Для лабораторий, использующих
Tina-quant IgG Gen.2
на анализаторе **cobas c** 311,
на модулях **cobas c** 501, **c** 502, **c** 702,
г. Москва

Дата: 15.07.2024
Исх.: 0260/1507/2024
Ref.: QN-RDS-CoreLab-2024-056

Уведомление по качеству
Касательно изменений в настройках Протокола методики и Инструкций по использованию для Tina-quant IgG Gen.2 (IGG-2)

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 Иммуноглобулин G (IGG2 / Tina-Quant IgG Gen.2)	03507432190		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 Иммуноглобулин G ген.2, 500 тестов (IGG-2/Tina-quant IgG Gen.2, 500)	05220718190		ФСЗ 2012/13068 от 19.10.2012	Sandhofer Strasse 116, D-68305, Mannheim, Germany
Инструмент/Система	Анализатор **cobas c** 311 Модуль **cobas c** 501 Модуль **cobas c** 502 Модуль **cobas c** 702			

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Уважаемый пользователь,

Сообщаем вам о том, что были внесены изменения в Протоколы методики и/или Инструкции по использованию реагентов Tina-quant IgG Gen.2 (IGG2) ввиду переназначения мастер-прибора с **cobas c** 501 на **cobas c** 503 (MN-RDS-CoreLab-2022-183).

Для всех стран

- Обновление Инструкций по использованию реагента IGG2

Описание ситуации

На основании рекламаций от пользователей и внутренних расследований в связи с недавно объявленным переназначением мастер-прибора с **cobas c** 501 на **cobas c** 503 (MN-RDS-CoreLab-2022-183) требуется следующее:

Обновление настроек Протокола методики и Инструкций по использованию для IGG2

a) Раздел «Ограничения – Интерференция»: интерференция в образцах с иктеричностью, (Протоколы методики для мочи и спинномозговой жидкости):

Формулировка «Интерференция в образцах с иктеричностью» в разделах «Ограничения – Интерференция» в Инструкциях по использованию для Протоколов методики для определения IGG2 в моче (IGG2U) и CSF (IGG2C) для всех модулей **cobas c** будет обновлена в соответствии с текущим стандартным протоколом (удалена фраза «неконъюгированный билирубин»).

b) Раздел «Ограничения – Интерференция»: заявление о перекрестной реакции (Протоколы методики мочи): следующее заявление добавлено во все Инструкции по использованию всех модулей **cobas c** для Протоколов методики мочи (IGG2U):
«В условиях анализа не наблюдается перекрестной реакции между IgG и IgA или IgM».

Обратите внимание: это заявление уже добавлено для всех других затронутых Протоколов методики.

c) Сводный раздел: исправление опечатки в соотношении IgG/альбумин.
Как указано в разделе «Описание», «определение IgG в моче в сочетании с альбумином в моче помогает отделить селективные формы канальцевой протеинурии от неселективных, поскольку IgG заметно повышается только при неселективных формах клубочковой протеинурии (IgG/альбумин > 0,3 мг/мг)».

В Инструкциях по использованию для Протоколов методики мочи **cobas c** 311/501/502 есть опечатка в соотношении IgG/альбумин (IgG/альбумин > 0,03 мг/мг), которая была исправлена.

Примечание: это утверждение верно для всех Инструкций по использованию.

Обратите внимание, что для IGG-2 требования нового Регламента (ЕС) «О медицинских изделиях для диагностики IN VITRO» требуют обновления Инструкций по использованию, о котором было заявлено в MN-RDS-CoreLab2023-074. Объединение Инструкций по использованию и обновление сводного раздела будут реализованы в дальнейшем обновлении Инструкций по использованию IGG-2 для всех систем.

В следующей таблице представлен обзор всех обновлений:

Продукт	Значение	Затронутый Протокол методики	Затронутый модуль cobas	ACN	Прежнее значение	Новое значение	Обновление настроек	Обновление Инструкции по использованию реагента
Tina-quant IgG Gen.2 (IGG-2)	I-Index	IGG2U IGG2C	**c** 311/501/502 **c** 702	(8)673 (8)625	См. 3a	См. 3a	Нет	Да
	перекрёстная реактивность	IGG2U	c 311/501/502 c 702	(8)625	См. 3b	См. 3b	Нет	Да
	Раздел сводной информации	IGG2	c 311/501/502	(8)674 (8)673 (8)625	См. 3c	См. 3c	Нет	Да

Причина возникновения

Это изменение основано на недавних выводах мастер-проекта **cobas c** 503, о котором было объявлено в MNRDS-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.

Основная причина описанных проблем связана с ошибкой, обусловленной человеческим фактором. Проблемы были обнаружены во время проверки документации и Протоколов методики, проведенной в рамках мастер-проекта.

Оценка риска

Частота возникновения

Ни одна рекламация не была передана в Группу расследования рисков (CIR).

Вероятность обнаружения

Проблема не обнаруживается пользователями.

Серьезность последствий

Результаты пациентов также не затрагиваются. Риск, связанный с описанной проблемой, отсутствует.

Медицинский риск для пациентов и пользователей может быть исключен.

Важная информация

Важные примечания, относящиеся ко всем изменениям настроек Протокола методики, а также обновленным Инструкциям по использованию Tinaquant IgG Gen.2 (IGG-2), приложены к настоящему Уведомлению по качеству.

Обновленная электронная документация для затронутых Протоколов методики будет опубликована на Портале электронного контента со ссылкой на настоящее Уведомление по качеству.

Пакеты электронной документации для IGG-2 будут содержать обновленные Инструкции по использованию и неизмененные электронные штрихкоды, за исключением IGG2U (20743), который также содержит Важное примечание и обновленный электронный штрихкод.

Инструкции по использованию для Tina-quant IgG Gen.2 (IGG-2):
эта Инструкция уже приложена к настоящему Уведомлению по качеству.

Для всех стран, кроме США:

Анализатор	Версия Инструкции к реагенту	Срок публикации
cobas 311 **cobas** 501/502	16.0 Reiber: 5.0	Июнь 2024 г.
cobas c 702	13.0	

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
Иван Каргов
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Date: 2024.07.15 16:34:31 +03'00'

Медицинский менеджер
Тел: + 7 (495) 229-69-99
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Мария Косякова
Maria Kosyakova
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Date: 2024.07.16 17:06:15 +03'00'

IGG-2

cobas®

Tina-quant IgG Gen.2

Order information

REF	CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
03507432190	Tina-quant IgG Gen.2 150 tests	System-ID 07 6787 5	**cobas c** 311, **cobas c** 501/502

Materials required (but not provided):

11355279216	Calibrator f.a.s. Proteins (5 x 1 mL)	Code 656	
03121305122	Calibrator f.a.s. PUC (5 x 1 mL)	Code 489	
10557897122	Precinorm Protein (3 x 1 mL)	Code 302	
11333127122	Precipath Protein (3 x 1 mL)	Code 303	
03121313122	Precinorm PUC (4 x 3 mL)	Code 240	
03121291122	Precipath PUC (4 x 3 mL)	Code 241	
05117003190	PreciControl ClinChem Multi 1 (20 x 5 mL)	Code 391	
05947626190	PreciControl ClinChem Multi 1 (4 x 5 mL)	Code 391	
05117216190	PreciControl ClinChem Multi 2 (20 x 5 mL)	Code 392	
05947774190	PreciControl ClinChem Multi 2 (4 x 5 mL)	Code 392	
04489357190	Diluent NaCl 9 % (50 mL)	System-ID 07 6869 3	

English

System information

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

IGG-2: ACN 674 (Standard application for serum and plasma)

IGGC2: ACN 673 (Sensitive application for cerebrospinal fluid)

IGGU2: ACN 625 (Sensitive application for urine)

For **cobas c** 502 analyzer:

IGG-2: ACN 8674 (Standard application for serum and plasma)

IGGC2: ACN 8673 (Sensitive application for cerebrospinal fluid)

IGGU2: ACN 8625 (Sensitive application for urine)

Intended use

In vitro test for the quantitative determination of IgG in human serum, plasma, cerebrospinal fluid and urine on Roche/Hitachi **cobas c** systems.

Summary[1,2,3,4,5,6,7,8,9]

IgG molecules are composed of 2 light chains (kappa or lambda) and 2 gamma heavy chains. Approximately 80 % of serum immunoglobulin is IgG; its main tasks are the defense against microorganisms, direct neutralization of toxins and induction of complement fixation. IgG is the only immunoglobulin that can cross the placental barrier and provide passive immune protection for the fetus and newborn. This maternal protection gradually declines until the infant's own immunological system starts to develop (at about 6 months of age). Near-adult levels in serum/plasma are reached at 18 months.

Polyclonal IgG increases in serum/plasma may be present in systemic lupus erythematosis, chronic liver diseases (infectious hepatitis and Laennec's cirrhosis), infectious diseases and cystic fibrosis. Monoclonal IgG increases in IgG-myeloma.

Decreased synthesis of IgG is found in congenital and acquired immunodeficiency diseases and selective IgG subclass deficiencies, such as Bruton type agammaglobulinemia. Decreased IgG concentrations in serum and plasma are seen in protein-losing enteropathies, nephrotic syndrome and through the skin from burns. Increased IgG metabolism is found in Wiskott-Aldrich syndrome, myotonic dystrophy and with anti-immunoglobulin antibodies.

The determination of IgG in cerebrospinal fluid (CSF) is used for evaluation of infections involving the central nervous system (CNS), neoplasms or primary neurologic diseases (in particular, multiple sclerosis). Increased CSF IgG concentrations may occur because of either increased permeability of the blood-brain barrier or local/intrathecal production of IgG, or both.

Malfunction of the blood-brain barrier can be reliably quantified by means of the albumin CSF/serum ratio. An elevated albumin ratio is an indication of a disorder of the blood-brain barrier. If IgG and albumin are measured in CSF and serum simultaneously, differentiation between IgG originating from blood and IgG originating from intrathecal production is possible.

The determination of urine IgG aids, in combination with urinary albumin, to separate selective forms from unselective forms of tubular proteinuria, since IgG is markedly increased only in unselective forms of glomerular proteinuria (IgG/albumin > 0.3 mg/mg). Additionally, measurements of IgG in urine can be used in the monitoring and assessment of glomerular proreinuria.

The Roche IgG assay is based on the principle of immunological agglutination. In addition to the standard application (IGG-2), there are sensitive applications (IGGC2 and IGGU2) designed for the quantitative determination of IgG in CSF and urine.

It is known that the so-called paraproteins secreted in monoclonal gammopathies (monoclonal immunoglobulinemia) may differ from the respective immunoglobulins of polyclonal origin by amino acid composition and size. This may impair the binding to antibody and hence impair accurate quantitation.

Test principle

Immunoturbidimetric assay.

Anti-IgG antibodies react with antigen in the sample to form an antigen/antibody complex. Following agglutination, this is measured turbidimetrically. Addition of PEG allows the reaction to progress rapidly to the end point, increases sensitivity, and reduces the risk of samples containing excess antigen producing false negative results.

Reagents - working solutions

R1 TRIS buffer: 20 mmol/L, pH 8.0; NaCl: 200 mmol/L; polyethylene glycol: 3.6 %; preservative; stabilizers

R2 Anti-human IgG antibody (goat): dependent on titer; TRIS buffer: 20 mmol/L, pH 8.0; NaCl: 150 mmol/L; preservative

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.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

IGG-2

Tina-quant IgG Gen.2

Danger

H318 Causes serious eye damage.

Prevention:

P280 Wear eye protection/ face protection.

Response:

P305 + P351 + P338 + P310 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Immediately call a POISON CENTER/ doctor.

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590

Reagent handling

Ready for use

Storage and stability

IGG-2

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

Diluent NaCl 9 %

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 application (IGG-2)

Serum.

Plasma: Li-heparin and K_2-EDTA plasma

CSF application (IGGC2)

Cerebrospinal fluid.

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.

Urine application (IGGU2)

Urine.

Centrifuge samples containing precipitates before performing the assay.

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

Serum and plasma

Stability:[10]	4 months at 15-25 °C
	8 months at 2-8 °C
	8 months at -20 °C (±5 °C)

CSF

Samples should be as fresh as possible. Centrifuge samples containing particles and/or cells before performing the assay.

Stability:[10]	1 day at 15-25 °C
	7 days at 2-8 °C
	Storage at -20 °C (±5 °C) is not recommended.

Urine

Spontaneous, 24-hour urine or 2nd morning urine. Centrifuge the urine samples for 10 min at ≥ 800 g.

Stability:[11]	7 days at 15-25 °C
	1 month at 2-8 °C
	Storage at -20 °C (±5 °C) is not recommended.

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 (IGG-2)

cobas c 311 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10/6-16		
Wavelength (sub/main)	700/340 nm		
Reaction direction	Increase		
Units	g/L (µmol/L, mg/dL)		
Reagent pipetting		Diluent (H_2O)	
R1	120 µL	–	
R2	38 µL	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	5 µL	9 µL	180 µL
Decreased	3.9 µL	2 µL	180 µL
Increased	9.4 µL	20 µL	85 µL

cobas c 501/502 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10/10-46		
Wavelength (sub/main)	700/340 nm		
Reaction direction	Increase		
Units	g/L (µmol/L, mg/dL)		
Reagent pipetting		Diluent (H_2O)	
R1	120 µL	–	
R2	38 µL	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	5 µL	9 µL	180 µL
Decreased	3.9 µL	2 µL	180 µL
Increased	9.4 µL	20 µL	85 µL

Application for CSF (IGGC2)

cobas c 311 **test definition**

IGG-2

Tina-quant IgG Gen.2

Assay type	2-Point End		
Reaction time / Assay points	10/6-31		
Wavelength (sub/main)	700/340 nm		
Reaction direction	Increase		
Units	mg/L (nmol/L)		
Reagent pipetting		Diluent (H_2O)	
R1	120 µL	–	
R2	10 µL	20 µL	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	14.5 µL	–	–
Decreased	2.9 µL	–	–
Increased	14.5 µL	–	–

cobas c 501 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10/10-46		
Wavelength (sub/main)	700/340 nm		
Reaction direction	Increase		
Units	mg/L (nmol/L)		
Reagent pipetting		Diluent (H_2O)	
R1	120 µL	–	
R2	10 µL	20 µL	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	14.5 µL	–	–
Decreased	2.9 µL	–	–
Increased	14.5 µL	–	–

cobas c 502 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10/10-46		
Wavelength (sub/main)	700/340 nm		
Reaction direction	Increase		
Units	mg/L (nmol/L)		
Reagent pipetting		Diluent (H_2O)	
R1	120 µL	–	
R2	10 µL	20 µL	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	14.5 µL	–	–
Decreased	2.9 µL	–	–
Increased	29 µL	–	–

Application for urine (IGGU2)

cobas c 311 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10/6-31		
Wavelength (sub/main)	700/340 nm		
Reaction direction	Increase		
Units	mg/L (nmol/L)		
Reagent pipetting		Diluent (H_2O)	
R1	120 µL	–	
R2	38 µL	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	14.5 µL	–	–
Decreased	14.5 µL	15 µL	135 µL
Increased	14.5 µL	–	–

cobas c 501 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10/10-46		
Wavelength (sub/main)	700/340 nm		
Reaction direction	Increase		
Units	mg/L (nmol/L)		
Reagent pipetting		Diluent (H_2O)	
R1	120 µL	–	
R2	38 µL	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	14.5 µL	–	–
Decreased	14.5 µL	15 µL	135 µL
Increased	14.5 µL	–	–

cobas c 502 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10/10-46		
Wavelength (sub/main)	700/340 nm		
Reaction direction	Increase		
Units	mg/L (nmol/L)		
Reagent pipetting		Diluent (H_2O)	
R1	120 µL	–	
R2	38 µL	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	14.5 µL	–	–
Decreased	14.5 µL	15 µL	135 µL
Increased	29 µL	–	–

Calibration

Serum/plasma application (IGG-2) :

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: 0.100 S5: 1.00
	S3: 0.250 S6: 3.14
	S4: 0.501
Calibration mode	**cobas c** 311 analyzer: Spline
	cobas c 501/502 analyzer: RCM

IGG-2

Tina-quant IgG Gen.2

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

CSF (IGGC2) and urine (IGGU2) applications:

Calibrators	S1: H_2O	
	S2-S6: C.f.a.s. PUC	
	Multiply the lot-specific C.f.a.s. PUC calibrator value by the factors below to determine the standard concentrations for the 6-point calibration curve:	
	S2: 0.0431	S5: 0.331
	S3: 0.0862	S6: 1.00
	S4: 0.166	
Calibration mode	RCM	
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 certified reference material in human serum of the IRMM (Institute for Reference Materials and Measurements) ERM-DA470k/IFCC.

Quality control

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

IGG-2: Precinorm Protein, Precipath Protein, PreciControl ClinChem Multi 1, PreciControl ClinChem Multi 2

IGGC2 and IGGU2: Precinorm PUC, Precipath PUC

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/dL x 0.01 = g/L	g/L x 6.67 = µmol/L
	g/L x 100 = mg/dL	µmol/L x 0.15 = g/L
	mg/L x 6.67 = nmol/L	nmol/L x 0.15 = mg/L

Limitations - interference

Serum/plasma application (IGG-2):

Criterion: Recovery within ±10 % of initial value at an IgG concentration of 7.00 g/L (46.7 µmol/L, 700 mg/dL).

Icterus:[12] 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:[12] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 621 µmol/L or 1000 mg/dL).

Lipemia (Intralipid):[12] No significant interference up to an L index of 2000 (approximate intralipid concentration: 2000 mg/dL). 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 1200 IU/mL.

High dose hook-effect: No false result up to an IgG concentration of 400 g/L (2668 µmol/L, 40000 mg/dL) occurs due to an antigen excess within polyclonal specimens.

There is no cross-reaction between IgG and IgA or IgM under the assay conditions.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[13,14]

As with other turbidimetric or nephelometric procedures, this test may not provide accurate results in patients with monoclonal gammopathy, due to individual sample characteristics which can be assessed by electrophoresis.[15]

CSF application (IGGC2):

Criterion: Recovery within ±10 % of initial value at an IgG concentration of 15.00 mg/L (100 nmol/L).

Icterus: No significant interference up to a conjugated bilirubin concentration of 257 µmol/L or 15 mg/dL.

Hemolysis: No significant interference up to a hemoglobin concentration of 124 µmol/L or 200 mg/dL.

High dose hook-effect: Using the prozone check, no false result without a flag was observed up to an IgG concentration of 2500 mg/L (16675 nmol/L).

There is no cross-reaction between IgG and IgA or IgM under the assay conditions.

Urine application (IGGU2):

Criterion: Recovery within ±2 mg/L (±13.3 nmol/L) of initial value at an IgG concentration of ≤ 10 mg/L (≤ 66.7 nmol/L) and within ±10 % of initial value at an IgG concentration of > 10 mg/L (> 66.7 nmol/L).

Icterus: No significant interference up to a conjugated bilirubin concentration of 257 µmol/L or 15 mg/dL.

Hemolysis: No significant interference up to a hemoglobin concentration of 93.2 µmol/L or 150 mg/dL.

High dose hook-effect: No false result occurs up to an IgG concentration of 6000 mg/L (40020 nmol/L).

There is no cross-reaction between IgG and IgA or IgM under the assay conditions.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[14]

Exception: N-acetyl cysteine and ascorbic acid cause artificially low IgG results.

No interference by h-albumin ≤ 5000 mg/L, glucose ≤ 111 mmol/L, creatinine ≤ 44 mmol/L, urea ≤ 900 mmol/L, uric acid ≤ 6 mmol/L, oxalate ≤ 2.2 mmol/L, calcium ≤ 40 mmol/L, citrate ≤ 10 mmol/L, magnesium ≤ 75 mmol/L and phosphate ≤ 40 mmol/L.

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

Serum/plasma application (IGG-2):

3.00-50.0 g/L (20.0-334 µmol/L, 300-5000 mg/dL)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:5.5 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 5.5.

Determine samples having lower concentrations via the rerun function. For samples with lower concentrations, the re-run function increases the sample volume by a factor of 7.5. The results are automatically divided by this factor.

IGG-2

Tina-quant IgG Gen.2

cobas®

CSF application (IGGC2):

4.00-200 mg/L (26.7-1334 nmol/L)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:5 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 5.

Urine application (IGGU2):

4.00-200 mg/L (26.7-1334 nmol/L)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:10 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 10.

Lower limits of measurement

Lower detection limit of the test

Serum/plasma application (IGG-2):

0.30 g/L (2.00 µmol/L, 30 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).

CSF application (IGGC2):

4.00 mg/L (26.7 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 the lowest standard (standard 1 + 3 SD, repeatability, n = 21).

Urine application (IGGU2):

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank	= 3 mg/L (20.0 nmol/L)
Limit of Detection	= 4 mg/L (26.7 nmol/L)
Limit of Quantitation	= 7 mg/L (46.7 nmol/L)

The Limit of Blank and Limit of Detection were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A requirements.

The Limit of Blank is the 95th percentile value from n ≥ 60 measurements of analyte-free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte-free samples are found with a probability of 95 %.

The Limit of Detection is determined based on the Limit of Blank and the standard deviation of low concentration samples.

The Limit of Detection corresponds to the lowest analyte concentration which can be detected (value above the Limit of Blank with a probability of 95 %).

The Limit of Quantitation is the lowest analyte concentration that can be reproducibly measured with a total error of 30 %. It has been determined using low concentration IgG samples.

Expected values

Serum/plasma

Adults[16]	7-16 g/L	46.7-107 µmol/L	700-1600 mg/dL
Children/juveniles:[17]			
0 - 14 days:	3.20-12.1 g/L	21.3-80.4 µmol/L	320-1205 mg/dL
15 days - <1 yr:	1.48-6.31 g/L	9.87-42.1 µmol/L	148-631 mg/dL
1 - <4 yr:	3.17-9.94 g/L	21.1-66.3 µmol/L	317-994 mg/dL
4 - <10 yr:	5.01-11.7 g/L	33.4-77.7 µmol/L	501-1165 mg/dL
10 - <19 yr:	5.95-13.1 g/L	39.7-87.2 µmol/L	595-1308 mg/dL

CSF[18]

10-30 mg/L (66.7-200 nmol/L)

Urine

The upper normal 97.5th percentile limit was found to be 8.5 mg/24 h for IgG (0.90 confidence interval: 7.7-10.1 mg/24 h).[19]

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

Specific performance data

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

Precision

Serum/plasma and *CSF:*

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, one lot of reagent, 21 days).

Urine:

Precision was determined using human samples and controls in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP5 requirements with repeatability (n = 84) and intermediate precision (4 aliquots per run, 1 run per day, 21 days on **cobas c** 501 analyzer). The following results were obtained:

Serum/plasma application (IGG-2):

Repeatability	*Mean*	*SD*	*CV*
	g/L (µmol/L, mg/dL)	*g/L (µmol/L, mg/dL)*	*%*
Precinorm Protein	8.25 (55.0, 825)	0.08 (0.5, 8)	1.0
Precipath Protein	14.2 (94.7, 1420)	0.2 (1.3, 20)	1.2
Human serum 1	8.44 (56.3, 844)	0.05 (0.3, 5)	0.6
Human serum 2	21.5 (143, 2150)	0.3 (2, 30)	1.5
Intermediate precision	*Mean*	*SD*	*CV*
	g/L (µmol/L, mg/dL)	*g/L (µmol/L, mg/dL)*	*%*
Precinorm Protein	8.19 (54.6, 819)	0.12 (0.8, 12)	1.5
Precipath Protein	14.2 (94.7, 1420)	0.2 (1.3, 20)	1.5
Human serum 3	7.11 (47.4, 711)	0.08 (0.5, 8)	1.1
Human serum 4	21.1 (140, 2110)	0.4 (3, 40)	1.7

CSF application (IGGC2):

Repeatability	*Mean*	*SD*	*CV*
	mg/L (nmol/L)	*mg/L (nmol/L)*	*%*
Precinorm PUC	18.8 (125)	0.3 (2)	1.6
Precipath PUC	150 (1001)	2 (13)	1.1
CSF 1	7.62 (50.7)	0.25 (1.7)	3.3
CSF 2	95.0 (634)	0.5 (3)	0.5
Intermediate precision	*Mean*	*SD*	*CV*
	mg/L (nmol/L)	*mg/L (nmol/L)*	*%*
Precinorm PUC	20.1 (134)	0.5 (3)	2.5
Precipath PUC	160 (1067)	2 (13)	1.0
CSF 3	21.9 (146)	0.5 (3)	2.1
CSF 4	137 (914)	1 (7)	1.1

Urine application (IGGU2):

Repeatability	*Mean*	*SD*	*CV*
	mg/L (nmol/L)	*mg/L (nmol/L)*	*%*
Precinorm PUC	17.2 (115)	0.3 (2)	1.5

Precipath PUC	140 (934)	1 (7)	0.9
Urine 1	7.52 (50.2)	0.28 (1.9)	3.7
Urine 2	89.9 (600)	0.6 (4)	0.7
Urine 3	160 (1067)	1 (7)	0.7
Intermediate precision	*Mean*	*SD*	*CV*
	mg/L (nmol/L)	*mg/L (nmol/L)*	*%*
Precinorm PUC	17.2 (115)	0.4 (3)	2.5
Precipath PUC	140 (934)	1 (7)	0.9
Urine 1	7.52 (50.2)	0.36 (2.4)	4.8
Urine 2	89.9 (600)	0.9 (6)	1.0
Urine 3	160 (1067)	2 (13)	1.0

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

Method comparison

Serum/plasma application (IGG-2):

IgG 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) = 103

Passing/Bablok[20]	Linear regression
y = 0.981x + 0.256 g/L	y = 0.990x + 0.229 g/L
τ = 0.957	r = 0.995

The sample concentrations were between 3.16 and 48.2 g/L (21.1 and 321 µmol/L, 316 and 4820 mg/dL).

CSF application (IGGC2):

IgG values for human CSF 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) = 77

Passing/Bablok[20]	Linear regression
y = 1.007x - 2.17 mg/L	y = 0.997x - 1.70 mg/L
τ = 0.941	r = 1.000

The sample concentrations were between 10.7 and 186 mg/L (71.4 and 1241 nmol/L).

Urine application (IGGU2):

IgG values for human urine samples obtained on a **cobas c** 501 analyzer (y) were compared with those determined with a nephelometric IgG test (x).

Sample size (n) = 64

Passing/Bablok[20]	Linear regression
y = 0.957x + 1.03 mg/L	y = 0.948x + 1.43 mg/L
τ = 0.877	r = 0.982

The sample concentrations were between 3.75 and 57.9 mg/L (25.0 and 386 nmol/L).

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

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

IGG-2

Tina-quant IgG Gen.2

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

IGG-2

cobas®

Tina-quant IgG Gen.2

Order information

REF	CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
05220718190	Tina-quant IgG Gen.2 (500 tests)	System-ID 03 6787 5	**cobas c** 701/702

Materials required (but not provided):

11355279216	Calibrator f.a.s. Proteins (5 x 1 mL)	Code 656	
03121305122	Calibrator f.a.s. PUC (5 x 1 mL)	Code 489	
10557897122	Precinorm Protein (3 x 1 mL)	Code 302	
11333127122	Precipath Protein (3 x 1 mL)	Code 303	
03121313122	Precinorm PUC (4 x 3 mL)	Code 240	
03121291122	Precipath PUC (4 x 3 mL)	Code 241	
05117003190	PreciControl ClinChem Multi 1 (20 x 5 mL)	Code 391	
05947626190	PreciControl ClinChem Multi 1 (4 x 5 mL)	Code 391	
05117216190	PreciControl ClinChem Multi 2 (20 x 5 mL)	Code 392	
05947774190	PreciControl ClinChem Multi 2 (4 x 5 mL)	Code 392	
05172152190	Diluent NaCl 9 % (119 mL)	System-ID 08 6869 3	

English

System information

IGG-2: ACN 8674 (Standard application for serum and plasma)

IGGC2: ACN 8673 (Sensitive application for cerebrospinal fluid)

IGGU2: ACN 8625 (Sensitive application for urine)

Intended use

In vitro test for the quantitative determination of IgG in human serum, plasma, cerebrospinal fluid and urine on Roche/Hitachi **cobas c** systems.

Summary[1,2,3,4,5,6,7,8,9]

IgG molecules are composed of 2 light chains (kappa or lambda) and 2 gamma heavy chains. Approximately 80 % of serum immunoglobulin is IgG; its main tasks are the defense against microorganisms, direct neutralization of toxins and induction of complement fixation. IgG is the only immunoglobulin that can cross the placental barrier and provide passive immune protection for the fetus and newborn. This maternal protection gradually declines until the infant's own immunological system starts to develop (at about 6 months of age). Near-adult levels in serum/plasma are reached at 18 months.

Polyclonal IgG increases may be present in systemic lupus erythematosis, chronic liver diseases (infectious hepatitis and Laennec's cirrhosis), infectious diseases and cystic fibrosis. Monoclonal IgG increases in IgG-myeloma.

Decreased synthesis of IgG is found in congenital and acquired immunodeficiency diseases and selective IgG subclass deficiencies, such as Bruton type agammaglobulinemia. Decreased IgG concentrations in serum and plasma are seen in protein-losing enteropathies, nephrotic syndrome and through the skin from burns. Increased IgG metabolism is found in Wiskott-Aldrich syndrome, myotonic dystrophy and with anti-immunoglobulin antibodies.

The determination of IgG in cerebrospinal fluid (CSF) is used for evaluation of infections involving the central nervous system (CNS), neoplasms or primary neurologic diseases (in particular, multiple sclerosis). Increased CSF IgG concentrations may occur because of either increased permeability of the blood-brain barrier or local/intrathecal production of IgG, or both.

Malfunction of the blood-brain barrier can be reliably quantified by means of the albumin CSF/serum ratio. An elevated albumin ratio is an indication of a disorder of the blood-brain barrier. If IgG and albumin are measured in CSF and serum simultaneously, differentiation between IgG originating from blood and IgG originating from intrathecal production is possible.

The determination of urine IgG aids, in combination with urinary albumin, to separate selective forms from unselective forms of tubular proteinuria, since IgG is markedly increased only in unselective forms of glomerular proteinuria (IgG/albumin > 0.3 mg/mg). Additionally, measurements of IgG in urine can be used in the monitoring and assessment of glomerular proteinuria.

The Roche IgG assay is based on the principle of immunological agglutination. In addition to the standard application (IGG-2), there are sensitive applications (IGGC2 and IGGU2) designed for the quantitative determination of IgG in CSF and urine.

It is known that the so-called paraproteins secreted in monoclonal gammopathies (monoclonal immunoglobulinemia) may differ from the respective immunoglobulins of polyclonal origin by amino acid composition and size. This may impair the binding to antibody and hence impair accurate quantitation.

Test principle

Immunoturbidimetric assay.
Anti-IgG antibodies react with antigen in the sample to form an antigen/antibody complex. Following agglutination, this is measured turbidimetrically. Addition of PEG allows the reaction to progress rapidly to the end point, increases sensitivity, and reduces the risk of samples containing excess antigen producing false negative results.

Reagents - working solutions

R1 TRIS buffer: 20 mmol/L, pH 8.0; NaCl: 200 mmol/L; polyethylene glycol: 3.6 %; preservative; stabilizers

R3 Anti-human IgG antibody (goat): dependent on titer; TRIS buffer: 20 mmol/L, pH 8.0; NaCl: 150 mmol/L; preservative

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.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Danger

H318 Causes serious eye damage.

Prevention:

IGG-2

Tina-quant IgG Gen.2

P280	Wear eye protection/ face protection.

Response:

P305 + P351 + P338 + P310	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Immediately call a POISON CENTER/ doctor.

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590

Reagent handling

Ready for use

Storage and stability

IGG-2

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label.
On-board in use and refrigerated on the analyzer:	4 weeks
On board on the Reagent Manager:	24 hours

Diluent NaCl 9 %

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label.
On-board in use and refrigerated on the analyzer:	4 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 application (IGG-2)
Serum.
Plasma: Li-heparin and K_2-EDTA plasma
CSF application (IGGC2)
Cerebrospinal fluid.
Urine application (IGGU2)
Urine.

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.

Serum/plasma

Stability:[10]	4 months at 15-25 °C
	8 months at 2-8 °C
	8 months at -20 °C (± 5 °C)

CSF

Samples should be as fresh as possible. Centrifuge samples containing particles and/or cells before performing the assay.

Stability:[10]	1 day at 15-25 °C
	7 days at 2-8 °C
	Storage at -20 °C (± 5 °C) is not recommended.

Urine

Spontaneous, 24-hour urine or 2nd morning urine. Centrifuge the urine samples for 10 min at ≥ 800 g.

Stability:[11]	7 days at 15-25 °C
	1 month at 2-8 °C
	Storage at -20 °C (± 5 °C) is not recommended.

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 (IGG-2)

cobas c 701/702 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10/18-27		
Wavelength (sub/main)	700/340 nm		
Reaction direction	Increase		
Units	g/L (µmol/L, mg/dL)		
Reagent pipetting		Diluent (H_2O)	
R1	120 µL	–	
R3	38 µL	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	5 µL	9 µL	180 µL
Decreased	3.9 µL	2 µL	180 µL
Increased	9.4 µL	20 µL	85 µL

Application for CSF (IGGC2)

cobas c 701/702 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10/18-27		
Wavelength (sub/main)	700/340 nm		
Reaction direction	Increase		
Units	mg/L (nmol/L)		
Reagent pipetting		Diluent (H_2O)	
R1	120 µL	–	
R3	10 µL	20 µL	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	14.5 µL	–	–
Decreased	2.9 µL	–	–
Increased	29 µL	–	–

Application for urine (IGGU2)

cobas c 701/702 **test definition**

Assay type	2-Point End
Reaction time / Assay points	10/18-38

IGG-2

Tina-quant IgG Gen.2

cobas®

Wavelength (sub/main)	700/340 nm	
Reaction direction	Increase	
Units	mg/L (nmol/L)	
Reagent pipetting		Diluent (H_2O)
R1	120 µL	–
R3	38 µL	–

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	14.5 µL	–	–
Decreased	14.5 µL	15 µL	135 µL
Increased	29 µL	–	–

Calibration

Serum/plasma application (IGG-2):

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: 0.100	S5: 1.00
	S3: 0.250	S6: 3.14
	S4: 0.501	
Calibration mode	RCM	
Calibration frequency	Full calibration - after reagent lot change - as required following quality control procedures	

CSF (IGGC2) and urine (IGGU2) applications:

Calibrators	S1: H_2O	
	S2-S6: C.f.a.s. PUC	
	Multiply the lot-specific C.f.a.s. PUC calibrator value by the factors below to determine the standard concentrations for the 6-point calibration curve:	
	S2: 0.0431	S5: 0.331
	S3: 0.0862	S6: 1.00
	S4: 0.166	
Calibration mode	RCM	
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 certified reference material in human serum of the IRMM (Institute for Reference Materials and Measurements) ERM-DA470k/IFCC.

Quality control

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

IGG-2: Precinorm Protein, Precipath Protein, PreciControl ClinChem Multi 1, PreciControl ClinChem Multi 2

IGGC2 and IGGU2: Precinorm PUC, Precipath PUC

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/dL x 0.01 = g/L	g/L x 6.67 = µmol/L
	g/L x 100 = mg/dL	µmol/L x 0.15 = g/L
	mg/L x 6.67 = nmol/L	nmol/L x 0.15 = mg/L

Limitations - interference

Serum/plasma application (IGG-2) :

Criterion: Recovery within ± 10 % of initial value at an IgG concentration of 7.00 g/L (46.7 µmol/L, 700 mg/dL).

Icterus:[12] 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:[12] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 621 µmol/L or 1000 mg/dL).

Lipemia (Intralipid):[12] No significant interference up to an L index of 2000 (approximate Intralipid concentration: 2000 mg/dL). 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 1200 IU/mL.

High dose hook-effect: Using the prozone check, no false result without a flag up to an IgG concentration of 400 g/L (2668 µmol/L, 40000 mg/dL) occurs due to an antigen excess within polyclonal specimens.

There is no cross-reaction between IgG and IgA or IgM under the assay conditions.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[13,14]

As with other turbidimetric or nephelometric procedures, this test may not provide accurate results in patients with monoclonal gammopathy, due to individual sample characteristics which can be assessed by electrophoresis.[15]

CSF application (IGGC2):

Criterion: Recovery within ± 10 % of initial value at an IgG concentration of 15.00 mg/L (100 nmol/L).

Icterus: No significant interference up to a conjugated bilirubin concentration of 257 µmol/L or 15 mg/dL.

Hemolysis: No significant interference up to a hemoglobin concentration of 124 µmol/L or 200 mg/dL.

High dose hook-effect: Using the prozone check, no false result without a flag was observed up to an IgG concentration of 2500 mg/L (16675 nmol/L).

There is no cross-reaction between IgG and IgA or IgM under the assay conditions.

Urine application (IGGU2):

Criterion: Recovery within ± 2 mg/L (± 13.3 nmol/L) of initial value at an IgG concentration of ≤ 10 mg/L (≤ 66.7 nmol/L) and within ± 10 % of initial value at an IgG concentration of > 10 mg/L (> 66.7 nmol/L).

Icterus: No significant interference up to a conjugated bilirubin concentration of 257 µmol/L or 15 mg/dL.

Hemolysis: No significant interference up to a hemoglobin concentration of 93.2 µmol/L or 150 mg/dL.

High dose hook-effect: No false result up to an IgG concentration of 6000 mg/L (40020 nmol/L).

There is no cross-reaction between IgG and IgA or IgM under the assay conditions.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[14]

Exception: N-acetyl cystein and ascorbic acid cause artificially low IgG results.

No interference by h-albumin ≤ 5000 mg/L, glucose ≤ 111 mmol/L, creatinine ≤ 44 mmol/L, urea ≤ 900 mmol/L, uric acid ≤ 6 mmol/L, oxalate ≤ 2.2 mmol/L, calcium ≤ 40 mmol/L, citrate ≤ 10 mmol/L, magnesium ≤ 75 mmol/L and phosphate ≤ 40 mmol/L.

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

Serum/plasma application (IGG-2):

3.00-50.0 g/L (20.0-334 µmol/L, 300-5000 mg/dL)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:5.5 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 5.5.

Determine samples having lower concentrations via the rerun function. For samples with lower concentrations, the rerun function increases the sample volume by a factor of 7.5. The results are automatically divided by this factor.

CSF application (IGGC2):

4.00-200 mg/L (26.7-1334 nmol/L)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:5 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 5.

Urine application (IGGU2):

4.00-200 mg/L (26.7-1334 nmol/L)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:10 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 10.

Lower limits of measurement

Lower detection limit of the test

Serum/plasma application (IGG-2):

0.30 g/L (2.00 µmol/L, 30 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 (< 0.30 g/L) will not be flagged by the instrument.

CSF application (IGGC2):

4.00 mg/L (26.7 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 the lowest standard (standard 1 + 3 SD, repeatability, n = 21).

Values below the lower detection limit (< 4.00 mg/L) will not be flagged by the instrument.

Urine application (IGGU2):

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank	= 3 mg/L (20.0 nmol/L)
Limit of Detection	= 4 mg/L (26.7 nmol/L)
Limit of Quantitation	= 7 mg/L (46.7 nmol/L)

The Limit of Blank and Limit of Detection were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A requirements.

The Limit of Blank is the 95th percentile value from n ≥ 60 measurements of analyte-free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte-free samples are found with a probability of 95 %.

The Limit of Detection is determined based on the Limit of Blank and the standard deviation of low concentration samples.

The Limit of Detection corresponds to the lowest analyte concentration which can be detected (value above the Limit of Blank with a probability of 95 %).

Values below the Limit of Detection (< 4 mg/L) will not be flagged by the instrument.

The Limit of Quantitation is the lowest analyte concentration that can be reproducibly measured with a total error of 30 %. It has been determined using low concentration IgG samples.

Expected values

Serum/plasma

Adults[16]	7-16 g/L	46.7-107 µmol/L	700-1600 mg/dL
Children/juveniles:[17]			
0 - 14 days:	3.20-12.1 g/L	21.3-80.4 µmol/L	320-1205 mg/dL
15 days - <1 yr:	1.48-6.31 g/L	9.87-42.1 µmol/L	148-631 mg/dL
1 - <4 yr:	3.17-9.94 g/L	21.1-66.3 µmol/L	317-994 mg/dL
4 - <10 yr:	5.01-11.7 g/L	33.4-77.7 µmol/L	501-1165 mg/dL
10 - <19 yr:	5.95-13.1 g/L	39.7-87.2 µmol/L	595-1308 mg/dL

CSF[18]

10-30 mg/L (66.7-200 nmol/L)

Urine

The upper normal 97.5th percentile limits were found to be 8.5 mg/24 h for IgG (0.90 confidence interval: 7.7-10.1 mg/24 h).[19]

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

Specific performance data

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

Precision

Serum/plasma and *CSF:*

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).

Urine:

Precision was determined using human samples and controls in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP5 requirements with repeatability (n = 84) and intermediate precision (4 aliquots per run, 1 run per day, one lot of reagent, 21 days, on **cobas c** 501 analyzer). The following results were obtained:

Serum/plasma application (IGG-2)

Repeatability	*Mean*	*SD*	*CV*
	g/L (µmol/L, mg/dL)	*g/L (µmol/L, mg/dL)*	*%*
Precinorm Protein	9.33 (62.3, 933)	0.04 (0.3, 4)	0.4
Precipath Protein	14.9 (99.5, 1492)	0.1 (0.6, 9)	0.6
Human serum A	37.4 (249, 3740)	0.5 (3, 50)	1.2
Human serum B	12.5 (83.4, 1250)	0.1 (0.7, 10)	0.9
Human serum C	3.40 (22.7, 340)	0.03 (0.2, 3)	0.8

IGG-2

Tina-quant IgG Gen.2

Intermediate precision	*Mean*	*SD*	*CV*
	g/L (µmol/L, mg/dL)	*g/L (µmol/L, mg/dL)*	*%*
Precinorm Protein	8.19 (54.6, 819)	0.12 (0.8, 12)	1.5
Precipath Protein	14.2 (94.7, 1420)	0.2 (1.3, 20)	1.5
Human serum 3	7.11 (47.4, 711)	0.08 (0.5, 8)	1.1
Human serum 4	21.1 (140, 2110)	0.4 (3, 40)	1.7

CSF application (IGGC2)

Repeatability	*Mean*	*SD*	*CV*
	mg/L (nmol/L)	*mg/L (nmol/L)*	*%*
Precinorm PUC	19.5 (130)	0.4 (3)	2.0
Precipath PUC	137 (914)	1 (7)	0.8
CSF A	14.8 (98.7)	0.3 (2.0)	2.1
CSF B	126 (840)	1 (7)	0.9
CSF C	179 (1194)	2 (13)	1.4

Intermediate precision	*Mean*	*SD*	*CV*
	mg/L (nmol/L)	*mg/L (nmol/L)*	*%*
Precinorm PUC	20.1 (134)	0.5 (3)	2.5
Precipath PUC	160 (1067)	2 (13)	1.0
CSF 3	21.9 (146)	0.5 (3)	2.1
CSF 4	137 (914)	1 (7)	1.1

Urine application (IGGU2)

Repeatability	*Mean*	*SD*	*CV*
	mg/L (nmol/L)	*mg/L (nmol/L)*	*%*
Precinorm PUC	17.7 (118)	0.2 (1)	0.9
Precipath PUC	140 (934)	1 (7)	1.0
Urine 1	7.30 (48.7)	0.11 (0.7)	1.5
Urine 2	87.5 (584)	0.5 (3)	0.5
Urine 3	159 (1061)	1 (7)	0.7

Intermediate precision	*Mean*	*SD*	*CV*
	mg/L (nmol/L)	*mg/L (nmol/L)*	*%*
Precinorm PUC	17.2 (115)	0.4 (3)	2.5
Precipath PUC	140 (934)	1 (7)	0.9
Urine 1	7.52 (50.2)	0.36 (2.4)	4.8
Urine 2	89.9 (600)	0.9 (6)	1.0
Urine 3	160 (1067)	2 (13)	1.0

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

Method comparison

Serum/plasma application (IGG-2):

IgG 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) = 183

Passing/Bablok[20]	Linear regression
y = 1.035x - 0.024 g/L	y = 1.004x + 0.29 g/L
τ = 0.9796	r = 0.997

The sample concentrations were between 3.30 and 47.1 g/L (22.0 and 314 µmol/L, 330 and 4710 mg/dL).

CSF application (IGGC2):

IgG values for human CSF 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) = 81

Passing/Bablok[20]	Linear regression
y = 0.994x - 1.40 mg/L	y = 0.973x - 0.403 mg/L
τ = 0.965	r = 0.999

The sample concentrations were between 4.97 and 197 mg/L (33.1 and 1314 nmol/L).

Urine application (IGGU2):

IgG values for human urine 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) = 66

Passing/Bablok[20]	Linear regression
y = 0.975x + 0.042 mg/L	y = 0.970x + 0.314 mg/L
τ = 0.983	r = 0.999

The sample concentrations were between 5.80 and 197 mg/L (38.7 and 1314 nmol/L).

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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.

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

IGG-2

cobas®

Tina-quant IgG CSF

Order information

REF	CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
03507432190	Tina-quant IgG Gen.2 (150 tests)	System-ID 07 6787 5	**cobas c** 501/502

Materials required (but not provided):

03121305122	Calibrator f.a.s. PUC (5 x 1 mL)	Code 489	
03121313122	Precinorm PUC (4 x 3 mL)	Code 240	
03121291122	Precipath PUC (4 x 3 mL)	Code 241	
05117003190	PreciControl ClinChem Multi 1 (20 x 5 mL)	Code 391	
05947626190	PreciControl ClinChem Multi 1 (4 x 5 mL)	Code 391	
05117216190	PreciControl ClinChem Multi 2 (20 x 5 mL)	Code 392	
05947774190	PreciControl ClinChem Multi 2 (4 x 5 mL)	Code 392	
04489357190	Diluent NaCl 9 % (50 mL)	System-ID 07 6869 3	

English

System information

For **cobas c** 501 analyzer:

IGG-C: ACN 119

For **cobas c** 502 analyzer:

IGG-C: ACN 8119

Intended use

In vitro test for the quantitative determination of IgG specifically in human cerebrospinal fluid and corresponding human serum/plasma on Roche/Hitachi **cobas c** 501/502 systems.

Summary[1,2,3]

Cerebrospinal fluid (CSF) analysis is a basic tool for diagnosis of neurological diseases.
The diffusion of proteins through the blood-brain barrier normally occurs at a steady rate. The rate is influenced by the permeability of the blood-brain barrier and CSF flow rate. Changes in protein concentration in the CSF can be an indication for various neurological diseases.
Disease-related immunoglobulin patterns (IgG, IgA, IgM with reference to albumin) allow for the differential diagnosis of neurological disorders with the aid of Reiber quotient schemes.
Elevated levels of IgG in CSF are often associated with opportunistic infections of the central nervous system (CNS) and neurotuberculosis. Increased CSF IgG concentrations may occur because of either increased permeability of the blood-brain barrier or local/intrathecal production of IgG, or both. Malfunction of the blood-brain barrier can be reliably quantified by means of the albumin CSF/serum ratio.
Albumin is an ideal reference protein for blood-brain barrier function, since it is solely synthesized outside the brain and thereby provides an excellent measure for proteins passing the blood-brain barrier. An elevated albumin CSF/serum ratio is an indication of disorders of the blood-brain barrier. Measuring IgG and albumin in CSF/serum pairs, a differentiation between IgG originating from blood and IgG originating from intrathecal production is possible. The results of the CSF/serum ratio for IgG and Albumin, in conjunction with Reiber quotient scheme provide an aid in the diagnosis of functional blood-brain barriers disorders and/or intrathecal IgG synthesis.
IgG molecules are composed of 2 light chains (kappa or lambda) and 2 gamma heavy chains. Approximately 80 % of serum immunoglobulin is IgG; its main tasks are the defense against microorganisms, direct neutralization of toxins and induction of complement fixation.

Test principle

Immunoturbidimetric assay.

Anti-IgG antibodies react with antigen in the sample to form an antigen/antibody complex. Following agglutination, this is measured turbidimetrically. Addition of PEG allows the reaction to progress rapidly to the end point, increases sensitivity, and reduces the risk of samples containing excess antigen producing false negative results.

Reagents - working solutions

R1 TRIS buffer: 20 mmol/L, pH 8.0; NaCl: 200 mmol/L; polyethylene glycol: 3.6 %; preservative; stabilizers

R2 Anti-human IgG antibody (goat): dependent on titer; TRIS buffer: 20 mmol/L, pH 8.0; NaCl: 150 mmol/L; preservative

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.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Danger

H318 Causes serious eye damage.

Prevention:

P280 Wear eye protection/ face protection.

Response:

P305 + P351 + P338 + P310 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Immediately call a POISON CENTER/ doctor.

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590

Reagent handling

Ready for use

Storage and stability

IGG-2

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

Diluent NaCl 9 %

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label.

IGG-2

Tina-quant IgG CSF

cobas®

On-board in use and refrigerated on the analyzer:	12 weeks

Specimen collection and preparation

Pairs of CSF/serum or CSF/plasma should be collected at the same time.

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

Cerebrospinal fluid

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.

Serum and plasma

Stability:[4]	4 months at 15-25 °C
	8 months at 2-8 °C
	8 months at -20 °C (±5 °C)

CSF

Samples should be as fresh as possible. Centrifuge samples containing particles and/or cells before performing the assay.

Stability:[4]	1 day at 15-25 °C
	7 days at 2-8 °C
	Storage at -20 °C (±5 °C) is not recommended.

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 sample type CSF

cobas c 501 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10/10-46		
Wavelength (sub/main)	700/340 nm		
Reaction direction	Increase		
Units	mg/L		
Reagent pipetting		Diluent (H_2O)	
R1	120 µL	–	
R2	10 µL	20 µL	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	14.5 µL	–	–
Decreased	2.9 µL	–	–
Increased	14.5 µL	–	–

cobas c 502 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10/10-46		
Wavelength (sub/main)	700/340 nm		
Reaction direction	Increase		
Units	mg/L		
Reagent pipetting		Diluent (H_2O)	
R1	120 µL	–	
R2	10 µL	20 µL	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	14.5 µL	–	–
Decreased	2.9 µL	–	–
Increased	29 µL	–	–

Application for sample type serum and plasma

cobas c 501 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10/10-46		
Wavelength (sub/main)	700/340 nm		
Reaction direction	Increase		
Units	mg/L		
Reagent pipetting		Diluent (H_2O)	
R1	120 µL	–	
R2	10 µL	20 µL	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	2.9 µL	3 µL	147 µL
Decreased	2.9 µL	3 µL	147 µL
Increased	2.9 µL	3 µL	147 µL

cobas c 502 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10/10-46		
Wavelength (sub/main)	700/340 nm		
Reaction direction	Increase		
Units	mg/L		
Reagent pipetting		Diluent (H_2O)	
R1	120 µL	–	
R2	10 µL	20 µL	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	2.9 µL	3 µL	147 µL
Decreased	2.9 µL	3 µL	147 µL
Increased	5.8 µL	3 µL	147 µL

Calibration

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

IGG-2

Tina-quant IgG CSF

	Multiply the lot-specific C.f.a.s. PUC calibrator value by the factors below to determine the standard calibration curve:
	S2: 0.0431 S5: 0.331
	S3: 0.0862 S6: 1.00
	S4: 0.166
Calibration mode	RCM
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 certified reference material in human serum of the IRMM (Institute for Reference Materials and Measurements) ERM-DA470k/IFCC.[5]

Quality control

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

In addition, other suitable control material can be used.

CSF	Precinorm PUC
	Precipath PUC
Serum, plasma	PreciControl ClinChem Multi 1
	PreciControl ClinChem Multi 2

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 CSF sample.

To calculate serum/plasma samples in g/L a calculated test must be programmed under Utility > Calculated Test on the **cobas c** 501 analyzer. Please use the following settings.

cobas c 501

Sample Type	Ser/Pl
Unit of Measure	g/L
Report Name	IgG Serum
Item	IGGS
Formula	IGG-C/1000

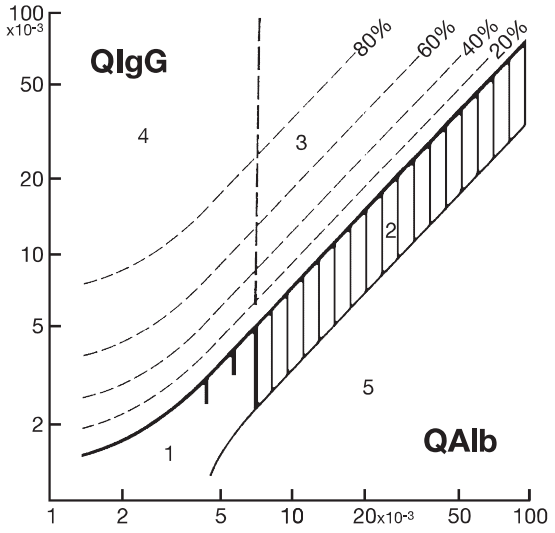
The values for serum/plasma in g/L will be automatically calculated after result output. It is recommended to report the IgG values in serum/plasma to 2 decimal places, which can be entered in the editable field "Expected Values".

For the definition of the calculated test on the **cobas c** 502 analyzer, refer to the operator's manual of the **cobas** 8000 Data Manager.

Reiber Quotient Graph

With the aid of commercially available software, Reiber Quotient Diagrams can be automatically generated.

The calculation employs a ratio diagram including hyperbolic functions as differential lines according to Reiber and Felgenhauer. Results from the determination of IgG and albumin in CSF and serum (IgG and albumin ratios)[6] are plotted.



1. Reference range. 2. Blood brain barrier functional disorder without local IgG synthesis. 3. Blood brain barrier functional disorder with concomitant IgG-synthesis in the CNS. 4. IgG synthesis in the CNS without blood brain barrier functional disorder. 5. As confirmed empirically, there are no values in this region (i.e. values here are due to errors introduced by blood sampling or analytical errors). Generally speaking, cases not associated with local IgG synthesis in the CNS lie below the bold line (hyperbolic function). The percentage values indicate what percentage of the total IgG in CSF (minimum) originates in the CNS relative to the statistically-defined 0 % differential lines.

Limitations - interference

Serum/plasma

Criterion: Recovery within ±10 % of initial value at an IgG concentration of 7.00 g/L.

Icterus:[7] 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:[7] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 621 µmol/L or 1000 mg/dL).

Lipemia (Intralipid):[7] No significant interference up to an L index of 2000 (approximate intralipid concentration: 2000 mg/dL). 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 1200 IU/mL.

High dose hook-effect: No false result occurs up to an IgG concentration of 400 g/L.

There is no cross-reaction between IgG and IgA or IgM under the assay conditions.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[8,9]

As with other turbidimetric or nephelometric procedures, this test may not provide accurate results in patients with monoclonal gammopathy, due to individual sample characteristics which can be assessed by electrophoresis.[10]

The assay was designed for the determination of IgG in serum/CSF or plasma/CSF pairs only. This assay shall not be used to determine IgG in serum or plasma alone, but always in combination with the matching CSF samples.

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

CSF

Criterion: Recovery within ± 10 % of initial value at an IgG concentration of 15.00 mg/L.

Icterus: No significant interference up to a conjugated bilirubin concentration of 257 µmol/L or 15 mg/dL.

IGG-2

Tina-quant IgG CSF

Hemolysis: No significant interference up to a hemoglobin concentration of 124 µmol/L or 200 mg/dL.

High dose hook-effect: No false result occurs up to an IgG concentration of 2500 mg/L.

There is no cross-reaction between IgG and IgA or IgM under the assay conditions.

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

CSF

4.00-200 mg/L

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:5 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 5.

Serum/plasma

3.00-50.0 g/L

Lower limits of measurement

Lower detection limit of the test

CSF

4.00 mg/L

Serum/plasma

0.30 g/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 the lowest standard (standard 1 + 3 SD, repeatability, n = 21).

Expected values

CSF[11]

10-30 mg/L

These values are only for orientation. The only relevant values are the CSF/serum ratios.

Serum/plasma

Adults[12]	7-16 g/L
Children/juveniles:[13]	
0 - 14 days:	3.20-12.1 g/L
15 days - <1 yr:	1.48-6.31 g/L
1 - <4 yr:	3.17-9.94 g/L
4 - <10 yr:	5.01-11.7 g/L
10 - <19 yr:	5.95-13.1 g/L

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

Specific performance data

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

Precision

CSF

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, one lot of reagent, 21 days).

Repeatability	*Mean*	*SD*	*CV*
	mg/L	mg/L	%
Precinorm PUC	18.8	0.3	1.6
Precipath PUC	150	2	1.1
CSF 1	7.62	0.25	3.3
CSF 2	95.0	0.5	0.5
Intermediate precision	*Mean*	*SD*	*CV*
	mg/L	mg/L	%
Precinorm PUC	20.1	0.5	2.5
Precipath PUC	160	2	1.0
CSF 3	21.9	0.5	2.1
CSF 4	137	1	1.1

Serum/plasma

Repeatability and intermediate precision were determined using human samples and controls in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP5 requirements (2 aliquots per run, 2 runs per day, 21 days). The following results were obtained:

Repeatability	*Mean*	*SD*	*CV*
	g/L	g/L	%
PreciControl CC[a)] Multi 1	8.07	0.14	1.7
PreciControl CC Multi 2	12.4	0.3	2.1
Human Serum 1	9.58	0.22	2.3
Human Serum 2	7.48	0.18	2.4
Human Serum 3	4.01	0.16	3.9
Human Serum 4	16.0	0.3	1.9
Human Serum 5	24.7	0.5	2.1
Human Serum 6	40.0	1.0	2.5

a) CC = ClinChem

Intermediate precision	*Mean*	*SD*	*CV*
	g/L	g/L	%
PreciControl CC Multi 1	8.07	0.17	2.2
PreciControl CC Multi 2	12.4	0.3	2.3
Human Serum 1	9.58	0.23	2.4
Human Serum 2	7.48	0.18	2.4
Human Serum 3	4.01	0.18	4.4
Human Serum 4	16.0	0.4	2.2
Human Serum 5	24.7	0.6	2.4
Human Serum 6	40.0	1.1	2.8

Method comparison

CSF

IgG values for human CSF 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) = 77

Passing/Bablok[14]	Linear regression
y = 1.007x - 2.17 mg/L	y = 0.997x - 1.70 mg/L
τ = 0.941	r = 1.000

The sample concentrations were between 10.7 and 186 mg/L.

Serum/plasma

IGG-2

Tina-quant IgG CSF

IgG values for human serum and plasma samples obtained on a **cobas c** 501 analyzer (y) were compared with those determined with IGG-2 Serum/plasma application (x).

Sample size (n) = 139

Passing/Bablok[14]	Linear regression
y = 0.982x + 0.601 g/L	y = 0.952x + 1.018 g/L
τ = 0.974	r = 0.997

The sample concentrations were between 3.12 and 49.8 g/L.

References

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2 Thomas L. Labor und Diagnose. 7. Auflage; TH-Books Verlagsgesellschaft mbH, Frankfurt/Main, 2007;1743-1784.

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7 Glick MR, Ryder KW, Jackson SA. Graphical Comparisons of Interferences in Clinical Chemistry Instrumentation. Clin Chem 1986;32:470-475.

8 Breuer J. Report on the Symposium "Drug effects in Clinical Chemistry Methods". Eur J Clin Chem Clin Biochem 1996;34:385-386.

9 Sonntag O, Scholer A. Drug interference in clinical chemistry: recommendation of drugs and their concentrations to be used in drug interference studies. Ann Clin Biochem 2001;38:376-385.

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11 Reiber H, Thompson EJ, Grimsley G, et al. Quality Assurance for Cerebrospinal Fluid Protein Analysis: International Consensus by an Internet-based Group Discussion. Clin Chem Lab Med 2003;41:331-337.

12 Dati F, Schumann G, Thomas L, et al. Consensus of a group of professional societies and diagnostic companies on guidelines for interim reference ranges for 14 proteins in serum based on the standardization against the IFCC/BCR/CAP reference material (CRM 470). Eur J Clin Chem Clin Biochem 1996;34:517-520.

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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.

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

IGG-2

cobas®

Tina-quant IgG Gen.2

Order information

REF	CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
03507432190	Tina-quant IgG Gen.2, 150 tests	System-ID 07 6787 5	**cobas c** 311, **cobas c** 501/502

Materials required (but not provided):

11355279160	Calibrator f.a.s. Proteins (5 x 1 mL)	Code 656	
03121305122	Calibrator f.a.s. Proteins, Urine/CSF (5 x 1 mL)	Code 489	
10557897160	Precinorm Protein (3 x 1 mL)	Code 302	
11333127160	Precipath Protein (3 x 1 mL)	Code 303	
03121313122	Precinorm PUC (4 x 3 mL)	Code 240	
03121291122	Precipath PUC (4 x 3 mL)	Code 241	
05947626160	PreciControl ClinChem Multi 1 (4 x 5 mL)	Code 391	
05947774160	PreciControl ClinChem Multi 2 (4 x 5 mL)	Code 392	
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:

IGG-2: ACN 674 (Standard application for serum and plasma)

IGGC2: ACN 673 (Sensitive application for cerebrospinal fluid)

For **cobas c** 502 analyzer:

IGG-2: ACN 8674 (Standard application for serum and plasma)

IGGC2: ACN 8673 (Sensitive application for cerebrospinal fluid)

Intended use

In vitro test for the quantitative determination of IgG in human serum, plasma and cerebrospinal fluid on Roche/Hitachi **cobas c** systems.

Summary[1,2,3,4,5,6,7]

IgG molecules are composed of 2 light chains (kappa or lambda) and 2 gamma heavy chains. Approximately 80 % of serum immunoglobulin is IgG; its main tasks are the defense against microorganisms, direct neutralization of toxins and induction of complement fixation. IgG is the only immunoglobulin that can cross the placental barrier and provide passive immune protection for the fetus and newborn. This maternal protection gradually declines until the infant's own immunological system starts to develop (at about six months of age). Near-adult levels in serum/plasma are reached at 18 months.

Polyclonal IgG increases in serum/plasma may be present in systemic lupus erythematosis, chronic liver diseases (infectious hepatitis and Laennec's cirrhosis), infectious diseases and cystic fibrosis. Monoclonal IgG increases in IgG-myeloma.

Decreased synthesis of IgG is found in congenital and acquired immunodeficiency diseases and selective IgG subclass deficiencies, such as Bruton type agammaglobulinemia. Decreased IgG concentrations in serum and plasma are seen in protein-losing enteropathies, nephrotic syndrome and through the skin from burns. Increased IgG metabolism is found in Wiskott-Aldrich syndrome, myotonic dystrophy and with anti-immunoglobulin antibodies.

The determination of IgG in cerebrospinal fluid (CSF) is used for evaluation of infections involving the central nervous system (CNS), neoplasms or primary neurologic diseases (in particular, multiple sclerosis). Increased CSF IgG concentrations may occur because of either increased permeability of the blood-brain barrier or local/intrathecal production of IgG, or both.

Malfunction of the blood-brain barrier can be reliably quantified by means of the albumin CSF/serum ratio. An elevated albumin ratio is an indication of a disorder of the blood-brain barrier. If IgG and albumin are measured in CSF and serum simultaneously, differentiation between IgG originating from blood and IgG originating from intrathecal production is possible.

The Roche IgG assay is based on the principle of immunological agglutination. In addition to the standard application (IGG-2), there is a sensitive application (IGGC2) designed for the quantitative determination of IgG in CSF.

It is known that the so-called paraproteins secreted in monoclonal gammopathies (monoclonal immunoglobulinemia) may differ from the respective immunoglobulins of polyclonal origin by amino acid composition and size. This may impair the binding to antibody and hence impair accurate quantitation.

Test principle

Immunoturbidimetric assay.

Anti-IgG antibodies react with antigen in the sample to form an antigen/antibody complex. Following agglutination, this is measured turbidimetrically. Addition of PEG allows the reaction to progress rapidly to the end point, increases sensitivity, and reduces the risk of samples containing excess antigen producing false negative results.

Reagents - working solutions

R1 TRIS buffer: 20 mmol/L, pH 8.0; NaCl: 200 mmol/L; polyethylene glycol: 3.6 %; preservative; stabilizers

R2 Anti-human IgG antibody (goat): dependent on titer; TRIS buffer: 20 mmol/L, pH 8.0; NaCl: 150 mmol/L; preservative

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.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Danger

H318	Causes serious eye damage.

Prevention:

P280	Wear eye protection/ face protection.

Response:

P305 + P351 + P338 + P310	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Immediately call a POISON CENTER/ doctor.

Product safety labeling follows EU GHS guidance.

IGG-2

Tina-quant IgG Gen.2

Contact phone: 1-800-428-2336

Reagent handling

Ready for use

Storage and stability

IGG-2

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

Diluent NaCl 9 %

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 application (IGG-2)

Serum.

Plasma: Li-heparin and K_2-EDTA plasma

CSF application (IGGC2)

Cerebrospinal fluid.

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.

Serum and plasma

Stability:[8]	4 months at 20-25 °C
	8 months at 4-8 °C
	8 months at -20 °C

CSF

Samples should be as fresh as possible. Centrifuge samples containing particles and/or cells before performing the assay.

Stability:[8]	1 day at 20-25 °C
	7 days at 4-8 °C
	Storage at -20 °C is not recommended.

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.

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 (IGG-2)

cobas c 311 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10 / 6-16		
Wavelength (sub/main)	700/340 nm		
Reaction direction	Increase		
Units	g/L (µmol/L, mg/dL)		
Reagent pipetting		Diluent (H_2O)	
R1	120 µL	–	
R2	38 µL	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	5 µL	9 µL	180 µL
Decreased	3.9 µL	2 µL	180 µL
Increased	9.4 µL	20 µL	85 µL

cobas c 501/502 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10 / 10-46		
Wavelength (sub/main)	700/340 nm		
Reaction direction	Increase		
Units	g/L (µmol/L, mg/dL)		
Reagent pipetting		Diluent (H_2O)	
R1	120 µL	–	
R2	38 µL	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	5 µL	9 µL	180 µL
Decreased	3.9 µL	2 µL	180 µL
Increased	9.4 µL	20 µL	85 µL

Application for CSF (IGGC2)

cobas c 311 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10 / 6-31		
Wavelength (sub/main)	700/340 nm		
Reaction direction	Increase		
Units	mg/L (nmol/L)		
Reagent pipetting		Diluent (H_2O)	
R1	120 µL	–	
R2	10 µL	20 µL	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	14.5 µL	–	–
Decreased	2.9 µL	–	–
Increased	14.5 µL	–	–

cobas c 501 **test definition**

Assay type	2-Point End

IGG-2

Tina-quant IgG Gen.2

Reaction time / Assay points	10 / 10-46	
Wavelength (sub/main)	700/340 nm	
Reaction direction	Increase	
Units	mg/L (nmol/L)	
Reagent pipetting		Diluent (H_2O)
R1	120 µL	–
R2	10 µL	20 µL

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	14.5 µL	–	–
Decreased	2.9 µL	–	–
Increased	14.5 µL	–	–

cobas c 502 **test definition**

Assay type	2-Point End	
Reaction time / Assay points	10 / 10-46	
Wavelength (sub/main)	700/340 nm	
Reaction direction	Increase	
Units	mg/L (nmol/L)	
Reagent pipetting		Diluent (H_2O)
R1	120 µL	–
R2	10 µL	20 µL

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	14.5 µL	–	–
Decreased	2.9 µL	–	–
Increased	29 µL	–	–

Calibration

Serum/plasma application (IGG-2)

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: 0.100	S5: 1.00
	S3: 0.250	S6: 3.14
	S4: 0.501	
Calibration mode	**cobas c** 311 analyzer: Spline **cobas c** 501/502 analyzers: RCM	
Calibration frequency	Full calibration	
	- after reagent lot change	
	- as required following quality control procedures	

CSF application (IGGC2)

Calibrators	S1: H_2O	
	S2-S6: C.f.a.s. PUC	
	Multiply the lot-specific C.f.a.s. PUC calibrator value by the factors below to determine the standard concentrations for the 6-point calibration curve:	
	S2: 0.0431	S5: 0.331
	S3: 0.0862	S6: 1.00
	S4: 0.166	
Calibration mode	RCM	
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 certified reference material in human serum of the IRMM (Institute for Reference Materials and Measurements) ERM-DA470k/IFCC.

Quality control

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

IGG-2: Precinorm Protein, Precipath Protein, PreciControl ClinChem Multi 1, PreciControl ClinChem Multi 2

IGGC2: Precinorm PUC, Precipath PUC

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/dL x 0.01 = g/L	g/L x 6.67 = µmol/L
	g/L x 100 = mg/dL	µmol/L x 0.15 = g/L
	mg/L x 6.67 = nmol/L	nmol/L x 0.15 = mg/L

Limitations - interference

Serum/plasma application (IGG-2):

Criterion: Recovery within ± 10 % of initial value at an IgG concentration of 7.00 g/L (46.7 µmol/L, 700 mg/dL).

Icterus:[9] 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:[9] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 621 µmol/L or 1000 mg/dL).

Lipemia (Intralipid):[9] No significant interference up to an L index of 2000 (approximate Intralipid concentration: 2000 mg/dL). 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 1200 IU/mL.

High dose hook-effect: No false result up to an IgG concentration of 400 g/L (2668 µmol/L, 40000 mg/dL) occurs due to an antigen excess within polyclonal specimens.

There is no cross-reaction between IgG and IgA or IgM under the assay conditions.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[10,11]

As with other turbidimetric or nephelometric procedures, this test may not provide accurate results in patients with monoclonal gammopathy, due to individual sample characteristics which can be assessed by electrophoresis.[12]

CSF application (IGGC2):

Criterion: Recovery within ± 10 % of initial value at an IgG concentration of 15.00 mg/L (100 nmol/L).

IGG-2

Tina-quant IgG Gen.2

Icterus: No significant interference up to a conjugated bilirubin concentration of 257 µmol/L or 15 mg/dL.

Hemolysis: No significant interference up to a hemoglobin concentration of 124 µmol/L or 200 mg/dL.

High dose hook-effect: No false result up to an IgG concentration of 2500 mg/L (16675 nmol/L) occurs due to an antigen excess within polyclonal specimens.

There is no cross-reaction between IgG and IgA or IgM under the assay conditions.

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

Serum/plasma application (IGG-2):

3.00-50.0 g/L (20.0-334 µmol/L, 300-5000 mg/dL)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:5.5 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 5.5.

Determine samples having lower concentrations via the rerun function. For samples with lower concentrations, the rerun function increases the sample volume by a factor of 7.5. The results are automatically divided by this factor.

CSF application (IGGC2):

4.00-200 mg/L (26.7-1334 nmol/L)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:5 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 5.

Lower limits of measurement

Lower detection limit of the test

Serum/plasma application (IGG-2):

0.30 g/L (2.00 µmol/L, 30 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).

CSF application (IGGC2):

4.00 mg/L (26.7 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 the lowest standard (standard 1 + 3 SD, repeatability, n = 21).

Expected values

Serum/plasma

Adults[13]	7-16 g/L	46.7-107 µmol/L	700-1600 mg/dL

CSF[14]

10-30 mg/L (66.7-200 nmol/L)

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

Specific performance data

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

Precision

Serum/plasma and *CSF:*

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:

Serum/plasma application (IGG-2):			
Repeatability	*Mean g/L (µmol/L, mg/dL)*	*SD g/L (µmol/L, mg/dL)*	*CV %*
Precinorm Protein	8.25 (55.0, 825)	0.08 (0.5, 8)	1.0
Precipath Protein	14.2 (94.7, 1420)	0.2 (1.3, 20)	1.2
Human serum 1	8.44 (56.3, 844)	0.05 (0.3, 5)	0.6
Human serum 2	21.5 (143, 2150)	0.3 (2, 30)	1.5

Serum/plasma application (IGG-2):			
Intermediate precision	*Mean g/L (µmol/L, mg/dL)*	*SD g/L (µmol/L, mg/dL)*	*CV %*
Precinorm Protein	8.19 (54.6, 819)	0.12 (0.8, 12)	1.5
Precipath Protein	14.2 (94.7, 1420)	0.2 (1.3, 20)	1.5
Human serum 3	7.11 (47.4, 711)	0.08 (0.5, 8)	1.1
Human serum 4	21.1 (140, 2110)	0.4 (3, 40)	1.7

CSF application (IGGC2):			
Repeatability	*Mean mg/L (nmol/L)*	*SD mg/L (nmol/L)*	*CV %*
Precinorm PUC	18.8 (125)	0.3 (2)	1.6
Precipath PUC	150 (1001)	2 (13)	1.1
CSF 1	7.62 (50.7)	0.25 (1.7)	3.3
CSF 2	95.0 (634)	0.5 (3)	0.5

CSF application (IGGC2):			
Intermediate precision	*Mean mg/L (nmol/L)*	*SD mg/L (nmol/L)*	*CV %*
Precinorm PUC	20.1 (134)	0.5 (3)	2.5
Precipath PUC	160 (1067)	2 (13)	1.0
CSF 3	21.9 (146)	0.5 (3)	2.1
CSF 4	137 (914)	1 (7)	1.1

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

Method comparison

Serum/plasma application (IGG-2):

IgG 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) = 103

Passing/Bablok[15]	Linear regression
y = 0.981x + 0.256 g/L	y = 0.990x + 0.229 g/L
τ = 0.957	r = 0.995

The sample concentrations were between 3.16 and 48.2 g/L (21.1 and 321 µmol/L, 316 and 4820 mg/dL).

CSF application (IGGC2):

IgG values for human CSF 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) = 77

IGG-2

Tina-quant IgG Gen.2

Passing/Bablok[15]	Linear regression
y = 1.007x - 2.17 mg/L	y = 0.997x - 1.70 mg/L
r = 0.941	r = 1.000

The sample concentrations were between 10.7 and 186 mg/L (71.4 and 1241 nmol/L).

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

References

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3 Tietz NW, ed. Clinical Guide to Laboratory Tests, 4th ed. Philadelphia. WB Saunders Co 2006;604-606.

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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.

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.

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.

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

IGG-2

cobas®

Tina-quant IgG Gen.2

Order information

REF	CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
05220718190	Tina-quant IgG Gen.2 (500 tests)	System-ID 03 6787 5	**cobas c** 701/702

Materials required (but not provided):

11355279160	Calibrator f.a.s. Proteins (5 x 1 mL)	Code 656	
03121305122	Calibrator f.a.s. PUC (5 x 1 mL)	Code 489	
10557897160	Precinorm Protein (3 x 1 mL)	Code 302	
11333127160	Precipath Protein (3 x 1 mL)	Code 303	
03121313122	Precinorm PUC (4 x 3 mL)	Code 240	
03121291122	Precipath PUC (4 x 3 mL)	Code 241	
05947626160	PreciControl ClinChem Multi 1 (4 x 5 mL)	Code 391	
05947774160	PreciControl ClinChem Multi 2 (4 x 5 mL)	Code 392	
05172152190	Diluent NaCl 9 % (119 mL)	System-ID 08 6869 3	

English

For use in the USA only

System information

IGG-2: ACN 8674 (Standard application for serum and plasma)

IGGC2: ACN 8673 (Sensitive application for cerebrospinal fluid)

Intended use

In vitro test for the quantitative determination of IgG in human serum, plasma, and cerebrospinal fluid on Roche/Hitachi **cobas c** systems.

Summary[1,2,3,4,5,6,7]

IgG molecules are composed of 2 light chains (kappa or lambda) and 2 gamma heavy chains. Approximately 80 % of serum immunoglobulin is IgG; its main tasks are the defense against microorganisms, direct neutralization of toxins and induction of complement fixation. IgG is the only immunoglobulin that can cross the placental barrier and provide passive immune protection for the fetus and newborn. This maternal protection gradually declines until the infant's own immunological system starts to develop (at about six months of age). Near-adult levels in serum/plasma are reached at 18 months.

Polyclonal IgG increases may be present in systemic lupus erythematosis, chronic liver diseases (infectious hepatitis and Laennec's cirrhosis), infectious diseases and cystic fibrosis. Monoclonal IgG increases in IgG-myeloma.

Decreased synthesis of IgG is found in congenital and acquired immunodeficiency diseases and selective IgG subclass deficiencies, such as Bruton type agammaglobulinemia. Decreased IgG concentrations in serum and plasma are seen in protein-losing enteropathies, nephrotic syndrome and through the skin from burns. Increased IgG metabolism is found in Wiskott-Aldrich syndrome, myotonic dystrophy and with anti-immunoglobulin antibodies.

The determination of IgG in cerebrospinal fluid (CSF) is used for evaluation of infections involving the central nervous system (CNS), neoplasms or primary neurologic diseases (in particular, multiple sclerosis). Increased CSF IgG concentrations may occur because of either increased permeability of the blood-brain barrier or local/intrathecal production of IgG, or both.

Malfunction of the blood-brain barrier can be reliably quantified by means of the albumin CSF/serum ratio. An elevated albumin ratio is an indication of a disorder of the blood-brain barrier. If IgG and albumin are measured in CSF and serum simultaneously, differentiation between IgG originating from blood and IgG originating from intrathecal production is possible.

The Roche IgG assay is based on the principle of immunological agglutination. In addition to the standard application (IGG-2), there is a sensitive application (IGGC2) designed for the quantitative determination of IgG in CSF.

It is known that the so-called paraproteins secreted in monoclonal gammopathies (monoclonal immunoglobulinemia) may differ from the respective immunoglobulins of polyclonal origin by amino acid composition and size. This may impair the binding to antibody and hence impair accurate quantitation.

Test principle

Immunoturbidimetric assay.

Anti-IgG antibodies react with antigen in the sample to form an antigen/antibody complex. Following agglutination, this is measured turbidimetrically. Addition of PEG allows the reaction to progress rapidly to the end point, increases sensitivity, and reduces the risk of samples containing excess antigen producing false negative results.

Reagents - working solutions

R1 TRIS buffer: 20 mmol/L, pH 8.0; NaCl: 200 mmol/L; polyethylene glycol: 3.6 %; preservative; stabilizers

R3 Anti-human IgG antibody (goat): dependent on titer; TRIS buffer: 20 mmol/L, pH 8.0; NaCl: 150 mmol/L; preservative

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.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Danger

H318 Causes serious eye damage.

Prevention:

P280 Wear eye protection/ face protection.

Response:

P305 + P351 + P338 + P310 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Immediately call a POISON CENTER/ doctor.

Product safety labeling follows EU GHS guidance.

Contact phone: 1-800-428-2336

Reagent handling

Ready for use

IGG-2

Tina-quant IgG Gen.2

cobas®

Storage and stability

IGG-2

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label.
On-board in use and refrigerated on the analyzer:	4 weeks
On-board on the Reagent Manager:	24 hours

Diluent NaCl 9 %

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label.
On-board in use and refrigerated on the analyzer:	4 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 application (IGG-2)

Serum.

Plasma: Li-heparin and K_2-EDTA plasma

CSF application (IGGC2)

Cerebrospinal fluid.

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.

Serum/plasma

Stability:[8] 4 months at 20-25 °C
8 months at 4-8 °C
8 months at -20 °C

CSF

Samples should be as fresh as possible. Centrifuge samples containing particles and/or cells before performing the assay.

Stability:[8] 1 day at 20-25 °C
7 days at 4-8 °C
Storage at -20 °C is not recommended.

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.

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 (IGG-2)

cobas c 701/702 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10 / 18-27		
Wavelength (sub/main)	700/340 nm		
Reaction direction	Increase		
Units	g/L (µmol/L, mg/dL)		
Reagent pipetting		Diluent (H_2O)	
R1	120 µL	–	
R3	38 µL	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	5 µL	9 µL	180 µL
Decreased	3.9 µL	2 µL	180 µL
Increased	9.4 µL	20 µL	85 µL

Application for CSF (IGGC2)

cobas c 701/702 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10 / 18-27		
Wavelength (sub/main)	700/340 nm		
Reaction direction	Increase		
Units	mg/L (nmol/L)		
Reagent pipetting		Diluent (H_2O)	
R1	120 µL	–	
R3	10 µL	20 µL	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	14.5 µL	–	–
Decreased	2.9 µL	–	–
Increased	29 µL	–	–

Calibration

Serum/plasma application (IGG-2):

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: 0.100 S5: 1.00
	S3: 0.250 S6: 3.14
	S4: 0.501
Calibration mode	RCM
Calibration frequency	Full calibration
	- after reagent lot change
	- as required following quality control procedures

CSF application (IGGC2):

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

	Multiply the lot-specific C.f.a.s. PUC calibrator value by the factors below to determine the standard concentrations for the 6-point calibration curve:	
	S2: 0.0431	S5: 0.331
	S3: 0.0862	S6: 1.00
	S4: 0.166	
Calibration mode	RCM	
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).[9]

Quality control

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

IGG-2: Precinorm Protein, Precipath Protein, PreciControl ClinChem Multi 1, PreciControl ClinChem Multi 2

IGGC2: Precinorm PUC, Precipath PUC

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/dL x 0.01 = g/L	g/L x 6.67 = µmol/L
	g/L x 100 = mg/dL	µmol/L x 0.15 = g/L
	mg/L x 6.67 = nmol/L	nmol/L x 0.15 = mg/L

Limitations - interference

Serum/plasma application (IGG-2):

Criterion: Recovery within ± 10 % of initial value at an IgG concentration of 7.00 g/L (46.7 µmol/L, 700 mg/dL).

Icterus:[10] 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:[10] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 621 µmol/L or 1000 mg/dL).

Lipemia (Intralipid):[10] No significant interference up to an L index of 2000 (approximate Intralipid concentration: 2000 mg/dL). 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 1200 IU/mL.

High dose hook-effect: No false result up to an IgG concentration of 400 g/L (2668 µmol/L, 40000 mg/dL) occurs due to an antigen excess within polyclonal specimens.

There is no cross-reaction between IgG and IgA or IgM under the assay conditions.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[11,12]

As with other turbidimetric or nephelometric procedures, this test may not provide accurate results in patients with monoclonal gammopathy, due to individual sample characteristics which can be assessed by electrophoresis.[13]

CSF application (IGGC2):

Criterion: Recovery within ± 10 % of initial value at an IgG concentration of 15.00 mg/L (100 nmol/L).

Icterus: No significant interference up to a conjugated bilirubin concentration of 257 µmol/L or 15 mg/dL.

Hemolysis: No significant interference up to a hemoglobin concentration of 124 µmol/L or 200 mg/dL.

High dose hook-effect: No false result up to an IgG concentration of 2500 mg/L (16675 nmol/L) occurs due to an antigen excess within polyclonal specimens.

There is no cross-reaction between IgG and IgA or IgM under the assay conditions.

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

Serum/plasma application (IGG-2):

3.00-50.0 g/L (20.0-334 µmol/L, 300-5000 mg/dL)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:5.5 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 5.5.

Determine samples having lower concentrations via the rerun function. For samples with lower concentrations, the rerun function increases the sample volume by a factor of 7.5. The results are automatically divided by this factor.

CSF application (IGGC2):

4.00-200 mg/L (26.7-1334 nmol/L)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:5 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 5.

Lower limits of measurement

Lower detection limit of the test

Serum/plasma application (IGG-2):

0.30 g/L (2.00 µmol/L, 30 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 (< 0.30 g/L) will not be flagged by the instrument.

CSF application (IGGC2):

4.00 mg/L (26.7 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 the lowest standard (standard 1 + 3 SD, repeatability, n = 21).

Values below the lower detection limit (< 4.00 mg/L) will not be flagged by the instrument.

Expected values

Serum/plasma

IGG-2

Tina-quant IgG Gen.2

cobas®

Adults[14]	7-16 g/L	46.7-107 µmol/L	700-1600 mg/dL

CSF [15]

10-30 mg/L (66.7-200 nmol/L, 0.010-0.030 g/L)

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

Specific performance data

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

Precision

Serum/plasma and CSF:

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:

Serum/plasma application (IGG-2)

Repeatability	*Mean* *g/L* *(µmol/L, mg/dL)*	*SD* *g/L* *(µmol/L, mg/dL)*	*CV* *%*
Precinorm Protein	9.33 (62.3, 933)	0.04 (0.3, 4)	0.4
Precipath Protein	14.9 (99.5, 1492)	0.1 (0.6, 9)	0.6
Human serum A	37.4 (249, 3740)	0.5 (3, 50)	1.2
Human serum B	12.5 (83.4, 1250)	0.1 (0.7, 10)	0.9
Human serum C	3.40 (22.7, 340)	0.03 (0.2, 3)	0.8

Intermediate precision	*Mean* *g/L* *(µmol/L, mg/dL)*	*SD* *g/L* *(µmol/L, mg/dL)*	*CV* *%*
Precinorm Protein	8.19 (54.6, 819)	0.12 (0.8, 12)	1.5
Precipath Protein	14.2 (94.7, 1420)	0.2 (1.3, 20)	1.5
Human serum 3	7.11 (47.4, 711)	0.08 (0.5, 8)	1.1
Human serum 4	21.1 (140, 2110)	0.4 (3, 40)	1.7

CSF application (IGGC2)

Repeatability	*Mean* *mg/L* *(nmol/L)*	*SD* *mg/L* *(nmol/L)*	*CV* *%*
Precinorm PUC	19.5 (130)	0.4 (3)	2.0
Precipath PUC	137 (914)	1 (7)	0.8
CSF A	14.8 (98.7)	0.3 (2)	2.1
CSF B	126 (840)	1 (7)	0.9
CSF C	179 (1194)	2 (13)	1.4

Intermediate precision	*Mean* *mg/L* *(nmol/L)*	*SD* *mg/L* *(nmol/L)*	*CV* *%*
Precinorm PUC	20.1 (134)	0.5 (3)	2.5
Precipath PUC	160 (1067)	2 (13)	1.0
CSF 3	21.9 (146)	0.5 (3)	2.1
CSF 4	137 (914)	1 (7)	1.1

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

Method comparison

Serum/plasma application (IGG-2):

IgG 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) = 183

Passing/Bablok[16]	Linear regression
y = 1.035x - 0.024 g/L	y = 1.004x + 0.29 g/L
τ = 0.9796	r = 0.997

The sample concentrations were between 3.30 and 47.1 g/L (22.0 and 314 µmol/L, 330 and 4710 mg/dL).

CSF application (IGGC2):

IgG values for human CSF 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) = 81

Passing/Bablok[16]	Linear regression
y = 0.994x - 1.40 mg/L	y = 0.973x - 0.403 mg/L
τ = 0.965	r = 0.999

The sample concentrations were between 4.97 and 197 mg/L (33.1 and 1314 nmol/L).

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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.

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):

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