Performance Characteristics
artus® CT/NG QS-RGQ Kit

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Version management

This document is the *artus* CT/NG QS-RGQ Kit Application Sheet for urine, Version 1, R3.

Check availability of new electronic labeling revisions at www.qiagen.com/products/artusctngqsrgqkitce.aspx before test execution. The current revision status is indicated by the issue date (format: month/year).

Limit of detection

The limit of detection (LOD) in consideration of the purification was assessed for the *artus* CT/NG QS-RGQ Kit using CT/NG-positive specimens in combination with the extraction on the QIAsymphony® SP.

For swabs in eNAT™ transport medium (Copan, Italy), the limit of detection in consideration of the purification of the *artus* CT/NG QS-RGQ Kit was determined using a dilution series of *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) cells (DSMZ) from 14.5 to nominal 0.0145 EB/ml (CT) and 35.3 to nominal 0.0112 cfu/ml (NG) spiked in eNAT medium. These were subjected to DNA extraction using the QIAsymphony DSP Virus/Pathogen Midi Kit in combination with the Complex400_DSP protocol (extraction volume: 400 µl, elution volume: 60 µl). Each of the 9 (10 for NG) dilutions was analyzed with the *artus* CT/NG QS-RGQ Kit on 4 different days in 4 runs with 9 replicates each. The results were determined by a probit analysis. The limit of detection in consideration of the purification of the *artus* CT/NG QS-RGQ Kit in combination with the Rotor-Gene® Q MDx 5plex HRM instrument is 5 EB/ml (p = 0.05) for *C. trachomatis* and 3 cfu/ml (p = 0.05) for *N. gonorrhoeae*. This means that there is a 95% probability that 5 EB/ml and 3 cfu/ml will be detected, respectively.

Specificity - swabs

The specificity of the *artus* CT/NG QS-RGQ Kit is first and foremost ensured by the selection of the primers and probes, as well as the selection of stringent reaction conditions. The primers and probes were checked for possible homologies to all sequences published in public sequence databases by sequence comparison analysis. The detectability of all relevant genotypes has thus been ensured by a database alignment and by a PCR run on Rotor-Gene Q MDx 5plex HRM instruments with the following strains/serovars (Table 1).

Table 1. Testing the specificity for relevant strains

ATCC* number	Name	CT (Cycling Green)	NG (Cycling Orange	Internal control (Cycling Yellow)
VR-1477	*Chlamydia trachomatis*	+	–	+
VR-346	*Chlamydia trachomatis* trachoma type F	+	–	+
VR-348B	*Chlamydia trachomatis* trachoma type E	+	–	+
VR-886	*Chlamydia trachomatis*	+	–	+
VR-902B	*Chlamydia trachomatis*	+	–	+
VR-1500	*Chlamydia trachomatis*	+	–	+
VR-901B	*Chlamydia trachomatis* LGV	+	–	+
VR-577	*Chlamydia trachomatis* LGV II	+	–	+
VR-903	*Chlamydia trachomatis* LGV III	+	–	+
VR-571B	*Chlamydia trachomatis* trachoma serotype a	+	–	+
VR-573	*Chlamydia trachomatis* trachoma serotype b	+	–	+
VR-347	*Chlamydia trachomatis* trachoma serotype ba	+	–	+
VR-878	*Chlamydia trachomatis* trachoma serotype g	+	–	+
VR-879	*Chlamydia trachomatis* trachoma serotype h	+	–	+
VR-880	*Chlamydia trachomatis* trachoma serotype i	+	–	+
VR-887	*Chlamydia trachomatis* trachoma serotype k	+	–	+
VR-885	*Chlamydia trachomatis* trachoma serotype d	+	–	+
53420	*Neisseria gonorrhoeae*	–	+	+
53421	*Neisseria gonorrhoeae*	–	+	+
53422	*Neisseria gonorrhoeae*	–	+	+
53423	*Neisseria gonorrhoeae*	–	+	+
53424	*Neisseria gonorrhoeae*	–	+	+
53425	*Neisseria gonorrhoeae*	–	+	+
700717	*Neisseria gonorrhoeae*	–	+	+
700718	*Neisseria gonorrhoeae*	–	+	+
700719	*Neisseria gonorrhoeae*	–	+	+
700825	*Neisseria gonorrhoeae*	–	+	+
BAA-1833	*Neisseria gonorrhoeae*	–	+	+
BAA-1838	*Neisseria gonorrhoeae*	–	+	+
BAA-1839	*Neisseria gonorrhoeae*	–	+	+
BAA-1840	*Neisseria gonorrhoeae*	–	+	+

* American Type Culture Collection.

Table continued on next page

Table 1. Continued

ATCC* number	Name	CT (Cycling Green)	NG (Cycling Orange	Internal control (Cycling Yellow)
BAA-1841	*Neisseria gonorrhoeae*	–	+	+
9793	*Neisseria gonorrhoeae*	–	+	+
9826	*Neisseria gonorrhoeae*	–	+	+
9827	*Neisseria gonorrhoeae*	–	+	+
9828	*Neisseria gonorrhoeae*	–	+	+
9830	*Neisseria gonorrhoeae*	–	+	+
10150	*Neisseria gonorrhoeae*	–	+	+
10874	*Neisseria gonorrhoeae*	–	+	+
11688	*Neisseria gonorrhoeae*	–	+	+
11689	*Neisseria gonorrhoeae*	–	+	+
19088	*Neisseria gonorrhoeae*	–	+	+
19424	*Neisseria gonorrhoeae*	–	+	+
19999	*Neisseria gonorrhoeae*	–	+	+
21823	*Neisseria gonorrhoeae*	–	+	+
23050	*Neisseria gonorrhoeae*	–	+	+
31356	*Neisseria gonorrhoeae*	–	+	+
31397	*Neisseria gonorrhoeae*	–	+	+
31398	*Neisseria gonorrhoeae*	–	+	+
31399	*Neisseria gonorrhoeae*	–	+	+
31400	*Neisseria gonorrhoeae*	–	+	+
31401	*Neisseria gonorrhoeae*	–	+	+
31402	*Neisseria gonorrhoeae*	–	+	+
31403	*Neisseria gonorrhoeae*	–	+	+
31404	*Neisseria gonorrhoeae*	–	+	+
31405	*Neisseria gonorrhoeae*	–	+	+
31406	*Neisseria gonorrhoeae*	–	+	+
31407	*Neisseria gonorrhoeae*	–	+	+
31426	*Neisseria gonorrhoeae*	–	+	+
43069	*Neisseria gonorrhoeae*	–	+	+
49226	*Neisseria gonorrhoeae*	–	+	+
49498	*Neisseria gonorrhoeae*	–	+	+
49981	*Neisseria gonorrhoeae*	–	+	+
51109	*Neisseria gonorrhoeae*	–	+	+

* American Type Culture Collection.

Moreover, the specificity was validated with 30 different CT/NG-negative clinical swab samples. None of these samples generated a signal with the CT/NG specific primers and probes, which are included in the CT/NG RG Master.

A potential cross-reactivity of the *artus* CT/NG QS-RGQ Kit was tested using the control group listed in Table 2. None of the tested pathogens was reactive.

Table 2. Testing the specificity of the kit with potentially cross-reactive pathogens

ATCC* number	Name	CT (Cycling Green)	NG (Cycling Orange	Internal control (Cycling Yellow)
14987	*Acinetobacter calcoaceticus*	–	–	+
17925	*Acinetobacter lwoffii*	–	–	+
10048	*Actinomyces israelii*	–	–	+
7965	*Aeromonas hydrophila*	–	–	+
8750	*Alcaligenes faecalis*	–	–	+
6051	*Bacillus subtilis*	–	–	+
753	*Candida albicans*	–	–	+
2001	*Candida glabrata*	–	–	+
750	*Candida tropicalis*	–	–	+
VR-1310	*Chlamydia pneumoniae*	–	–	+
8090	*Citrobacter freundii*	–	–	+
2344	*Cryptococcus neoformans*	–	–	+
VR-538	Cytomegalovirus	–	–	+
13047	*Enterobacter cloacae*	–	–	+
19433	*Enterococcus faecalis*	–	–	+
19434	*Enterococcus faecium*	–	–	+
11775	*Escherichia coli*	–	–	+
14018	*Gardnerella vaginalis*	–	–	+
10379	*Gemella haemolysans*	–	–	+
33940	*Haemophilis ducreyi*	–	–	+
9006	*Haemophilus influenzae*	–	–	+
VR-260	Herpes simplex virus 1	–	–	+
VR-540	Herpes simplex virus 2	–	–	+
45113	HPV type 16	–	–	+
45152	HPV type 18	–	–	+
23330	*Kingella kingae*	–	–	+
4356	*Lactobacillus acidophilus*	–	–	+
14869	*Lactobacillus brevis*	–	–	+
25258	*Lactobacillus jensenii*	–	–	+
10973	*Moraxella osloensis*	–	–	+
23114	*Mycoplasma hominis*	–	–	+
14685	*Neisseria cinerea*	–	–	+
25295	*Neisseria elongata* subsp. elongata	–	–	+
29315	*Neisseria elongata* subsp. glycolytica	–	–	+
49377	*Neisseria elongata* subsp. nitroreducens	–	–	+
14221	*Neisseria flava*	–	–	+
13120	*Neisseria flavescens*	–	–	+
23970	*Neisseria lactamica*	–	–	+
23971	*Neisseria lactamica*	–	–	+
23972	*Neisseria lactamica*	–	–	+

* American Type Culture Collection.

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Table 2. Continued

ATCC* number	Name	CT (Cycling Green)	NG (Cycling Orange	Internal control (Cycling Yellow)
49142	*Neisseria lactamica*	–	–	+
13077	*Neisseria meningitidis*	–	–	+
13102	*Neisseria meningitidis*	–	–	+
13113	*Neisseria meningitidis*	–	–	+
35558	*Neisseria meningitidis*	–	–	+
35560	*Neisseria meningitidis*	–	–	+
35561	*Neisseria meningitidis*	–	–	+
35562	*Neisseria meningitidis*	–	–	+
43744	*Neisseria meningitidis*	–	–	+
43828	*Neisseria meningitidis*	–	–	+
53415	*Neisseria meningitidis*	–	–	+
17937	*Neisseria meningitidis* L-Phase Variant	–	–	+
10555	*Neisseria perflava*	–	–	+
43768	*Neisseria polysaccharea*	–	–	+
9913	*Neisseria sicca*	–	–	+
29193	*Neisseria sicca*	–	–	+
29256	*Neisseria sicca*	–	–	+
29259	*Neisseria sicca*	–	–	+
49275	*Neisseria subflava*	–	–	+
27337	*Peptostreptococcus anaerobius*	–	–	+
6919	*Propionibacterium acnes*	–	–	+
29906	*Proteus mirabilis*	–	–	+
29914	*Providencia stuartii*	–	–	+
10145	*Pseudomonas aeruginosa*	–	–	+
14028	*Salmonella typhimurium*	–	–	+
6538	*Staphylococcus aureus*	–	–	+
12228	*Staphylococcus epidermidis*	–	–	+
13813	*Streptococcus agalactiae*	–	–	+
49456	*Streptococcus mitis*	–	–	+
25175	*Streptococcus mutans*	–	–	+
49619	*Streptococcus pneumoniae*	–	–	+
23345	*Streptomyces griseus*	–	–	+
30001	*Trichomonas vaginalis*	–	–	+
27618	*Ureaplasma urealyticum*	–	–	+
17802	*Vibrio parahaemolyticus*	–	–	+
9610	*Yersinia enterocolitica*	–	–	+

* American Type Culture Collection.

Robustness - swabs

The verification of the robustness allows the determination of the total failure rate of the *artus* CT/NG QS-RGQ Kit. To verify the robustness, 30 CT/NG-negative swab samples were spiked with 15 EB/ml of *C. trachomatis* and 8 cfu/ml of

N. gonorrhoeae material (approximately threefold concentration of the limit of detection). After DNA extraction using the QIAsymphony DSP Virus/Pathogen Midi Kit in combination with the Complex400_DSP protocol (extraction volume: 400 ml, elution volume: 60 µl), these samples were analyzed with the *artus* CT/NG QS-RGQ Kit. In addition, the robustness of the internal control was assessed by purification and analysis of the 30 spiked swab samples. Inhibitions were not observed. Thus, the robustness of the *artus* CT/NG QS RGQ Kit is ≥99%.

Limit of detection - urine, 400 µl

For urine, the limit of detection (LOD) in consideration of the purification of the *artus* CT/NG QS-RGQ Kit was determined using a dilution series of CT and NG cells (DSMZ) from 45.8 to nominal 0.0458 EB/ml (CT) and 11.2 to nominal 0.0112 cfu/ml spiked in urine samples containing eNAT as stabilization reagent (1 part eNAT to 2 parts of urine simulating a urine sample in an eNAT tube containing 2 ml of eNAT, Copan, cat. no. 606C). These samples were subjected to DNA extraction using the QIAsymphony DSP Virus/Pathogen Midi Kit in combination with the Complex400_DSP protocol (extraction volume: 400 µl, elution volume: 60 µl). Each of the 9 dilutions was analyzed with the *artus* CT/NG QS-RGQ Kit on 4 different days in 4 runs for CT and 6 runs for NG with 9 replicates each. The results were determined by a probit analysis. The limit of detection in consideration of the purification of the *artus* CT/NG QS-RGQ Kit in combination with the Rotor-Gene Q MDx 5plex HRM instrument is 7.65 EB/ml (p = 0.05) for *C. trachomatis* and 10.32 cfu/ml (p = 0.05) for *N. gonorrhoeae*. This means that there is a 95% probability that 7.65 EB/ml and 10.32 cfu/ml will be detected, respectively.

Specificity - urine, 400 µl

The specificity of the *artus* CT/NG QS-RGQ Kit is first and foremost ensured by the selection of the primers and probes, as well as the selection of stringent reaction conditions. The primers and probes were checked for possible homologies to all sequences published in public sequence databases by sequence comparison analysis. The detectability of all relevant genotypes has thus been ensured by a database alignment and by a PCR run on Rotor-Gene Q MDx 5plex HRM instruments with the strains/serovars shown in Table 1 (beginning on page 2).

Moreover, the specificity was validated with more than 100 CT/NG-negative urine samples. None of these samples generated a signal with the CT/NG specific primers and probes, which are included in the CT/NG RG Master.

A potential cross-reactivity of the *artus* CT/NG QS-RGQ Kit was tested using the control group listed in Table 2 (beginning on page 4). None of the tested pathogens was reactive.

Robustness - urine, 400 µl

The verification of the robustness allows the determination of the total failure rate of the *artus* CT/NG QS-RGQ Kit. To verify the robustness, 100 CT/NG-negative urine samples were spiked with 23 EB/ml of *C. trachomatis* and 20 cfu/ml of *N. gonorrhoeae* material (approximately threefold concentration of the limit of detection). After DNA extraction using the QIAsymphony DSP Virus/Pathogen Midi Kit in combination with the Complex400_DSP protocol (extraction volume: 400 µl, elution volume: 60 µl), these samples were analyzed with the *artus* CT/NG QS-RGQ Kit. In addition, the robustness of the internal control was assessed by purification and analysis of the 100 spiked urine samples. Inhibitions were not observed. Thus, the robustness of the *artus* CT/NG QS-RGQ Kit is ≥99%.

Precision

The precision data of the *artus* CT/NG QS-RGQ Kit allows determination of the total variance of the assay. The total variance consists of the intra-assay variability (variability of multiple results of samples of the same concentration within one experiment), the inter-assay variability (variability of multiple results of the assay generated on different instruments of the same type by different operators within one laboratory), and the inter-batch variability (variability of multiple results of the assay using various batches). The data obtained were used to determine the standard deviation (SD), the variance, and the coefficient of variation (CV) for the pathogen-specific and the internal-control PCR.

Analytical precision data of the *artus* CT/NG QS-RGQ Kit were collected using the samples and concentrations shown in Tables 3 and 4. Testing was performed with 9 replicates. The precision data were calculated on basis of the C_T values of the amplification curves (C_T: threshold cycle, see Table 5). Based on these results, the overall statistical spread of any given sample with the mentioned concentration is shown in Tables 5–7. These values are based on the totality of all single values of the determined variability.

Table 3. *C. trachomatis* samples and concentrations used for precision experiments

Matrix	Concentration
Urine and eNAT	0.316 EB/ml
eNAT	0.100 EB/ml

Table 4. *N. gonorrhoeae* samples and concentrations used for precision experiments

Matrix	Concentration
Urine and eNAT	10 cfu/ml
eNAT	10 cfu/ml

Table 5. *C. trachomatis* total variance and statistical spread for both sample types

Matrix	Concentration (EB/ml)	Variance	CV (%)
Urine and eNAT	0.316	0.42	1.90
eNAT	0.1	0.79	2.51

Table 6. *N. gonorrhoeae* total variance and statistical spread for both sample types

Matrix	Concentration (cfu/ml)	Variance	CV (%)
Urine and eNAT	10	0.96	3.06
eNAT	10	0.40	2.00

Table 7. Internal control total variance and statistical spread for both sample types

Matrix	Variance	CV (%)
Urine and eNAT	0.16	1.37
eNAT	0.13	1.26

Table 8. Precision data for *C. trachomatis*, urine and eNAT, on the basis of the C_T values

0.316 EB/ml urine and eNAT	C_T value	SD	CV (%)
Intra-assay variability: CT signal	33.69	0.47	1.39
Intra-assay variability: internal control	28.32	0.15	0.51
Inter-assay variability: CT signal	33.92	0.59	1.74
Inter-assay variability: internal control	28.67	0.31	1.07
Inter-batch variability: CT signal	34.31	0.66	1.91
Inter-batch variability: internal control	28.72	0.29	1.01

Table 9. Precision data for *C. trachomatis*, eNAT, on the basis of the C_T values

0.1 EB/ml eNAT	C_T value	SD	CV (%)
Intra-assay variability: CT signal	34.90	0.55	1.58
Intra-assay variability: internal control	28.81	0.08	0.29
Inter-assay variability: CT signal	35.14	0.56	1.61
Inter-assay variability: internal control	28.73	0.21	0.73
Inter-batch variability: CT signal	35.87	1.01	2.81
Inter-batch variability: internal control	28.83	0.23	0.79

Table 10. Precision data for *N. gonorrhoeae*, urine and eNAT, on the basis of the C_T values

10 cfu/ml urine and eNAT	C_T value	SD	CV (%)
Intra-assay variability: NG signal	31.92	0.76	2.38
Intra-assay variability: internal control	29.40	0.47	1.61
Inter-assay variability: NG signal	32.14	0.65	2.03
Inter-assay variability: internal control	29.24	0.38	1.30
Inter-batch variability: NG signal	31.84	1.21	3.80
Inter-batch variability: internal control	28.68	0.28	0.99

Table 11. Precision data for *N. gonorrhoeae*, eNAT, on the basis of the C_T values

10 cfu/ml eNAT	C_T value	SD	CV (%)
Intra-assay variability: NG signal	31.84	0.23	0.72
Intra-assay variability: internal control	29.53	0.10	0.33
Inter-assay variability: NG signal	32.11	0.37	1.16
Inter-assay variability: internal control	29.48	0.20	0.67
Inter-batch variability: NG signal	35.87	1.01	2.81
Inter-batch variability: internal control	28.79	0.22	0.76

Reproducibility

One part of the validation study conducted with the *artus* CT/NG QS-RGQ Kit was an experiment where a standardized proficiency panel (provided by QCMD) with defined CT and NG was tested. The results of these tests are highly comparable throughout the different sites and the CV over all sites was <10% in all cases.

Carryover

Absence of carryover (cross-contamination) between samples for the entire workflow was proven by the correct detection of all known positive and negative samples in alternating positions. Simulated swab and urine samples were spiked with positive control plasmids in concentrations of 1 x 10^7 copies/ml (CT) and 1 x 10^6 copies/ml (NG). These samples were processed with the complete *artus* CT/NG workflow. All samples were detected correctly.

Inhibitory substances

During the verification, a set of samples spiked with potentially inhibitory substances was tested with the *artus* CT/NG QS-RGQ Kit. The samples and brands are shown in Table 12. All substances were tested in samples containing CT and NG cells in the 10x LOD concentrations. None of the substances showed an inhibitory effect on the signals of the internal control and the pathogen signals.

Table 12. Substances tested for potential inhibition

Substance	Sample type	Highest concentration tested
Acidovir (Rathioparm 50mg/g)	Swab	0.25%
CLOTRIMAZOLE 2% Vaginal Cream	Swab	0.25%
Monistat®-1 Dose Treatment	Swab	0.25%
Gyno-Daktar Kombi (100mg suppository)	Swab	0.25%
Antifungol Hexal 3 Vag. Creme	Swab	0.25%
Terazol 7 Vag. Creme (0.4%)	Swab	0.25%
Yeast gard®	Swab	0.25%
Metrogel®-Vaginal 0.75% (Galderna)	Swab	0.25%
Betaisodona Lsg. (Mundipharma)	Swab	0.25%
K-Y® Jelly (personal lubricant)	Swab	0.25%
Vagisan™ FeuchtCreme Combi (suppository)	Swab	0.25%
Vagisan FeuchtCreme Combi (Creme)	Swab	0.25%
Vagisil® Intimate Lubricant	Swab	0.25%
Patentec oval suppository (Merz)	Swab	0.25%
Norforms® Deodorant Suppositories	Swab	0.25%
Hydrocortison Hexal 1%	Swab	0.25%
Mucus	Swab	n.a.
Blood	Swab	5%
Leukocytes	Swab	1 x 10^6 cells/ml
Mucus	Urine	n.a.
Blood	Urine	5%
Leukocytes	Urine	1 x 10^6 cells/ml
Bilirubin	Urine	10 mg/ml
Glucose	Urine	10 mg/ml
pH 4 urine	Urine	n.a.
pH 9 urine	Urine	n.a.
Protein (albumin) from human serum	Urine	5%
Talcum powder	Urine	0.15%
Phenazopyridine hydrochloride	Urine	3 mg/ml

n/a: not applicable.

Diagnostic performance evaluation

Diagnostic performance characteristics were established in a study with retrospectively collected samples conducted in Tilburg, The Netherlands. During this validation study, 612 different samples were tested, comprising all claimed sampling sites and materials (urine [male/female], urethral swabs [male], cervical and vaginal swabs).

With the clinical samples tested, the *artus* CT/NG QS-RGQ Kit showed an overall clinical specificity of 99.8% and sensitivity of 98.1% for CT and 100% specificity and 100% sensitivity for NG in comparison with the Abbott® CT/NG assay (Table 13 and Table 14). A detailed overview of the sensitivity and specificity for the particular sample types is shown in Table 15 and Table 16.

Table 13. Positive and negative samples with each assay (*C. trachomatis*)

		Abbott CT/NG assay		
		+	–	Total
artus CT/NG QS-RGQ Kit	+	103	1	104
	–	2	506	508
	Total	105	507	612

Table 14. Positive and negative samples with each assay (*N. gonorrhoeae*)

		Abbott CT/NG assay		
		+	–	Total
artus CT/NG QS-RGQ Kit	+	26	0	26
	–	0	586	586
	Total	26	586	612

Table 15. Clinical sensitivity and specificity for female and male samples (*C. trachomatis*)

Specimen		n	TP	FP	TN	FN	Sensitivity (%)	Specificity (%)
Female	Urine	51	9	0	42	0	100.00	100.00
	Cervical	186	9	0	177	0	100.00	100.00
	Vaginal	49	4	0	45	0	100.00	100.00
Male	Urine	309	78	1	231	2	97.50	99.57
	Urethral	17	5	0	12	0	100.00	100.00

TP: true positive samples; FP: false positive samples; TN: true negative samples; FN: false negative samples.

Table 16. Clinical sensitivity and specificity for female and male samples (*N. gonorrhoeae*)

Specimen		n	TP	FP	TN	FN	Sensitivity (%)	Specificity (%)
Female	Urine	51	3	0	48	0	100.00	100.00
	Cervical	186	3	0	183	0	100.00	100.00
	Vaginal	49	0	0	49	0	100.00	100.00
Male	Urine	309	18	0	291	0	100.00	100.00
	Urethral	17	2	0	15	0	100.00	100.00

TP: true positive samples; FP: false positive samples; TN: true negative samples; FN: false negative samples.

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