Для лабораторий, использующих
Cardiac C-Reactive Protein (Latex) High Sensitive
на анализаторе **cobas c** 311,
на модулях **cobas c** 501, **c** 502,
на модуле **cobas c** 702,
COBAS INTEGRA 400 plus
и cobas **c** 111

Дата: 17.06.2024 г. Москва
Исх.: 0222/1706/2024
Ref.: QN-RDS-CoreLab-2024-029

Уведомление по качеству
Касательно теста Cardiac C-Reactive Protein (Latex) High Sensitive (CRPHS) для cobas c and COBAS INTEGRA 400 plus:
Обновленная информация об интерференции, обусловленной ревматоидным фактором

Название продукта	**GMMI / Кат. №**	**Идентификатор продукта (Номер лота или серийный номер)**	**Номер РУ, Дата РУ**	**Производитель**
Реагенты, стандарты, калибраторы, контроли и расходные материалы для биохимических анализаторов Hitachi 902, 902 ISE, 912, 912 ISE, 917 ISE, Cobas c 311, Cobas c 111, Cobas c 111 ISE, Cobas Integra 400 Plus/ 800 и платформ модульных MODULAR ANALYTICS, cobas 6000 С-реактивный белок (высокочувствительный) (CRPHS / CPR High Sensitive)	04628918190		ФСЗ 2011/08936 от 04.05.2021	Sandhofer Strasse 116, 68305 Mannheim, Germany
Реагенты для анализаторов биохимических Hitachi 902, 902 ISE, 912, 912 ISE, 917 ISE, Cobas c 311, Cobas c 111, Cobas c 111 ISE, Cobas Integra 400 plus, Cobas Integra 800 и платформ модульных MODULAR ANALYTICS, cobas 6000, cobas 8000 С-реактивный белок высокой чувствительности, 250 тестов (С-реактивный белок высокой чувствительности, 250 тестов)	05950864190		ФСЗ 2012/13068 от 19.10.2012	Sandhofer Strasse 116, D-68305, Mannheim, Germany
Sandhofer Strasse 116, 68305 Mannheim, Germany С-реактивный белок высокочувствительный (C-reactive protein (High sensitive) cobas c system (CRPHS))	05401607190		ФСЗ 2007/00476 от 21.06.2016	Sandhofer Strasse 116, 68305 Mannheim, Germany
Инструмент/Система	Анализатор **cobas c** 111 Анализатор **cobas c** 311 Модуль **cobas c** 501 Модуль **cobas c** 502			

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Уважаемый пользователь,

Сообщаем вам о том, что были проведены внутренние исследования эффективности высокочувствительного теста на сердечный С-реактивный белок (латекс) (CRPHS). Результаты показали, что данные об интерференции, обусловленной ревматоидными факторами, больше не актуальны в связи с новой более строгой процедурой тестирования. Таким образом, спецификация в Инструкции по использованию реагента была обновлена.

Это изменение основано на недавних результатах мастер-проекта **cobas c** 503, о котором было объявлено в MN-RDS-CoreLab-2022-183.

Описание ситуации

На основе внутренних исследований в контексте недавно объявленного переназначения мастер-прибора с **cobas c** 501 на **cobas c** 503 (MN-RDS-CoreLab-2022-183) была проведена оценка эффективности теста CRPHS.

Было обнаружено, что спецификации по интерференции, обусловленной ревматоидными факторами, больше не соответствуют новой, более строгой процедуре тестирования, и нуждаются в корректировке:

- В диапазоне низкого относительного риска для оценки риска ишемической болезни сердца (<1 мг/л CRPHS) и при ожидаемой истинной концентрации CRPHS 0,298 мг/л результаты для образцов со значениями ревматоидного фактора >200 МЕ/мл были ошибочно завышены до +0,181 мг/л CRPHS (максимальное абсолютное отклонение). При ожидаемой истинной концентрации CRPHS 0,831 мг/л результат измерения был завышен на 14%.
- При значениях CRPHS >1 мг/л результаты всех измерений находились в пределах допустимых значений.

Ситуация касается теста CRPHS для **cobas c** (ACN 217 для **cobas c** 111/311/501; ACN 8217 для **cobas c** 502/702) и COBAS INTEGRA 400 plus (идентификатор теста 0-033).

Инструкции по использованию реагента были обновлены с учетом новой спецификации в разделе «Ограничения – интерференция»: **«Ревматоидные факторы: значимая интерференция, обусловленная ревматоидными факторами, отсутствует до концентрации 200 МЕ/мл».**

Причина возникновения

Изменение процедуры оценки основано на недавних результатах мастер-проекта **cobas c** 503, о котором было объявлено в MN-RDS-CoreLab-2022-183:

Поскольку мы собираем дополнительные данные о **cobas c** 503, нам необходимо соблюдать новейшие нормативные требования (например, IVDR), а некоторые рабочие процедуры изменились из-за обновленных версий основных международных рекомендаций (например, CLSI). Новые внешние требования могут привести к другим настройкам Протокола методики и различиям в результатах, полученных на **cobas c** 503 по сравнению со старыми данными **cobas c** 501.

Частота возникновения

Ни одна рекламация не была передана в группу расследования рекламаций (CIR).

Вероятность обнаружения

Проблема не может быть надежно обнаружена. Для профессиональных пользователей не существует регулярно применяемых мер по определению концентрации ревматоидных факторов в отдельном образце. Следовательно, невозможно идентифицировать затронутые образцы.

Серьезность последствий

Согласно заявленному назначению, высокочувствительное измерение уровня сердечного С-реактивного белка (СРБ) может использоваться в качестве вспомогательного средства при оценке риска развития ишемической болезни сердца в будущем. Более конкретно, высокочувствительное измерение уровня СРБ можно использовать в качестве маркера для прогнозирования риска ишемической болезни сердца у практически здоровых людей и в качестве индикатора прогноза повторных событий. Однако, важно отметить, что высокочувствительный С-реактивный белок (вчСРБ) является лишь одним из многих факторов, влияющих на общий риск, и его следует интерпретировать в сочетании с другой клинической и диагностической информацией: вчСРБ имеет дополнительную прогностическую ценность, например, при оценке липидного спектра, риска по шкале Фрамингема, тяжести метаболического синдрома, артериального давления, а также у лиц с субклиническим атеросклерозом и без него. Тест на вчСРБ обычно назначается медицинскими работниками для оценки риска сердечно-сосудистых заболеваний, особенно у лиц с промежуточным риском.

Исследование может помочь принять решение о лечении и таких модификациях образа жизни, как корректировка питания и физической нагрузки, для того чтобы снизить риск сердечно-сосудистых заболеваний. Стоит отметить, что на уровень вчСРБ также могут влиять другие факторы, например, инфекции, некоторые препараты и хронические заболевания, поэтому результаты теста следует интерпретировать в контексте общего состояния здоровья.

В описанной ситуации противоречивые завышенные результаты вчСРБ наблюдались в диапазоне вчСРБ <1 мг/л из-за интерференции, обусловленной ревматоидными факторами (РФ) >200 МЕ/мл. В частности, было обнаружено абсолютное отклонение +0,1810 мг/л (при ожидаемой истинной концентрации аналита 0,298 мг/л) и максимальное значение +14% при самом низком пороге (при ожидаемой истинной концентрации аналита 0,831 мг/л). Никаких противоречивых результатов не наблюдалось при значениях вчСРБ >1 мг/л.

Учитывая ограниченную фазу максимального абсолютного отклонения (+0,181 мг/л) и затронутый нижний диапазон (<1 мг/л), маловероятно, что однократное измерение вчСРБ повлияет на какое-либо медицинское решение. Кроме того, согласно заявленному назначению, при использовании вчСРБ для оценки риска ишемической болезни сердца измерения следует проводить на метаболически стабильных пациентах и сравнивать с предыдущими значениями. В идеале для оценки риска следует использовать среднее значение результатов вчСРБ, повторенных с интервалом в две недели. Скрининг всего взрослого населения на вчСРБ не рекомендуется, и оценка уровня вчСРБ не заменяет оценку традиционных факторов риска сердечно-сосудистых заболеваний. Лечение острого коронарного синдрома не должно зависеть исключительно от измерения вчСРБ. Аналогичным образом, применение мер вторичной профилактики должно основываться на глобальной оценке риска, а не только на измерениях вчСРБ. Серийные измерения вчСРБ не следует использовать для мониторинга лечения.

<u>Важная информация</u>

Пользователи, проводящие высокочувствительный тест на сердечный С-реактивный белок (латекс) (CRPHS) на **cobas c** 111/311/501/502/702 или COBAS INTEGRA 400 plus, должны быть

проинформированы об обновленных заявлениях об интерференции, обусловленной ревматоидными факторами.
К настоящему Уведомлению по качеству прилагаются обновленные Инструкции по использованию реагента для всех затронутых систем.

Обновленная электронная документация будут опубликована на портале электронного контента со ссылкой на настоящее Уведомление по качеству.

Срок публикации для разных анализаторов:

Новая Инструкция по использованию реагента уже приложена к настоящему Уведомлению по качеству.

Версия Инструкции по использованию реагента	Анализатор	Срок публикации
10.0	**cobas c** 111	Май 2024 г.
15.0	**cobas c** 311 **cobas c** 501/502 **COBAS INTEGRA 400 plus**	
11.0	**cobas c** 702	

Распространение настоящего уведомления по качеству на местах

Настоящее Уведомление по качеству предназначено для всех заинтересованных лиц в Вашей организации или других организациях, которые получали данную продукцию.

Пожалуйста, перешлите данное уведомление другим организациям/лицам, которых она может касаться.

Приносим свои извинения за причиненные неудобства, которые могут быть связаны с данной ситуацией, и надеемся на Ваше понимание и поддержку.

Контакты

В случае возникновения вопросов обратитесь, пожалуйста, в службу поддержки Roche:
Бесплатная линия: 8 800 100-68-96
Время работы: понедельник – пятница с 08:00 до 18:00 по Московскому времени
e-mail: russia.rcsc@roche.com.

С уважением,

Менеджер по продукции
Тел: +7 (916) 922-64-09
Электронная почта: ivan.kargov@roche.com

Иван Каргов
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Медицинский менеджер
Тел: + 7 (495) 229-69-99
Электронная почта: maria.kosyakova@roche.com

Мария Косякова
Maria Kosyakova Digitally signed by Maria Kosyakova Date: 2024.06.18 15:02:34 +03'00'

CRPHS

cobas®

Cardiac C-Reactive Protein (Latex) High Sensitive

Order information

REF		CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
04628918190	04628918500	Cardiac C-Reactive Protein (Latex) High Sensitive (300 tests)	System-ID 07 6866 9	**cobas c** 311, **cobas c** 501/502, COBAS INTEGRA 400 plus

Materials required (but not provided):

		cobas c 311, **cobas c** 501/502	COBAS INTEGRA 400 plus
11355279216	Calibrator f.a.s. Proteins (5 x 1 mL)	Code 656	System-ID 07 6557 0
20766321322	CRP T Control N (5 x 0.5 mL)	Code 235	System-ID 07 6632 1
10557897122	Precinorm Protein (3 x 1 mL)	Code 302	System-ID 07 9105 9
05117003190	PreciControl ClinChem Multi 1 (20 x 5 mL)	Code 391	System-ID 07 7469 3
05947626190	PreciControl ClinChem Multi 1 (4 x 5 mL)	Code 391	System-ID 07 7469 3
04489357190	Diluent NaCl 9 % (50 mL)	System-ID 07 6869 3	n.a.
20756350322	Diluent NaCl 9 % (6 x 22 mL)	n.a.	System-ID 07 5635 0

English

Intended use

In vitro test for the quantitative determination of C-reactive protein (CRP) in human serum and plasma on **cobas c** and COBAS INTEGRA systems. Measurement of CRP is of use for the detection and evaluation of inflammatory disorders and associated diseases, infection and tissue injury. Highly sensitive measurement of CRP may also be used as an aid in the assessment of the risk of future coronary heart disease. When used as an adjunct to other laboratory evaluation methods of acute coronary syndromes, it may also be an additional independent indicator of recurrent event prognosis in patients with stable coronary disease or acute coronary syndrome.

Summary

C-reactive protein is the classic acute phase protein in inflammatory reactions.[1] It is synthesized by the liver and consists of five identical polypeptide chains that form a five-member ring having a molecular weight of 105000 daltons.[1,2,3,4] CRP is the most sensitive of the acute phase reactants and its concentration increases rapidly during inflammatory processes.[2,3] Complexed CRP activates the classical complement pathway. The CRP response frequently precedes clinical symptoms, including fever.[1,3] After onset of an acute phase response the serum CRP concentration rises rapidly and extensively.[2,3,4] The increase begins within 6 to 12 hours and the peak value is reached within 24 to 48 hours.[1,3,5] CRP response may be less pronounced in patients suffering from liver disease.[6]

CRP assays are used to detect systemic inflammatory processes (apart from certain types of inflammation such as systemic lupus erythematosus (SLE) and Colitis ulcerosa);[1,3,4,6] to assess treatment of bacterial infections with antibiotics;[1,4,6,7] to detect intrauterine infections with concomitant premature amniorrhexis;[4,6] to differentiate between active and inactive forms of disease with concurrent infection, e.g. in patients suffering from SLE or Colitis ulcerosa;[3,4,6] to therapeutically monitor rheumatic disease and assess anti-inflammatory therapy;[1,4,6] to determine the presence of post-operative complications at an early stage, such as infected wounds, thrombosis and pneumonia, and to distinguish between infection and bone marrow transplant rejection.[1,4,6]

Sensitive CRP measurements have been used and discussed for early detection of infection in pediatrics and risk assessment of coronary heart disease.[8,9,10,11] Several studies came to the conclusion that the highly sensitive measurement of CRP could be used as a marker to predict the risk of coronary heart disease in apparently healthy persons and as an indicator of recurrent event prognosis.[10,12,13,14,15,16] Increases in CRP values are non-specific and should not be interpreted without a complete clinical history.[17] The American Heart Association and the Centers for Disease Control and Prevention have made several recommendations concerning the use of high sensitivity C-Reactive Protein (hsCRP) in cardiovascular risk assessment.[17,18] Measurement of hsCRP may also be used as an aid in the assessment of the risk of future coronary heart disease and as a risk-enhancing factor in patients with borderline- or intermediate-risk for atherosclerotic cardiovascular disease.[19] When used as an adjunct to other laboratory evaluation methods of acute coronary syndromes, it may also be an additional independent indicator of recurrent event prognosis in patients with stable coronary disease or acute coronary syndrome.[17,20]

Testing for any risk assessment should not be performed while there is an indication of infection, systemic inflammation or trauma.[11,17,21] Patients with persistently unexplained hsCRP levels above 10 mg/L (95.2 nmol/L) should be evaluated for non-cardiovascular etiologies.[13,17] When using hsCRP to assess the risk of coronary heart disease, measurements should be made on metabolically stable patients and compared to previous values.[17] Optimally, the average of hsCRP results repeated two weeks apart should be used for risk assessment.[17] Screening the entire adult population for hsCRP is not recommended, and hsCRP is not a substitute for traditional cardiovascular risk factors.[17] Acute coronary syndrome management should not depend solely on hsCRP measurements.[14,17] Similarly, application of secondary prevention measures should be based on global risk assessment and not solely on hsCRP measurements.[17] Serial measurements of hsCRP should not be used to monitor treatment.[17]

Studies indicate an influence of gestational age on the kinetics of CRP in preterm infants, which may materialize as a blunted response to infection when comparing preterm and term newborns.[22,23,24] This phenomenon, most likely due to immature liver function, may result in a lower sensitivity of CRP in the diagnosis of neonatal sepsis in preterm compared to term newborns.[25] In adult patients with advanced liver dysfunction, CRP levels are reduced in response to acute infection, however production is nevertheless maintained.[26] Although the liver is considered the main source of CRP, serum levels are not significantly lower in patients with cirrhosis than in other patients, and the predictive performance for infection is similar for patients with and without cirrhosis.[27]

Various assay methods are available for CRP determination, such as nephelometry and turbidimetry.[28,29] The Roche CRP assay is based on the principle of particle-enhanced immunological agglutination.

Test principle[28,29]

Particle enhanced immunoturbidimetric assay.

Human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies. The precipitate is determined turbidimetrically.

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:
Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

Reagent handling

cobas c systems:

Ready for use

Carefully invert reagent container several times prior to use to ensure that the reagent components are mixed.

CRPHS

Cardiac C-Reactive Protein (Latex) High Sensitive

COBAS INTEGRA systems:

Mix all new (non-punctured) **cobas c** packs for 1 minute on a cassette mixer before loading on the analyzer. All in-use **cobas c** packs must also be mixed in the same manner at the beginning of each week (once a week).

Specimen collection and preparation

For specimen collection and preparation only use suitable tubes or collection containers.

Only the specimens listed below were tested and found acceptable.
Serum.
Plasma: Li-heparin and K_2-EDTA plasma

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Centrifuge samples containing precipitates before performing the assay.

See the limitations and interferences section for details about possible sample interferences.

Stability:[30]	11 days at 15-25 °C
	2 months at 2-8 °C
	3 years at –20 °C (± 5 °C)

Freeze only once.

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

- See "Order information" section
- General laboratory equipment

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

The performance of applications not validated by Roche is not warranted and must be defined by the user.

Calculation

The systems automatically calculate the analyte concentration of each sample. For more details, please refer to Data Analysis in the Online Help.

Conversion factors:	mg/L x 9.52 = nmol/L
	mg/L x 0.1 = mg/dL
	nmol/L x 0.001 = µmol/L

Expected values

Consensus reference interval for adults:[31]

IFCC/CRM 470

mg/dL	mg/L	nmol/L
< 0.5	< 5.0	< 47.6

The CDC/AHA recommended the following hsCRP cut-off points (tertiles) for CVD risk assessment:[17,32]

hsCRP level (mg/L)	hsCRP level (nmol/L)	Relative risk
< 1.0	< 9.52	low
1.0-3.0	9.52-28.6	average
> 3.0	> 28.6	high

Patients with higher hsCRP concentrations are more likely to develop myocardial infarction and severe peripheral vascular disease.

5-95 % reference intervals of neonates and children:[33]

Neonates (0-3 weeks): 0.1-4.1 mg/L (0.95-39.0 nmol/L)

Children (2 months-15 years): 0.1-2.8 mg/L (0.95-26.7 nmol/L)

It is important to monitor the CRP concentration during the acute phase of the illness.

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

Increases in CRP values are non-specific and should not be interpreted without a complete clinical history.

When using hsCRP to assess the risk of coronary heart disease, measurements should be made on metabolically stable patients and compared to previous values. Optimally, the average of hsCRP results repeated two weeks apart should be used for risk assessment. Measurements should be compared to previous values. When the results are being used for risk assessment, patients with persistently unexplained hsCRP levels of above 10 mg/L (95.2 nmol/L) should be evaluated for non-cardiovascular origins. Testing for any risk assessment should not be performed while there is indication of infection, systemic inflammation or trauma.[17]

cobas c systems

System information

For **cobas c** 311/501 analyzers:

CRPHS: ACN 217

For **cobas c** 502 analyzer:

CRPHS: ACN 8217

Reagents - working solutions

R1	TRIS buffer with bovine serum albumin and immunoglobulins (mouse); preservative; stabilizers
R2	Latex particles coated with anti-CRP (mouse) in glycine buffer; preservative; stabilizers

R1 is in position B and R2 is in position C.

Storage and stability

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label.
On-board in use and refrigerated on the analyzer:	12 weeks

Application for serum and plasma

cobas c 311 **test definition**

Assay type	Rate A	
Reaction time / Assay points	10/7-57	
Wavelength (sub/main)	– /546 nm	
Reaction direction	Increase	
Units	mg/L (nmol/L, mg/dL)	
Reagent pipetting		Diluent (H_2O)
R1	82 µL	42 µL
R2	28 µL	20 µL

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	6 µL	–	–
Decreased	6 µL	10 µL	140 µL
Increased	6 µL	–	–

cobas c 501 **test definition**

Assay type	Rate A
Reaction time / Assay points	10/12-70
Wavelength (sub/main)	– /546 nm

CRPHS

Cardiac C-Reactive Protein (Latex) High Sensitive

Reaction direction	Increase	
Units	mg/L (nmol/L, mg/dL)	
Reagent pipetting		Diluent (H_2O)
R1	82 µL	42 µL
R2	28 µL	20 µL

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	6 µL	–	–
Decreased	6 µL	10 µL	140 µL
Increased	6 µL	–	–

cobas c 502 **test definition**

Assay type	Rate A
Reaction time / Assay points	10/12-70
Wavelength (sub/main)	– /546 nm
Reaction direction	Increase
Units	mg/L (nmol/L, mg/dL)
Reagent pipetting	Diluent (H_2O)
R1	82 µL 42 µL
R2	28 µL 20 µL

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	6 µL	–	–
Decreased	6 µL	10 µL	140 µL
Increased	12 µL	–	–

Calibration

Calibrators	S1: H_2O
	S2: C.f.a.s. Proteins
	Multiply the lot-specific C.f.a.s. Proteins calibrator value by the factors below to determine the standard concentrations for the 6-point calibration curve:
	S2: 0.0125 S5: 0.100
	S3: 0.0250 S6: 0.200
	S4: 0.0500
Calibration mode	Line Graph
Calibration frequency	Full calibration • after reagent lot change • as required following quality control procedures

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Traceability: This method has been standardized against the reference preparation of the IRMM (Institute for Reference Materials and Measurements) BCR470/CRM470 (RPPHS - Reference Preparation for Proteins in Human Serum).[34]

Quality control

For quality control, use control materials as listed in the "Order information" section.

In addition, other suitable control material can be used.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

Follow the applicable government regulations and local guidelines for quality control.

Limitations - interference

Criterion: Recovery within ± 10 % of initial values at CRP levels of 1.0 mg/L.

Icterus:[35] No significant interference up to an I index of 60 for conjugated bilirubin and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 60 mg/dL or 1026 µmol/L).

Hemolysis:[35] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 622 µmol/L or 1000 mg/dL).

Lipemia (Intralipid):[35] No significant interference up to an L index of 600. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Rheumatoid factors: No significant interference from rheumatoid factors up to a concentration of 200 IU/mL.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[36,37]

Therapeutic drugs: Significantly decreased CRP values may be obtained from samples taken from patients who have been treated with carboxypenicillins.

High dose hook-effect: No false result occurs up to a CRP concentration of 1000 mg/L.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[38]

Although measures were taken to minimize interference caused by human anti-mouse antibodies, erroneous findings may be obtained from samples taken from patients who have been treated with monoclonal mouse antibodies or have received them for diagnostic purposes.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

ACTION REQUIRED

Special Wash Programming: The use of special wash steps is mandatory when certain test combinations are run together on **cobas c** systems. The latest version of the carry-over evasion list can be found with the NaOHD-SMS-SmpCln1+2-SCCS Method Sheets. For further instructions refer to the operator's manual. **cobas c** 502 analyzer: All special wash programming necessary for avoiding carry-over is available via the **cobas** link, manual input is required in certain cases.

Where required, special wash/carry-over evasion programming must be implemented prior to reporting results with this test.

Limits and ranges

Measuring range

0.15-20.0 mg/L (1.43-190 nmol/L, 0.015-2.0 mg/dL)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:15 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 15.

Lower limits of measurement

Lower detection limit of the test

0.15 mg/L (1.43 nmol/L, 0.015 mg/dL)

The lower detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying 3 standard deviations above that of the lowest standard (standard 1 + 3 SD, repeatability, n = 21).

Functional sensitivity

0.3 mg/L (2.96 nmol/L, 0.03 mg/dL)

The functional sensitivity is the lowest CRP concentration that can be reproducibly measured with an inter-assay coefficient of variation of < 10 %.

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using human samples and controls in an internal protocol with repeatability (n = 21) and intermediate precision (3 aliquots

CRPHS

Cardiac C-Reactive Protein (Latex) High Sensitive

per run, 1 run per day, 21 days). The following results were obtained on the **cobas c** 501 analyzer:

Repeatability	*Mean*	*SD*	*CV*
	mg/L (nmol/L, mg/dL)	*mg/L (nmol/L, mg/dL)*	*%*
Precinorm Protein	9.00 (85.7, 0.900)	0.10 (1.0, 0.010)	1.2
CRP T Control N	4.34 (41.3, 0.434)	0.04 (0.4, 0.004)	1.0
Human serum 1	15.9 (151, 1.59)	0.1 (1, 0.01)	0.4
Human serum 2	0.54 (5.14, 0.054)	0.01 (0.10, 0.001)	1.6
Intermediate precision	*Mean*	*SD*	*CV*
	mg/L (nmol/L, mg/dL)	*mg/L (nmol/L, mg/dL)*	*%*
Precinorm Protein	9.06 (86.3, 0.906)	0.11 (1.1, 0.011)	1.3
CRP T Control N	4.28 (40.8, 0.428)	0.11 (1.1, 0.011)	2.6
Human serum 3	13.3 (126, 1.33)	0.3 (3, 0.03)	2.1
Human serum 4	0.53 (5.05, 0.053)	0.05 (0.48, 0.005)	8.4

The data obtained on **cobas c** 501 analyzer(s) are representative for **cobas c** 311 analyzer(s).

Method comparison

CRP values for human serum and plasma samples obtained on a **cobas c** 501 analyzer (y) were compared with those determined using the corresponding reagent on a Roche/Hitachi 917 analyzer (x).

Sample size (n) = 192

Passing/Bablok[39]	Linear regression
y = 0.992x + 0.254 mg/L	y = 0.946x + 0.514 mg/L
τ = 0.944	r = 0.996

The sample concentrations were between 0.500 and 19.7 mg/L (4.76 and 188 nmol/L, 0.050 and 1.97 mg/dL).

The data obtained on **cobas c** 501 analyzer(s) are representative for **cobas c** 311 analyzer(s).

COBAS INTEGRA systems

System information

COBAS INTEGRA Cardiac C-Reactive Protein (Latex) High Sensitive (CRPHS)

Test CRPHS: Test ID 0-033

Reagents - working solutions

R1 TRIS buffer with bovine serum albumin and immunoglobulins (mouse); preservative; stabilizers.

SR Latex particles coated with anti-CRP (mouse) in glycine buffer; preservative; stabilizers.

R1 is in position B and SR is in position C.

Storage and stability

Shelf life at 2-8 °C	See expiration date on **cobas c** pack label
On-board in use at 10-15 °C	12 weeks

Application for serum and plasma

Measuring mode	Absorbance
Abs. calculation mode	Kinetic
Reaction mode	R1-S-SR
Reaction direction	Increase
Wavelength A	552 nm
Calc. first/last	35/63
Typical prozone effect	> 40 mg/L (> 380 nmol/L)
Antigen excess check	Yes[a)]
Unit	mg/L

Pipetting parameters

		Diluent (H_2O)
R1	82 µL	48 µL
Sample	6 µL	
SR	28 µL	14 µL
Total volume	178 µL	

a) Samples with concentrations > 40 mg/L are flagged either >TEST RNG or "HIGH ACT". Rerun the sample with postdilution or, if the sample has already been postdiluted, rerun the sample with a higher postdilution factor.

Calibration

Calibrator	Calibrator f.a.s. Proteins
Calibration dilution ratio	1:5, 1:10, 1:20, 1:40, 1:80 and 0 mg/L performed automatically by the instrument.
Calibration mode	Linear interpolation
Calibration replicate	Duplicate recommended
Calibration interval	Each lot and as required following quality control procedures

Enter the assigned lot-specific CRP value for the Calibrator f.a.s. Proteins.

Traceability: This method has been standardized by method comparison to the Tina-Quant CRPLX high sensitive assay. The Tina-Quant CRPLX high sensitive assay has been standardized with regard to the IFCC/BCR/CAP reference preparation CRM 470 (RPPHS 91/0619) for 14 serum proteins.

Quality control

Reference range	CRP T Control N
Pathological range	Precinorm Protein or PreciControl ClinChem Multi 1
Control interval	24 hours recommended
Control sequence	User defined
Control after calibration	Recommended

For quality control, use control materials as listed in the "Order information" section. In addition, other suitable control material can be used.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

Follow the applicable government regulations and local guidelines for quality control.

Limitations - interference

Criterion: Recovery within ± 10 % of initial value.

Serum, plasma

Icterus:[35] No significant interference up to an I index of 60 for conjugated and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 60 mg/dL or 1026 µmol/L).

Hemolysis:[35] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 1000 mg/dL or 621 µmol/L).

Lipemia (Intralipid):[35] No significant interference up to an L index of 500 (at 2 mg/L or 19 nmol/L CRP). There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

High-dose hook effect: Does not occur at CRP concentrations below 40 mg/L or 380 nmol/L. Samples with concentrations > 40 mg/L are flagged either >TEST RNG or "HIGH ACT".

Rheumatoid factors: No interference up to 200 IU/mL.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[36,37]
Therapeutic drugs: Significantly decreased CRP values may be obtained

from samples taken from patients who have been treated with carboxypenicillins.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[38]

Although measures were taken to minimize interference caused by human anti-mouse antibodies, erroneous findings may be obtained from samples taken from patients who have been treated with monoclonal mouse antibodies or have received them for diagnostic purposes.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

ACTION REQUIRED
Special Wash Programming: The use of special wash steps is mandatory when certain test combinations are run together on COBAS INTEGRA analyzers. Refer to the CLEAN Method Sheet for further instructions and for the latest version of the Extra wash cycle list.
Where required, special wash/carry-over evasion programming must be implemented prior to reporting results with this test.

Limits and ranges

Measuring range

0.1-20 mg/L (0.952-190 nmol/L) (typical measuring range)

The upper and lower limits of the measuring range depend on the actual calibrator value.

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:15 dilution. Results from samples diluted by the rerun function are automatically multiplied by a factor of 15.

Lower limits of measurement

Lower detection limit of the test

0.1 mg/L (0.952 nmol/L)

The lower detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying 3 standard deviations above that of a zero sample (zero sample + 3 SD, repeatability, n = 21).

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using human samples and controls in an internal protocol with repeatability (n = 21) and intermediate precision (3 aliquots per run, 1 run per day, 21 days). Results for repeatability and intermediate precision were obtained on the COBAS INTEGRA 700 analyzer.

	Repeatability		Intermediate precision	
Sample	Mean	CV	Mean	CV
	mg/L (nmol/L)	%	mg/L (nmol/L)	%
Control Level 1	3.3 (31.4)	0.9	3.3 (31.4)	3.5
Control Level 2	8.0 (76.2)	0.7	8.0 (76.2)	2.2
Human pool 1	1.6 (15.2)	1.3	1.5 (14.3)	3.1
Human pool 2	11.4 (109)	0.6	11.4 (109)	2.3

The data obtained on COBAS INTEGRA 700 analyzer(s) are representative for COBAS INTEGRA 400 analyzer(s).

Functional sensitivity (limit of quantitation)

0.3 mg/L (2.96 nmol/L)

The functional sensitivity (limit of quantitation) is the lowest CRP concentration that can be reproducibly measured with an inter-assay coefficient of variation of < 10 %.

Method comparison

CRP values for human serum and plasma samples obtained on a COBAS INTEGRA 700 analyzer using the COBAS INTEGRA Cardiac C-Reactive Protein (Latex) High Sensitive reagent (y) were compared to two commercially available alternative automated systems (x). Sample size (n) represents all replicates.

System 1

Sample size (n) = 58

Passing/Bablok[39]	Linear regression
y = 1.0548x + 0.0414	y = 0.9877x + 0.1264
τ = 0.956	r = 0.996

The sample concentrations were between 0.2 and 16.3 mg/L (1.9 and 15.5 nmol/L).

System 2

Sample size (n) = 54

Passing/Bablok[39]	Linear regression
y = 0.9715x + 0.0211	y = 0.9941x + 0.0295
τ = 0.935	r = 0.998

The sample concentrations were between 0.1 and 9.0 mg/L (1.0 and 8.6 nmol/L).

The data obtained on COBAS INTEGRA 700 analyzer(s) are representative for COBAS INTEGRA 400 analyzer(s).

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A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

The Summary of Safety & Performance Report can be found here: https://ec.europa.eu/tools/eudamed

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see navifyportal.roche.com for definition of symbols used):

CONTENT	Contents of kit
→	Volume for reconstitution
GTIN	Global Trade Item Number
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

CE 0123

Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim
www.roche.com
+800 5505 6606

CRPHS

cobas®

Cardiac C-Reactive Protein (Latex) High Sensitive

Order information

REF		CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
05950864190	05950864500	Cardiac C-Reactive Protein (Latex) High Sensitive (250 tests)	System-ID 01 6866 9	**cobas c** 701/702

Materials required (but not provided):

11355279216	Calibrator f.a.s. Proteins (5 x 1 mL)	Code 656	
20766321322	CRP T Control N (5 x 0.5 mL)	Code 235	
10557897122	Precinorm Protein (3 x 1 mL)	Code 302	
05117003190	PreciControl ClinChem Multi 1 (20 x 5 mL)	Code 391	
05947626190	PreciControl ClinChem Multi 1 (4 x 5 mL)	Code 391	
05172152190	Diluent NaCl 9 % (119 mL)	System-ID 08 6869 3	

English

System information

CRPHS: ACN 8217

Intended use

In vitro test for the quantitative determination of C-reactive protein (CRP) in human serum and plasma on **cobas c** systems. Measurement of CRP is of use for the detection and evaluation of inflammatory disorders and associated diseases, infection and tissue injury. Highly sensitive measurement of CRP may also be used as an aid in the assessment of the risk of future coronary heart disease. When used as an adjunct to other laboratory evaluation methods of acute coronary syndromes, it may also be an additional independent indicator of recurrent event prognosis in patients with stable coronary disease or acute coronary syndrome.

Summary

C-reactive protein is the classic acute phase protein in inflammatory reactions.[1] It is synthesized by the liver and consists of five identical polypeptide chains that form a five-member ring having a molecular weight of 105000 daltons.[1,2,3,4] CRP is the most sensitive of the acute phase reactants and its concentration increases rapidly during inflammatory processes.[2,3] Complexed CRP activates the classical complement pathway. The CRP response frequently precedes clinical symptoms, including fever.[1,3] After onset of an acute phase response the serum CRP concentration rises rapidly and extensively.[2,3,4] The increase begins within 6 to 12 hours and the peak value is reached within 24 to 48 hours.[1,3,5] CRP response may be less pronounced in patients suffering from liver disease.[6]

CRP assays are used to detect systemic inflammatory processes (apart from certain types of inflammation such as systemic lupus erythematosus (SLE) and Colitis ulcerosa);[1,3,4,6] to assess treatment of bacterial infections with antibiotics;[1,4,6,7] to detect intrauterine infections with concomitant premature amniorrhexis;[4,6] to differentiate between active and inactive forms of disease with concurrent infection, e.g. in patients suffering from SLE or Colitis ulcerosa;[3,4,6] to therapeutically monitor rheumatic disease and assess anti-inflammatory therapy;[1,4,6] to determine the presence of post-operative complications at an early stage, such as infected wounds, thrombosis and pneumonia, and to distinguish between infection and bone marrow transplant rejection.[1,4,6]

Sensitive CRP measurements have been used and discussed for early detection of infection in pediatrics and risk assessment of coronary heart disease.[8,9,10,11] Several studies came to the conclusion that the highly sensitive measurement of CRP could be used as a marker to predict the risk of coronary heart disease in apparently healthy persons and as an indicator of recurrent event prognosis.[10,12,13,14,15,16] Increases in CRP values are non-specific and should not be interpreted without a complete clinical history.[17] The American Heart Association and the Centers for Disease Control and Prevention have made several recommendations concerning the use of high sensitivity C-Reactive Protein (hsCRP) in cardiovascular risk assessment.[17,18] Measurement of hsCRP may also be used as an aid in the assessment of the risk of future coronary heart disease and as a risk-enhancing factor in patients with borderline- or intermediate-risk for atherosclerotic cardiovascular disease.[19] When used as an adjunct to other laboratory evaluation methods of acute coronary syndromes, it may also be an additional independent indicator of recurrent event prognosis in patients with stable coronary disease or acute coronary syndrome.[17,20]

Testing for any risk assessment should not be performed while there is an indication of infection, systemic inflammation or trauma.[11,17,21] Patients with persistently unexplained hsCRP levels above 10 mg/L (95.2 nmol/L) should be evaluated for non-cardiovascular etiologies.[13,17] When using hsCRP to assess the risk of coronary heart disease, measurements should be made on metabolically stable patients and compared to previous values.[17] Optimally, the average of hsCRP results repeated two weeks apart should be used for risk assessment.[17] Screening the entire adult population for hsCRP is not recommended, and hsCRP is not a substitute for traditional cardiovascular risk factors.[17] Acute coronary syndrome management should not depend solely on hsCRP measurements.[14,17] Similarly, application of secondary prevention measures should be based on global risk assessment and not solely on hsCRP measurements.[17] Serial measurements of hsCRP should not be used to monitor treatment.[17]

Studies indicate an influence of gestational age on the kinetics of CRP in preterm infants, which may materialize as a blunted response to infection when comparing preterm and term newborns.[22,23,24] This phenomenon, most likely due to immature liver function, may result in a lower sensitivity of CRP in the diagnosis of neonatal sepsis in preterm compared to term newborns.[25] In adult patients with advanced liver dysfunction, CRP levels are reduced in response to acute infection, however production is nevertheless maintained.[26] Although the liver is considered the main source of CRP, serum levels are not significantly lower in patients with cirrhosis than in other patients, and the predictive performance for infection is similar for patients with and without cirrhosis.[27]

Various assay methods are available for CRP determination, such as nephelometry and turbidimetry.[28,29] The Roche CRP assay is based on the principle of particle-enhanced immunological agglutination.

Test principle[28,29]

Particle enhanced immunoturbidimetric assay.

Human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies. The precipitate is determined turbidimetrically.

Reagents - working solutions

R1 TRIS buffer with bovine serum albumin and immunoglobulins (mouse); preservative; stabilizers

R3 Latex particles coated with anti-CRP (mouse) in glycine buffer; preservative; stabilizers

R1 is in position B and R3 is in position C.

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:
Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

Reagent handling

Ready for use

Carefully invert reagent container several times prior to use to ensure that the reagent components are mixed.

CRPHS

Cardiac C-Reactive Protein (Latex) High Sensitive

cobas®

Storage and stability

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label.
On-board in use and refrigerated on the analyzer:	12 weeks
On-board on the Reagent Manager:	24 hours

Specimen collection and preparation

For specimen collection and preparation only use suitable tubes or collection containers.

Only the specimens listed below were tested and found acceptable.
Serum.
Plasma: Li-heparin and K_2-EDTA plasma

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Centrifuge samples containing precipitates before performing the assay.

See the limitations and interferences section for details about possible sample interferences.

Stability:[30]	11 days at 15-25 °C 2 months at 2-8 °C 3 years at –20 °C (± 5 °C)

Freeze only once.

Materials provided

See “Reagents – working solutions” section for reagents.

Materials required (but not provided)

See “Order information” section

General laboratory equipment

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator’s manual for analyzer-specific assay instructions.

The performance of applications not validated by Roche is not warranted and must be defined by the user.

Application for serum and plasma

cobas c 701/702 **test definition**

Assay type	Rate A	
Reaction time / Assay points	10 / 22-38	
Wavelength (sub/main)	– /546 nm	
Reaction direction	Increase	
Units	mg/L (nmol/L, mg/dL)	
Reagent pipetting		Diluent (H_2O)
R1	82 µL	42 µL
R3	28 µL	20 µL

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	6 µL	–	–
Decreased	6 µL	10 µL	140 µL
Increased	12 µL	–	–

Calibration

Calibrators	S1: H_2O S2-S6: C.f.a.s. Proteins

Multiply the lot-specific C.f.a.s. Proteins calibrator value by the factors below to determine the standard concentrations for the 6-point calibration curve:

S2: 0.0125	S5: 0.100
S3: 0.0250	S6: 0.200
S4: 0.0500	

Calibration mode	Line Graph
Calibration frequency	Full calibration - after reagent lot change - as required following quality control procedures

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Traceability: This method has been standardized against the reference preparation of the IRMM (Institute for Reference Materials and Measurements) BCR470/CRM470 (RPPHS - Reference Preparation for Proteins in Human Serum).[31]

Quality control

For quality control, use control materials as listed in the "Order information" section.

In addition, other suitable control material can be used.

The control intervals and limits should be adapted to each laboratory’s individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

Follow the applicable government regulations and local guidelines for quality control.

Calculation

cobas c systems automatically calculate the analyte concentration of each sample.

Conversion factors:	mg/L x 9.52 = nmol/L mg/L x 0.1 = mg/dL

Limitations - interference

Criterion: Recovery within ± 10 % of initial values at CRP levels of 1.0 mg/L.

Icterus:[32] No significant interference up to an I index of 60 for conjugated and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 1026 µmol/L or 60 mg/dL).

Hemolysis:[32] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 622 µmol/L or 1000 mg/dL).

Lipemia (Intralipid):[32] No significant interference up to an L index of 600. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Rheumatoid factors: No significant interference from rheumatoid factors up to a concentration of 200 IU/mL.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[33,34]

Therapeutic drugs: Significantly decreased CRP values may be obtained from samples taken from patients who have been treated with carboxypenicillins.

High dose hook-effect: No false result occurs up to a CRP concentration of 1000 mg/L.

In very rare cases, gammopathy, in particular type IgM (Waldenström’s macroglobulinemia), may cause unreliable results.[35]

Although measures were taken to minimize interference caused by human anti-mouse antibodies, erroneous findings may be obtained from samples taken from patients who have been treated with monoclonal mouse antibodies or have received them for diagnostic purposes.

CRPHS

Cardiac C-Reactive Protein (Latex) High Sensitive

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

ACTION REQUIRED

Special Wash Programming: The use of special wash steps is mandatory when certain test combinations are run together on **cobas c** systems. All special wash programming necessary for avoiding carry-over is available via the **cobas** link, manual input is required in certain cases. The latest version of the carry-over evasion list can be found with the NaOHD/SMS/SmpCln1+2/SCCS Method Sheet and for further instructions refer to the operator's manual.

Where required, special wash/carry-over evasion programming must be implemented prior to reporting results with this test.

Limits and ranges

Measuring range

0.15-20.0 mg/L (1.43-190 nmol/L, 0.015-2.0 mg/dL)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:15 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 15.

Lower limits of measurement

Lower detection limit of the test

0.15 mg/L (1.43 nmol/L, 0.015 mg/dL)

The lower detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying 3 standard deviations above that of the lowest standard (standard 1 + 3 SD, repeatability, n = 21).

Values below the lower detection limit (< 0.15 mg/L) will not be flagged by the instrument.

Functional sensitivity

0.3 mg/L (2.96 nmol/L, 0.03 mg/dL)

The functional sensitivity is the lowest CRP concentration that can be reproducibly measured with an inter-assay coefficient of variation of < 10 %.

Expected values

Consensus reference interval for adults:[36]

IFCC/CRM 470

mg/dL	mg/L	nmol/L
< 0.5	< 5.0	< 47.6

The CDC/AHA recommended the following hsCRP cut-off points (tertiles) for CVD risk assessment:[17,37]

hsCRP level (mg/L)	hsCRP level (nmol/L)	Relative risk
< 1.0	< 9.52	low
1.0-3.0	9.52-28.6	average
> 3.0	> 28.6	high

Patients with higher hsCRP concentrations are more likely to develop myocardial infarction and severe peripheral vascular disease.

5-95 % reference intervals of neonates and children:[38]

Neonates (0-3 weeks): 0.1-4.1 mg/L (0.95-39.0 nmol/L)

Children (2 months-15 years): 0.1-2.8 mg/L (0.95-26.7 nmol/L)

It is important to monitor the CRP concentration during the acute phase of the illness.

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

Increases in CRP values are non-specific and should not be interpreted without a complete clinical history.

When using hsCRP to assess the risk of coronary heart disease, measurements should be made on metabolically stable patients and compared to previous values. Optimally, the average of hsCRP results repeated two weeks apart should be used for risk assessment. Measurements should be compared to previous values. When the results are being used for risk assessment, patients with persistently unexplained hsCRP levels of above 10 mg/L (95.2 nmol/L) should be evaluated for non-cardiovascular origins. Testing for any risk assessment should not be performed while there is indication of infection, systemic inflammation or trauma.[17]

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using human samples and controls in an internal protocol with repeatability (n = 21) and intermediate precision (3 aliquots per run, 1 run per day, 21 days). The following results were obtained:

Repeatability	*Mean*	*SD*	*CV*
	mg/L (nmol/L, mg/dL)	*mg/L (nmol/L, mg/dL)*	*%*
Precinorm Protein	14.0 (133, 1.40)	0.1 (0.952, 0.010)	0.3
CRP T Control N	4.13 (39.3, 0.413)	0.04 (0.381, 0.004)	1.0
Human serum A	6.58 (62.6, 0.658)	0.05 (0.476, 0.005)	0.7
Human serum B	13.0 (124, 1.30)	0.1 (0.952, 0.010)	0.7
Human serum C	0.511 (4.86, 0.051)	0.012 (0.114, 0.001)	2.3

Intermediate precision	*Mean*	*SD*	*CV*
	mg/L (nmol/L, mg/dL)	*mg/L (nmol/L, mg/dL)*	*%*
Precinorm Protein	9.06 (86.3, 0.906)	0.11 (1.1, 0.011)	1.3
CRP T Control N	4.28 (40.8, 0.428)	0.11 (1.1, 0.011)	2.6
Human serum 3	13.3 (126, 1.33)	0.3 (3, 0.03)	2.1
Human serum 4	0.53 (5.05, 0.053)	0.05 (0.48, 0.005)	8.4

Results for intermediate precision were obtained on the **cobas c** 501 analyzer.

Method comparison

CRP values for human serum and plasma samples obtained on a **cobas c** 701 analyzer (y) were compared with those determined using the corresponding reagent on a **cobas c** 501 analyzer (x).

Sample size (n) = 231

Passing/Bablok[39]	Linear regression
y = 0.996x - 0.074 mg/L	y = 0.998x - 0.079 mg/L
τ = 0.987	r = 1.000

The sample concentrations were between 0.180 and 17.8 mg/L (1.71 and 169 nmol/L, 0.018 and 1.78 mg/dL).

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A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

The Summary of Safety & Performance Report can be found here: https://ec.europa.eu/tools/eudamed

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see navifyportal.roche.com for definition of symbols used):

CONTENT	Contents of kit
→	Volume for reconstitution
GTIN	Global Trade Item Number
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

CRPHS

Cardiac C-Reactive Protein (Latex) High Sensitive

CE 0123

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05403138001V10.0

CRPHS

cobas®

Cardiac C-Reactive Protein (Latex) High Sensitive

Order information

REF	CONTENT		Analyzer(s) on which kit(s) can be used
05401607190	Cardiac C-Reactive Protein (Latex) High Sensitive (2 x 50 tests)		**cobas c** 111

Materials required (but not provided):

11355279216	Calibrator f.a.s. Proteins (5 x 1 mL)	Code 656	
20766321322	CRP T Control N (5 x 0.5 mL)	Code 235	
10557897122	Precinorm Protein (3 x 1 mL)	Code 302	
05117003190	PreciControl ClinChem Multi 1 (20 x 5 mL)	Code 391	
05947626190	PreciControl ClinChem Multi 1 (4 x 5 mL)	Code 391	
04774230190	NaCl Diluent 9 % (4 x 12 mL)	Code 951	

English

System information

CRPHS: ACN 217

Intended use

In vitro test for the quantitative determination of C-reactive protein (CRP) in human serum and plasma on the **cobas c** 111 system. Measurement of CRP is of use for the detection and evaluation of inflammatory disorders and associated diseases, infection and tissue injury. Highly sensitive measurement of CRP may also be used as an aid in the assessment of the risk of future coronary heart disease. When used as an adjunct to other laboratory evaluation methods of acute coronary syndromes, it may also be an additional independent indicator of recurrent event prognosis in patients with stable coronary disease or acute coronary syndrome.

Summary

C-reactive protein is the classic acute phase protein in inflammatory reactions.[1] It is synthesized by the liver and consists of five identical polypeptide chains that form a five-member ring having a molecular weight of 105000 daltons.[1,2,3,4] CRP is the most sensitive of the acute phase reactants and its concentration increases rapidly during inflammatory processes.[2,3] Complexed CRP activates the classical complement pathway. The CRP response frequently precedes clinical symptoms, including fever.[1,3] After onset of an acute phase response the serum CRP concentration rises rapidly and extensively.[2,3,4] The increase begins within 6 to 12 hours and the peak value is reached within 24 to 48 hours.[1,3,5] CRP response may be less pronounced in patients suffering from liver disease.[6]

CRP assays are used to detect systemic inflammatory processes (apart from certain types of inflammation such as systemic lupus erythematosus (SLE) and Colitis ulcerosa);[1,3,4,6] to assess treatment of bacterial infections with antibiotics;[1,4,6,7] to detect intrauterine infections with concomitant premature amniorrhexis;[4,6] to differentiate between active and inactive forms of disease with concurrent infection, e.g. in patients suffering from SLE or Colitis ulcerosa;[3,4,6] to therapeutically monitor rheumatic disease and assess anti-inflammatory therapy;[1,4,6] to determine the presence of post-operative complications at an early stage, such as infected wounds, thrombosis and pneumonia, and to distinguish between infection and bone marrow transplant rejection.[1,4,6]

Sensitive CRP measurements have been used and discussed for early detection of infection in pediatrics and risk assessment of coronary heart disease.[8,9,10,11] Several studies came to the conclusion that the highly sensitive measurement of CRP could be used as a marker to predict the risk of coronary heart disease in apparently healthy persons and as an indicator of recurrent event prognosis.[10,12,13,14,15,16] Increases in CRP values are non-specific and should not be interpreted without a complete clinical history.[17] The American Heart Association and the Centers for Disease Control and Prevention have made several recommendations concerning the use of high sensitivity C-Reactive Protein (hsCRP) in cardiovascular risk assessment.[17,18] Measurement of hsCRP may also be used as an aid in the assessment of the risk of future coronary heart disease and as a risk-enhancing factor in patients with borderline- or intermediate-risk for atherosclerotic cardiovascular disease.[19] When used as an adjunct to other laboratory evaluation methods of acute coronary syndromes, it may also be an additional independent indicator of recurrent event prognosis in patients with stable coronary disease or acute coronary syndrome.[17,20]

Testing for any risk assessment should not be performed while there is an indication of infection, systemic inflammation or trauma.[11,17,21] Patients with persistently unexplained hsCRP levels above 10 mg/L (95.2 nmol/L) should be evaluated for non-cardiovascular etiologies.[13,17] When using hsCRP to assess the risk of coronary heart disease, measurements should be made on metabolically stable patients and compared to previous values.[17] Optimally, the average of hsCRP results repeated two weeks apart should be used for risk assessment.[17] Screening the entire adult population for hsCRP is not recommended, and hsCRP is not a substitute for traditional cardiovascular risk factors.[17] Acute coronary syndrome management should not depend solely on hsCRP measurements.[14,17] Similarly, application of secondary prevention measures should be based on global risk assessment and not solely on hsCRP measurements.[17] Serial measurements of hsCRP should not be used to monitor treatment.[17]

Studies indicate an influence of gestational age on the kinetics of CRP in preterm infants, which may materialize as a blunted response to infection when comparing preterm and term newborns.[22,23,24] This phenomenon, most likely due to immature liver function, may result in a lower sensitivity of CRP in the diagnosis of neonatal sepsis in preterm compared to term newborns.[25] In adult patients with advanced liver dysfunction, CRP levels are reduced in response to acute infection, however production is nevertheless maintained.[26] Although the liver is considered the main source of CRP, serum levels are not significantly lower in patients with cirrhosis than in other patients, and the predictive performance for infection is similar for patients with and without cirrhosis.[27]

Various assay methods are available for CRP determination, such as nephelometry and turbidimetry.[28,29] The Roche CRP assay is based on the principle of particle-enhanced immunological agglutination.

Test principle[28,29]

Particle enhanced immuno-turbidimetric assay.

Human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies. The precipitate is determined turbidimetrically.

Reagents - working solutions

R1 TRIS buffer with bovine serum albumin and immunoglobulins (mouse); preservative; stabilizers

SR Latex particles coated with anti-CRP (mouse) in glycine buffer; preservative; stabilizers

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:
Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

Reagent handling

R1 Ready for use.

SR Ready for use.
Carefully invert reagent container several times prior to use to ensure that the reagent components are mixed. Avoid the formation of foam.

Storage and stability

Shelf life at 2-8 °C:	See expiration date on reagent

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On-board in use and refrigerated on the analyzer:	4 weeks

Specimen collection and preparation

For specimen collection and preparation only use suitable tubes or collection containers.

Only the specimens listed below were tested and found acceptable.

Serum

Plasma: Li-heparin, K_2-EDTA plasma

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Centrifuge samples containing precipitates before performing the assay.

See the limitations and interferences section for details about possible sample interferences.

Stability:[30]	11 days at 15-25 °C
	2 months at 2-8 °C
	3 years at –20 °C (± 5 °C)

Freeze only once.

Materials provided

See “Reagents – working solutions” section for reagents.

Materials required (but not provided)

See “Order information” section

General laboratory equipment

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator’s manual for analyzer-specific assay instructions.

The performance of applications not validated by Roche is not warranted and must be defined by the user.

Application for serum and plasma

cobas c 111 **test definition**

Measuring mode	Absorbance
Abs. calculation mode	Kinetic
Reaction direction	Increase
Wavelength A	552 nm
Calc. first/last	17/34
Unit	mg/L (nmol/L, mg/dL)
Reaction mode	R1-S-SR

Pipetting parameters

		Diluent (H_2O)
R1	82 µL	48 µL
Sample	6 µL	
SR	28 µL	14 µL
Total volume	178 µL	

Calibration

Calibrator	Calibrator f.a.s. Proteins
Calibration dilution ratio	1:5, 1:10, 1:20, 1:40, 1:80, performed automatically by the instrument, and Standard 6 = 0 mg/L.
Calibration mode	Linear interpolation
Calibration interval	Each lot and as required following quality control procedures

Enter the assigned lot-specific CRPHS value of the undiluted calibrator (mg/L), indicated in the package insert of C.f.a.s. Proteins.

Traceability: This method has been standardized against the reference preparation of the IRMM (Institute for Reference Materials and Measurements) BCR470/CRM470 (RPPHS -Reference Preparation for Proteins in Human Serum).[31]

Quality control

For quality control, use control materials as listed in the "Order information" section.

In addition, other suitable control material can be used.

The control intervals and limits should be adapted to each laboratory’s individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

Follow the applicable government regulations and local guidelines for quality control.

Calculation

The **cobas c** 111 analyzer automatically calculates the analyte concentration of each sample.

Conversion factors:	mg/L x 9.52 = nmol/L
	mg/L x 0.1 = mg/dL

Limitations - interference

Criterion: Recovery within ± 10 % of initial value at CRP levels of 3.0 mg/L.

Icterus:[32] No significant interference up to an I index of 60 for conjugated and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 1026 µmol/L or 60 mg/dL).

Hemolysis:[32] No significant interference up to an H index of 700 (approximate hemoglobin concentration: 435 µmol/L or 700 mg/dL).

Lipemia (Intralipid):[32] No significant interference up to an L index of 500. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Rheumatoid factors up to 200 IU/mL do not interfere.

High-dose hook effect: does not occur at CRP concentrations below 40 mg/L or 380 nmol/L. Samples with concentrations > 40 mg/L are flagged either ">TEST RNG" or “HIGH ACT”.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[33,34]

Therapeutic drugs: Significantly decreased CRP values may be obtained from samples taken from patients who have been treated with carboxypenicillins.

In very rare cases, gammopathy, in particular type IgM (Waldenström’s macroglobulinemia), may cause unreliable results.[35]

Although measures were taken to minimize interference caused by human anti-mouse antibodies, erroneous findings may be obtained from samples taken from patients who have been treated with monoclonal mouse antibodies or have received them for diagnostic purposes.

For diagnostic purposes, the results should always be assessed in conjunction with the patient’s medical history, clinical examination and other findings.

ACTION REQUIRED

Special Wash Programming: The use of special wash steps is mandatory when certain test combinations are run together on the **cobas c** 111 analyzer. For information about test combinations requiring special wash steps, please refer to the latest version of the carry over evasion list found with the CLEAN Method Sheet and the operator’s manual for further instructions.

Where required, special wash/carry-over evasion programming must be implemented prior to reporting results with this test.

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Cardiac C-Reactive Protein (Latex) High Sensitive

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Limits and ranges

Measuring range

0.15-20.0 mg/L (1.43-190 nmol/L, 0.015-2.0 mg/dL)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:15 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 15.

Lower limits of measurement

Lower detection limit of the test:
0.15 mg/L (1.43 nmol/L, 0.015 mg/dL)

The lower detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying 3 standard deviations above that of the lowest standard (standard 1 + 3 SD, repeatability, n = 21).

Functional sensitivity (Limit of Quantitation)

0.3 mg/L (2.86 nmol/L)

The functional sensitivity (Limit of Quantitation) is the lowest CRP concentration that can be reproducibly measured with an inter-assay coefficient of variation < 10 %.

Expected values

Consensus reference interval for adults:[36]

IFCC/CRM 470

mg/dL	mg/L	nmol/L
< 0.5	< 5.0	< 47.6

The CDC/AHA recommended the following hsCRP cut-off points (tertiles) for CVD risk assessment:[17,37]

hsCRP level (mg/L)	hsCRP level (nmol/L)	Relative risk
< 1.0	< 9.52	low
1.0-3.0	9.52-28.6	average
> 3.0	> 28.6	high

Patients with higher hsCRP concentrations are more likely to develop myocardial infarction and severe peripheral vascular disease.

5-95 % reference intervals of neonates and children:[38]

Neonates (0-3 weeks): 0.1-4.1 mg/L (0.95-39.0 nmol/L)

Children (2 months-15 years): 0.1-2.8 mg/L (0.95-26.7 nmol/L)

It is important to monitor the CRP concentration during the acute phase of the illness.

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

Increases in CRP values are non-specific and should not be interpreted without a complete clinical history.

When using hsCRP to assess the risk of coronary heart disease, measurements should be made on metabolically stable patients and compared to previous values. Optimally, the average of hsCRP results repeated two weeks apart should be used for risk assessment. Measurements should be compared to previous values. When the results are being used for risk assessment, patients with persistently unexplained hsCRP levels of above 10 mg/L (95.2 nmol/L) should be evaluated for non-cardiovascular origins. Testing for any risk assessment should not be performed while there is indication of infection, systemic inflammation or trauma.[17]

Specific performance data

Representative performance data on the **cobas c** 111 analyzer are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using human samples and controls in an internal protocol with repeatability (n = 21) and intermediate precision (3 aliquots per run, 1 run per day, 10 days). The following results were obtained:

Repeatability	*Mean mg/L (nmol/L, mg/dL)*	*SD mg/L (nmol/L, mg/dL)*	*CV %*
Precinorm Protein	11.4 (109, 1.14)	0.0 (0, 0.0)	0.4
CRP T Control N	4.06 (38.7, 0.406)	0.01 (0.1, 0.01)	0.3
Human serum 1	0.49 (4.66, 0.049)	0.01 (0.07, 0.001)	1.5
Human serum 2	4.02 (38.3, 0.402)	0.02 (0.2, 0.002)	0.6
Human serum 3	16.9 (161, 1.69)	0.1 (1, 0.01)	0.3

Intermediate precision	*Mean mg/L (nmol/L, mg/dL)*	*SD mg/L (nmol/L, mg/dL)*	*CV %*
Precinorm Protein	11.3 (108, 1.13)	0.1 (1, 0.01)	0.5
CRP T Control N	3.90 (37.1, 0.39)	0.04 (0.4, 0.004)	1.0
Human serum 4	0.48 (4.57, 0.048)	0.01 (0.10, 0.001)	2.0
Human serum 5	3.91 (37.2, 0.39)	0.05 (0.5, 0.005)	1.4
Human serum 6	16.8 (160, 1.68)	0.1 (1, 0.01)	0.7

Method comparison

CRP values for human serum and plasma samples obtained on a **cobas c** 111 analyzer using the Roche CRPHS reagent (y) were compared with those determined using the same reagent on a COBAS INTEGRA 400 analyzer (x).

Sample size (n) = 79

Passing/Bablok[39]	Linear regression
y = 1.035x – 0.111 mg/L	y = 1.051x – 0.202 mg/L
τ = 0.962	r = 0.999

The sample concentrations of the reference system (x) were between 0.21 and 18.6 mg/L (2.0 and 177 nmol/L, 0.021 and 1.86 mg/dL).

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A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

The Summary of Safety & Performance Report can be found here: https://ec.europa.eu/tools/eudamed

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see navifyportal.roche.com for definition of symbols used):

CONTENT	Contents of kit
REAGENT	Reagent
→	Volume for reconstitution
GTIN	Global Trade Item Number
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

CE 0123

Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim
www.roche.com
+800 5505 6606

CRPHS

cobas®

Cardiac C-Reactive Protein (Latex) High Sensitive

Order information

REF	CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
04628918190	Cardiac C-Reactive Protein (Latex) High Sensitive (300 tests)	System-ID 07 6866 9	**cobas c** 311, **cobas c** 501/502

Materials required (but not provided):

11355279160	Calibrator f.a.s. Proteins (5 x 1 mL)	Code 656	
20766321322	CRP T Control N (5 x 0.5 mL)	Code 235	
10557897160	Precinorm Protein (3 x 1 mL)	Code 302	
05947626160	PreciControl ClinChem Multi 1 (4 x 5 mL)	Code 391	
04489357190	Diluent NaCl 9 % (50 mL)	System-ID 07 6869 3	

English

For use in the USA only

System information

For **cobas c** 311/501 analyzers:

CRPHS: ACN 217

For **cobas c** 502 analyzer:

CRPHS: ACN 8217

Intended use

In vitro test for the quantitative determination of C-reactive protein (CRP) in human serum and plasma on **cobas c** systems. Measurement of CRP is of use for the detection and evaluation of inflammatory disorders and associated diseases, infection and tissue injury. Highly sensitive measurement of CRP may also be used as an aid in the assessment of the risk of future coronary heart disease. When used as an adjunct to other laboratory evaluation methods of acute coronary syndromes, it may also be an additional independent indicator of recurrent event prognosis in patients with stable coronary disease or acute coronary syndrome.

Summary[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21]

C-reactive protein is the classic acute phase protein in inflammatory reactions. It is synthesized by the liver and consists of five identical polypeptide chains that form a five-member ring having a molecular weight of 105000 daltons. CRP is the most sensitive of the acute phase reactants and its concentration increases rapidly during inflammatory processes. Complexed CRP activates the complement system beginning with C1q. CRP then initiates opsonization and phagocytosis of invading cells, but its main function is to bind and detoxify endogenous toxic substances produced as a result of tissue damage.

CRP assays are used to detect systemic inflammatory processes (apart from certain types of inflammation such as SLE and Colitis ulcerosa); to assess treatment of bacterial infections with antibiotics; to detect intrauterine infections with concomitant premature amniorrhexis; to differentiate between active and inactive forms of disease with concurrent infection, e.g. in patients suffering from SLE or Colitis ulcerosa; to therapeutically monitor rheumatic disease and assess anti-inflammatory therapy; to determine the presence of post-operative complications at an early stage, such as infected wounds, thrombosis and pneumonia, and to distinguish between infection and bone marrow transplant rejection.

Sensitive CRP measurements have been used and discussed for early detection of infection in pediatrics and risk assessment of coronary heart disease. Several studies came to the conclusion that the highly sensitive measurement of CRP could be used as a marker to predict the risk of coronary heart disease in apparently healthy persons and as an indicator of recurrent event prognosis. Increases in CRP values are non-specific and should not be interpreted without a complete clinical history. The American Heart Association and the Centers for Disease Control and Prevention have made several recommendations concerning the use of high sensitivity C-Reactive Protein (hsCRP) in cardiovascular risk assessment.[21] Testing for any risk assessment should not be performed while there is an indication of infection, systemic inflammation or trauma. Patients with persistently unexplained hsCRP levels above 10 mg/L (95.2 nmol/L) should be evaluated for non-cardiovascular etiologies. When using hsCRP to assess the risk of coronary heart disease, measurements should be made on metabolically stable patients and compared to previous values. Optimally, the average of hsCRP results repeated two weeks apart should be used for risk assessment. Screening the entire adult population for hsCRP is not recommended, and hsCRP is not a substitute for traditional cardiovascular risk factors. Acute coronary syndrome management should not depend solely on hsCRP measurements. Similarly, application of secondary prevention measures should be based on global risk assessment and not solely on hsCRP measurements. Serial measurements of hsCRP should not be used to monitor treatment.

Various assay methods are available for CRP determination, such as nephelometry and turbidimetry. The Roche CRP assay is based on the principle of particle-enhanced immunological agglutination.

Test principle[22,23]

Particle enhanced immunoturbidimetric assay.

Human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies. The precipitate is determined turbidimetrically.

Reagents - working solutions

R1 TRIS buffer with bovine serum albumin and immunoglobulins (mouse); preservative; stabilizers

R2 Latex particles coated with anti-CRP (mouse) in glycine buffer; preservative; stabilizers

R1 is in position B and R2 is in position C.

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:
Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

Reagent handling

Ready for use

Carefully invert reagent container several times prior to use to ensure that the reagent components are mixed.

Storage and stability

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label.
On-board in use and refrigerated on the analyzer:	12 weeks

Specimen collection and preparation

For specimen collection and preparation only use suitable tubes or collection containers.

Only the specimens listed below were tested and found acceptable.
Serum.
Plasma: Li-heparin and K_2-EDTA plasma

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

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Centrifuge samples containing precipitates before performing the assay.

See the limitations and interferences section for details about possible sample interferences.

Sample stability claims were established by experimental data by the manufacturer or based on reference literature and only for the temperatures/time frames as stated in the method sheet. It is the responsibility of the individual laboratory to use all available references and/or its own studies to determine specific stability criteria for its laboratory.

Stability:[24]	11 days at 15-25 °C
	2 months at 2-8 °C
	3 years at (-15)-(-25) °C

Freeze only once.

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

See "Order information" section

General laboratory equipment

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

The performance of applications not validated by Roche is not warranted and must be defined by the user.

Application for serum and plasma

cobas c 311 **test definition**

Assay type	Rate A	
Reaction time / Assay points	10/7-57	
Wavelength (sub/main)	– /546 nm	
Reaction direction	Increase	
Units	mg/L (nmol/L, mg/dL)	
Reagent pipetting		Diluent (H_2O)
R1	82 µL	42 µL
R2	28 µL	20 µL

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	6 µL	–	–
Decreased	6 µL	10 µL	140 µL
Increased	6 µL	–	–

cobas c 501 **test definition**

Assay type	Rate A	
Reaction time / Assay points	10/12-70	
Wavelength (sub/main)	– /546 nm	
Reaction direction	Increase	
Units	mg/L (nmol/L, mg/dL)	
Reagent pipetting		Diluent (H_2O)
R1	82 µL	42 µL
R2	28 µL	20 µL

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	6 µL	–	–
Decreased	6 µL	10 µL	140 µL
Increased	6 µL	–	–

cobas c 502 **test definition**

Assay type	Rate A	
Reaction time / Assay points	10/12-70	
Wavelength (sub/main)	– /546 nm	
Reaction direction	Increase	
Units	mg/L (nmol/L, mg/dL)	
Reagent pipetting		Diluent (H_2O)
R1	82 µL	42 µL
R2	28 µL	20 µL

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	6 µL	–	–
Decreased	6 µL	10 µL	140 µL
Increased	12 µL	–	–

Calibration

Calibrators	S1: H_2O
	S2: C.f.a.s. Proteins
	Multiply the lot-specific C.f.a.s. Proteins calibrator value by the factors below to determine the standard concentrations for the 6-point calibration curve:
	S2: 0.0125 S5: 0.100
	S3: 0.0250 S6: 0.200
	S4: 0.0500
Calibration mode	Line Graph
Calibration frequency	Full calibration - after reagent lot change - as required following quality control procedures

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Traceability: This method has been standardized against the reference preparation of the IRMM (Institute for Reference Materials and Measurements) BCR470/CRM470 (RPPHS - Reference Preparation for Proteins in Human Serum).[25]

Quality control

For quality control, use control materials as listed in the "Order information" section.

In addition, other suitable control material can be used.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

Follow the applicable government regulations and local guidelines for quality control.

Calculation

cobas c systems automatically calculate the analyte concentration of each sample.

Conversion factors:	mg/L x 9.52 = nmol/L
	mg/L x 0.1 = mg/dL

Limitations - interference

Criterion: Recovery within ± 10 % of initial values at CRP levels of 1.0 mg/L.

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Icterus:[26] No significant interference up to an I index of 60 for conjugated bilirubin and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 60 mg/dL or 1026 µmol/L).

Hemolysis:[26] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 622 µmol/L or 1000 mg/dL).

Lipemia (Intralipid):[26] No significant interference up to an L index of 600. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Rheumatoid factors: No significant interference from rheumatoid factors up to a concentration of 200 IU/mL.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[27,28]

Therapeutic drugs: Significantly decreased CRP values may be obtained from samples taken from patients who have been treated with carboxypenicillins.

High dose hook-effect: No false result occurs up to a CRP concentration of 1000 mg/L.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[29]

Although measures were taken to minimize interference caused by human anti-mouse antibodies, erroneous findings may be obtained from samples taken from patients who have been treated with monoclonal mouse antibodies or have received them for diagnostic purposes.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

ACTION REQUIRED

Special Wash Programming: The use of special wash steps is mandatory when certain test combinations are run together on **cobas c** systems. The latest version of the carry-over evasion list can be found with the NaOHD-SMS-SmpCln1+2-SCCS Method Sheets. For further instructions refer to the operator's manual. **cobas c** 502 analyzer: All special wash programming necessary for avoiding carry-over is available via the **cobas** link, manual input is required in certain cases.

Where required, special wash/carry-over evasion programming must be implemented prior to reporting results with this test.

Limits and ranges

Measuring range

0.15-20.0 mg/L (1.43-190 nmol/L, 0.015-2.0 mg/dL)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:15 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 15.

Lower limits of measurement

Lower detection limit of the test

0.15 mg/L (1.43 nmol/L, 0.015 mg/dL)

The lower detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying 3 standard deviations above that of the lowest standard (standard 1 + 3 SD, repeatability, n = 21).

Functional sensitivity

0.3 mg/L (2.96 nmol/L, 0.03 mg/dL)

The functional sensitivity is the lowest CRP concentration that can be reproducibly measured with an inter-assay coefficient of variation of < 10 %.

Expected values

Consensus reference interval for adults:[30]

IFCC/CRM 470

mg/dL	mg/L	nmol/L
< 0.5	< 5.0	< 47.6

The CDC/AHA recommended the following hsCRP cut-off points (tertiles) for CVD risk assessment:[21,31]

hsCRP level (mg/L)	hsCRP level (nmol/L)	Relative risk
< 1.0	< 9.52	low
1.0-3.0	9.52-28.6	average
> 3.0	> 28.6	high

Patients with higher hsCRP concentrations are more likely to develop myocardial infarction and severe peripheral vascular disease.

5-95 % reference intervals of neonates and children:[32]

Neonates (0-3 weeks): 0.1-4.1 mg/L (0.95-39.0 nmol/L)

Children (2 months-15 years): 0.1-2.8 mg/L (0.95-26.7 nmol/L)

It is important to monitor the CRP concentration during the acute phase of the illness.

Roche has not evaluated reference ranges in a pediatric population.

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

Increases in CRP values are non-specific and should not be interpreted without a complete clinical history.

When using hsCRP to assess the risk of coronary heart disease, measurements should be made on metabolically stable patients and compared to previous values. Optimally, the average of hsCRP results repeated two weeks apart should be used for risk assessment. Measurements should be compared to previous values. When the results are being used for risk assessment, patients with persistently unexplained hsCRP levels of above 10 mg/L (95.2 nmol/L) should be evaluated for non-cardiovascular origins. Testing for any risk assessment should not be performed while there is indication of infection, systemic inflammation or trauma.[21]

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using human samples and controls in an internal protocol with repeatability (n = 21) and intermediate precision (3 aliquots per run, 1 run per day, 21 days). The following results were obtained on the **cobas c** 501 analyzer:

Repeatability	*Mean*	*SD*	*CV*
	mg/L (nmol/L, mg/dL)	*mg/L (nmol/L, mg/dL)*	*%*
Precinorm Protein	9.00 (85.7, 0.900)	0.10 (1.0, 0.010)	1.2
CRP T Control N	4.34 (41.3, 0.434)	0.04 (0.4, 0.004)	1.0
Human serum 1	15.9 (151, 1.59)	0.1 (1, 0.01)	0.4
Human serum 2	0.54 (5.14, 0.054)	0.01 (0.10, 0.001)	1.6
Intermediate precision	*Mean*	*SD*	*CV*
	mg/L (nmol/L, mg/dL)	*mg/L (nmol/L, mg/dL)*	*%*
Precinorm Protein	9.06 (86.3, 0.906)	0.11 (1.1, 0.011)	1.3
CRP T Control N	4.28 (40.8, 0.428)	0.11 (1.1, 0.011)	2.6
Human serum 3	13.3 (126, 1.33)	0.3 (3, 0.03)	2.1
Human serum 4	0.53 (5.05, 0.053)	0.05 (0.48, 0.005)	8.4

The data obtained on **cobas c** 501 analyzer(s) are representative for **cobas c** 311 analyzer(s).

Method comparison

CRP values for human serum and plasma samples obtained on a **cobas c** 501 analyzer (y) were compared with those determined using the corresponding reagent on a Roche/Hitachi 917 analyzer (x).

Sample size (n) = 192

Passing/Bablok[33]	Linear regression
y = 0.992x + 0.254 mg/L	y = 0.946x + 0.514 mg/L
τ = 0.944	r = 0.996

The sample concentrations were between 0.500 and 19.7 mg/L (4.76 and 188 nmol/L, 0.050 and 1.97 mg/dL).

CRPHS

Cardiac C-Reactive Protein (Latex) High Sensitive

The data obtained on **cobas c** 501 analyzer(s) are representative for **cobas c** 311 analyzer(s).

References

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FOR US CUSTOMERS ONLY: LIMITED WARRANTY

Roche Diagnostics warrants that this product will meet the specifications stated in the labeling when used in accordance with such labeling and will be free from defects in material and workmanship until the expiration date printed on the label. THIS LIMITED WARRANTY IS IN LIEU OF ANY OTHER WARRANTY, EXPRESS OR IMPLIED, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR PARTICULAR PURPOSE. IN NO EVENT SHALL ROCHE DIAGNOSTICS BE LIABLE FOR INCIDENTAL, INDIRECT, SPECIAL OR CONSEQUENTIAL DAMAGES.

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Cardiac C-Reactive Protein (Latex) High Sensitive

For USA: Rx only

Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim
www.roche.com
+800 5505 6606

Distribution in USA by:
Roche Diagnostics, Indianapolis, IN
US Customer Technical Support 1-800-428-2336

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cobas®

Cardiac C-Reactive Protein (Latex) High Sensitive

Order information

REF	CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
05950864190	Cardiac C-Reactive Protein (Latex) High Sensitive (250 tests)	System-ID 01 6866 9	**cobas c** 701/702

Materials required (but not provided):

11355279160	Calibrator f.a.s. Proteins (5 x 1 mL)	Code 656	
20766321322	CRP T Control N (5 x 0.5 mL)	Code 235	
10557897160	Precinorm Protein (3 x 1 mL)	Code 302	
05947626160	PreciControl ClinChem Multi 1 (4 x 5 mL)	Code 391	
05172152190	Diluent NaCl 9 % (119 mL)	System-ID 08 6869 3	

English

For use in the USA only

System information

CRPHS: ACN 8217

Intended use

In vitro test for the quantitative determination of C-reactive protein (CRP) in human serum and plasma on **cobas c** systems. Measurement of CRP is of use for the detection and evaluation of inflammatory disorders and associated diseases, infection and tissue injury. Highly sensitive measurement of CRP may also be used as an aid in the assessment of the risk of future coronary heart disease. When used as an adjunct to other laboratory evaluation methods of acute coronary syndromes, it may also be an additional independent indicator of recurrent event prognosis in patients with stable coronary disease or acute coronary syndrome.

Summary[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21]

C-reactive protein is the classic acute phase protein in inflammatory reactions. It is synthesized by the liver and consists of five identical polypeptide chains that form a five-member ring having a molecular weight of 105000 Daltons. CRP is the most sensitive of the acute phase reactants and its concentration increases rapidly during inflammatory processes. Complexed CRP activates the complement system beginning with C1q. CRP then initiates opsonization and phagocytosis of invading cells, but its main function is to bind and detoxify endogenous toxic substances produced as a result of tissue damage.

CRP assays are used to detect systemic inflammatory processes (apart from certain types of inflammation such as SLE and Colitis ulcerosa); to assess treatment of bacterial infections with antibiotics; to detect intrauterine infections with concomitant premature amniorrhexis; to differentiate between active and inactive forms of disease with concurrent infection, e.g. in patients suffering from SLE or Colitis ulcerosa; to therapeutically monitor rheumatic disease and assess anti-inflammatory therapy; to determine the presence of post-operative complications at an early stage, such as infected wounds, thrombosis and pneumonia, and to distinguish between infection and bone marrow transplant rejection.

Sensitive CRP measurements have been used and discussed for early detection of infection in pediatrics and risk assessment of coronary heart disease. Several studies came to the conclusion that the highly sensitive measurement of CRP could be used as a marker to predict the risk of coronary heart disease in apparently healthy persons and as an indicator of recurrent event prognosis. Increases in CRP values are non-specific and should not be interpreted without a complete clinical history. The American Heart Association and the Centers for Disease Control and Prevention have made several recommendations concerning the use of high sensitivity C-Reactive Protein (hsCRP) in cardiovascular risk assessment. Testing for any risk assessment should not be performed while there is an indication of infection, systemic inflammation or trauma. Patients with persistently unexplained hsCRP levels above 10 mg/L (95.2 nmol/L) should be evaluated for non-cardiovascular etiologies. When using hsCRP to assess the risk of coronary heart disease, measurements should be made on metabolically stable patients and compared to previous values. Optimally, the average of hsCRP results repeated two weeks apart should be used for risk assessment. Screening the entire adult population for hsCRP is not recommended, and hsCRP is not a substitute for traditional cardiovascular risk factors. Acute coronary syndrome management should not depend solely on hsCRP measurements. Similarly, application of secondary prevention measures should be based on global risk assessment and not solely on hsCRP measurements. Serial measurements of hsCRP should not be used to monitor treatment.

Various assay methods are available for CRP determination, such as nephelometry and turbidimetry. The Roche CRP assay is based on the principle of particle-enhanced immunological agglutination.

Test principle[22,23]

Particle enhanced immunoturbidimetric assay.

Human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies. The precipitate is determined turbidimetrically.

Reagents - working solutions

R1 TRIS buffer with bovine serum albumin and immunoglobulins (mouse); preservative; stabilizers

R3 Latex particles coated with anti-CRP (mouse) in glycine buffer; preservative; stabilizers

R1 is in position B and R3 is in position C.

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:
Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

Reagent handling

Ready for use

Carefully invert reagent container several times prior to use to ensure that the reagent components are mixed.

Storage and stability

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label.
On-board in use and refrigerated on the analyzer:	12 weeks
On-board on the Reagent Manager:	24 hours

Specimen collection and preparation

For specimen collection and preparation only use suitable tubes or collection containers.

Only the specimens listed below were tested and found acceptable.
Serum.
Plasma: Li-heparin and K_2-EDTA plasma

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Centrifuge samples containing precipitates before performing the assay.

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See the limitations and interferences section for details about possible sample interferences.

Sample stability claims were established by experimental data by the manufacturer or based on reference literature and only for the temperatures/time frames as stated in the method sheet. It is the responsibility of the individual laboratory to use all available references and/or its own studies to determine specific stability criteria for its laboratory.

Stability:[24]	11 days at 15-25 °C
	2 months at 2-8 °C
	3 years at (-15)-(-25) °C

Freeze only once.

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

See "Order information" section

General laboratory equipment

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

The performance of applications not validated by Roche is not warranted and must be defined by the user.

Application for serum and plasma

cobas c 701/702 **test definition**

Assay type	Rate A	
Reaction time / Assay points	10 / 22-38	
Wavelength (sub/main)	– /546 nm	
Reaction direction	Increase	
Units	mg/L (nmol/L, mg/dL)	
Reagent pipetting		Diluent (H_2O)
R1	82 µL	42 µL
R3	28 µL	20 µL

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	6 µL	–	–
Decreased	6 µL	10 µL	140 µL
Increased	12 µL	–	–

Calibration

Calibrators	S1: H_2O S2-S6: C.f.a.s. Proteins Multiply the lot-specific C.f.a.s. Proteins calibrator value by the factors below to determine the standard concentrations for the 6-point calibration curve: S2: 0.0125 S5: 0.100 S3: 0.0250 S6: 0.200 S4: 0.0500
Calibration mode	Line Graph
Calibration frequency	Full calibration - after reagent lot change - as required following quality control procedures

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Traceability: This method has been standardized against the reference preparation of the IRMM (Institute for Reference Materials and Measurements) BCR470/CRM470 (RPPHS - Reference Preparation for Proteins in Human Serum).[25]

Quality control

For quality control, use control materials as listed in the "Order information" section.

In addition, other suitable control material can be used.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

Follow the applicable government regulations and local guidelines for quality control.

Calculation

cobas c systems automatically calculate the analyte concentration of each sample.

Conversion factors:	mg/L x 9.52 = nmol/L
	mg/L x 0.1 = mg/dL

Limitations - interference

Criterion: Recovery within ± 10 % of initial values at CRP levels of 1.0 mg/L.

Icterus:[26] No significant interference up to an I index of 60 for conjugated and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 1026 µmol/L or 60 mg/dL).

Hemolysis:[26] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 622 µmol/L or 1000 mg/dL).

Lipemia (Intralipid):[26] No significant interference up to an L index of 600. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Rheumatoid factors: No significant interference from rheumatoid factors up to a concentration of 200 IU/mL.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[27,28]

Therapeutic drugs: Significantly decreased CRP values may be obtained from samples taken from patients who have been treated with carboxypenicillins.

High dose hook-effect: No false result occurs up to a CRP concentration of 1000 mg/L.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[29]

Although measures were taken to minimize interference caused by human anti-mouse antibodies, erroneous findings may be obtained from samples taken from patients who have been treated with monoclonal mouse antibodies or have received them for diagnostic purposes.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

ACTION REQUIRED

Special Wash Programming: The use of special wash steps is mandatory when certain test combinations are run together on **cobas c** systems. All special wash programming necessary for avoiding carry-over is available via the **cobas** link, manual input is required in certain cases. The latest version of the carry-over evasion list can be found with the NaOHD/SMS/SmpCln1+2/SCCS Method Sheet and for further instructions refer to the operator's manual.

Where required, special wash/carry-over evasion programming must be implemented prior to reporting results with this test.

Limits and ranges

Measuring range

0.15-20.0 mg/L (1.43-190 nmol/L, 0.015-2.0 mg/dL)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:15 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 15.

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Lower limits of measurement

Lower detection limit of the test

0.15 mg/L (1.43 nmol/L, 0.015 mg/dL)

The lower detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying 3 standard deviations above that of the lowest standard (standard 1 + 3 SD, repeatability, n = 21).

Values below the lower detection limit (< 0.15 mg/L) will not be flagged by the instrument.

Functional sensitivity

0.3 mg/L (2.96 nmol/L, 0.03 mg/dL)

The functional sensitivity is the lowest CRP concentration that can be reproducibly measured with an inter-assay coefficient of variation of < 10 %.

Expected values

Consensus reference interval for adults:[30]

IFCC/CRM 470

mg/dL	mg/L	nmol/L
< 0.5	< 5.0	< 47.6

The CDC/AHA recommended the following hsCRP cut-off points (tertiles) for CVD risk assessment:[21,31]

hsCRP level (mg/L)	hsCRP level (nmol/L)	Relative risk
< 1.0	< 9.52	low
1.0-3.0	9.52-28.6	average
> 3.0	> 28.6	high

Patients with higher hsCRP concentrations are more likely to develop myocardial infarction and severe peripheral vascular disease.

5-95 % reference intervals of neonates and children:[32]

Neonates (0-3 weeks): 0.1-4.1 mg/L (0.95-39.0 nmol/L)

Children (2 months-15 years): 0.1-2.8 mg/L (0.95-26.7 nmol/L)

It is important to monitor the CRP concentration during the acute phase of the illness.

Roche has not evaluated reference ranges in a pediatric population.

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

Increases in CRP values are non-specific and should not be interpreted without a complete clinical history.

When using hsCRP to assess the risk of coronary heart disease, measurements should be made on metabolically stable patients and compared to previous values. Optimally, the average of hsCRP results repeated two weeks apart should be used for risk assessment. Measurements should be compared to previous values. When the results are being used for risk assessment, patients with persistently unexplained hsCRP levels of above 10 mg/L (95.2 nmol/L) should be evaluated for non-cardiovascular origins. Testing for any risk assessment should not be performed while there is indication of infection, systemic inflammation or trauma.[21]

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using human samples and controls in an internal protocol with repeatability (n = 21) and intermediate precision (3 aliquots per run, 1 run per day, 21 days). The following results were obtained:

Repeatability	*Mean* *mg/L (nmol/L, mg/dL)*	*SD* *mg/L (nmol/L, mg/dL)*	*CV* *%*
Precinorm Protein	14.0 (133, 1.40)	0.1 (0.952, 0.010)	0.3
CRP T Control N	4.13 (39.3, 0.413)	0.04 (0.381, 0.004)	1.0
Human serum A	6.58 (62.6, 0.658)	0.05 (0.476, 0.005)	0.7
Human serum B	13.0 (124, 1.30)	0.1 (0.952, 0.010)	0.7
Human serum C	0.511 (4.86, 0.051)	0.012 (0.114, 0.001)	2.3

Intermediate precision	*Mean* *mg/L (nmol/L, mg/dL)*	*SD* *mg/L (nmol/L, mg/dL)*	*CV* *%*
Precinorm Protein	9.06 (86.3, 0.906)	0.11 (1.1, 0.011)	1.3
CRP T Control N	4.28 (40.8, 0.428)	0.11 (1.1, 0.011)	2.6
Human serum 3	13.3 (126, 1.33)	0.3 (3, 0.03)	2.1
Human serum 4	0.53 (5.05, 0.053)	0.05 (0.48, 0.005)	8.4

Results for intermediate precision were obtained on the **cobas c** 501 analyzer.

Method comparison

CRP values for human serum and plasma samples obtained on a **cobas c** 701 analyzer (y) were compared with those determined using the corresponding reagent on a **cobas c** 501 analyzer (x).

Sample size (n) = 231

Passing/Bablok[33]	Linear regression
y = 0.996x - 0.074 mg/L	y = 0.998x - 0.079 mg/L
τ = 0.987	r = 1.000

The sample concentrations were between 0.180 and 17.8 mg/L (1.71 and 169 nmol/L, 0.018 and 1.78 mg/dL).

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