Extra INSTAND EQA Scheme (340) - April 2020

Virus Genome Detection SARS-CoV-2

Final Evaluation of Results

Submitted by 463 out of 487 Laboratories

from 36 Countries

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[3]IQVD GmbH - Institut für Qualitätssicherung in der Virusdiagnostik
[4]GBD Gesellschaft für Biotechnologische Diagnostik mbH, Berlin

Disclosure

Heinz Zeichhardt is share-holder

of

GBD Gesellschaft für Biotechnologische Diagnostik mbH, Berlin

and

IQVD GmbH - Institut für Qualitätssicherung in der Virusdiagnostik, Berlin

INSTAND
accredited by DAkkS
Deutsche
Akkreditierungsstelle
D-EP-15027-02-00

Coronavirus Standards Working Group
15 May 2020
Heinz Zeichhardt, Martin Kammel and Hans-Peter Grunert

GBD IQVD

EQA Network

Scientific umbrella
German Association for Prevention of Virus Diseases (DVV e.V.)
Society of Virology (GfV e.V.)
German Society for Hygiene and Microbiology (DGHM e.V.)

Partners

Berlin

Teams of

GBD Gesellschaft für Biotechnologische Diagnostik mbH, Berlin

and

IQVD GmbH - Institut für Qualitätssicherung in der Virusdiagnostik, Berlin

and

Düsseldorf

INSTAND-Team

and

38 INSTAND Expert Laboratories
incl.
Robert Koch-Institut
Paul-Ehrlich-Institut
National Reference and Consiliary Labs

and

EMPIR AntiMicroResist EMRP European Metrology Research Programme ▶ Programme of EURAMET The EMRP is jointly funded by the EMRP participating countries within EURAMET and the European Union EURAMET European Association of National Metrology Institutes
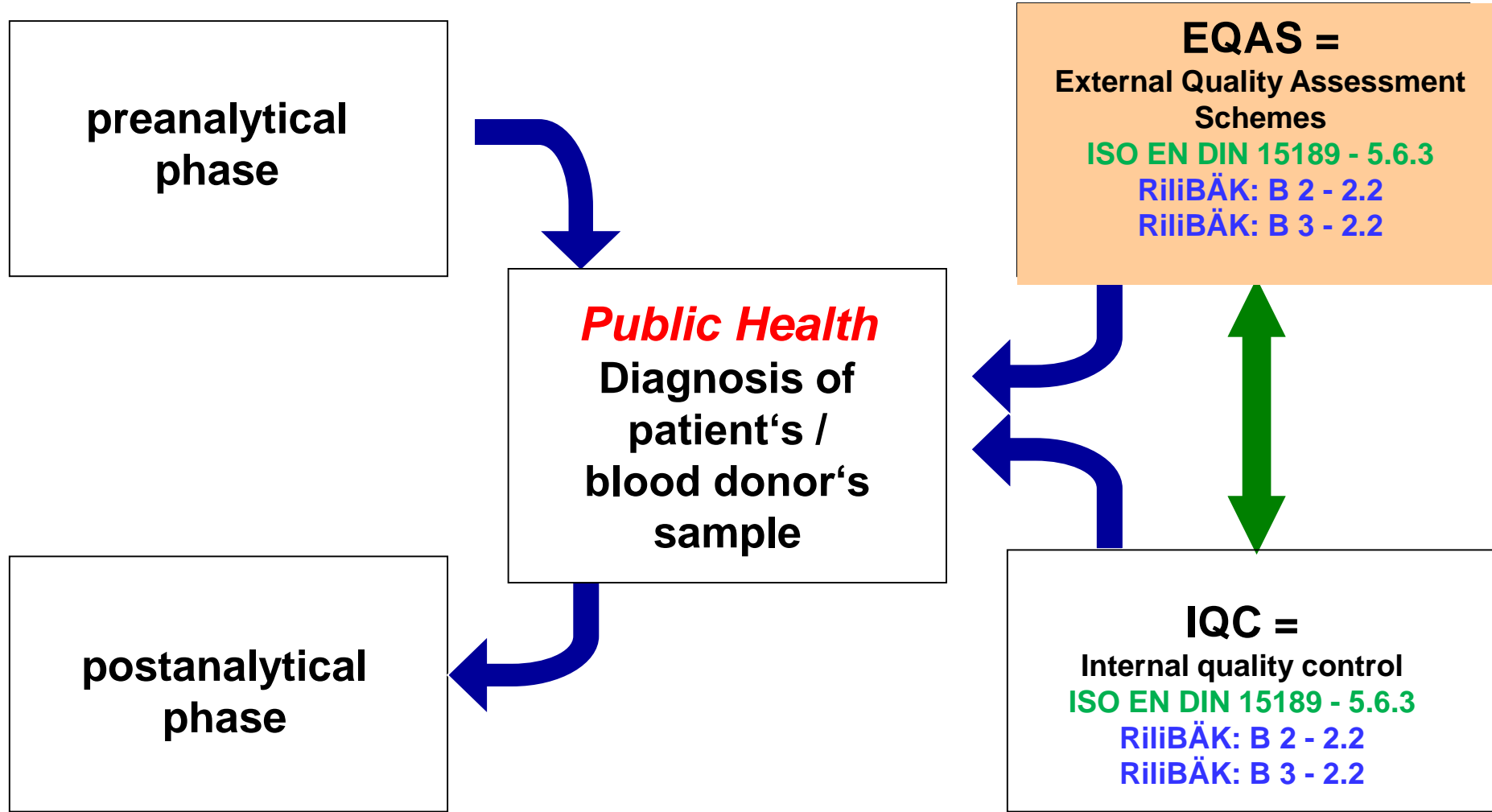
JRC – Joint Research Centre (BE)
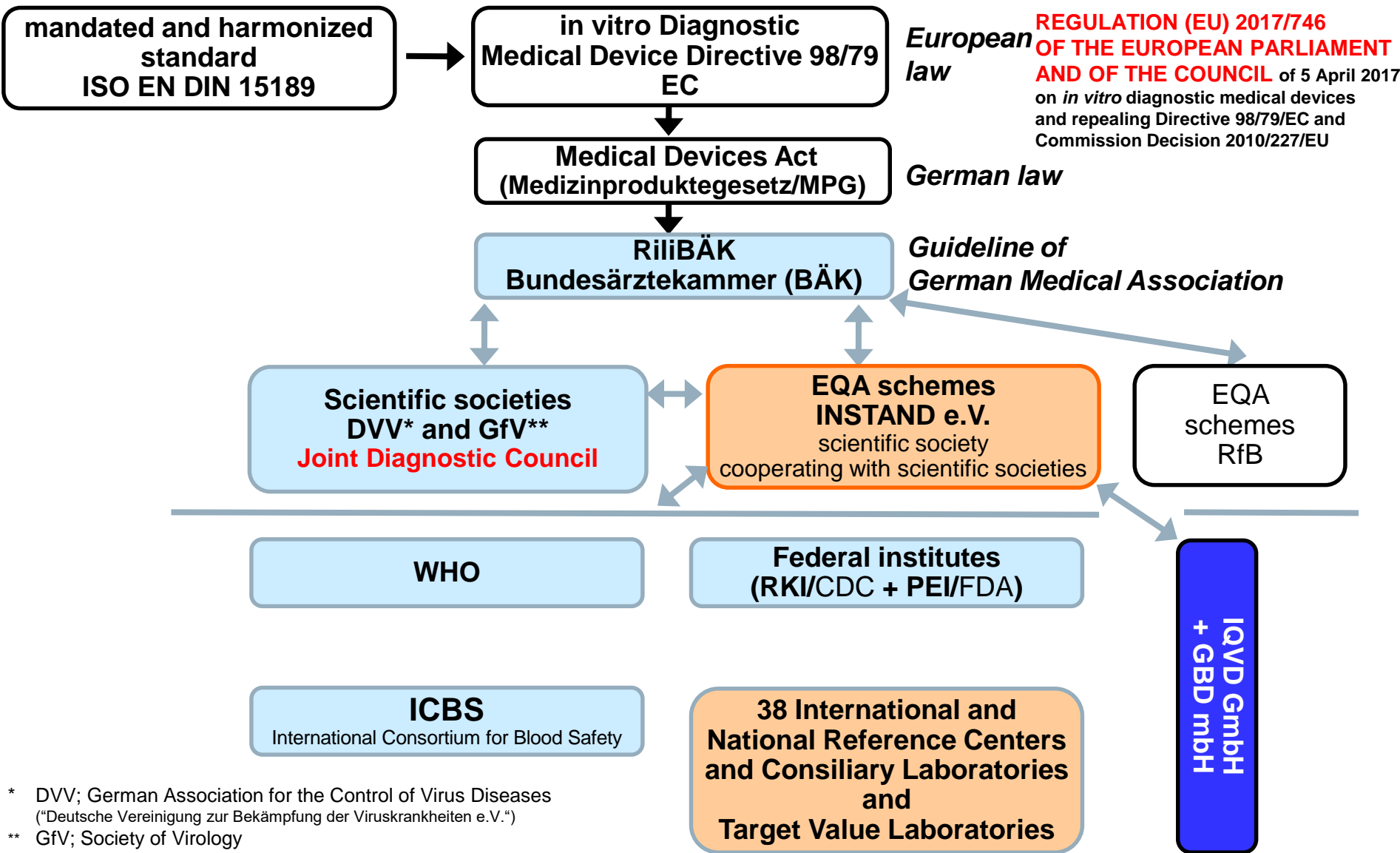
➡ **LGC – National Measurement Laboratory (UK)**

NIB – National Institute of Biology (SI)

PTB - Physikalisch-Technische Bundesanstalt (DE)

The Role of Quality Control for Public Health and Quality Improvement of Diagnostics and Blood Safety

preanalytical phase

Public Health
Diagnosis of patient's / blood donor's sample

postanalytical phase

EQAS =
External Quality Assessment Schemes
ISO EN DIN 15189 - 5.6.3
RiliBÄK: B 2 - 2.2
RiliBÄK: B 3 - 2.2

IQC =
Internal quality control
ISO EN DIN 15189 - 5.6.3
RiliBÄK: B 2 - 2.2
RiliBÄK: B 3 - 2.2

INSTAND e.V. - Quality Assurance in (Virus) Diagnostics

mandated and harmonized standard ISO EN DIN 15189 → **in vitro Diagnostic Medical Device Directive 98/79 EC**

European law

REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

Medical Devices Act (Medizinproduktegesetz/MPG)

German law

RiliBÄK Bundesärztekammer (BÄK)

Guideline of German Medical Association

Scientific societies DVV* and GfV** Joint Diagnostic Council

EQA schemes INSTAND e.V. scientific society cooperating with scientific societies

EQA schemes RfB

WHO

Federal institutes (RKI/CDC **+ PEI/**FDA**)**

IQVD GmbH + GBD mbH

ICBS International Consortium for Blood Safety

38 International and National Reference Centers and Consiliary Laboratories and Target Value Laboratories

*   DVV; German Association for the Control of Virus Diseases ("Deutsche Vereinigung zur Bekämpfung der Viruskrankheiten e.V.")

** GfV; Society of Virology ("Gesellschaft für Virologie e.V.")

INSTAND EQA Schemes (78 Schemes)
in Virus Immunology and Genome Detection 2020

Serology and Antigen Detection		Virus Genome Detection and Typing	
HIV-1/2	Herpes simplex Viruses	HIV-1 (RNA) HIV-2 (RNA)	Measles Rubella Mumps Viruses
HIV-1 p24 Ag	Varicella Zoster Virus	HIV-1 Resistance + Tropism	Adenoviruses
HTLV-1/2	Epstein Barr Virus	Hepatitis A Virus	Norovirus Rotavirus
Hepatitis A Virus	Resp. Sync. Virus Ag	Hepatitis B Virus + Genotyping + Resistance	CoV incl. MERS CoV **SARS-CoV-2 NEW**
Hepatitis B Virus, Prg. I	Influenza A and B Ag + A/H1N1 pdm 2009 + A/H5N1+A/H7N9	Hepatitis C Virus + Genotyping + Resistance	Enteroviruses + Enterovirus (WHO/RKI) Parechovirus **NEW**
Hepatitis B Virus, Prg. II	Rubella Virus Measles Virus Mumps Virus	Hepatitis D Virus Hepatitis E Virus	Human Rhinoviruses Resp. Syncytial Virus Hum. Metapneumovirus Parainfluenza viruses
Hepatitis C Virus	TBE Virus	Torque Teno Virus **NEW**	Influenza A and B incl avian
Hepatitis D Virus	Hantavirus	Cytomegalovirus + Resistance	BK Virus JC Virus
Hepatitis E Virus	Dengue Virus Chikungunya Virus Zika Virus	Epstein-Barr Virus Herpes simplex Viruses HHV-6 **NEW** HHV-8 **NEW**	Dengue Virus West Nile Virus Chikungunya Virus Zika Virus
Parvovirus B19	Rabies Virus	Varicella Zoster Virus	Hum. Papilloma Viruses
Cytomegalovirus	Borna Virus **NEW**	Parvovirus B19	Rabies Virus
SARS-CoV-2 NEW	BSE (PrPsc) (2002-2007)	Multiplex: Respiratory Viruses (2 programs)	Multiplex: **NEW** Viral Meningitis/Encephalitis
		Multiplex: Gastrointestinal Viruses	Borna Viruses **NEW**

INSTAND   *GBD   IQVD*

Extra INSTAND EQA Scheme (340) - April 2020 Virus Genome Detection SARS-CoV-2

Cooperation partner

National Consultant Laboratory for Coronaviruses
Institute of Virology, Charité – University Medicine Berlin, Campus Charité Mitte
   Prof. Dr. Christian Drosten
   Dr. Victor M. Corman
   Dr. Daniela Niemeyer

Expert Laboratories

Universitätsklinikum Frankfurt, Institut für Medizinische Virologie (DE)
   Prof. Dr. Sandra Ciesek
   Prof. Dr. Holger F. Rabenau
   Prof. Dr. Annemarie Berger

Uniklinik Köln, Institut für Virologie Nationales Referenzzentrum für Papillom- und Polyomaviren (DE)
   Prof. Dr. Florian Klein
   Dr. Rolf Kaiser
   Dr. Eva Heger

Medizinisches Infektiologiezentrum Berlin (DE)
   Dr. M. Obermeier
   Dr. R. Ehret

LGC
National Measurement Laboratory
Teddington, Middlesex (UK)
   Dr. Jim Huggett
   Dr. Denise O'Sullivan
and
University of Surrey, Guildford, Surrey (UK)
   Dr. Jim Huggett

Physikalisch-Technische Bundesanstalt, Berlin (DE)
   Prof. Dr. Rainer Macdonald
   Dr. Andreas Kummrow
   Dr. Anabell Plauth
   Dr. Samreen Falak

INSTAND   accredited by DAkkS Deutsche Akkreditierungsstelle D-EP-15027-02-00   Coronavirus Standards Working Group
15 May 2020
Heinz Zeichhardt, Martin Kammel and Hans-Peter Grunert   *GBD IQVD*

Final Evaluation
Based on the Results of 463 out of 487 Laboratories

Sample no.	Sample properties	Sample evaluated
340059	SARS-CoV-2 / 1 : 1 000 diluted$^{\$}$	no
340060	HCoV OC43 / 1 : 2 500 diluted / specificity control	no
340061	SARS-CoV-2 / 1 : 1 000 000 diluted$^{\$}$	yes
340062	CoV negative / specificity control	yes
340063	SARS-CoV-2 / 1 : 10 000 diluted$^{\$}$	yes
340064	SARS-CoV-2 / 1 : 100 000 diluted$^{\$}$	no
340065	HCoV 229E / 1 : 2 500 diluted specificity control	yes

$ The SARS-CoV-2 positive samples 340059, 340061, 340063 and 340064 represent different dilution steps from a dilution series of a lysate from cells, infected with SARS-CoV-2 (inactivated).

Results of sensitivity panel
- qualitative results
  ct/cp/cq/CN values
- quantitative results in copies/ml
  qPCR and dPCR
- what can we learn from quantification of CMV and HIV-1?

Results of specificity panel

$ The SARS-CoV-2 positive samples 340059, 340061, 340063 and 340064 represent different dilution steps from a dilution series of a lysate from cells, infected with SARS-CoV-2 (inactivated).

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340064	SARS-CoV-2 / 1 : 100 000 diluted$^{\$}$	no
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Final Evaluation
Based on the Results of 463 out of 487 Laboratories

Sample no.	Sample properties	Expected qualitative result for SARS-CoV-2	Gene region	Correct results per reported results differentiated by gene region	*Correct results per reported results differentiated by gene region (reduced by the no. of incorrect result assignments (mix-ups) for samples 340064 and 340065)*	Reported Ct/Cp/Cq/CN-results differentiated by gene region median (min − max)
Sample 340059$,*	SARS-CoV-2 1 : 1 000 diluted	positive	E	373/373 (100%)	n.a.	22.6 (16.8-34.0)
			N	165/167 (98.8%)		23.6 (17.9-34.9)
	sample not evaluated$		ORF1a	45/46 (97.8%)		22.2 (20.8-28.7)
			ORF1ab	48/48 (100%)		21.8 (10.9-29.1)
			RdRP	185/185 (100%)		23.8 (10.0-34.5)
			S	100/100 (100%)		21.8 (17.5-27.8)
			n.s.§	64/64 (100%)		22.6 (9.4-33.0)
			total	980/983 (99.7%)$		22.8
Sample 340063*	SARS-CoV-2 1 : 10 000 diluted	positive	E	368/371 (99.2%)	n.a.	25.7 (19.8-35.3)
			N	165/167 (98.8%)		26.9 (20.0-39.6)
			ORF1a	45/46 (97.8%)		25.5 (24.0-31.5)
			ORF1ab	45/47 (95.7%)		24.7 (14.5-33.4)
			RdRP	184/184 (100%)		27.2 (13.4-38.3)
			S	100/100 (100%)		25.0 (18.0-30.0)
			n.s.§	64/64 (100%)		25.7 (12.8-35.9)
			total	971/983 (98.8%)		26.0
Sample 340064$,*	SARS-CoV-2 1 : 100 000 diluted	positive	E	356/373 (95.4%)	356/360 (98.9%)	29.2 (17.7-36.0)
			N	146/166 (88.0%)	145/147 (98.6%)	30.2 (20.0-41.5)
			ORF1a	44/46 (95.7%)	44/46 (95.7%)	28.8 (27.3-34.0)
	sample not evaluated$		ORF1ab	41/48 (85.4%)	41/41 (100%)	28.8 (18.4-37.0)
			RdRP	168/185 (90,8%)	168/173 (97.1%)	30.5 (16.0-41.4)
			S	97/100 (97.0%)	97/97 (100%)	28.6 (20.0-34.2)
			n.s.§	64/64 (100%)	64/64 (100%)	29.0 (16.5-40.0)
			total	916/983 (93.2%)$	915/929 (98.5%)$	29.5
Sample 340061*	SARS-CoV-2 1 : 1 000 000 diluted	positive	E	364/373 (97.6%)	n.a.	32.1 (15.0-40.0)
			N	153/167 (91.6%)		33.3 (20.0-40.7)
			ORF1a	44/46 (95.7%)		31.7 (30.6-36.0)
			ORF1ab	42/48 (87.5%)		31.5 (20.0-39.3)
			RdRP	158/185 (85.4%)		33.5 (19.5-42.8)
			S	97/100 (97.0%)		31.5 (20.0-39.0)
			n.s.§	56/64 (87.5%)		31.9 (19.3-37.5)
			total	914/983 (93.0%)		32.4

Final Evaluation
Based on the Results of 463 out of 487 Laboratories

Sample no.	Sample properties	Expected qualitative result for SARS-CoV-2	Gene region	Correct results per reported results differentiated by gene region	Correct results per reported results differentiated by gene region (reduced by the no. of incorrect result assignments (mix-ups) for samples 340064 and 340065)	Reported Ct/Cp/Cq/CN-results differentiated by gene region median (min – max)
Sample 340059$,*	SARS-CoV-2 1 : 1 000 diluted sample not evaluated$	positive	E	373/373 (100%)	n.a.	22.6 (16.8-34.0)
			N	165/167 (98.8%)		23.6 (17.9-34.9)
			ORF1a	45/46 (97.8%)		22.2 (20.8-28.7)
			ORF1ab	48/48 (100%)		21.8 (10.9-29.1)
			RdRP	185/185 (100%)		23.8 (10.0-34.5)
			S	100/100 (100%)		21.8 (17.5-27.8)
			n.s.$	64/64 (100%)		22.6 (9.4-33.0)
		total		980/983 (99.7%)$		22.8
Sample 340063*	SARS-CoV-2 1 : 10 000 diluted	positive	E	368/371 (99.2%)	n.a.	25.7 (19.8-35.3)
			N	165/167 (98.8%)		26.9 (20.0-39.6)
			ORF1a	45/46 (97.8%)		25.5 (24.0-31.5)
			ORF1ab	45/47 (95.7%)		24.7 (14.5-33.4)
			RdRP	184/184 (100%)		27.2 (13.4-38.3)
			S	100/100 (100%)		25.0 (18.0-30.0)
			n.s.$	64/64 (100%)		25.7 (12.8-35.9)
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			N	146/166 (88.0%)	145/147 (98.6%)	30.2 (20.0-41.5)
			ORF1a	44/46 (95.7%)	44/46 (95.7%)	28.8 (27.3-34.0)
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			RdRP	168/185 (90,8%)	168/173 (97.1%)	30.5 (16.0-41.4)
			S	97/100 (97.0%)	97/97 (100%)	28.6 (20.0-34.2)
			n.s.$	64/64 (100%)	64/64 (100%)	29.0 (16.5-40.0)
		total		916/983 (93.2%)$	915/929 (98.5%)$	29.5
Sample 340061*	SARS-CoV-2 1 : 1 000 000 diluted	positive	E	364/373 (97.6%)	n.a.	32.1 (15.0-40.0)
			N	153/167 (91.6%)		33.3 (20.0-40.7)
			ORF1a	44/46 (95.7%)		31.7 (30.6-36.0)
			ORF1ab	42/48 (87.5%)		31.5 (20.0-39.3)
			RdRP	158/185 (85.4%)		33.5 (19.5-42.8)
			S	97/100 (97.0%)		31.5 (20.0-39.0)
			n.s.$	56/64 (87.5%)		31.9 (19.3-37.5)
		total		914/983 (93.0%)		32.4

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Sample 340061 (Result (qual)) - SARS-CoV-2 positive (inactivated), 1 : 1 000 000 diluted

Reagent	Testkit	Total (N=983)	below detection limit/negative (N=58)	intermediate (N=11)	positive (N=914)	Quota (93%)	Ct/Cp/Ct/CN Median	Ct/Cp/Cq/CN Min	Ct/Cp/Cq/CN Max
E-Gene									
ALTONA DIAGNOSTIC	RealStar SARS-CoV-2 RT-PCR Kit 1.0	48	0	0	48	100,00%	31.7	28.7	36.0
ANATOLIA GENEWORKS	Bosphore Novel Coronavirus Detection Kit v2	4	1	0	3	75,00%	29.4	28.5	30.2
OTHER MANUFACTURERS		10	0	0	10	100,00%	33.0	32.4	36.5
BOSCH HEALTHCARE SOLUTIONS	Vivalytic VRI Multiplex Test	2	0	0	2	100,00%			
CEPHEID	Xpert Xpress SARS-CoV-2	11	0	0	11	100,00%	31.1	30.5	35.1
IN HOUSE (dPCR)		1	0	0	1	97,87%			
IN HOUSE		47	1	0	46	100,00%	32.9	25.7	37.5
ELITech	GeneFinder COVID-19 Plus	8	2	0	6	75,00%	31.2	30.4	35.5
EURO IMMUN	EURORealTime SARS-CoV-2	1	0	0	1	100,00%	33.7	33.7	33.7
EUROFINS TECHNOLOGIES	VirSeek SARS-CoV-2 Screen	1	0	0	1	100,00%	35.5	35.5	35.5
GENETIC SIGNATURES	EasyScreen SARS-CoV-2 Detection Kit	1	0	0	1	100,00%	32.2	32.2	32.2
GERBION	virellaSARS-CoV-2 seqc	5	0	0	5	100,00%	33.0	31.8	33.0
IMMUNDIAGNOSTIK	MutaPLEX Coronavirus	5	1	0	4	80,00%	33.5	31.4	37.9
LIFERIVER	Novel Coronavirus (2019-nCoV) Real Time Multiplex RT-PCR Kit	3	0	0	3	100,00%	30.0	27.0	30.5
LUMINEX	NxTAG CoV	1	0	0	1	100,00%			
MIKROGEN	ampliCube Coronavirus Panel	1	0	0	1	100,00%	32.0	32.0	32.0
MIKROGEN	ampliCube Coronavirus SARS-CoV-2 RUO	3	0	0	3	100,00%	31.4	30.8	35.3
Priv. Inst. f. Immunol. u. Mol.genetik	AmpliGnost CoV-2 E-Gen	4	0	0	4	100,00%	29.9	28.0	32.2
QIAGEN	QIAstat-Dx Respiratory 2019-nCoV Panel	3	0	0	3	100,00%	33.6	28.1	38.6
R-BIOPHARM	RIDA GENE SARS-CoV-2 RUO	55	1	0	54	98,18%	33.3	15.0	37.1
ROCHE DIAGNOSTICS	COBAS SARS-CoV-2 Test	39	0	0	39	100,00%	32.4	30.5	34.9
SEEGENE	Allplex 2019 n-CoV Assay	51	0	1	50	98,04%	31.1	19.2	36.3
TIB MOLBIOL	LightMix Modular SARS and Wuhan CoV E-gene	68	2	0	66	97,06%	32.7	29.6	40.0
TIB MOLBIOL	LightMix Sarbeco E-gene	1	0	0	1	100,00%	32.0	32.0	32.0
		373	8	1	364	97,59%	32.1	15.0	40.0

Results of sensitivity panel
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Sample 340060[$]	HCoV OC43 1 : 2 500 diluted specificity control sample not evaluated[§]	negative	E	368/373 (98.7%)		-
			N	162/166 (97.6%)		-
			ORF1a	45/46 (97.8%)		-
			ORF1ab	45/48 (93.8%)	n.a.	-
			RdRP	178/181 (98.3%)		-
			S	99/100 (99.0%)		-
			n.s.[§]	64/64 (100%)		-
			total	961/983 (97.8%)[$]		-
Sample 340065	HCoV 229E 1 : 2 500 diluted specificity control	negative	E	355/373 (95.2%)	354/360 (98.3%)	-
			N	146/166 (88.0%)	144/147 (98.0%)	-
			ORF1a	44/46 (95.7%)	44/46 (95.7%)	-
			ORF1ab	41/48 (85.4%)	40/41 (97.6%)	-
			RdRP	165/182 (90.7%)	165/170 (97.1%)	-
			S	93/100 (93.0%)	93/97 (95.9%)	-
			n.s.[§]	64/64 (100%)	64/64 (100%)	-
			total	908/983 (92.4%)	904/929 (97.3%)	-
Sample 340062	CoV negative specificity control	negative	E	371/373 (99.5%)		-
			N	164/167 (98.2%)		-
			ORF1a	46/46 (100%)		-
			ORF1ab	47/48 (97.9%)	n.a.	-
			RdRP	178/182 (97.8%)		-
			S	99/100 (99.0%)		-
			n.s.[§]	64/64 (100%)		-
			total	969/983 (98.6%)		-
Success rate for all 4 evaluated samples[&]					428/461 (92.8%)[&]	
Success rate for all 4 evaluated samples (corrected)[&]					428/439 (97.5%)[&]	

Thank you very much!

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Charité-Universitätsmedizin Berlin

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INSTAND EQA schemes in virus diagnostics
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