Product availability may vary from country to country and is subject to varying regulatory requirements. An N Latex Cystatin C assay standardized to ERM-DA471/IFCC reference is not available for sale in the U.S. Please contact your local representative for availability.

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Enabling Early Detection of Renal Function Decline

N Latex Cystatin C Assay

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Answers for life.

Diagnosing the Silent Threat: Chronic Kidney Disease

Chronic kidney disease is a major public-health problem across the world. In the U.S. and Western Europe, the incidence has tripled since 1990, a trend that seems likely to continue due to the increasing incidence of diabetes and hypertension—the major causes of kidney failure in today's aging population.[1]

Data from the 2013 USRDS annual report shows that the number of patients treated for end stage renal disease (ESRD) is 10 times higher than in 1980, with more than 600,000 in the U.S. alone.[2]

Intelligent laboratory-testing solutions not only provide valuable information for monitoring and monitoring kidney disease, but also contribute substantially to improved patient outcomes and reduced healthcare costs.

Kidney disease is painless

Renal disease often progresses undetected, because kidney impairment does not cause pain. This is why, for so many patients, kidney disease is not diagnosed until they show symptoms of an advanced stage of the disease. In the early stages of disease, laboratory testing is the most efficient and sensitive way to detect reduction in renal function.

Today, chronic kidney disease can be significantly detained if diagnosed early enough.

Laboratory testing for kidney disease can therefore have a crucial impact on patient management. It can reduce the risk of developing end-stage renal disease (requiring dialysis or transplantation) and cardiovascular disease (CVD), the leading cause of mortality in chronic kidney disease patients (Figure 1).

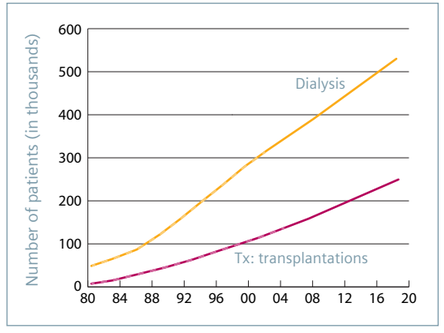

Figure 1. Projected growth of prevalent ESRD populations, by modality.[3]

Counts projected using a Markov model. Original projection uses data through 2000; new projection uses data through 2005.

GFR and chronic kidney disease

According to KDIGO* guidelines published in January 2013, glomerular filtration rate (GFR, Figure 2) is used for definition and classification of chronic kidney disease (CKD).[4]

Definition of chronic kidney disease:[1]

- GFR <60 mL/min/1.73 m^2 for ≥3 months, or
- Kidney damage for ≥3 months (structural or functional abnormalities; e.g., increased albumin excretion)

A reliable and sensitive method for GFR assessment is crucial to diagnose CKD at an early stage, because strategies to improve outcomes are more successful with earlier treatment.

Today, determination of serum creatinine is the most widely used method for estimating GFR. However, the creatinine level is strongly related to the patient's muscle mass and must be corrected for weight and age (e.g., using the Cockcroft-Gault formula) to allow accurate interpretation. Furthermore, creatinine is increasingly secreted by renal tubules with decreasing renal function. As a result, serum creatinine increases only when the full capacity of this alternative route of elimination is reached (the creatinine-blind range).

Advanced GFR determination with cystatin C

Cystatin C is a nonglycated, low-molecular-weight (13 kDa) protein that is synthesized by all nucleated cells. It is produced at a constant rate regulated by a housekeeping gene.[5]

Cystatin C is freely filtered by the glomerulus, and there is no tubular secretion or any extrarenal elimination. In addition, cystatin C is not affected by muscle mass, diet, gender, or inflammation.

Due to these factors, cystatin C shows increased sensitivity to renal dysfunction compared to serum creatinine, especially in the early stage of kidney disease characterized by a mild reduction of GFR.

After glomerular filtration, cystatin C is reabsorbed and metabolized by the proximal tubulus cells, resulting in a very low concentration in urine under normal conditions. However, an increase in urinary cystatin C may indicate a tubular injury or dysfunction.[5]

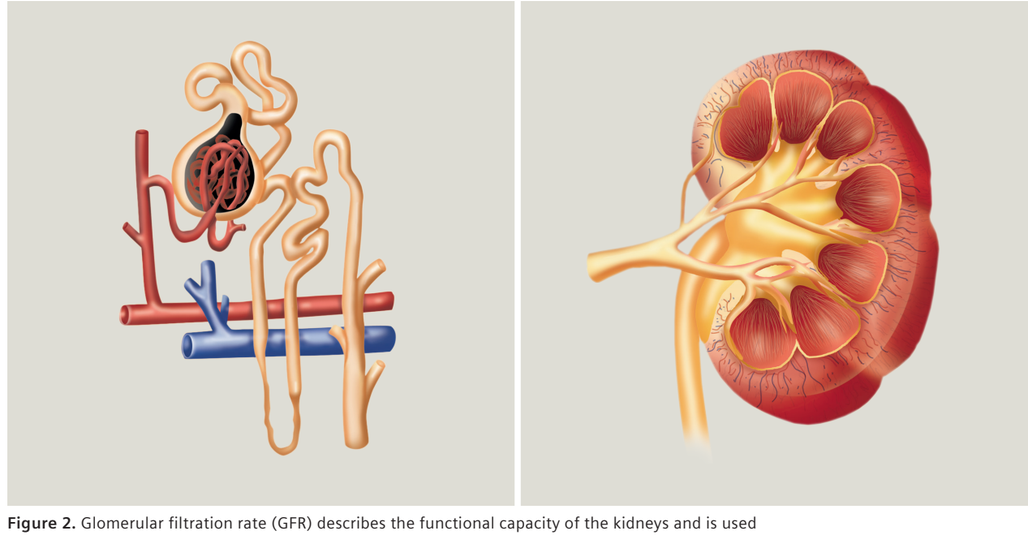

Figure 2. Glomerular filtration rate (GFR) describes the functional capacity of the kidneys and is used to define the severity of kidney dysfunction.

*KDIGO: Kidney Disease Improving Global Outcomes

Cystatin C: the More Sensitive Alternative for Estimating GFR

There are multiple studies and formulas available to calculate the estimated glomerular filtration rate (eGFR) from creatinine or cystatin C alone or in combination.

However, cystatin C offers clear advantages over serum creatinine and creatinine-based GFR formulas for a sensitive and reliable diagnosis of decreased GFR.

Determining cystatin C is now recommended in international guidelines

For the first time, the relevance of determining cystatin C for diagnosis for CKD (chronic kidney disease) is now included in the international KDIGO guidelines. Well-validated equations based on cystatin C and the combination of cystatin C and creatinine are provided.

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2012 formula for determination of eGFR from cystatin C is shown in Table 1.

Table 1. KDIGO/CKD-EPI 2012 cystatin C equation for adult GFR estimation.

	Serum Cystatin C	Equation for Estimating GFR
Male or female	≤0.8 mg/L	$133 \times (SCysC/0.8)^{-0.499} \times 0.996^{Age}$ [x 0.932 if female]
Male or female	>0.8 mg/L	$133 \times (SCysC/0.8)^{-1.328} \times 0.996^{Age}$ [x 0.932 if female]

GFR estimation from cystatin C

The IFCC SD Working Group on Standardization of Cystatin C has developed the Caucasian, Asian, Pediatric, and Adult (CAPA) equation for converting cystatin C values to body-surface-adjusted eGFR.[6] The utility of this formula was validated in a population of 4690 subjects using seven assays adjusted to the international cystatin C calibrator ERM-DA471/IFCC and is shown in Figure 3.

$$eGFRCys\ C\ (mL/min/1.73\ m^2) = 130 \times Cystatin\ C^{-1.069} \times age^{-0.117} - 7$$

Figure 3. CAPA equation for eGFR calculation based on IFCC standardized cystatin C assay.

New Internationally Certified Cystatin C Reference Material[6]

The IFCC Working Group on Standardization of Cystatin C, in collaboration with the Institute for Reference Materials and Measurements and Siemens Healthcare Diagnostics Products GmbH, developed the first internationally certified reference material: ERM-DA471/IFCC. The 2012 KDIGO Guidelines recommend that clinical laboratories that measure cystatin C should use an assay with calibration traceable to the international standard reference material.

Table 2. Classification of chronic kidney disease based on GFR and cystatin C level (60-year-old patient).

Stage	GFR	Cystatin C	Description
1	≥90	<0.84	Normal or elevated GFR
2	60–89	0.85–1.19	Mildly decreased GFR
3a	45–59	1.20–1.51	Mild to moderate GFR reduction
3b	30–44	1.52–2.09	Moderate to severe GFR reduction
4	15–29	2.10–3.42	Severely decreased GFR
5	<15	>3.43	Kidney failure

Cystatin C/GFR conversion based on CAPA equation.

Cystatin C for GFR Determination in Clinical Routine: Patients Who Benefit Most

Patients with suspected to moderate GFR reduction[7]

- GFR may decline by as much as 50% of normal before serum creatinine increases to levels above the reference range.
- A meta-analysis of 46 papers that compared a GFR reference method against cystatin C and serum creatinine concluded cystatin C to be clearly superior, providing a higher diagnostic efficiency (AUC 0.926 vs. 0.837 for serum creatinine). The higher AUC for cystatin C is a result of the higher sensitivity of cystatin C for mild to moderate renal dysfunction.

Elderly patients[8]

- Decrease in renal function is a normal process of aging. In parallel, muscle mass also decreases with aging, further reducing the sensitivity of creatinine.
- Decrease in GFR often requires adjustment of drug dosing.
- GFR (inulin clearance) in elderly patients was significantly reduced compared to a younger control group. While creatinine levels did not differ, cystatin C levels were significantly higher in the elderly and more closely correlated to GFR.

Children and young infants[9]

- In childhood, the age and muscle-mass dependency of serum creatinine complicates GFR assessment, even when body-length-to-creatinine ratios are used.
- EDTA-clearance determination in 225 children showed significantly higher correlation to cystatin C compared to the Schwartz formula (r = 0.765 vs. 0.706) and higher diagnostic efficiency (AUC 0.943 vs. 0.917).

Patients with diabetes and hypertension[10]

- Microalbuminuria and a decrease in GFR are predictors for progression to overt nephropathy.
- In diabetic patients, cystatin C was more closely correlated to Cr-EDTA-determined GFR (r = 0.84) than creatinine (r = 0.70).
- The diagnostic efficiency was 90% for cystatin C, 77% for creatinine, and 85% for the Cockcroft-Gault formula.

Acute renal failure[11]

- Incidence of acute renal failure is still high (30% in intensive care, 5% in hospital). Mortality is lower if diagnosed early.
- Current diagnosis by an increase in serum creatinine (50 or 100%) comes relatively late.
- Corresponding increases in cystatin C are observed 1 to 2 days earlier.

Kidney transplant recipients[12]

- Due to tubular secretion, serum creatinine overestimates GFR after transplantation by 30–40% compared to EDTA clearance, suggesting a false-normal GFR in approximately 25% of renal transplant patients.
- Cystatin C slightly underestimates GFR (by 14%); no false-normal GFR estimates were observed with cystatin C.

Patients with liver disease[13]

- Liver cirrhosis is often accompanied by functional renal failure.
- In cirrhotic patients, creatinine over-estimates GFR because of muscle wasting syndrome and an impaired conversion of creatine to creatinine.
- In 42 liver cirrhosis patients with reduced GFR (inulin clearance), sensitivity was 86% for cystatin C compared to 29% for creatinine.

Add Sensitivity and Reliability in Daily GFR Assessment with the N Latex Cystatin C Assay from Siemens Healthcare Diagnostics

Cystatin C: the more sensitive diagnostic test alternative to Creatinine for estimating glomerular filtration rate (GFR)

	Cystatin C	Creatinine
Filtration-independent elimination	**No tubular secretion; sensitive in the creatinine-blind range[5]** • Higher sensitivity in early disease	**In early disease, tubular secretion compensates for the decline of glomerular filtration** • Creatinine-blind range; creatinine levels increase only if more than 50% of renal function is lost • MDRD† or Cockcroft-Gault formula cannot compensate for this limitation
Influence of age, sex, and muscle mass	**Independent of age, sex, and muscle mass[5]** • Constant relationship between cystatin C and GFR at 1 year of age and older • Single reference range: 0.62–1.11 mg/L§ in children and adults • Sensitive detection of declining GFR with aging • Reliable in patients with spina bifida, paralysis, amputations, etc.	**Dependent on age, sex, and muscle mass** • Different relationships between creatinine and GFR; between men and women; in children, adults, and elderly; and in patients with low and high muscle mass • Different reference ranges for interpretation • Correction for age, sex, race, and weight in GFR estimation formulas • Due to declining muscle mass in old age, lower sensitivity to loss of renal function with aging • Not suited for patients with grossly abnormal muscle mass
Correlation to GFR reference methods	**High correlation to GFR reference methods;[5] high correlation to GFR decline** • High reliability and accuracy	**Correlation to GFR reference methods less narrow, especially in normal or only slightly abnormal GFR** • Limited reliability; lower sensitivity
Influence of liver disease	**Not influenced by liver disease or creatinine intake; may be influenced by high-dose steroid therapy or thyroid dysfunction**	**Strongly influenced by liver disease; dependent on creatinine (i.e., protein) intake**
Effect of analytical interferences	**No analytical interferences known**	**Many analytically interfering factors (e.g., bilirubin, ascorbic acid, various drugs) for common analytical methodologies**

†Modification of Diet in Renal Disease

§ Recommended reference range for N Latex Cystatin C assay standardized to ERM-DA471/IFCC reference. Product availability may vary from country to country.

Assay characteristics

- Suitable for both serum and plasma specimens
- No need for urine collection
- Low imprecision (total CV <5%)
- Latex-enhanced reagent for high sensitivity and lot-to-lot reproducibility
- Broad initial measuring ranges cover the entire physiological range of cystatin C; BN™ Systems: 0.23–8.0 mg/L
- Excellent linearity
- Closer correlation than creatinine to GFR reference methods such as Cr^{51}-EDTA clearance[7]
- Runs on BN™ II and BN ProSpec® Systems in full random access mode
- Assay with IFCC standardization available‡

Interpretation of cystatin C

Reference range for BN Systems: 0.62–1.11 mg/L§ cystatin C

Cystatin C is elevated in the newborn, but with maturation of kidney function over the first year, cystatin C levels decrease and reach adult levels at the end of the first year of life.

The age-related decline in GFR is considered part of normal aging (~10 mL/min per decade from 30 years). However, detection of reduced GFR in the elderly is important for prediction of adverse outcomes or drug dosage adjustments. In contrast to creatinine, the relationship between cystatin C and GFR does not change with aging.[8]

Siemens Renal Disease Management Panel

- Cystatin C in serum or plasma for GFR determination
- Albumin, IgG, and α1-microglobulin in urine for glomerular and tubular nephropathy
- PROTIS® Kidney Assessment software‡ for graphical display, formula application, and result interpretation of renal markers

‡Availability varies from country to country.

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