Hannsjörg Baum*, Sail Chun, Peter Findeisen, Hans Fleurkens, Hyunjung Gu, Jinyoung Hong, Franziska Prévôt, Dawid Radziszewski, Michel F. Rossier, Nico Vogt, Jan Furrer, Kai Klopprogge and Christian Schneider-Thauern

Performance evaluation of cobas pure integrated solutions at multiple sites in Europe and Asia

https://doi.org/10.1515/labmed-2022-0137
Received October 17, 2022; accepted April 14, 2023;
published online May 23, 2023

Abstract

Objectives: We evaluated analytical performance, functionality, reliability, and comparability of cobas® pure integrated solutions (Roche Diagnostics) under routine-like conditions.

Methods: The study was conducted in Europe and Asia (five sites). Seventy-six applications covering ion selective electrolytes (ISE), clinical chemistry (CC), and immunochemistry (IC) analytes were assessed using Elecsys® immunochemistry assays (Roche Diagnostics). Samples included control material and pseudonymized residual samples (plasma/serum/urine). Analytical performance, functionality, and system reliability were evaluated. An inter-laboratory survey, routine simulation imprecision (RSI) and method comparison experiments, and dedicated workflow runs were conducted.

Results: Most coefficients of variation (CVs) for repeatability were <1 % for ISE, ≤2 % for CC, and <2.5 % for IC assays; for intermediate precision were ≤2 % for ISE and CC, and <2.5 % for IC assays; and for reproducibility were ≤3 % for ISE and CC, and <2.5 % for IC assays. Most RSI reference (94 %) and random part (93 %) CVs were ≤2 %; 99 % of runs completed without system-related interruption. 218 method comparisons generated median Passing–Bablok slope of 1.00, median bias at the medical decision point of −0.1 %, and median Pearson's r of 0.998.

Conclusions: cobas pure integrated solutions demonstrated precise and accurate results under routine-like conditions and comparable results vs. commercial analyzers, supporting implementation into routine practice.

Keywords: accuracy; cobas pure; method comparison; precision; reliability; routine conditions.

Introduction

Accurate and timely diagnosis is critical for informed treatment and patient management. Standards are being raised across health care systems, as patient and physician satisfaction and fast clinical decision-making are becoming more prominent quality metrics. Choosing an analyzer that supports short and predictable turnaround times for diagnostic testing at periods of peak workload is key to meeting these standards [1]. Cost pressures, limited space, and the requirement for qualified technical personnel are increasing the demand for automation and consolidation of clinical chemistry and immunochemistry assays, not only in high-throughput laboratories, but also in low-to-medium throughput laboratories. The aim is to provide reliable and accurate results with acceptable analytical performance and short turnaround times using smaller sample volumes. Patient results should be robust over time for comparability between different operators and laboratories.

The novel cobas® pure integrated solutions (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) is an analyzer intended to quantify ion selective electrolyte (ISE), clinical chemistry, and immunochemistry parameters in biological fluids such as plasma, serum, urine, whole blood, and cerebrospinal fluid (CSF). The instrument combines a clinical chemistry analytical unit, cobas® c 303

Hans Fleurkens has since retired from Spital Wallis, Labor ICH-ZIS, Visp, Switzerland.

***Corresponding author: Prof. Hannsjörg Baum**, Institut für Laboratoriumsmedizin und Transfusionsmedizin, RKH Regionale Kliniken Holding und Services GmbH, Posilipostr. 4, 71640 Ludwigsburg, Germany, E-mail: hannsjoerg.baum@rkh-gesundheit.de
Sail Chun, Hyunjung Gu and Jinyoung Hong, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
Peter Findeisen, MVZ Limbach, Heidelberg, Germany
Hans Fleurkens, Spital Wallis, Labor ICH-ZIS, Visp, Switzerland
Franziska Prévôt and Nico Vogt, Institut für Laboratoriumsmedizin und Transfusionsmedizin, RKH Regionale Kliniken Holding und Services GmbH, Ludwigsburg, Germany
Dawid Radziszewski, Diagnostyka Sp. z o.o., Wroclaw, Poland
Michel F. Rossier, Spital Wallis, ICH-ZIS, Sion, Switzerland and University of Geneva, Geneva, Switzerland
Jan Furrer, Roche Diagnostics International Ltd, Rotkreuz, Switzerland
Kai Klopprogge and Christian Schneider-Thauern, Roche Diagnostics GmbH, Mannheim, Germany

(including an integrated ISE unit; Roche Diagnostics International Ltd, Rotkreuz, Switzerland), with an immunochemistry analytical unit, cobas e 402; both can be used as stand-alone analyzers or in combination as an integrated system. cobas pure integrated solutions is a serum work area solution designed for users with a small-to-medium workload (between 50 and 300 samples per day), or as support or a back-up solution for users with higher workloads using cobas® pro integrated solutions (Roche Diagnostics GmbH, Mannheim, Germany). cobas pure integrated solutions uses the same reagents as cobas pro integrated solutions, therefore, good comparability of results should be observed between the two, regardless of the size of the workload.

With a footprint of two square meters, cobas pure integrated solutions consolidates clinical chemistry and immunochemistry testing on a single, compact platform. The analyzer has a broad menu of >230 parameters that can be measured in plasma, serum, urine, whole blood, and CSF. The maximum throughput is 870 tests per hour: 750 tests per hour on the clinical chemistry analyzer (450 ISE and 300 photometric), and 120 tests per hour on the immunochemistry analyzer. The throughput may differ based on the mix of test orders per sample.

Thorough testing of a novel analyzer under routine-like conditions by the intended user population is critical in the development process, as is validation of the analyzer at multiple sites. We therefore evaluated the analytical performance, functionality, reliability, comparability (vs. respective routine analyzers), practicability, and usability of cobas pure integrated solutions under routine-like conditions at multiple sites in Europe and Asia.

Materials and methods

The study was conducted between August and December 2020 at five sites in Europe and Asia: Heidelberg and Ludwigsburg (Germany), Seoul (Republic of Korea), Visp (Switzerland), and Wroclaw (Poland). All sites were equipped with a cobas pure integrated solutions system, except the Visp site, which was equipped with stand-alone cobas c 303 and e 402 analyzers to verify that integrated system and stand-alone analyzers perform similarly under routine-like conditions.

Analytical performance, functionality, reliability, comparability, practicability, and usability of the cobas pure integrated solutions were assessed using 76 selected applications, which were chosen to challenge the system in different ways (Supplementary Table 1). Assays may have different applications for different sample materials (e.g. serum or urine) depending on the reagent. All immunochemistry assays were Elecsys® assays (Roche Diagnostics International Ltd, Rotkreuz, Switzerland). Roche-manufactured and BioRad quality control (QC) materials (stored at −20 °C) or pseudonymized residual patient samples from routine testing (plasma, serum, and urine; stored at 2–8 °C until testing) were used.

The study was approved by the Institutional Review Boards or equivalent committees for the respective study sites: Landesärztekammer Baden-Württemberg (Heidelberg and Ludwigsburg: approval no. F-2019-128), the Asan Medical Center Institutional Review Board (Seoul: approval no. 2020-0975), and La Commission cantonale d'éthique de la recherche sur l'être humain in Lausanne (Visp: project no. 2020-00424). For the Wroclaw site, no approval was required as only control materials were used. The study complied with all relevant national regulations and institutional policies, and was performed in accordance with the principles of the Declaration of Helsinki.

Daily QC

At all five sites, the Roche-manufactured and BioRad QC materials were measured using selected applications (ISE, clinical chemistry [including enzyme, substrate, and specific protein], and immunochemistry) at two analyte concentration levels over 14–16 weeks. Analyte recovery per QC was monitored; the recommended analyte recovery range was within ±2 standard deviation (SD) of the assigned target value, with the exception of chloride and urea, where the range was extended to ±3 SD (due to electrode exchange and adjustment of the rinse station).

Precision

At four sites (Ludwigsburg, Seoul, Visp, and Wroclaw), precision experiments based on the Clinical and Laboratory Standards Institute EP05-A3 protocol were conducted, with two runs per day over a 21-day period for 34 selected applications (ISE: 3 analytes/6 applications [serum/plasma and urine]; clinical chemistry: 10 analytes/15 applications [serum/plasma, urine]; immunochemistry: 13 analytes/13 applications [serum/plasma]) that represent a typical routine panel of assays and cover differences in assay protocols (such as different viscosity of reagents or pipetting volumes). Pooled control materials (Roche-manufactured and BioRad) were used to minimize the potential influence of sample handling between sites and operators; two control samples were measured per application (low and high concentration).

Coefficients of variation (CVs) for repeatability (within-run precision), intermediate precision (within-laboratory precision), and reproducibility (across-laboratory precision) were calculated and compared with study-specific acceptance criteria. The study-specific acceptance criteria are detailed in the supplementary materials (Supplementary Table 2).

System functionality

At four sites (Heidelberg, Ludwigsburg, Visp, and Wroclaw), routine simulation imprecision experiments were conducted to test the interaction of hardware, software, assays, and samples, and evaluate recovery and precision under various stressed routine-like conditions, including provocations.

These experiments comprised a reference part, where a defined number of aliquots per assay were processed consecutively (within-run batch), and a random part, where all assays and materials were requested in a randomized order (random access mode). For selected experimental runs (two per site), operators challenged the system functionality by applying provocations within the random part of the

experiment. The provocations performed represented typical user scenarios applicable to daily routine laboratory work, such as sample short, short turnaround time requests, reagent changeover, reagent short, sample clots, etc. CVs and median CVs of the reference part and random part were calculated and compared.

Reliability

At all five sites, system reliability – measured by the percentage of analysis runs completed without system-related interruption – was assessed.

Routine simulation method comparison

At four sites (Heidelberg, Ludwigsburg, Seoul, and Visp), routine simulation method comparison experiments using residual routine samples were conducted to evaluate overall functionality under routine-like conditions and comparability of cobas pure integrated solutions with respective routine analyzers: Beckman Coulter AU5800 Clinical Chemistry Analyzer (Seoul), Abbott Alinity i (Seoul), Siemens ADVIA Centaur XPT Immunoassay System (Seoul), and Roche COBAS INTEGRA® 400 plus (Roche Diagnostics GmbH, Mannheim, Germany; Visp), cobas e 411 (Visp), cobas pro (cobas c 503 and e 801; Ludwigsburg), and cobas 8000 (cobas c 702 and e 801; Ludwigsburg and Heidelberg). In total, 47 analytes with 53 applications covering ISE, clinical chemistry, and immunochemistry were assessed. To introduce variability within and across sites, testing was performed for up to 10 days at each site. The analyte concentration ranges covered per assay reflected those of the individual sites' routine samples at that time. The residual routine samples were independent from their specific matrices, including type of serum/plasma collection tube and type of urine specimen (e.g. spot samples and samples collected over 24 h). Pre-collected or spiked samples were not included.

Routine workloads (100–300 samples) were replicated and reprocessed, in part or total, on cobas pure integrated solutions using WinCAEv – a Code of Federal Regulations Title 21 Part 11 compliant electronic data capture software developed and validated for Roche-sponsored studies [2] – to capture routine analyzer requests via an electronic file from the Laboratory Information Systems (LIS, Host). This experimental design enabled laboratory personnel to assess overall system functionality, including sample and reagent handling, data flagging and alarm generation, and flow of workload processing [3], as well as reliability under different laboratory conditions. Samples were stored for 1–3 days at 4 °C between the initial routine measurement and the subsequent measurement on cobas pure integrated solutions.

Results per sample were compared with those previously generated during routine operation; data pairs were automatically evaluated using Passing–Bablok regression [4], and slopes, intercepts, and correlations for method comparisons were calculated and compared with study-specific acceptance criteria.

Workflow

At four sites (Heidelberg, Seoul, Visp, and Wroclaw), operational performance was evaluated by recording time to first result (from sample loading to first result), time to last result (from sample loading to last result of the entire workload), and output (results generated per hour). The results considered eight different workflows, with variable test request patterns and different clinical chemistry/immunochemistry test ratios. All runs were defined and performed as routine simulations to verify the throughput of cobas pure integrated solutions under user intended conditions, using pooled Roche-manufactured QC materials as samples. By loading the samples onto the analyzer as the starting point, the same conditions were ensured for all systems.

Inter-laboratory survey (ring trial)

At four sites (Heidelberg, Ludwigsburg, Visp, and Wroclaw), result accuracy for 48 selected applications (ISE: 3 analytes/3 applications; clinical chemistry: 26 analytes/26 applications; immunochemistry: 19 analytes/19 applications) was validated in a ring trial – a validation study that evaluates a diagnostic method using identical samples in several laboratories.

Ring trial samples included 16 commercial serum samples and two Roche-manufactured QC samples (low and high concentration anti-hepatitis A virus immunoglobulin M), which were measured in triplicate over 3 consecutive days. Commercial samples are often used for ring trials due to their availability for comparison measurements. The median percentage difference between site-specific recovery and overall recovery was calculated (maximum 10 % deviation permitted).

Practicability and usability

At the five sites, user feedback was captured at the end of the study via a 200-item questionnaire comprising 17 question categories: installation environment, location of components, operator training, user documentation and support, product design and labelling, daily workflow, reagent handling, workflow, timing/productivity, data processing environment, quality assurance, calibration, QC, maintenance, troubleshooting, versatility, and consolidation. Questions were graded on a 10-point scale, from 1 "does not meet expectations" to 10 "exceeds expectations". For each question, a mean score was calculated across the five sites; an approximate score of 1–3.3 = "does not meet expectations", >3.3–6.6 = "meets expectations", and >6.6–10 = "exceeds expectations". Users could provide qualitative feedback to report advantages of the analyzer, incidents of malfunction, and suggest possible improvements.

Formative usability testing was performed according to the ISO standard IEC 62366-1:2015. Trained operators completed tasks relying on their training and training material alone, while observed by trained test conductors from Roche Diagnostics.

Statistical analysis

Data were captured, analyzed, and stored by WinCAEv; data captured offline were verified using review by Roche Diagnostics.

Results

Daily QC

In total, 25,826 QC results were included in the analysis. Analyte recovery for all assays was within ±2 SD of the preliminary assigned target value; except for chloride and

urea, which showed QC recoveries within ±3 SD. The chloride electrode was exchanged and optimized adjustments were applied to the rinse station used for urea. Following this, chloride and urea showed recoveries within ±2 SD.

Precision

In total, 612 CVs were calculated, including repeatability (n=272), intermediate precision (n=272), and reproducibility (n=68) (Figure 1; Table 1). For repeatability, 34/48 CVs were <1 % for ISE assays, 116/120 CVs were ≤2 % for clinical chemistry assays, and 90/104 were <2.5 % for immunochemistry assays. For intermediate precision, 47/48 CVs were ≤2 % for ISE assays, 114/120 CVs were ≤2 % for clinical chemistry assays, and 77/104 were <2.5 % for immunochemistry assays. For reproducibility, 11/12 CVs were ≤3 % for ISE assays, 27/30 were ≤3 % for clinical chemistry assays, and 14/26 were <2.5 % for immunochemistry assays.

System functionality

For the routine simulation imprecision experiments, 18 runs with 604 CV pairs were included in the analysis. All introduced provocations were handled as expected by cobas pure integrated solutions. All runs including provocations are shown in Table 2.

Most reference and random part CVs were ≤2 % (reference part: 94 %; random part: 93 %) as shown in Figure 2; median reference and random part CVs were 0.58 and 0.74 %, respectively. cobas pure integrated solutions consistently demonstrated very good precision results in batch and random access mode over an experiment run time of ~4 h.

Reliability

The overall system reliability of cobas pure integrated solutions was 99 %. In total, 271/288 runs were completed without interruption across all five sites during the 4-month study period. Only three interruptions were system related, the additional 14 interruptions were due to human error and, therefore, excluded from the analysis.

Routine simulation method comparison

Four of the sites (Heidelberg, Ludwigsburg, Seoul, and Visp) participated in the comparison of routine results with those generated on cobas pure integrated solutions from the same routine samples. More than 55,000 data pairs were generated from 7,254 routine samples.

In total, 218 method comparisons generated a median slope of 1.00, median bias at the medical decision point of −0.1 %, and median Pearson's r of 0.998. The median bias at the medical decision point was 0.0 and −0.2 % for clinical chemistry and immunochemistry assays, respectively. For ISE, all comparisons were within ±5 % bias at the medical decision point. Overall, 168/187 method comparisons vs. Roche methods met the Passing–Bablok slope and intercept criteria for standard batch method comparisons (Table 3; Supplementary Table 3). Standard batch method comparison is where a number of samples are run in sequence, i.e., they are not randomized. This reduces the time between measurements taken on the investigational device and measurements taken on the reference (comparator) device and also limits potential interactions between different samples and reagents. In contrast, the routine simulation method comparison mimics the situation in real laboratories, where samples are tested in random access mode and multiple applications are used concurrently. Depending on the availability of samples, the time span between testing can be 1–3 days for the routine simulation method comparison.

These results were obtained even though the four sites used different reagent and calibrator lots for routine testing and there were delays of up to 3 days between measuring samples on cobas pure integrated solutions following routine analysis.

Workflow

Summaries of the workflow metrics for the eight different workloads analyzed are shown in Tables 4 and 5. The time to first result was as expected (0.5–2 min for ISE results and 20–21 min for the immunochemistry assays), and time to last result was highly dependent on workload (a rise in requests for immunochemistry testing from 14 to 17 % increased the time to last result from 45 to 55 min, while the absolute number of requests stayed the same). The introduction of two short turnaround samples per 200 samples did not significantly change the time to last result. However, the percentage of pre-dilution or 27-min assays in specific immunochemistry blood screening workloads did increase time to last result; these assays require additional pipetting steps, thus, affecting time to last result.

Output (results generated per hour) correlated with workload and immunochemistry/clinical chemistry ratio. Output for blood screening workflows correlated with the

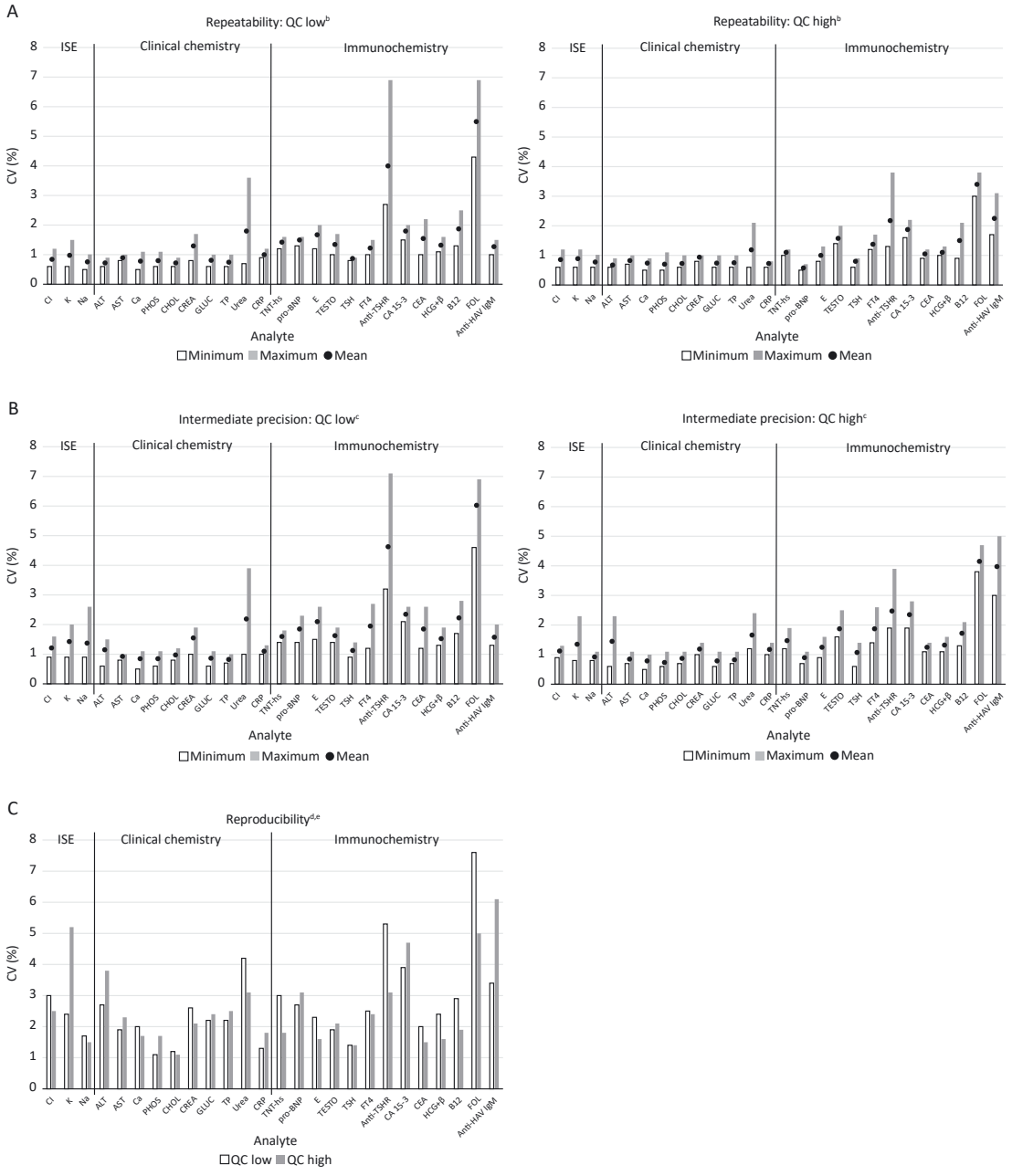

Figure 1: Distribution of (A) repeatability, (B) intermediate precision, and (C) reproducibility CVs for QC low and high concentration samples for ISE, clinical chemistry, and Elecsys immunochemistry assays[a]. [a]Combined dataset, including serum and urine matrices. [b]Target CVs for repeatability: ISE <1 %; enzyme and substrate assays <2 %; homogeneous immunoassays and urinalysis <3 %; heterogeneous immunoassays <5 %. [c]Target CVs for intermediate precision: ISE <2 %; enzyme and substrate assays <3 %; homogeneous immunoassays and urinalysis <4 %; heterogeneous immunoassays <8 %. [d]Target CVs for reproducibility: ISE <3 %; clinical chemistry, homogeneous immunoassays, and urinalysis <5 %; heterogeneous immunoassays <10 %. [e]The reproducibility analysis yielded two CVs per analyte (QC low and high), therefore, there is no variability (minimum, maximum, or mean). ALT, alanine aminotransferase; AST, aspartate aminotransferase; B12, vitamin B12; Ca, calcium; CA 15-3, cancer antigen 15-3; CEA, carcinoembryonic antigen; CHOL, cholesterol; Cl, chloride; CREA, creatinine; CRP, C-reactive protein; CV, coefficient of variation; E, estradiol; Fe, iron; FOL, folate; FT4, free thyroid hormone thyroxine; GLUC, glucose; HAV, hepatitis A virus; HCG+β, human chorionic gonadotropin; IgM, immunoglobulin M; ISE, ion selective electrolyte; K, potassium; Na, sodium; PHOS, phosphate; pro-BNP, pro-B-type natriuretic peptide; QC, quality control; TESTO, testosterone; TNT-hs, troponin T-high sensitive; TP, total protein; TSH, thyroid stimulating hormone; TSHR, thyroid stimulating hormone receptor.

Table 1: Distribution of repeatability, intermediate precision, and reproducibility CVs for QC low and high concentration samples for ISE, clinical chemistry, and Elecsys immunochemistry assays.[a]

Assay	QC concentration	Precision parameter	CV, n[b]				
			<1 %	1–2 %	>2–3 %	>3 %	Total
ISE assays	Low	Repeatability	17	7	0	0	24
		Intermediate precision	5	18	1	0	24
		Reproducibility	0	2	4	0	6
	High	Repeatability	17	7	0	0	24
		Intermediate precision	11	13	0	0	24
		Reproducibility	1	3	1	1	6
Clinical chemistry assays	Low	Repeatability	45	12	2	1	60
		Intermediate precision	33	24	0	3	60
		Reproducibility	0	7	7	1	15
	High	Repeatability	51	8	1	0	60
		Intermediate precision	34	23	3	0	60
		Reproducibility	0	7	6	2	15
			<2.5 %	2.5–3.5 %		>3.5 %	Total
Elecsys immunochemistry assays	Low	Repeatability	44	2		6	52
		Intermediate precision	37	9		6	52
		Reproducibility	6	4		3	13
	High	Repeatability	46	3		3	52
		Intermediate precision	40	6		6	52
		Reproducibility	8	2		3	13

[a]Details of the study-specific acceptance criteria and concentrations of the QC samples are provided in the supplementary materials. [b]Data show the number of parameters within the limit. CV, coefficient of variation; ISE, ion selective electrolyte; QC, quality control.

use of pre-dilution or 27-min assays. Output of serum work area workloads was not affected by an increase in immunochemistry/clinical chemistry ratio (from 14 to 17 %), nor the introduction of two short turnaround samples.

Inter-laboratory survey (ring trial)

For the 48 applications included in the result accuracy analysis using ring trial samples, 80.4 % of median recoveries per assay and site were within ±2 % of the median per assay for all sites, and 99.7 % of median recoveries per assay and site were within ±10 % of the median per assay for all sites. Only folate exhibited increased imprecision due to the complex assay format (Figure 3).

Practicability and usability

In total, 99 % of questions answered were graded as “meets expectations” or better. With a mean grading of 8.6 and a median grading of 9.0 across all sites, practicability was categorized by all sites combined as “exceed expectations” (Supplementary Figure 1). Usability testing did not reveal severe safety issues for operators or patient results; thus, no design change was required.

Discussion

In this study, the novel cobas pure integrated solutions, for clinical chemistry and immunochemistry testing (using Elecsys immunochemistry assays), was assessed extensively for overall precision, functionality, and comparability of results vs. data generated during routine operation on the COBAS INTEGRA 400 plus, cobas e 411, cobas pro, and cobas 8000 analyzers, as well as Beckman Coulter AU5822 Clinical Chemistry Analyzer, Abbott Alinity i, and Siemens ADVIA Centaur analyzers. Our findings show that under routine-like conditions, and when used as stand-alone analyzers (cobas c 303 and e 402) or in combination as an integrated system, cobas pure integrated solutions is reliable, safe, and practical with very good analytical performance, supporting its implementation into routine clinical laboratory practice.

Eight different workflows were analyzed during this study on stand-alone cobas c 303 and e 402 analyzers, as well as cobas pure integrated solutions: one clinical chemistry, four immunochemistry, and three mixed clinical chemistry and immunochemistry workflows. Throughput of the comprehensive metabolic panel on stand-alone c 303 and cobas pure integrated solutions was 516 and 510 results/hour, respectively, and, therefore, ~70 % of the maximal mixed ISE/clinical chemistry mode throughput of 750 results/hour.

Table 2: Summary of all provocations during routine simulation imprecision runs.

Provocation (event triggered by operator)	Visp				Ludwigsburg		Wroclaw			Heidelberg	
	Rep 2 cobas c 303	Rep 3 cobas c 303	Rep 2 cobas e 402	Rep 3 cobas e 402	Rep 2	Rep 3	Rep 2	Rep 3	Rep 4	Rep 2	Rep 3
Sample short (insufficient sample volume)	OK	–	OK	–	–	–	OK	OK	–	OK	–
STAT requests (introduction of priority sample)	–	OK	–	OK	–	OK	–	–	–	–	–
Module mask and load cassette	–	–	–	–	OK	–	OK	–	–	OK	–
Pmask (patient masking)	–	OK	–	OK	–	–	–	OK	–	–	OK
cobas c pack or e pack green masking (masking of the reagent pack)	OK	–	–	–	–	–	–	–	OK	–	–
Calibration via STAT port (introduction of priority calibration)	–	OK	–	OK	–	–	–	OK	–	–	OK
QC via STAT port (introduction of priority QC)	–	OK	–	OK	–	–	–	OK	–	OK	OK
System reagent short (insufficient volume of system reagent)	–	–	–	–	–	–	OK	OK	OK	OK	–
Use of micro-cup	–	–	–	–	–	OK	OK	–	–	OK	–
Sample clot	OK	–	OK	–	–	OK	–	–	–	–	OK
Sample barcode read error	OK	OK	OK	–	OK	–	–	–	–	–	OK
Load pack during operation	OK	–	–	–	OK	–	–	–	–	–	–
Add on sample requests	–	–	–	–	–	OK	–	–	–	OK	–

OK indicates that the provocation was handled by the instrument as per design. QC, quality control; Rep, repetition; STAT, short turnaround time.

Specific immunochemistry blood screening panels (1–4) differed in number of requests per sample and type of assays used. The throughput ranged from 69 (panel 2) to 121 (panel 4) results/hour, which corresponds to the theoretical throughput of 120 results/hour for the cobas e 402 analytical unit. The immunochemistry/clinical chemistry mixed panels differed in percentage of immunochemistry to clinical chemistry requests (14 and 17 %) and the addition of short turnaround samples during the 14 % immunochemistry/clinical chemistry run. Time to last result increased as more immunochemistry requests were added to the panel (2:34 h:min to 3:29 h:min), while the maximum throughput during the runs were similar (~640 results/hour). The addition of two short turnaround samples to the 14 % mixed immunochemistry/clinical chemistry panel did not change time to last result or the throughput, in comparison to the run without short turnaround samples. The short turnaround samples themselves had a fast turnaround time of 14–22 min, demonstrating the short turnaround capabilities of cobas pure integrated solutions.

cobas pure integrated solutions was designed by the manufacturer to provide prolonged calibration and reagent on-board stability compared with cobas e 411 and COBAS INTEGRA 400 plus, thereby promoting user convenience as well as high reliability of patient results. Throughout the current study, laboratory technicians assessed the system with respect to practicability and usability for their daily work. The outcome of this standardized assessment indicated high user satisfaction, with particular emphasis on the features that facilitate routine operation. Besides optimized daily workflow, space saved in terms of system dimensions, and reagent storage requirements, the laboratory technicians particularly valued the proficient reagent handling compared with cobas e 411 and COBAS INTEGRA 400 plus. Although improvements regarding the accessibility of some components for maintenance are still desired, cobas pure integrated solutions meets or even exceeds user expectations with regard to practicability and usability.

While increasing testing efficiency, maintenance of high-quality analytical performance is essential. The precision and method comparison data demonstrated the reliability of cobas pure integrated solutions in this respect. For repeatability, most CVs were <1 % for ISE assays, ≤2 % for clinical chemistry assays, and <2.5 % for immunochemistry assays. For intermediate precision, most CVs were ≤2 % for ISE assays, ≤2 % for clinical chemistry assays, and <2.5 % for immunochemistry assays. For reproducibility, most CVs were ≤3 % for ISE assays, ≤3 % for clinical chemistry assays, and <2.5 % for immunochemistry assays. Additionally, 80.4 % of median recoveries per assay and site were within 2 % of the median per assay for all sites, which

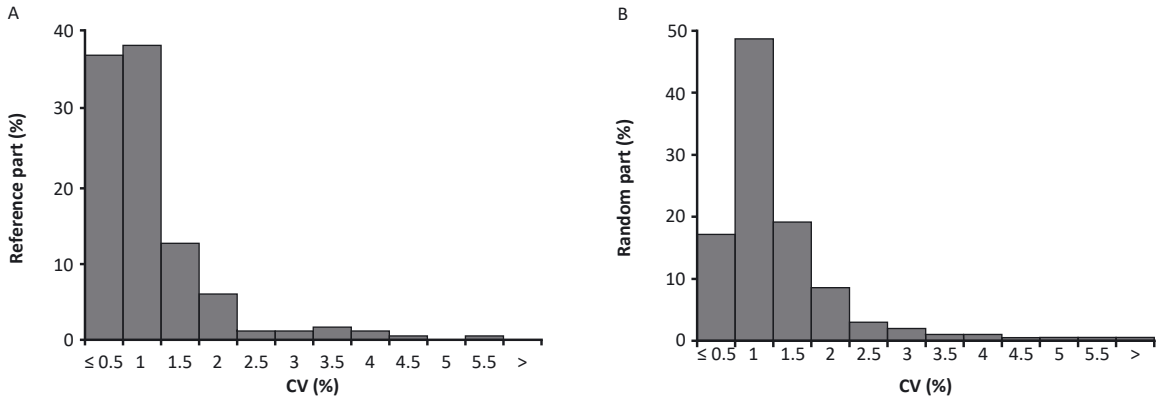

Figure 2: Distribution of (A) reference part and (B) random part CVs for cobas pure integrated solutions. CV, coefficient of variation.

Table 3: Method comparisons vs. Roche methods for ISE, clinical chemistry, and Elecsys immunochemistry assays at the Ludwigsburg site.

Assay[a]	Unit	Comparator instrument	Sample material	Number of samples	Passing–Bablok			
					Slope	Intercept	Bias at MDP, %	Pearson's r
Cl[b]	mmol/L	cobas pro	Serum/plasma	14	1.11	−12.9	−2	0.890
Cl	mmol/L	cobas 8000	Serum/plasma	61	1.03	−4.6	−2	0.968
K	mmol/L	cobas 8000	Serum/plasma	210	0.99	0.22	5	0.982
K	mmol/L	cobas pro	Serum/plasma	102	0.99	0.16	4	0.991
Na	mmol/L	cobas pro	Serum/plasma	129	1.00	2.8	2	0.952
Na	mmol/L	cobas 8000	Serum/plasma	219	0.99	2.1	1	0.873
Na	mmol/L	cobas 8000	Urine	26	0.99	−0.30	−2	0.999
ALB	g/L	cobas 8000	Serum/plasma	69	1.07	−3.92	−5	0.977
ALBT[b]	mg/L	cobas 8000	Urine	7	1.15	−2.50	6	1.000
ALP	U/L	cobas 8000	Serum/plasma	78	1.00	−0.55	−1	0.999
ALP	U/L	cobas pro	Serum/plasma	39	1.03	−1.45	1	1.000
ALT	U/L	cobas pro	Serum/plasma	49	1.03	−0.05	3	1.000
ALT	U/L	cobas 8000	Serum/plasma	122	0.99	−2.00	−7	1.000
AST	U/L	cobas pro	Serum/plasma	49	0.94	0.29	−6	1.000
AST	U/L	cobas 8000	Serum/plasma	105	1.02	−1.69	−3	1.000
Ca	mmol/L	cobas 8000	Serum/plasma	91	0.97	0.14	3	0.981
Ca	mmol/L	cobas pro	Serum/plasma	67	1.04	−0.03	3	0.968
CHE	U/L	cobas 8000	Serum/plasma	63	1.02	39.11	2	0.999
CHOL	mmol/L	cobas 8000	Serum/plasma	62	1.04	−0.08	3	0.998
CK	U/L	cobas pro	Serum/plasma	69	1.01	−2.47	0	1.000
CK	U/L	cobas 8000	Serum/plasma	75	1.00	0.80	1	1.000
CREA	µmol/L	cobas pro	Serum/plasma	152	1.03	−1.91	0	0.998
CREA	µmol/L	cobas 8000	Serum/plasma	174	1.00	−1.77	−2	0.998
CREA	µmol/L	cobas 8000	Urine	25	0.98	33.48	−1	0.998
CRP	mg/L	cobas 8000	Serum/plasma	126	1.05	−0.15	2	0.999
CRP	mg/L	cobas pro	Serum/plasma	108	1.02	−0.12	0	0.999
Fe	µmol/L	cobas 8000	Serum/plasma	89	1.06	−1.08	−12	0.998
GGT	U/L	cobas pro	Serum/plasma	46	1.00	0.00	0	1.000
GGT	U/L	cobas 8000	Serum/plasma	103	0.99	−0.64	−3	0.999
GLUC	mmol/L	cobas 8000	Serum/plasma	147	0.98	0.05	0	0.997
GLUC	mmol/L	cobas pro	Serum/plasma	30	1.01	0.09	3	0.997
HbA_{1c}	%	cobas pro	Whole Blood	82	1.01	−0.20	−2	0.993
HDL	mmol/L	cobas 8000	Serum/plasma	23	0.95	0.02	−3	0.998
LDH	U/L	cobas pro	Serum/plasma	31	1.04	−5.06	2	0.996
LDH	U/L	cobas 8000	Serum/plasma	72	1.01	−0.36	1	0.999
LDL	mmol/L	cobas 8000	Serum/plasma	23	1.01	−0.01	1	0.998
LIP	U/L	cobas 8000	Serum/plasma	81	0.96	0.06	−5	0.997
Mg	mmol/L	cobas 8000	Serum/plasma	65	1.05	−0.04	0	0.993
PHOS	mmol/L	cobas 8000	Serum/plasma	72	1.04	−0.01	3	0.811
TP	g/L	cobas 8000	Serum/plasma	61	1.06	0.23	6	0.982

Table 3: (continued)

Assay[a]	Unit	Comparator instrument	Sample material	Number of samples	Passing–Bablok			
					Slope	Intercept	Bias at MDP, %	Pearson's r
TRIGL	mmol/L	cobas 8000	Serum/plasma	73	1.01	0.05	3	0.998
UA	µmol/L	cobas 8000	Serum/plasma	35	1.00	5.93	1	0.999
Urea	mmol/L	cobas 8000	Serum/plasma	223	0.96	0.11	−3	0.998
Urea	mmol/L	cobas pro	Serum/plasma	133	0.99	0.03	−1	1.000
B12	pg/mL	cobas pro	Serum/plasma	68	0.96	−14.43	−13	0.997
CA 15-3	U/mL	cobas pro	Serum/plasma	13	0.99	1.97	7	0.996
CEA	ng/mL	cobas pro	Serum/plasma	80	1.06	0.08	7	1.000
FOL	ng/mL	cobas pro	Serum/plasma	63	1.07	0.03	6	0.985
FT3	pmol/L	cobas 8000	Serum/plasma	64	0.91	0.32	2	0.997
FT4	pmol/L	cobas 8000	Serum/plasma	64	1.02	0.81	8	0.994
HCG+β	mIU/mL	cobas 8000	Serum/plasma	62	0.95	0.14	8	0.999
pro-BNP	pg/mL	cobas 8000	Serum/plasma	81	1.02	−6.60	−3	1.000
TNT-hs	pg/mL	cobas pro	Serum/plasma	17	0.99	−0.70	−2	1.000
TNT-hs	pg/mL	cobas 8000	Serum/plasma	48	0.96	0.20	−4	0.999
TPSA	ng/mL	cobas pro	Serum/plasma	107	0.98	−0.01	−3	0.997
TSH	mIU/L	cobas 8000	Serum/plasma	60	1.03	0.00	3	0.999
TSH	mIU/L	cobas pro	Serum/plasma	14	1.01	0.00	3	0.995

[a]Multiple method comparisons for each assay were ran at different time points. [b]Analytical performance can be negatively affected by sample aging effects, reduced number of samples, uneven distribution of samples, and multiple calibrations and runs on routine systems. ALB, albumin; ALBT, Tina-quant albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; B12, vitamin B12; Ca, calcium; CA 15-3, cancer antigen 15-3; CEA, carcinoembryonic antigen; CHE, cholinesterase; CHOL, cholesterol; CK, creatine; Cl, chloride; CREA, creatinine; CRP, C-reactive protein; Fe, iron; FOL, folate; FT3, free thyroid hormone triiodothyronine; FT4, free thyroid hormone thyroxine; GGT, γ-glutamyltransferase; GLUC, glucose; HbA_{1c}, hemoglobin A1c; HCG+β, human chorionic gonadotropin; HDL, high density lipoprotein cholesterol; ISE, ion selective electrolyte; K, potassium; LDH, diglycosylated luteinizing hormone; LDL, low density lipoprotein cholesterol; LIP, lipase; MDP, medical decision point; Mg, magnesium; Na, sodium; PHOS, phosphate; pro-BNP, pro-B-type natriuretic peptide; TNT-hs, troponin T-high sensitive; TP, total protein; TPSA, total prostate-specific antigen; TRIGL, triglycerides; TSH, thyroid stimulating hormone; UA, uric acid.

Table 4: Summary of workflow metrics for blood screening and metabolic panels.

Workflow (number of samples; requests)	Assays	Time to first result, min		Time to last result, h:min		Output, results/h		Median sample processing time, min	
		Visp/ Wroclaw	Seoul/ Heidelberg	Visp/ Wroclaw	Seoul/ Heidelberg	Visp/ Wroclaw	Seoul/ Heidelberg	Visp/ Wroclaw	Seoul/ Heidelberg
Comprehensive metabolic panel (n=50; 700)	GLUC, Ca, ALB, TP, Na, K, CO2, Cl, Urea, CREA, ALP, ALT, AST, BILT	2	0.5	1:28	1:33	516	510	51	51
Blood screening panel 1 (n=50; 300)	HBsAg II, HIV Duo[a], TOXO IgG, TOXO IgM, Rubella IgG, Syphilis	21	21	2:16	2:18	105	107	101	120
Blood screening panel 2 (n=50; 350)	Anti-HAV, Anti-HAV IgM, Anti-HBc IgM, Anti-HBc II, Anti-HCV II, HBsAg II, HIV Duo[a]	21	20	6:11	6:17	69	70	201	200
Blood screening panel 3 (n=50; 250)	HIV Duo[a], HBsAg II, Anti-HCV II, Syphilis, Anti-HBc II	21	20	3:19	3:21	103	104	115	114
Blood screening panel 4 (n=50; 200)	HIV Duo[a], HBsAg II, Anti-HCV II, Syphilis	21	20	2:21	2:24	120	121	82	81

[a]HIV Duo is an assay for the parallel detection of HIV-1 p24 antigen, as well as antibodies to HIV-1 and HIV-2, with two separate determinations. ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILT, bilirubin total; Ca, calcium; Cl, chloride; CO2, bicarbonate; CREA, creatinine; GLUC, glucose; HAV, hepatitis A virus; HBc, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgG, immunoglobulin G; IgM, immunoglobulin M; K, potassium; Na, sodium; TOXO, toxoplasma; TP, total protein.

Table 5: Summary of workflow metrics for combined immunochemistry and clinical chemistry panels

Workflow (number of samples; requests)	Assays	Time to first result, min		Time to last result, h:min		Output, results/h		Median sample processing time, min	
		Visp/ Wroclaw	Seoul/ Heidelberg	Visp/ Wroclaw	Seoul/ Heidelberg	Visp/ Wroclaw	Seoul/ Heidelberg	Visp/ Wroclaw	Seoul/ Heidelberg
14 % IC/CC (n=200; 1347)	ALB, ALP, ALT, AST, B12, BILT, Ca, CHOL, CO2, CREA, CRP, Ca, Cl, FT4, GLUC, K, LH, Na, PHOS, PROG, pro-BNP, TNT-hs, TP, TSH, UA, Urea	2	2	2:34	2:34	639	641	59	65
14 % IC/ CC + STAT (n=200; 1381)	ALB, ALP, ALT, AST, B12, BILT, CHOL, CO2, CREA, CRP, Ca, Cl, FT4, GLUC, K, LH, Na, PHOS, PROG, pro-BNP, TNT-hs, TP, TSH, UA, Urea	2	2	2:34	3:11 (2:39)[a]	649	640	58 (STAT 18, 14)	62 (STAT 18, 22)
17 % IC/CC (n=200; 1403)	ALB, ALP, ALT, AST, B12, BILT, CHOL, CO2, CREA, CRP, Ca, Cl, FT4, GLUC, K, LH, Na, PHOS, PROG, Pro-BNP, TNT-hs, TP, TSH, UA, Urea	2	2	3:29[b]	3:19[b]	637	646	65	67

[a]Including reruns; 2:39 without reruns. [b]Time to last result increased by 45 and 55 min at the Visp/Wroclaw and Seoul/Heidelberg sites, respectively, due to an increase in immunochemistry requests from 14 % to 17 %. ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; B12, vitamin B12; BILT, bilirubin total; Ca, calcium; CC, clinical chemistry; CHOL, cholesterol; Cl, chloride; CO2, bicarbonate; CREA, creatinine; CRP, C-reactive protein; FT4, free thyroid hormone thyroxine; GLUC, glucose; IC, immunochemistry; K, potassium; LH, luteinizing hormone; Na, sodium; PHOS, phosphate; pro-BNP, pro-B-type natriuretic peptide; PROG, progesterone; STAT, short turnaround time; TNT-hs, troponin T-high sensitive; TP, total protein; TSH, thyroid stimulating hormone; UA, uric acid.

demonstrated high overall accuracy of cobas pure integrated solutions.

When comparing results from cobas pure integrated solutions with results from routine, randomly selected samples, the 53 applications chosen for inclusion in this study showed consistent results. This experimental design tested the overall system performance by automatically generating method comparisons using the evaluation tool WinCAEv. Although, the achieved analyte concentration ranges solely rely on the distribution within routine workloads at the time of testing, rather than an evenly spread distribution, the derived Passing–Bablok slopes and intercepts demonstrated good agreement. For the method comparisons vs. Roche analyzers, the median Passing–Bablok slopes for both clinical chemistry and immunochemistry assays were 1.00. The median bias at the medical decision point was 0.0 and −0.2 % for clinical chemistry and immunochemistry assays, respectively. For ISE, all comparisons were within ±5 % bias at the medical decision point. As these results demonstrate no systematic deviations at medical decision points, there should be a seamless transition from older Roche analyzers to the new cobas pure integrated solutions.

One strength of this study is the multi-center, multi-national design. The applications selected for inclusion were specifically chosen to broadly challenge the system in different ways (e.g. different viscosity of reagents or pipetting techniques) and a variety of assessment types were conducted to evaluate all aspects of performance. One limitation was the user feedback questionnaire, as answers may have reflected the personal preferences of the operators rather than more broadly-applicable information relating to the routine use of the system within busy analytical laboratories. As this study was conducted under routine-like conditions in real-world settings, pre-analytical effects could not be avoided; for example, for the routine simulation method comparisons, use of routine samples that were stored for 1–3 days at 4 °C before remeasurement on cobas pure integrated solutions, and which might require several calibrations on the routine systems, introduced additional bias. Nevertheless, the routine-like, real-world design is a strength, as all experiments were executed under these conditions and the results were able to provide a holistic picture of cobas pure integrated solutions in routine practice.

In conclusion, cobas pure integrated solutions demonstrates robust overall performance, supporting its

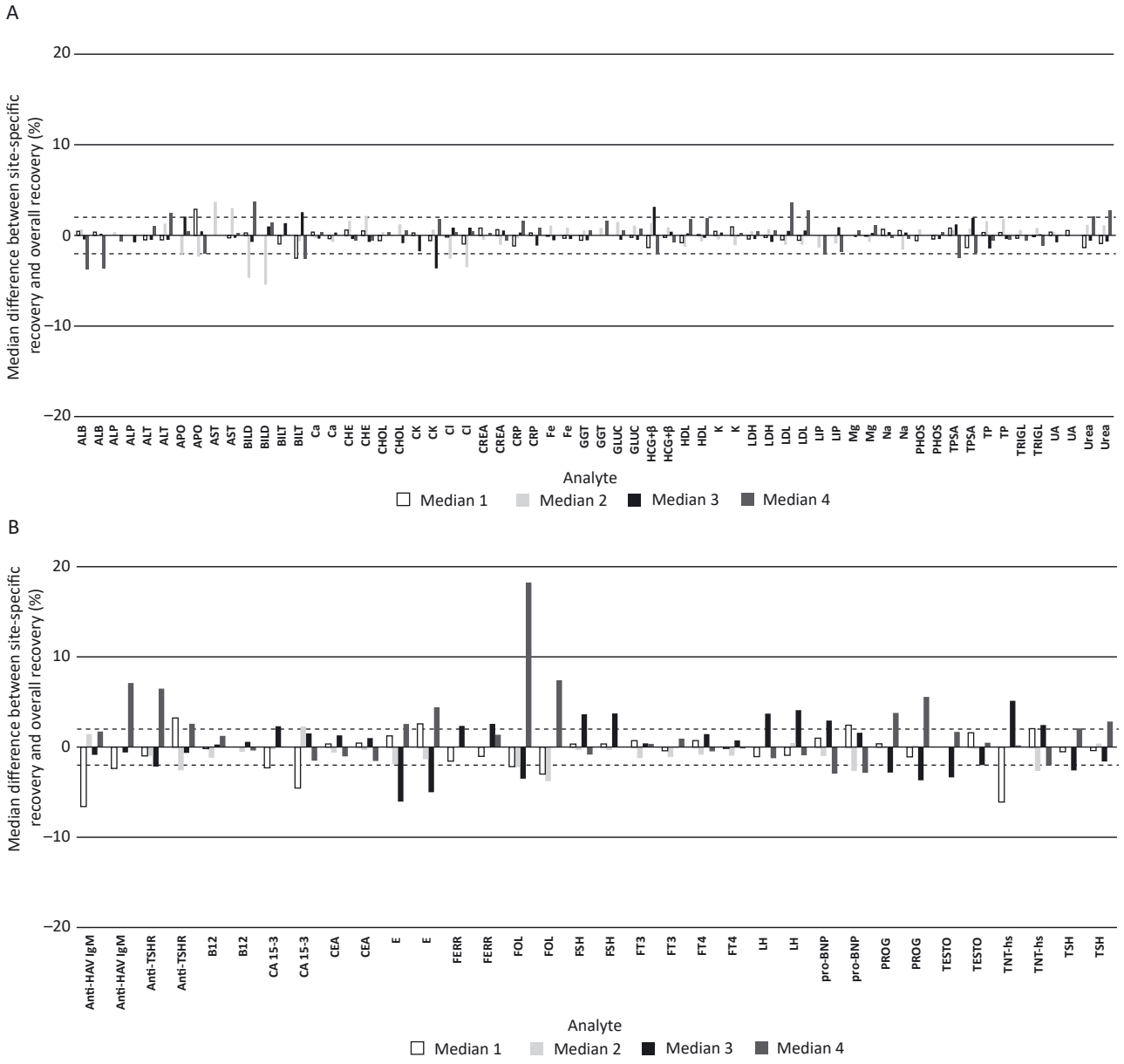

Figure 3: Inter-laboratory survey (ring trial): Median within-lab recovery vs. median across all sites for (A) clinical chemistry and (B) Elecsys immunochemistry assays. The dashed lines represent median recoveries within ±2 % of the median per assay for all sites. ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APO, apolipoprotein A1; AST, aspartate aminotransferase; B12, vitamin B12; BILD, bilirubin direct; BILT, bilirubin total; Ca, calcium; CA 15-3, cancer antigen 15-3; CEA, carcinoembryonic antigen; CHE, cholinesterase; CHOL, cholesterol; CK, creatine; Cl, chloride; CREA, creatinine; CRP, C-reactive protein; E, estradiol; Fe, iron; FERR, ferritin; FOL, folate; FSH, follicle stimulating hormone; FT3, free thyroid hormone triiodothyronine; FT4, free thyroid hormone thyroxine; GGT, γ-glutamyltransferase; GLUC, glucose; HAV, hepatitis A virus; HCG+β, human chorionic gonadotropin; HDL, high density lipoprotein cholesterol; IgM, immunoglobulin M; K, potassium; LDH, diglycosylated luteinizing hormone; LDL, low density lipoprotein cholesterol; LH, luteinizing hormone; LIP, lipase; Mg, magnesium; Na, sodium; PHOS, phosphate; pro-BNP, pro-B-type natriuretic peptide; PROG, progesterone; TESTO, testosterone; TNT-hs, troponin T-high sensitive; TP, total protein; TPSA, total prostate-specific antigen; TRIGL, triglycerides; TSH, thyroid stimulating hormone; TSHR, thyroid stimulating hormone receptor; UA, uric acid.

implementation into routine clinical laboratory practice and potential to further consolidate *in vitro* diagnostic testing in small-to-medium sized laboratories.

Acknowledgments: The planning and execution of this study required the dedication and support of many colleagues and staff across sites. The authors wish to thank their

staff at the five testing sites for study execution: Claudine Steiner-Weissen, Martin Furrer, Elke Sasse, Aleksandra Strzala, Aleksandra Znamiec, Hyojeong Nam, and David Krempel. The authors also wish to thank the following individuals at Roche Diagnostics for study management, monitoring, and support: Anita Blanche Ogolong, Flavio Bizzozzero, Claudia Stieber, Athanasios Sofianidis, Tanja Wolf, Heike Sauter, Sabine Mathis, Claudia Greinwald, Andrea Knorr, Claire Moon, and Min-Ji Kim. Third-party medical writing assistance, under the direction of the authors, was provided by Sophie Lavelle, MSc, of Ashfield MedComms, (Macclesfield, UK), an Inizio company, and was funded by Roche Diagnostics International Ltd (Rotkreuz, Switzerland). ELECSYS, COBAS, COBAS INTEGRA, COBAS PRO, and COBAS PURE are trademarks of Roche. All other product names and trademarks are the property of their respective owners. The Elecsys FT4 III assay is not approved for clinical use in the US.

Research funding: This study was funded by Roche Diagnostics GmbH (Mannheim, Germany).

Author contributions: H.B., F.P., and N.V. contributed to data acquisition, data analysis and interpretation, and manuscript writing and critical review. S.C., P.F., H.F., H.G., J.H., and D.R. contributed to data acquisition and manuscript writing and critical review. M.F.R. contributed to data analysis and interpretation, and manuscript writing and critical review. J.F., K.K., and C.S-T. contributed to study conception and design, data acquisition, data analysis and interpretation, and manuscript writing and critical review. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: H.B., S.C., P.F., H.F., H.G., J.H., F.P., D.R., M.F.R. and N.V. report provision of funding for the present study from Roche Diagnostics to their institute. J.F. is an employee of Roche Diagnostics International Ltd (Rotkreuz, Switzerland) and holds stocks in F. Hoffman-La Roche Ltd. K.K. and C.S-T. are employees of Roche Diagnostics GmbH (Mannheim, Germany) and hold stocks in F. Hoffmann-La Roche Ltd.

Ethical approval: The study was approved by the Institutional Review Boards or Equivalent Committees for the respective study sites: Landesärztekammer Baden-Württemberg (Heidelberg and Ludwigsburg: approval no. F-2019-128), the Asan Medical Center Institutional Review Board (Seoul: approval no. 2020-0975), and La Commission cantonale d'éthique de la recherche sur l'être humain in Lausanne (Visp: project no. 2020-00424). For the Wroclaw site, no approval was required as only control materials were used. The study complied with all relevant national regulations and institutional policies, and was performed in accordance with the principles of the Declaration of Helsinki.

References

1. Findeisen P, Zahn I, Fiedler GM, Leichtle AB, Wang S, Soria G, et al. Doubling immunochemistry laboratory testing efficiency with the cobas e 801 module while maintaining consistency in analytical performance. Clin Biochem 2018;58:86–93.
2. Kunst A, Grawitz AB, Engeldinger W, Koch W, Luthe H, Stockmann W. WinCAEv—a new program supporting evaluations of reagents and analyzers. Clin Chim Acta 2005;355S:361. (Abstract WP6.04).
3. Stockmann W, Engeldinger W, Kunst A, McGovern M. An innovative approach to functionality testing of analysers in the clinical laboratory. J Autom Methods Manag Chem 2008;2008:183747.
4. Passing H, Bablok W. A new biometrical procedure for testing the equality of measurements from two different analytical methods. Application of linear regression procedures for method comparison studies in clinical chemistry, Part I. J Clin Chem Clin Biochem 1983;21: 709–20.

Supplementary Material: This article contains supplementary material (https://doi.org/10.1515/labmed-2022-0137).