

CREATININE

Diagnostic reagent for determination of Creatinine concentration.

Liquid. Dual reagents (*Ratio: R1/R2: 4/1*). Store at +15/+25°C. For in Vitro Diagnostic Use (IVD). **Do not freeze.**

Ref No	Pack
MH-152	100 mL
MH-153	75 mL

Changes made in the instructions for use are marked as grey.

INTENDED USE

The test is applied for the quantitative determination of Creatinine in serum and urine.

GENERAL INFORMATION

Some of the free creatine in muscle is spontaneously and irreversibly converted into creatinine, the anhydride waste product. Thus, the amount of creatinine produced each day in an individual is fairly constant and correlates with muscle mass. In a healthy individual, the blood concentration of creatinine is also fairly constant, although it can be influenced by diet. Creatinine is present in all body fluids and secretions and is freely filtered through the glomeruli. Although it is largely not reabsorbed by the renal tubules, there is a small but significant tubular secretion as well as concentration-dependent losses in the intestine.¹ Creatinine production also decreases as the concentration of circulating creatinine increases. Several mechanisms have been proposed for this, including feedback inhibition of creatinine production, recycling of creatinine to creatine and conversion to other metabolites.²⁻⁴ Serum creatinine concentration is a product of the rate of release from muscle into circulation and the rate of removal. Creatinine measurement is easy and inexpensive. However, its production is influenced by age, sex, race, muscle mass and diet, as well as various preanalytical and analytical effects.^{5,6} An important issue is that the serum creatinine level may remain within the reference range until renal function is substantially lost.⁵

Glomerular filtration rate (GFR) is most commonly assessed using methods based on measurement of serum creatinine. Creatinine is freely filtered through the glomeruli and its concentration is inversely related to GFR, i.e. for the same creatinine production, halving the GFR leads to approximately doubling the serum creatinine concentration.¹ A small (but significant) and variable proportion (≈7-10%) of the amount of creatinine seen in urine is due to tubular secretion.⁷ However, this amount increases in the presence of renal impairment and is inhibited by some drugs (e.g. cimetidine⁷ and trimethoprim⁸).

Creatinine measurements are used in the diagnosis, treatment and follow-up of some renal diseases, in the monitoring of renal dialysis, and in the measurement of some other analytes and their interpretation based on

Rev: V1.1 Date: 03.2024

their ratio to creatinine.^{1,9} Measurement of serum creatinine is very important in the detection of acute kidney injury (AKI), the definition and classification of AKI is predominantly based on changes in serum creatinine concentration over time.¹ Kidney Disease Improving Global Outcomes (KDIGO) defines ABH as an increase in serum creatinine of ≥0.3 mg/dL (≥26.5 mmol/L) within 48 hours or an increase in serum creatinine of ≥1.5 times baseline within the previous 7 days.¹⁰ The KDIGO guidelines also recommend the use of serum creatinine and the GFR estimation equation (eGFR) in the initial evaluation of chronic kidney disease (CKD). Categorized GFR values (G1 to G5 classification) and albuminuria values (A1 to A3 classification) categorized according to the albumin/creatinine ratio (ACR) are used in the prognosis of CKD, prediction of cardiovascular and all-cause mortality, diagnosis and follow-up of end-stage renal failure, and evaluation of CKD progression and acute kidney injury. In addition to ACR values, protein creatinine ratio (PCR) is also used in the evaluation of diseases such as nephrotic syndrome.

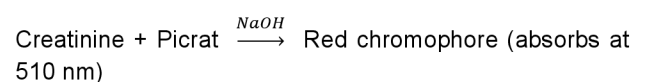
Serum creatinine is not exactly an ideal marker for the calculation of GFR, so equations derived from creatinine, such as Modification of Diet in Renal Disease (MDRD) and GFR-EPI_{crea}, are not appropriate for use in patients with diseases such as ABH, where serum creatinine concentrations can change rapidly.¹

TEST PRINCIPLE

Colorimetric measurement

A modified version of the kinetic Jaffe reaction is used in the creatinine method. This method has been reported to be less sensitive to interference caused by non-creatinine, Jaffe-positive compounds than conventional methods. Creatinine is generally considered the most useful endogenous substance in the evaluation of renal function.

Creatinine reacts with picric acid in alkaline environment to form a color complex. Developing of this red color can be followed by photometrically at 500-520 nm. The association on surfactant and sodium tetraborate keeps interferences at minimum.



Annotation:

- Most chemical methods for the measurement of creatinine are based primarily on the reaction with alkaline picrate. In this reaction, first described by Jaffe in 1886, creatinine reacts with picrate ion in an alkaline medium to give the equimolar orange-red Janovski complex.¹¹
- The use of this reaction to measure creatinine in urine was first described by Folin in 1904.¹²

REAGENT COMPONENTS**Reagent 1:**

Carbonate Buffer : ≤ 120 mmol/L
Sodium Hydroxide : ≤ 360 mmol/L

Reagent 2:

Picric Acid : ≤ 7.8 mmol/L

REAGENT PREPARATION

Reagents are ready for use.

REAGENT STABILITY AND STORAGE

Reagents are stable at +2/+8°C till the expiration date stated on the label which is only for closed vials.

Once opened vials are stable for 30 days at +2/+8°C in optimum conditions. On board stability is strongly related to auto analyzers' cooling specification and carry-over values.

Reagent stability and storage data have been verified by using Clinical and Laboratory Standards Institute (CLSI) EP25-A protocol.¹³

SAMPLE REQUIREMENTS

Serum and urine collected by standard procedure can be used. Multiple sample freezing and thawing should be avoided.

Additives should not be used when collecting urine. However, if urine needs to be preserved for other analytes, only hydrochloric acid can be used.

Creatinine activity stability in serum:

7 days at +2/+8°C
7 days at +20/+25°C
3 months at -20°C

Creatinine activity stability in urine (without preservatives):

6 days at +2/+8°C
2 days at +20/+25°C
6 months at -20°C

Creatinine activity stability in urine (with preservatives):

8 days at +2/+8°C
3 days at +20/+25°C
3 weeks at -20°C

Annotation:

- Acidified urine is not suitable for creatinine determination.
- Bacterial contamination of long-stored samples has been reported to falsely lower creatinine values measured by the Jaffe method, allegedly due to bacterial production of a reaction retarding agent.¹⁴
- The concentration of creatinine in the blood increases after meals containing cooked meat or fish because creatine is converted to creatinine. Ideally, blood for serum creatinine measurement should be taken in the fasting state.¹⁵⁻²¹ Although the effect depends on the amount and type of meat consumed and the time of sampling, it can increase the creatinine concentration by 25%,²⁰ with a similar reduction in creatinine-based GFR estimates.¹

CALIBRATION AND QUALITY CONTROL

Calibration: The assay requires the use of Creatinine Calibrators.:

Creatinine Calibrator Level I

Ref.No: VT-043

Creatinine Calibrator Level II

Ref No: VT-044

Calibration stability is 20 days. Calibration stability depends on the application characteristics and cooling capacity of the autoanalyzer used.

Serum calibrator creatinine can be traced using the Isotope Dilution Mass Spectroscopy (IDMS) method via National Institute of Standards and Technology (NIST) SRM 967. For urine, traceability is provided using NIST SRM 914.

Control: Commercially available control material with established values determined by this method can be used. We recommend:

Arcon N Level 1 Control- Lyophilized

Ref.No: VT-001

Arcon P Level 2 Control- Lyophilized

Ref.No: VT-002

At least two level controls must be run once in every 24 hours. Each laboratory should determine its own quality control scheme and procedures. If quality control results are not within acceptable limits, calibration is required.

REFERENCE INTERVALS / MEDICAL DECISION LEVELS

Serum:

Men	: 0.70 - 1.20 mg/dL
Women	: 0.60 - 1.10 mg/dL
Children	
0 - <15 day old	: 0.42 - 1.05 mg/dL
15 day - <1 year old	: 0.45 - 0.70 mg/dL
1 - < 4 year old	: 0.50 - 0.74 mg/dL
4 - <7 year old	: 0.65 - 0.80 mg/dL
7 - <12 year old	: 0.70 - 0.88 mg/dL
12 - <15 year old	: 0.70 - 0.93 mg/dL
15 - <17 year old	: 0.72 - 1.05 mg/dL

Urine, random:

Men < 40 years	: 24 - 392 mg/dL
Men ≥ 40 years	: 22 - 328 mg/dL
Women < 40 years	: 16 - 327 mg/dL
Women ≥ 40 years	: 15 - 278 mg/dL

24 hour urine:

Men	: 1040 - 2350 mg/24-hour
Women	: 740 - 1570 mg/24-hour

For 24-hour urine excretion, to convert results from mg/dL to mg/24-hour;

$$24 \text{ h urine} = [(V \times c) / 100] \text{ mg/24-hour (or day)}$$

V = 24 hour urine volume

c = analyte concentration (mg/dL)

Annotation:

- Serum creatinine reference intervals depend on the method.²²
- Since most creatine is found in muscle, the amount of creatinine in a person reflects muscle mass. This is why women have lower serum creatinine concentrations than men, and children and infants have lower serum creatinine concentrations than adults.²²
- Reference intervals in older people are, on average, similar to those of young adults, despite the decline in renal function that occurs with aging.²²

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary, determine its own reference range.

Reference interval has been verified by using CLSI EP28-A3c protocol.²³

Unit Conversion:

Serum

mg/dL x 88.4 = μmol/L

μmol/L x 0.001 = mmol/L

Urine

mg/dL x 0.0884 = mmol/L

PERFORMANCE CHARACTERISTICS

Measuring Interval

According to CLSI EP34-ED1:2018, "Measuring Interval" refers to the interval where the analyte concentration is measured with intended accuracy in terms of medical and laboratory requirements without dilution, concentrating or any kind of pre-treatment that is between the analyte's lower limit of quantitation (LLOQ) and upper limit of quantitation (ULOQ).²⁴

The determined analytic measuring interval for Creatinine is 0.20 – 20 mg/dL.

Detection Capability

Limit of Detection (LoD): 0.15 mg/dL

Limit of Quantitation (LoQ): 0.20 mg/dL

Note: LoQ values are based on Coefficient of Variation Percentage (CV) ≤ 20%.

LoD and LoQ values have been verified by using CLSI EP17-A2:2012 protocol.²⁵

Linearity

This method shows measurement linearity in the activities up to 20 mg/dL. Autoanalyzer's auto-dilution system can be used if the concentrations have higher values. See device manual for further information.

For the manual dilution procedure, dilute the sample 1:5 using 0.90% isotonic. After this process, multiply the result of the reworked sample by the dilution factor. Do not report the sample result after dilution if it is marked as lower than the linear lower limit. Rerun with a suitable dilution.

Linearity Studies data have been verified by using CLSI EP06-A:2003 protocol.²⁶

Precision

Running system has been developed according to 20x2x2 "The Single Site" protocol. Repeatability and Within-Laboratory Precision/Within-Device values have been obtained according to the running results.

According to the protocol in use, 2 separate runs per day have been made for 20 days (no obligation for being consecutive days). This protocol has been applied to each low and high samples separately and 80 results have been obtained for each one. Statistically, the results have been obtained using 2-factor Nested-ANOVA model.²⁷

Repeatability (Within Run) and Repeatability (Day to Day) SD (standard deviation) and CV% values of Creatinine have been given in the table 1 and 2 respectively.

Table 1. Cholesterol Repeatability (Within Run) results obtained from samples in two different concentrations

Mean Concentration	SD	CV%	n
0.74 mg/dL	0.01	1.04	80
4.95 mg/dL	0.05	1.07	80

Note: This working system has been named “Within-Run Precision” in the previous CLSI - EP05-A2 manual.²⁸

Table 2. Cholesterol Repeatability (Day to Day) results obtained from samples in two different concentrations

Mean Concentration	SD	CV%	n
0.74 mg/dL	0.03	4.05	80
4.95 mg/dL	0.14	2.82	80

Note: This working system has been named “Total Precision” in the previous CLSI - EP05-A2 manual.²⁸

Method Comparison

As a result of the statistical evaluation of the method comparison data:

Passing-Bablok equation:²⁹
 $y = 1.032x - 0.039 \text{ mg/dL}$
 $r = 0.999$

Interference

Endogenous interferant and analyte concentrations that have been used in the Creatinine scanning tests has been determined according to “CLSI EP37-ED1:2018” and “CLSI EP07-ED3:2018” manuals.^{30,31}

The total acceptable error rate, which is going to be used to detect whether the observed differential value obtained from Creatinine interference scanning test is appropriate, is determined as $\pm 10\%$.³²

In Creatinine test results, no significant interaction has been observed in the determined endogenous interferant and analyte concentrations or between interferants and analyte.

Interferant-Concentration	Creatinine Target (mg/dL)	N*	Observed Recovery %
Hemoglobin 1080 mg/dL	1.06	3	91
Bilirubin 3.67 mg/dL	1.38	3	91
Lipemia 2179 mg/dL	0.89	3	98
Glucose 530 mg/dL	2.51	3	107

* Total acceptable error rate determined as interference limit and repeatability (within run) pre-detected for the related method were used for the calculations of how many times the control and test samples prepared as a serum pool are going to be run repetitively. In the calculations, the accepted error rate for type 1 (α error) was 5% and for type 2 (β error) was 10% (90% power).³¹

Rev: V1.1 Date: 03.2024

Annotation:

- The Jaffe reaction is not specific for creatinine. Several compounds have been reported to produce a Jaffe-like chromogen, including protein,^{33,34} glucose, ascorbic acid,³⁵ ketone bodies,³⁶ pyruvate,³⁵ guanidine, hemoglobin F,³⁴ blood substitutes,³⁷ streptomycin,³⁸ acetaminophen, aspirin, metamazole³⁹ and cephalosporin.⁴⁰
- The degree of interference from these compounds depends on the precise reaction conditions chosen and the concentration of the interferant present in the patient's sample. It is generally accepted that non-creatinine chromogens can contribute up to approximately 20% of the creatinine concentration measured by Jaffe in normal serum samples.²²
- Non-creatinine chromogens usually do not contribute to the measured urinary creatinine concentration.²²
- Bilirubin or other hemoglobin degradation products produce negative interference in the Jaffe reaction, probably due to their oxidation to colorless compounds in strong bases.⁴¹

It should be noted that endogenous interferants, as well as various medicines and metabolites, anticoagulants (e.g. Heparin, EDTA, citrate, oxalate) and preservatives (e.g. sodium floride, iodoacetate, hydrochloride acide) such as additives, materials that may contact with samples during collection and processing (serum separator devices, sample collection containers and contents, catheters, catheter wash solutions, skin disinfectants, hand cleaners and lotions, glass washing detergents, powder gloves), dietary substances known to affect some specific tests (caffeine, beta-carotene, poppy seeds, etc.), or some substances present in a sample that cause foreign proteins (heterophilic antibodies, etc.), autoimmune response (autoantibodies, etc.), or due to malignancy (for example, interference by paraproteins with phosphate testing and indirect ion selective electrode methods) may show some negative effects that will cause various attempts and some misjudgements.³¹

These performance characteristics have been obtained using an autoanalyzer. Results may vary slightly when using different equipment or manual procedures.

WARNINGS AND PRECAUTIONS

IVD: For in Vitro Diagnostic use only.

Do not use expired reagents.

Reagents with two different lot numbers should not be interchanged.

For professional use.

Follow Good Laboratory Practice (GLP) guidelines.

Contains sodium azide.

CAUTION: Human source samples are processed with this product. All human source samples must be treated as potentially infectious materials and must be handled in

accordance with OSHA (Occupational Safety and Health Administration) standards.

Danger

- EUH032 :Releases a very toxic gas if contacts with acid.
- H317 :May cause allergic skin reaction.

Precaution

- P280 :Use protective gloves / clothes / glasses / mask.
- P264 :Wash your hands properly after using.
- P272 :Contaminated work clothes should not be allowed to be used outside of the workplace.

Intervention

- P302+P352 :Wash with plenty of water and soap if it contacts with skin.
- P333+P313 :Seek medical help if it irritates your skin or develops rash.
- P362+P364 :Remove contaminated clothes and wash properly before using.

Disposal

- P501 :Dispose the vials and contents according to the local regulations.

REFERENCES

- Rifai, N., Chiu, R. W., & Young, I., et al., (2023) Tietz Textbook of Laboratory Medicine (7th ed.), Chapter 34: Kidney Function Tests, p.352-352.e60, Elsevier, St. Louis, Missouri 63043
- Goldman R. Creatinine excretion in renal failure. Proc Soc Exp Biol Med 1954;85:446–8.
- Heymsfield SB, Arteaga C, McManus C, et al. Measurement of muscle mass in humans: validity of the 24-hour urinary creatinine method. Am J Clin Nutr 1983;37:478–94.
- Wyss M, Kaddurah-Daouk R. Creatine and creatinine metabolism. Physiol Rev 2000;80:1107–213.
- Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. Clin Chem 1992;38:1933–53.
- Spencer K. Analytical reviews in clinical biochemistry: the estimation of creatinine. Ann Clin Biochem 1986;23 (Pt 1):1–25.
- Miller BF, Winkler AW. The Renal Excretion of Endogenous Creatinine in Man. Comparison with Exogenous Creatinine and Inulin. J Clin Invest 1938;17:31–40.
- Naderer O, Nafziger AN, Bertino JS, Jr. Effects of moderate dose versus high-dose trimethoprim on serum creatinine and creatinine clearance and adverse reactions. Antimicrob Agents Chemother 1997;41:2466–70.
- KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (Issue 1, Vol. 3). (2013). National Kidney Foundation.
- Kidney Disease Improving Global Outcomes Acute Kidney Injury Working Group. KDIGO Clinical Practice

Guideline for Acute Kidney Injury. Kidney Int 2012 suppl.; 2:1–138.

- Jaffe M. Über den Niederschlag welchen Pikrinsäure in normalen Harn erzeugt und über eine neue Reaction des Kreatinins. Z Physiol Chem 1886;10:391-400.
- Folin O. Beitrag zur Chemie des Kreatinins und Kreatins in Harn. Z Physiol Chem 1904;41:223-4.
- Clinical and Laboratory Standards Institute (CLSI). Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline. CLSI Document EP25-A. Wayne, PA: CLSI; 2009.
- Dilena BA. Bacterial interference with measurement of creatinine in stored plasma. Clin Chem 1988;34:1007-8.
- Preiss DJ, Godber IM, Lamb EJ, Dalton RN, Gunn IR. The influence of a cooked-meat meal on estimated glomerular filtration rate. Ann Clin Biochem 2007;44:35-42.
- Jacobsen FK, Christensen CK, Mogensen CE, et al. Pronounced increase in serum creatinine concentration after eating cooked meat. Br Med J 1979;1:1049–50.
- Jacobsen FK, Christensen CK, Mogensen CE, et al. Evaluation of kidney function after meals. Lancet 1980;1:319.
- Mayersohn M, Conrad KA, Achari R. The influence of a cooked meat meal on creatinine plasma concentration and creatinine clearance. Br J Clin Pharmacol 1983;15:227–30.
- Pasternack A, Kuhlback B. Diurnal variations of serum and urine creatine and creatinine. Scand J Clin Lab Invest 1971;27:1–7.
- Preiss DJ, Godber IM, Lamb EJ, et al. The influence of a cooked-meat meal on estimated glomerular filtration rate. Ann Clin Biochem 2007;44:35–42.
- Shah KF, Stevens PE, Lamb EJ. The influence of a cooked-fish meal on estimated glomerular filtration rate. Ann Clin Biochem 2020;57:182–5.
- Pesce, A. J., & Kaplan, L. D. (2009). Methods in Clinical Chemistry: Kaplan and Pesce's: Clinical Chemistry: Theory, Analysis, Correlation: Vol. I (5th ed.), Chapter: Creatinine, p.440-51. Elseviers.
- Clinical and Laboratory Standards Institute (CLSI). Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline – Third Edition. CLSI Document EP28-A3c. Wayne, PA: CLSI; 2010.
- Clinical and Laboratory Standards Institute (CLSI). Establishing and Verifying an Extended Measuring Interval Through Specimen Dilution and Spiking – 1st Edition. CLSI Document EP34. Wayne, PA: CLSI; 2018.
- Clinical and Laboratory Standards Institute (CLSI). Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition. CLSI Document EP17-A2. Wayne, PA: CLSI; 2012.
- Clinical and Laboratory Standards Institute (CLSI). Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach - 1st Edition. CLSI Document EP06-A. Wayne, PA: CLSI; 2003.
- Clinical and Laboratory Standards Institute (CLSI). Evaluation of Precision of Quantitative Measurement

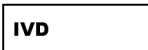


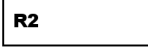

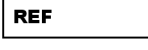
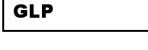










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- Procedures; Approved Guideline – Third Edition. CLSI Document EP05-A3. Wayne, PA: CLSI; 2014.
28. Clinical and Laboratory Standards Institute (CLSI). Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline - Second Edition. CLSI Document EP05-A2. Wayne, PA: CLSI; 2004.
 29. Bablok W et al. A General Regression Procedure for Method Transformation. J Clin Chem Clin Biochem 1988;26:783-790.
 30. Clinical and Laboratory Standards Institute (CLSI). Supplemental Tables for Interference Testing in Clinical Chemistry - First Edition. CLSI Document EP37. Wayne, PA: CLSI; 2018.
 31. Clinical and Laboratory Standards Institute (CLSI). Interference Testing in Clinical Chemistry - Third Edition. CLSI Document EP07. Wayne, PA: CLSI; 2018.
 32. CLIA proficiency testing criteria for acceptable analytical performance, as printed in the Federal Register July 11, 2022;87(131:41194-242.
 33. Carobene A, Ferrero C, Ceriotti F, et al. Creatinine measurement proficiency testing: assignment of matrix-adjusted ID GC-MS target values. Clin Chem 1997;43:1342–7.
 34. Cobbaert CM, Baadenhuijsen H, Weykamp CW. Prime time for enzymatic creatinine methods in pediatrics. Clin Chem 2009;55:549–58.
 35. Greenberg N, Roberts WL, Bachmann LM, et al. Specificity characteristics of 7 commercial creatinine measurement procedures by enzymatic and jaffe method principles. Clin Chem 2012;58:391–401.
 36. Weatherburn MW, Trotman RB, Jackson SH. Specific method for serum creatinine determination based on ion Exchange chromatography and an automated alkaline picrate reaction - a proposed reference method. Clin Biochem 1978;11:159–66.
 37. Ali AC, Mihas CC, Campbell JA. Interferences of o-raffinose cross-linked hemoglobin in three methods for serum creatinine. Clin Chem 1997;43:1738–43.
 38. Syal K, Srinivasan A, Banerjee D. Streptomycin interference in Jaffe reaction - possible false positive creatinine estimation in excessive dose exposure. Clin Biochem 2012;46:177–9.
 39. Luna-Zaizar H, Virgen-Montelongo M, Cortez-Alvarez CR, et al. In vitro interference by acetaminophen, aspirin, and metamizole in serum measurements of glucose, urea, and creatinine. Clin Biochem 2015;48:538–41.
 40. Swain RR, Briggs SL. Positive interference with the Jaffe reaction by cephalosporin antibiotics. Clin Chem 1977;23:1340–2.
 41. Kroll MH, Elin RJ. Interference with clinical laboratory analyses. Clin Chem 1994;40:1996-2005.

SYMBOLS

	In Vitro Diagnostic Medical Device
	Lot Number
	Reagent 1
	Reagent 2
	Global Trade Item Number
	Reference Number
	Good Laboratory Practices
	Identifies Products to Be Used Together
	Product of Turkey
	Manufacturer
	Expiration Date
	Temperature Limits
	Consult Instructions for Use
	Caution
	Number of Tests