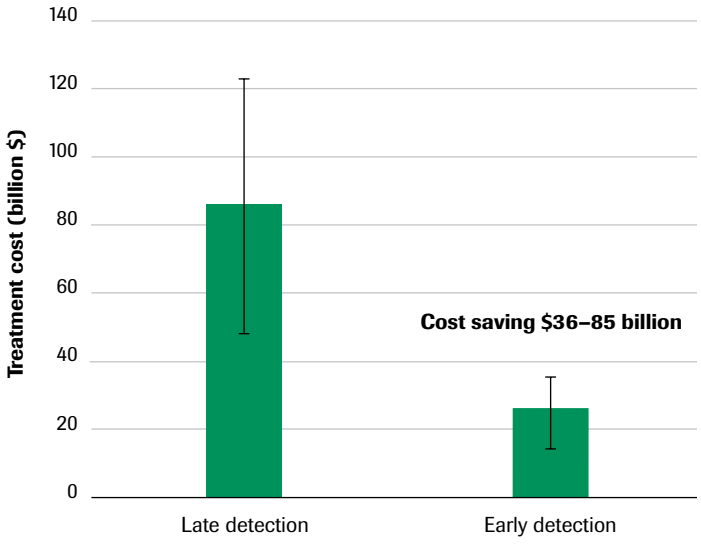

Figure 1: Early intervention reduces the cost of treating CKD[5]

Chronic kidney disease

Diagnosis and classification

Chronic kidney disease is defined as a decreased level of kidney function and/or the presence of kidney damage for longer than 3 months;[8] however, it is often characterized clinically by a progressive loss in renal function over a period of months or years. Physical symptoms of CKD are non-specific, such as reduced appetite and feeling unwell, which means that it is often not diagnosed unless the patient develops an associated complication such as CVD. Guidelines recommend that individuals with associated risk factors, including diabetes, hypertension or a familial link to CKD, should be screened regularly[8] as making the diagnosis early in the disease course allows therapy to be initiated before more severe damage occurs and the therapeutic window is missed.

Kidney function is assessed clinically by determining the glomerular filtration rate, or GFR.[9] This is a measure of the volume of liquid filtered from the blood by the kidneys each minute, standardized for the average body surface area of 1.73 m^2. GFR is calculated by quantifying the clearance of chemicals that have steady levels in the blood and are renally filtered, but not renally absorbed or secreted. In a clinical setting, GFR is usually estimated (eGFR) using measurements of endogenous substances, such as creatinine or cystatin C. Decreasing GFR is known to correlate with the pathologic severity of kidney disease and, in most cases, GFR declines progressively over time leading to complications such as hypertension and CVD. As such, GFR can be used both to help diagnose and classify CKD. However, GFR alone is often not sufficient to provide a diagnosis of CKD as the definition also includes the presence of kidney damage. Kidney damage is detected by measuring the amount of protein in the urine: in a healthy individual the protein level is very low, however it increases when the kidney is damaged.

Individuals with kidney damage for more than 3 months, with or without reduced GFR, or with a GFR <60 mL/min/1.73 m^2 for more than 3 months in the presence or absence of kidney damage are considered to have CKD.[8] CKD is further classified according to the reduction of kidney function, as shown in Table 1.

Stage	GFR	Proteinuria detectable	Proteinuria not detectable
1	>89	Kidney disease with normal renal function	Normal finding
2	60–89	Kidney disease with mild renal impairment	Mild renal impairment, but NO kidney disease
3	30–59	Kidney disease with moderate renal impairment	
4	15–29	Kidney disease with severe renal impairment	
5	<15	Chronic renal failure	

Table 1: Classification of CKD[8]

Stages 1–2 represent mild kidney disease, stages 3–4 represent more severe kidney disease, and stage 5 represents ESRD which requires Renal Replacement Therapy (RRT; dialysis or kidney transplantation). However, patients do not always progress from stage 1 to stage 5. Very rapid progression to kidney failure is indicative of acute kidney failure, often occurring due to injury or infection for example. This is usually reversible, although dialysis may be required for a short time.[10]

Monitoring

Kidney function should be monitored in all patients with CKD and those considered at risk of developing the condition so that any changes can be identified early and managed accordingly. Timely diagnosis requires a test that accurately detects the subtle changes in kidney function observed in the early stages of the disease.

Determining creatinine clearance (CrCl) and estimating GFR using serum creatinine levels are the current mainstays for the clinical assessment of kidney function today. However, there is growing interest in using cystatin C as a marker for CKD because it offers several advantages over creatinine.

Limitations of creatinine

While creatinine has been widely used to date to assess renal function, it is subject to variation due to a number of factors including age, gender, race, chronic illness, diet, and muscle mass[9] (Table 2).

Factors causing a decrease in serum creatinine	Factors causing an increase in serum creatinine
Increasing age	Black ethnicity
Female gender	Increased muscle mass
Asian ethnicity	Black ethnicity
Hispanic ethnicity	
Inflammation	
Neuromuscular illness	
Amputation of limbs	
Malnutrititon	
Vegetarian diet	

Table 2: Factors that cause variation in serum creatinine levels[9]

As a result, CrCl and serum creatinine measurements show a relatively low diagnostic sensitivity and specificity compared with cystatin C (levels of which are much less influenced by these factors) for early diagnosis of CKD [11] (stages 1 and 2; Figure 2).

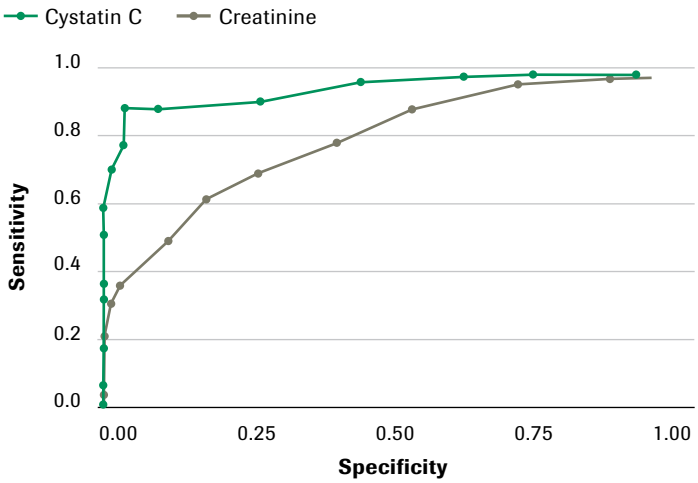

Figure 2: Serum creatinine shows relatively low diagnostic sensitivity and specificity vs. cystatin C for the diagnosis of CKD [11]

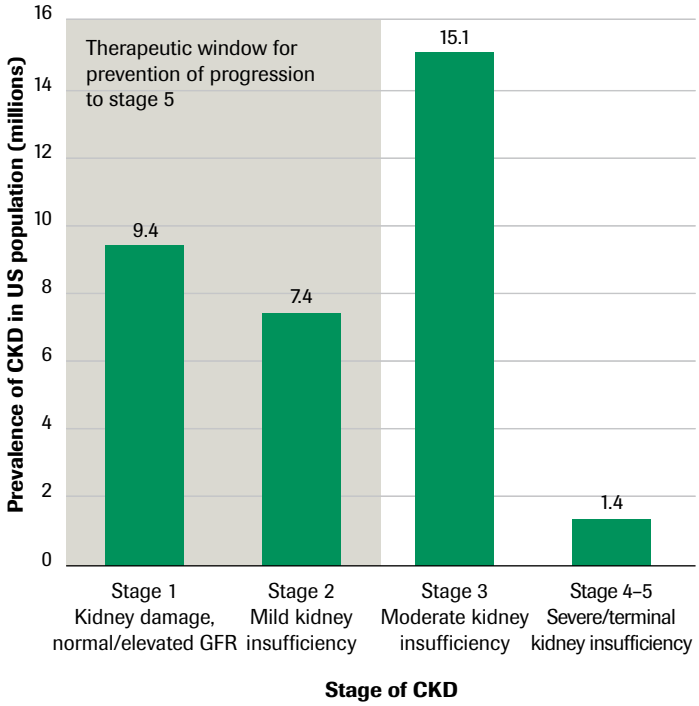

Figure 4: Not detecting CKD in the early stages (stages 1 and 2) means that half of patients miss the advantages of early treatment [2,16]

The inability of creatinine to detect mild kidney insufficiency (stages 1 and 2) is due to the fact that serum creatinine levels only begin to rise above the normal value when approximately 50% of renal function is already lost;[12] this is known as the **creatinine-blind area** (Figure 3). Using creatinine alone as the diagnostic test for kidney disease means that many patients with stage 1 or stage 2 may go undetected and the important early therapeutic window may be missed (Figure 4).[13,14]

So, although creatinine is a good marker for detecting stages 3–5 of CKD, it is not useful in patients in the early stages of CKD due to the creatinine-blind area (Figure 3). An additional diagnostic method, such as cystatin C, would be extremely valuable to use alongside creatinine to cover patients in the early stages of CKD.

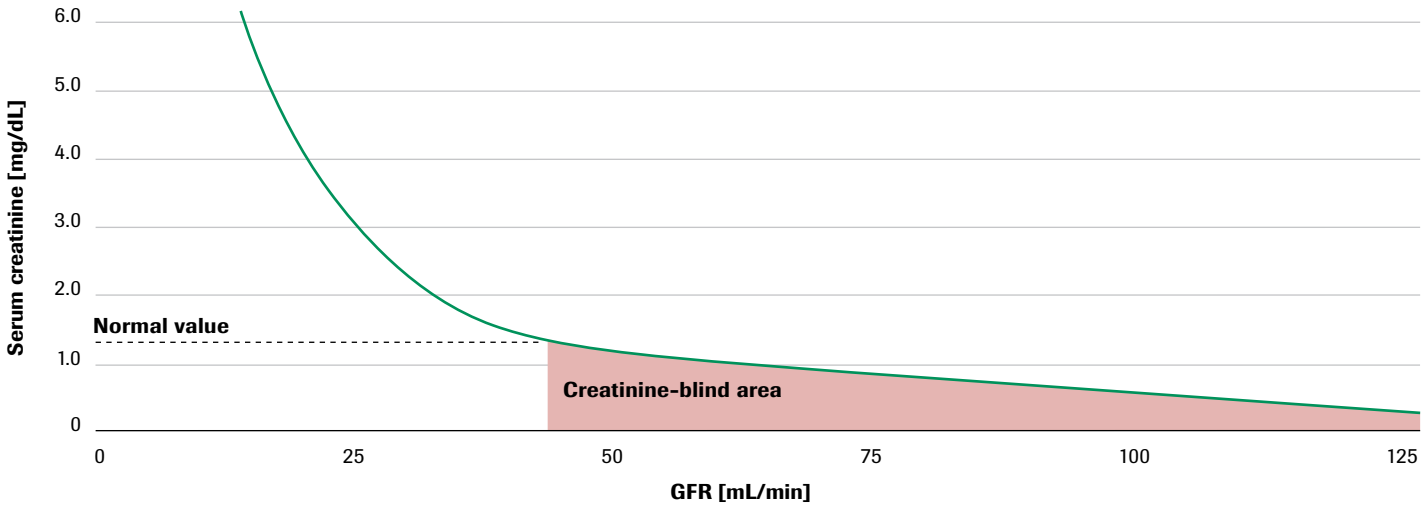

Figure 3: The limitations of serum creatinine mean that patients with early stage kidney disease may go undetected [13–15]

Tina-quant® Cystatin C

A new marker with higher medical value compared with creatinine

The early stages of CKD are characterized by subtle reductions in GFR that creatinine-based measurements are not able to detect. In contrast, these small GFR changes are reflected in altered levels of serum cystatin C, allowing earlier detection and diagnosis.[11] Furthermore, as there is no variation in cystatin C due to gender, muscle mass or inflammation,[9] it shows superior performance as a marker compared with creatinine in children with renal disease, the elderly, diabetic patients, transplant patients and cancer patients (independent of the presence of metastases or chemotherapy).[17–25]

The enhanced detection of early CKD (stages 1 and 2) using cystatin C allows physicians to provide patients with a much improved prognosis. The aim of therapy is to slow disease progression to stage 5 (ESRD), and the sooner treatment is initiated, the greater the benefit. The early detection and initiation of therapy afforded by using cystatin C as a marker for CKD has been shown to prolong ESRD-free survival for up to 2 years compared with treatment following creatinine-based detection, and up to 4 years compared with no treatment[26,27] (Figure 5).

Once a patient reaches stage 5, treatment options are limited to dialysis or transplantation, both of which are associated with poor outcomes for the patient and are extremely costly. In addition, as CKD is associated with an increased risk of CVD and other risk factors for heart disease (e.g., hyperlipidemia), patients are more likely to suffer from comorbidities at more advanced stages of CKD.[28] By detecting CKD earlier using cystatin C, disease progression can be delayed and even prevented, to provide patients with a longer life free of kidney failure.

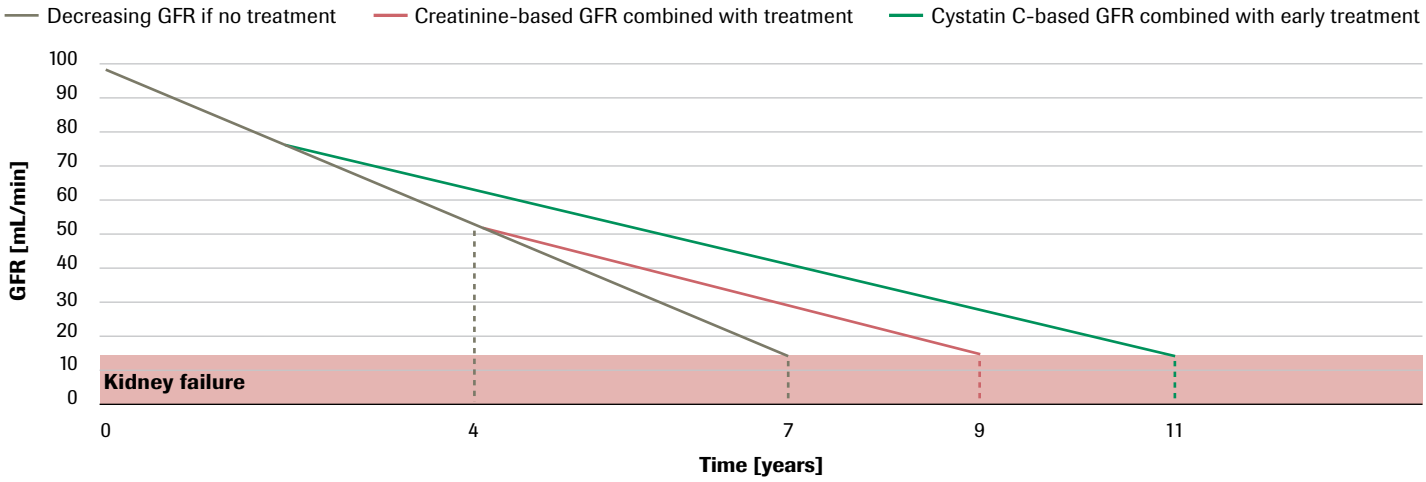

Figure 5: Cystatin C is the marker of choice for early detection of CKD (stages 1 and 2), contributing to improved patient outcome[26,27]

Early detection of CKD using cystatin C allows early therapeutic intervention and can delay ESRD by up to 2 years compared with creatinine-based detection[26,27]

Conclusion

The Tina-quant® Cystatin C assay is valuable for the early detection of CKD

Chronic kidney disease can be treated more effectively if detected early enough, leading to improved patient outcomes and a significantly diminished economic burden worldwide.

The Roche **cobas®** diagnostic markers portfolio contains both cystatin C and creatinine as markers for CKD, to allow detection across all 5 stages of CKD (Figure 6). The inclusion of the Tina-quant Cystatin C assay allows the critical early detection of CKD.

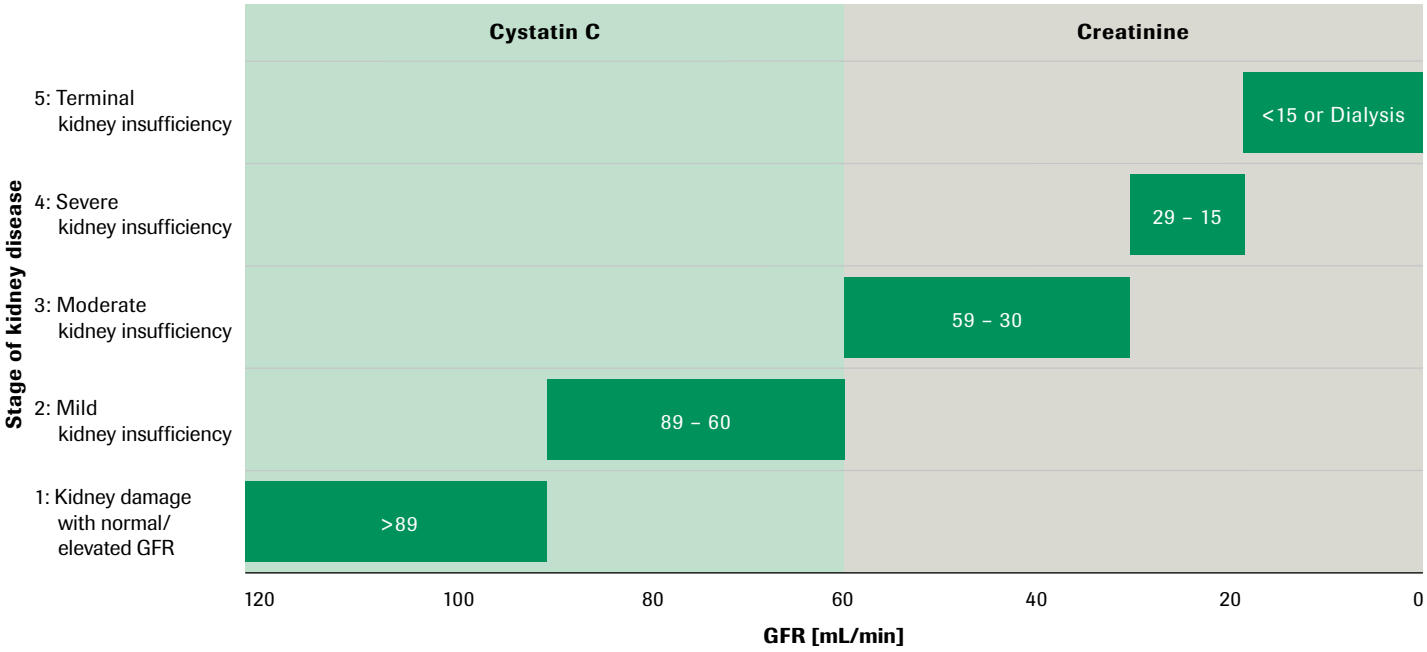

Figure 6: Cystatin C combined with creatinine detects all stages of CKD

Get excellent medical value

- Tina-quant Cystatin C is the assay of choice for early detection when creatinine is still in the normal range – offering patients a longer life without kidney failure
- Tina-quant Cystatin C is not influenced by gender, muscle mass or inflammation
- Tina-quant Cystatin C, together with creatinine measurement, provides detection of CKD across the complete range of renal function

Potential clinical uses for Tina-quant® Cystatin C

GFR estimation in mild renal impairment

- Creatinine and modification of diet in renal disease (MDRD) are of limited use when the GFR is 60–90 mL/min because of the creatinine-blind area [13,14]
- Cystatin C permits earlier recognition of chronic renal impairment in high-risk populations (e.g. patients with diabetes, hypertension) [8,22]
- Early detection permits earlier therapeutic intervention when GFR is only mildly impaired

GFR measurement before and after contrast administration

- Accurate renal function testing is essential both before and after contrast administration to avoid contrast-induced nephropathy [29]
- A cystatin C increase of <10% at 24 hours after contrast administration excludes contrast-induced nephropathy; an increase of >10% at 24 hours after administration is an independent predictor of major adverse events at 1 year after treatment [29]
- High-risk populations can be classified more exactly, and prophylactic therapeutic measures better controlled, with cystatin C

Renal function testing in children and the elderly

- In adults, the Cockcroft-Gault and MDRD equations are recommended for eGFR calculated from creatinine measurements; however in patients <18 and >70 years the Schwartz and Counahan-Barratt equations are recommended [8]
- With its constant rate of synthesis, cystatin C permits more reliable and exact estimation of GFR in children and the elderly where the relationship between cystatin C and GFR is more complex [30,31]
- This avoids use of time-consuming methods such as 24-hour urine collection

Monitoring of drug dosage

- In the case of drugs whose dosage depends on renal function, more accurate estimation of renal function with cystatin C allows more accurate adjustment of dosages, thus avoiding major side effects [32,33]
- It also permits earlier and more exact detection of kidney damage due to nephrotoxic drugs [34,35]

GFR measurement in renal transplant recipients

- Transplant nephropathy requires early and reliable detection. In this patient population, cystatin C identifies renal impairment with high certainty, thereby contributing to improved management of renal transplant recipients [36]

Renal function testing using Tina-quant® Cystatin C provides excellent medical value for your laboratory

- Cystatin C is a more reliable, early marker of renal dysfunction, compared with creatinine [11]
- Adverse outcomes of renal failure can be prevented or delayed through early detection and treatment [37–42]
- Cystatin C concentration is not influenced by inflammation, muscle mass, gender, or age [9]
- Cystatin C is a better indicator of mild changes in GFR; at which stage creatinine values are still within the normal range [19]
- Cystatin C as a measure of renal function enhances the early detection, prevention, and treatment of diabetic kidney damage [22]
- Cystatin C exhibits superior diagnostic accuracy for decreased GFR compared with that of creatinine in children under 3 years old with renal disease [18]
- Constant production of cystatin C makes it an ideal marker of GFR, especially in patients with reduced muscle mass or conditions that produce rapid change in muscle mass [43,44]
- Cystatin C is a superior marker of early stages of renal impairment in the elderly population [45]
- Cystatin C is the preferred method for testing renal function in certain patient groups, such as patients with diabetes and the critically ill [21]
- Cystatin C is superior to creatinine for assessing GFR in patients with cancer [25]

Glossary and abbreviations

Chronic kidney disease – decreased kidney function and/or kidney damage for a continuous period of 3 months

Glomerular filtration rate – the rate of fluid filtration from the blood into the kidneys

Estimated GFR – calculation of GFR using the concentration of an endogenous substance, such as creatinine or cystatin C, which is freely filtered by the kidneys

End-stage renal disease – renal failure, treated by dialysis or kidney transplantation

CKD chronic kidney disease

CrCl creatinine clearance

CVD cardiovascular disease

ESRD end-stage renal disease

GFR glomerular filtration rate

eGFR estimated GFR

RRT renal replacement therapy

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