SIEMENS Healthineers

Cystatin C_2 (CYSC_2)

Current Revision and Date[a]	Rev. 04, 2020-08	
Product Name	Atellica CH Cystatin C_2 (CYSC_2)	REF 11097647 (800 tests)
Abbreviated Product Name	Atellica CH CYSC_2	
Test Name/ID	CYSC_2	
Systems	Atellica CH Analyzer	
Materials Required but Not Provided	Atellica CH CYSC_2 CAL	REF 11097648
Specimen Types	Human serum and plasma (lithium heparin, potassium EDTA)	
Sample Volume	5.2 µL	
Measuring Interval	0.25–8.93 mg/L	

[a] A vertical bar in the page margin indicates technical content that differs from the previous version.

CE

Intended Use

The Atellica® CH Cystatin C_2 (CYSC_2) assay is for *in vitro* diagnostic use in the quantitative determination of cystatin C in human serum and plasma (lithium heparin, potassium EDTA) using the Atellica® CH Analyzer. Measurement of cystatin C aids in the diagnosis and treatment of renal disease.

Summary and Explanation

Cystatin C is a cysteine proteinase inhibitor with a relative molecular weight of 13,250 daltons and is formed by all nucleated cells investigated.[1,2] Since it is formed at a constant rate and freely filtered by the healthy kidney, this protein is a good marker of renal function. Serum concentrations of cystatin C are almost totally dependent on the glomerular filtration rate.[3,4] A reduction in the glomerular filtration rate (GFR) causes a rise in the concentration of cystatin C. Cystatin C has not been shown to be affected by factors such as muscle mass and nutrition, factors which have been demonstrated to affect creatinine values. In addition, a rise in creatinine does not become evident until the GFR has fallen by approximately 50%.

Principles of the Procedure

The Atellica CH CYSC_2 latex reagent is a suspension of uniform latex particles coated with anti-cystatin C antibody. When serum or plasma containing cystatin C is mixed with the latex reagent, agglutination takes place resulting in an increase in turbidity. This turbidity is measured at 571/805 nm. The cystatin C concentration in serum or plasma is determined from a calibration curve that is generated with the calibrators.

Reagents

Material Description	Storage	Stability[a]
Atellica CH CYSC_2 **Pack 1 (P1)** Well 1 (W1) Reagent 1 (R1) 12.8 mL Buffer; Methylisothiazolone (MIT) (0.03%) (*w/v*) Well 2 (W2) Reagent 1 (R1) 12.8 mL Buffer; Methylisothiazolone (MIT) (0.03%) (*w/v*) **Pack 2 (P2)** Well 1 (W1) Reagent 2 (R2) 5.0 mL Latex particles coated with anti-cystatin C antibody (rabbit) (variable by lot); sodium azide (0.09%) (*w/v*) Well 2 (W2) Reagent 2 (R2) 5.0 mL Latex particles coated with anti-cystatin C antibody (rabbit) (variable by lot); sodium azide (0.09%) (*w/v*)	Unopened at 2–8°C Onboard per well	Until expiration date on product 40 days

[a] Refer to *Storage and Stability*.

Warnings and Precautions

For *in vitro* diagnostic use.

For Professional Use.

CAUTION

Federal (USA) law restricts this device to sale by or on the order of a licensed healthcare professional.

Safety data sheets (SDS) available on siemens.com/healthineers.

H412	Harmful to aquatic life with long lasting effects.
P273, P501	Avoid release to the environment. Dispose of contents and container in accordance with all local, regional, and national regulations. **Contains:** 2-methyl-2H-isothiazol-3-one. (R1)

CAUTION

This device contains material of animal origin and should be handled as a potential carrier and transmitter of disease.

Contains sodium azide as a preservative. Sodium azide can react with copper or lead plumbing to form explosive metal azides. On disposal, flush reagents with a large volume of water to prevent buildup of azides. Disposal into drain systems must be in compliance with prevailing regulatory requirements.

Dispose of hazardous or biologically contaminated materials according to the practices of your institution. Discard all materials in a safe and acceptable manner and in compliance with prevailing regulatory requirements.

Note For information about reagent preparation, refer to *Preparing the Reagents* in the *Procedure* section.

Storage and Stability

Unopened reagents are stable until the expiration date on the product when stored at 2–8°C.

Do not use products beyond the expiration date printed on the product labeling.

Onboard Stability

Reagents are stable onboard the system for 40 days per well. Discard reagents at the end of the onboard stability interval. Do not use products beyond the expiration date printed on the product labeling.

Specimen Collection and Handling

Serum and plasma (lithium heparin, potassium EDTA) are the recommended sample types for this assay.

Collecting the Specimen

- Observe universal precautions when collecting specimens. Handle all specimens as if they are capable of transmitting disease.[5]
- Follow recommended procedures for collection of diagnostic blood specimens by venipuncture.[6]
- Follow the instructions provided with your specimen collection device for use and processing.[7]
- Allow blood specimens to clot completely before centrifugation.[8]
- Keep tubes capped at all times.[8]

Storing the Specimen

Specimens shall be stable for at least 7 days when tightly capped and stored at 2–8°C,[9] or stored frozen for at least 3 months at or below -20°C if they are frozen within 24 hours after collection and if repeated freeze-thaw cycles are avoided.[9]

The handling and storage information provided here is based on data or references maintained by the manufacturer. It is the responsibility of the individual laboratory to use all available references and/or its own studies when establishing alternate stability criteria to meet specific needs.

Transporting the Specimen

Package and label specimens for shipment in compliance with applicable federal and international regulations covering the transport of clinical specimens and etiological agents.

Preparing the Samples

This assay requires 5.2 µL of sample for a single determination. This volume does not include the unusable volume in the sample container or the additional volume required when performing duplicates or other tests on the same sample. For information about determining the minimum required volume, refer to the online help.

Note Do not use specimens with apparent contamination.

Before placing samples on the system, ensure that samples are free of:

- Bubbles or foam.
- Fibrin or other particulate matter.

Note Remove particulates by centrifugation according to CLSI guidance and the collection device manufacturer's recommendations.[8]

Note For a complete list of appropriate sample containers, refer to the online help.

Procedure

Materials Provided

The following materials are provided:

REF	Contents	Number of Tests
11097647	**Pack 1 (P1)** Well 1 (W1) 12.8 mL of Atellica CH CYSC_2 Reagent 1 Well 2 (W2) 12.8 mL of Atellica CH CYSC_2 Reagent 1 **Pack 2 (P2)** Well 1 (W1) 5.0 mL of Atellica CH CYSC_2 Reagent 2 Well 2 (W2) 5.0 mL of Atellica CH CYSC_2 Reagent 2	4 x 200

Materials Required but Not Provided

The following materials are required to perform this assay, but are not provided:

REF	Description	
	Atellica CH Analyzer[a]	
11097648	Atellica CH CYSC_2 CAL (calibrator)	1 x 2.0 mL calibrator level 2 CAL 2 1 x 2.0 mL calibrator level 3 CAL 3 1 x 2.0 mL calibrator level 4 CAL 4 1 x 2.0 mL calibrator level 5 CAL 5 1 x 2.0 mL calibrator level 6 CAL 6 Calibrator lot-specific value sheet CAL LOT VAL
	Commercially available quality control materials	

[a] Additional system fluids are required to operate the system: Atellica CH Diluent, Atellica CH Wash, Atellica CH Conditioner, Atellica CH Cleaner, Atellica CH Reagent Probe Cleaner 1, Atellica CH Reagent Probe Cleaner 2, Atellica CH Reagent Probe Cleaner 4, Atellica CH Lamp Coolant, and Atellica CH Water Bath Additive. For system fluid instructions for use, refer to the Document Library.

Assay Procedure

The system automatically performs the following steps:

1. For serum/plasma, dispenses 50 µL of primary sample and 200 µL of Atellica CH Diluent into a dilution cuvette.
2. Dispenses 80 µL of Reagent 1 into a reaction cuvette.
3. Dispenses 5.2 µL of pre-diluted sample into a reaction cuvette.
4. Dispenses 17.4 µL of Reagent 2 into a reaction cuvette.
5. Mixes and incubates the mixture at 37°C.

6. Measures the absorbance after Reagent 2 addition.
7. Reports results.

Test Duration: 10 minutes

Preparing the Reagents

All reagents are liquid and ready to use.

Preparing the System

Ensure that the system has sufficient reagent packs loaded in the reagent compartment. For information about loading reagent packs, refer to the online help.

Performing Calibration

For calibration of the Atellica CH CYSC_2 assay, use Atellica CH CYSC_2 CAL. Use the calibrators in accordance with the calibrator instructions for use.

Calibration Frequency

Perform a calibration if one or more of the following conditions exist:

- When changing lot numbers of primary reagent packs.
- At the end of the lot calibration interval, for a specified lot of calibrated reagent on the system.
- At the end of the pack calibration interval, for calibrated reagent packs on the system.
- When indicated by quality control results.
- After major maintenance or service, if indicated by quality control results.

At the end of the onboard stability interval, replace the reagent pack on the system with a new reagent pack. Recalibration is not required, unless the lot calibration interval is exceeded.

Stability Interval	Days
Lot Calibration	61
Pack Calibration	40
Reagent Onboard Stability	40

For information about lot calibration and pack calibration intervals, refer to the online help.

Follow government regulations or accreditation requirements for calibration frequency. Individual laboratory quality control programs and procedures may require more frequent calibration.

Performing Quality Control

For quality control of the Atellica CH CYSC_2 assay, use at least two levels (low and high) of the appropriate quality control material of known analyte concentration. Use the quality control material in accordance with the quality control instructions for use.

For the assigned values, refer to the lot-specific value sheet provided. A satisfactory level of performance is achieved when the analyte values obtained are within the expected control range for the system or within your range, as determined by an appropriate internal laboratory quality control scheme. Follow your laboratory's quality control procedures if the results obtained do not fall within the acceptable limits. For information about entering quality control definitions, refer to the online help.

Follow government regulations or accreditation requirements for quality control frequency. Individual laboratory quality control programs and procedures may require more frequent quality control testing.

Taking Corrective Action

If the quality control results do not fall within the assigned values, do not report results. Perform corrective actions in accordance with established laboratory protocol. For suggested protocol, refer to the online help.

Results

Calculation of Results

The system determines the result using the calculation scheme described in the online help. The system reports results in mg/L.

For information about results outside the specified measuring interval, refer to *Measuring Interval*.

Cystatin C concentration measurements have shown utility in the calculation of the estimated glomerular filtration rate (eGFR). National and international professional groups have recommended that clinical laboratories report (eGFR) along with the analytical value of the marker of kidney function.[10-12] Several formulas for converting cystatin C values to (eGFR) have been developed both with adjustments for body surface area (mL/min/1.73m^2) and without adjustment (mL/min). Two of these formulas published by Grubb *et al*. (CAPA equation)[13] and the KDIGO guideline[10] are noted below:

eGFR (mL/min/1.73m^2) = 130 x CYSC_2$^{-1.069}$ x age$^{-0.117}$ - 7

eGFR according to KDIGO (2012 CKD-EPI):[10]

if CYSC_2 ≤ 0.8:

eGFR (mL/min/1.73m^2) = 133 x (CYSC_2/0.8)$^{-0.499}$ x 0.996^{age}(x 0.932 if female)

if CYSC_2 > 0.8:

eGFR (mL/min/1.73m^2) = 133 x (CYSC_2/0.8)$^{-1.3289}$ x 0.996^{age}(x 0.932 if female)

Interpretation of Results

Results of this assay should always be interpreted in conjunction with the patient's medical history, clinical presentation, and other findings.

Limitations

The Atellica CH CYSC_2 assay is limited to the detection of cystatin C in human serum and plasma (lithium heparin, potassium EDTA).

Expected Values

Reference Interval

A reference interval for healthy adults was established in accordance with CLSI Document EP28-A3c and verified for the Atellica CH Analyzer.[14]

The reference interval for cystatin C is 0.64–1.23 mg/L for adults.[9]

As with all *in vitro* diagnostic assays, each laboratory should determine its own reference interval for the diagnostic evaluation of patient results. Consider these values as guidance only.[14]

Performance Characteristics

Measuring Interval

The Atellica CH CYSC_2 assay provides results from 0.25–8.93 mg/L. The system flags all values that are outside the specified measuring interval.

Extended Measuring Interval

An automatic repeat condition for this assay extends the measuring interval to 26.79 mg/L for serum and plasma. You may configure the system to trigger an automatic repeat. Automatic repeat results will be flagged **Autorepeat**.

Detection Capability

Detection capability was determined in accordance with CLSI Document EP17-A2.[15]

The limit of detection (LoD) corresponds to the lowest concentration of cystatin C that can be detected with a probability of 95%. The LoD for the Atellica CH CYSC_2 assay is 0.12 mg/L, and was determined using 480 determinations, and a LoB of 0.08 mg/L.

The LoQ is the lowest amount of cystatin C that can be determined quantitatively at < 10% CV, which corresponds to a value of 0.25 mg/L for the Atellica CH CYSC_2 assay.

Assay results obtained at individual laboratories may vary from the data presented.

Precision

Precision was determined in accordance with CLSI Document EP05-A3.[16] Samples were assayed on an Atellica CH Analyzer in duplicate in 2 runs per day for 20 days (N ≥ 80 for each sample). The following results were obtained:

			Repeatability		Within-Lab Precision	
Sample Type	**N**	**Mean (mg/L)**	**SD[a] (mg/L)**	**CV[b] (%)**	**SD (mg/L)**	**CV (%)**
QC 1	80	0.55	0.020	3.6	0.020	3.7
QC 2	80	0.75	0.016	2.2	0.018	2.4
QC 3	80	0.86	0.018	2.1	0.019	2.2
Serum	80	0.91	0.016	1.7	0.020	2.2
Potassium EDTA plasma	80	2.94	0.020	0.7	0.032	1.1
QC 4	80	3.86	0.021	0.6	0.030	0.8
Lithium heparin plasma	80	6.61	0.044	0.7	0.073	1.1

[a] Standard deviation.

[b] Coefficient of variation.

Assay results obtained at individual laboratories may vary from the data presented.

Assay Comparison

The Atellica CH CYSC_2 assay is compared to ADVIA® Chemistry 1800 CYSC_2. Assay comparison was determined using the Deming linear regression model in accordance with CLSI Document EP09-A3.[17] The following results were obtained:

Specimen	Comparative Assay (x)	Regression Equation	Sample Interval	N[a]	r[b]
Serum	ADVIA Chemistry 1800 CYSC_2	y = 1.01x + 0.04 mg/L	0.72–8.17 mg/L	100	0.999

[a] Number of samples tested.

[b] Correlation coefficient.

The agreement of the assay may vary depending on the study design, comparative assay, and sample population. Assay results obtained at individual laboratories may vary from the data presented.

Specimen Equivalency

The equivalency of sample types was confirmed by comparing the performance of the Atellica CH CYSC_2 assay for serum and plasma (lithium heparin or potassium EDTA) samples. Testing was performed using one lot of reagents with analysis of a single replicate from a matched set of serum and plasma samples in accordance with CLSI Document EP09-A3.[17]

Interferences

Hemolysis, Icterus, and Lipemia (HIL)

The Atellica CH CYSC_2 assay is designed to have ≤ 10% interference from hemoglobin, bilirubin, and lipemia. Interfering substances at the levels indicated in the table below were tested in accordance with CLSI Document EP07-A2 using the Atellica CH CYSC_2 assay.[18]

Bias is the difference in the results between the control sample (does not contain the interferent) and the test sample (contains the interferent) expressed in percent. Bias > 10% is considered interference. Analyte results should not be corrected based on this bias.

Substance	Substance Test Concentration Common Units (SI Units)	Analyte Concentration (mg/L)	Percent Bias
Hemoglobin	1000 mg/dL (0.621 mmol/L) 1000 mg/dL (0.621 mmol/L)	1.03 3.10	-5.8 -2.9
Bilirubin, conjugated	60 mg/dL (1026 µmol/L) 60 mg/dL (1026 µmol/L)	1.02 3.16	3.9 1.6
Bilirubin, unconjugated	60 mg/dL (1026 µmol/L) 60 mg/dL (1026 µmol/L)	1.02 3.18	2.0 0.6
Lipemia (Intralipid®)	1000 mg/dL (11.3 mmol/L) 1000 mg/dL (11.3 mmol/L)	1.05 3.13	-5.7 -3.2

Assay results obtained at individual laboratories may vary from the data presented.

Non-Interfering Substances

The following substances do not interfere with the Atellica CH CYSC_2 assay at the concentrations indicated in the table below. Bias due to these substances is ≤ 10%.

Substance Tested	Concentration Tested	Analyte Concentration (mg/L)	Percent Bias
Rheumatoid Factor	508 IU/mL	1.09	-1.8
	508 IU/mL	3.34	1.2

Assay results obtained at individual laboratories may vary from the data presented.

High-Dose Hook Effect

High cystatin C levels can cause a paradoxical decrease in signal as a result of the high-dose hook effect. In the Atellica CH CYSC_2 assay, cystatin C levels as high as 56.00 mg/L will read > 8.93 mg/L.

Standardization

The Atellica CH CYSC_2 assay is traceable to the International Federation of Clinical Chemistry (IFCC) Standard ERM–DA471.[9]

Assigned values for calibrators are traceable to this standardization.[9]

Technical Assistance

For customer support, contact your local technical support provider or distributor.

siemens.com/healthineers

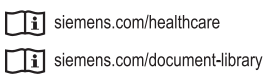
References

1. Simonsen O, Grubb A, Thysell H. The blood serum concentration of cystatin C (gamma-trace) as a measure of the glomerular filtration rate. *Scand J Clin Lab Invest.* 1985;45(2):97-101.
2. Randers E, Erlandsen EJ. Serum cystatin C as an endogenous marker of the renal function: A Review. *Clin Chem Lab Med.* 1999;37(4):389-395.
3. Grubb A. Diagnostic value of analysis of cystatin C and protein HC in biological fluids. *Clin Nephrol.* 1992;38 Suppl 1:S20-S27.
4. Coll E, Botey A, Alvarez L, et al. Serum cystatin C as a new marker for noninvasive estimation of glomerular filtration rate and as a marker of early renal impairment. *Am J Kidney Dis.* 2000;36(1):29–34.
5. Clinical and Laboratory Standards Institute. *Protection of Laboratory Workers from Occupationally Acquired Infections; Approved Guideline—Fourth Edition*. Wayne, PA: Clinical and Laboratory Standards Institute; 2014. CLSI Document M29-A4.
6. Clinical and Laboratory Standards Institute. *Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture; Approved Standard—Sixth Edition*. Wayne, PA: Clinical and Laboratory Standards Institute; 2007. CLSI Document GP41-A6.
7. Clinical and Laboratory Standards Institute. *Tubes and Additives for Venous and Capillary Blood Specimen Collection; Approved Standard—Sixth Edition*. Wayne, PA: Clinical and Laboratory Standards Institute; 2010. CLSI Document GP39-A6.
8. Clinical and Laboratory Standards Institute. *Procedures for the Handling and Processing of Blood Specimens for Common Laboratory Tests; Approved Guideline—Fourth Edition*. Wayne, PA: Clinical and Laboratory Standards Institute; 2010. CLSI Document GP44-A4.
9. Data on file at Siemens Healthcare Diagnostics.

10. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl.* 2013;3(1):1–150.
11. Mathew TH; Australasian Creatinine Consensus Working Group. Chronic kidney disease and automatic reporting of estimated glomerularfiltration rate: a position statement. *Med J Aust.* 2005;183(3):138-141.
12. Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* 2005;67(6):2089-2100.
13. Grubb A, Horio M, Hansson LO, et al. Generation of a new cystatin C-based estimating equation for glomerular filtration rate by use of 7 assays standardized to the international calibrator. *Clin Chem.* 2014;60(7):974-986.
14. Clinical and Laboratory Standards Institute. *Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition*. Wayne, PA: Clinical and Laboratory Standards Institute; 2010. CLSI Document EP28-A3c.
15. Clinical and Laboratory Standards Institute. *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition*. Wayne, PA: Clinical and Laboratory Standards Institute; 2012. CLSI Document EP17-A2.
16. Clinical and Laboratory Standards Institute. *Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition*. Wayne, PA: Clinical and Laboratory Standards Institute; 2014. CLSI Document EP05-A3.
17. Clinical and Laboratory Standards Institute. *Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Third Edition*. Wayne, PA: Clinical and Laboratory Standards Institute; 2013. CLSI Document EP09-A3.
18. Clinical and Laboratory Standards Institute. *Interference Testing in Clinical Chemistry; Approved Guideline—Second Edition*. Wayne, PA: Clinical and Laboratory Standards Institute; 2005. CLSI Document EP07-A2.

Definition of Symbols

The following symbols may appear on the product labeling:

Symbol	Symbol Title and Description
	Consult instructions for use
	Version of instructions for use
	Internet URL address to access the electronic instructions for use
	Revision
	Caution Consult instructions for use or accompanying documents for cautionary information such as warnings and precautions that cannot, for a variety of reasons, be presented on the medical device.
	Biological risks Potential biological risks are associated with the medical device.

Symbol	Symbol Title and Description
	Corrosive
	Dangerous to environment
	Irritant Oral, dermal, or inhalation hazard
	Inhalation hazard Respiratory or internal health
	Flammable Flammable to extremely flammable
	Oxidizing
	Explosive
	Toxic
	Compressed gas
	Keep away from sunlight Prevent exposure to sunlight and heat.
	Up Store in an upright position.
	Do not freeze
	Temperature limit Upper and lower limits of temperature indicators are adjacent to the upper and lower horizontal lines.
	Handheld barcode scanner
	*In vitro* diagnostic medical device
	Contains sufficient for <n> tests Total number of IVD tests the system can perform with the IVD kit reagents appears adjacent to the symbol.

Symbol	Symbol Title and Description
RxOnly	Prescription device (US only) Applies only to United States-registered IVD assays. CAUTION: Federal (USA) law restricts this device to sale by or on the order of a licensed healthcare professional.
	Mixing of substances Mix product before use.
	Reconstitute and mix lyophilized product before use.
	Target
	Interval
	Legal Manufacturer
EC REP	Authorized Representative in the European Community
	Use-by date Use by the designated date.
LOT	Batch code
REF	Catalog number
	Recycle
	Printed with soy ink
CE	CE Mark
CE 0088	CE Mark with notified body ID number Notified body ID number can vary.
YYYY-MM-DD	Date format (year-month-day)
CHECKSUM	Variable hexadecimal number that ensures the Master Curve and Calibrator definition values entered are valid.
UNITS C	Common Units
UNITS SI	International System of Units
MATERIAL	Material
MATERIAL ID	Unique material identification number

Symbol	Symbol Title and Description
CONTROL NAME	Name of control
CONTROL TYPE	Type of control

Legal Information

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