VILNIUS UNIVERSITY

Dalius Vitkus

DEVELOPMENT, TESTING AND IMPLEMENTATION OF QUALITY ASSURANCE MODEL FOR LABORATORY ASSAYS

Summary of Doctoral Dissertation
Biomedical Sciences, Medicine (07B)

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VILNIAUS UNIVERSITETAS

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LABORATORINIŲ TYRIMŲ KOKYBĖS UŽTIKRINIMO MODELIO SUKŪRIMAS, IŠBANDYMAS IR ĮDIEGIMAS

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List of Abbreviations

ALT – alanine aminotransferase

ALP – alkaline phosphatase

AST – aspartate aminotransferase

CDC – Centers for Disease Control and Prevention

CLIA – Clinical Laboratory Improvement Amendments

CSN – normal level of control serum

CSP – pathological level of control serum

CLSI – Clinical and Laboratory Standards Institute formerly NCCLS

EQA – External quality assessment

GGT – γ-glutamiltransferase

IFCC – International Federation of Clinical Chemistry and Laboratory Medicine

ISO – International Organization for Standardization

IVD – *in vitro* diagnostics

LIS – laboratory information system

QC – quality control

RMSDI – Running Mean of Standard Deviation Index

SCE – Scandinavian Committee for Enzymes

SDI – Standard Deviation Index

STAT – short turn around time

TAT – turn around time

TQM – total quality management

Table of Contents

1. Introduction

According to the definition of International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) clinical chemistry is the discipline with the application of chemical, molecular and cellular concepts and techniques to the understanding and the evaluation of human health and disease. At the core of the discipline is the provision of results of measurements and observations relevant to the cause of disease, maintenance of health, and conversion of this data into specific and general patient- and disease-related information at the laboratory-clinician interface. Today laboratories of clinical chemistry are capable to provide customers wide spectrum of tests counting more than 1000 specific measurable quantities on the list. Results of laboratory tests usually are background for clinical decision making. Therefore it is of major importance to achieve reliable accuracy, precision, repeatability, reproducibility and comparability of tests results. It becomes critical when laboratory tests are performed for the same patient and different measurement procedures or different *in vitro* diagnostic (IVD) medical devices are applied for the same purpose. Highly effective quality system and methods for quality assurance have to be implemented to achieve satisfactory results.

Different topics on quality management systems have been widely reviewed in the scientific literature. Various approaches for quality assurance have been described in details and have got an acceptance by the professionals in different countries. But still there is no method alone capable to assure and assess agreement of tests results then analyzing patient samples on different IVD devices or by different measurement procedures. To achieve that purpose reference materials and reference measurement procedures have been introduced for some analytes and the numbers of these materials and measurement procedures are growing constantly. Sophisticated statistical approaches and extended external quality assessment schemes are available for the same purpose. All these improvements have led to remarkable improvement in quality of clinical laboratory test results.

Different IVD instruments and measurement procedures applications for the same analyte remain common for bigger laboratories and health care institutions where decentralized testing is being used. Even in small laboratories or health care institutions separate IVD devices are dedicated for day and night shifts. Set of traditional quality assurance tools could be inadequate to achieve acceptable comparability when results originate from different testing sites or different IVD instruments.

Almost three decades clinical laboratories in Lithuania have been under pressure to introduce measures for quality improvement but only with quite simple QC procedures were succeeded in most of them. Critical changes have taken place in most of Lithuanian clinical laboratories during last two decades: manual methods were replaced by standardized automated procedures; in-house reagents were displaced by commercial reagent kits and number of new tests and measurement procedures were introduced. While the analytical quality aspects at the same time remained at the status of 1980-ies – 1990-ies and are limited with daily QC and formal participation in EQA scheme predominantly. Lack of scientific approach to analytical quality requirements, absence of national EQA scheme and slow movements towards standardization are the major weakness spread between Lithuanian clinical laboratories. This makes reason for scientific research in the field of analytical quality requirements, models for quality assurance and total quality management.

Under the strong economical pressure and constantly rising expectations of customers (clinicians and patients) clinical laboratories are faced with the challenge: to do as much as possible tests with the best quality in the short period of time. This makes scientific approach to be applied not only in analytical quality but in total quality management obviously. There were no scientific papers on total quality management in clinical laboratories published in Lithuania so far.

2. Aim of the study

The aim of the study was to evaluate effectiveness of traditional quality control methods applied in laboratories of clinical chemistry using native samples, assess the comparability of test results received by different type of equipment and/or by different measurement procedures and propose the quality assurance model for the detection and minimization of numbers of incompliance's and rational use of resources at the laboratories of clinical chemistry.

3. Tasks of the study

1. To evaluate how the results of native sample measurements in the group of most common clinical chemistry analytes from separate instruments and/or different measurement procedures meet the recommended analytical quality requirements.
2. To evaluate the QC results of same group of analytes and compare with the evaluation of the results from native samples.
3. To test split-sample model for use in quality assessment of the same laboratory tests performed on separate instruments.
4. To investigate process improvement possibilities and its impact on laboratory workflow and analytical performance.
5. To develop unsophisticated quality assurance model for routine laboratories of clinical chemistry, suitable to detect and minimize incomparability of test results and assure rational use of laboratory resources.

4. Significance and novelty of research work

Comparability of QC and native sample test results, performed on separate instruments or by different measurement procedures at the same laboratory was investigated and evaluated.

Quality of laboratory investigations was studied by original way – not only through the analytical quality control and assurance, but also through the workflow in different laboratory activities and process improvement. Process improvement implementing lean thinking was performed for the very first time in Lithuania.

There were no research studies on process improvement as tool for quality management in Lithuanian clinical laboratories carried out. Simple and practical model

for quality assurance in routine clinical laboratories under rapidly changing laboratory environment was developed.

5. Materials and methods

5.1. Blood serum samples

For experiments with native samples remainders of the serum from laboratory testing were used with no evidence of hemolysis and lipemia. Specimens were collected in plastic evacuated tubes with inert gel barrier (BD, USA) by standard venepuncture. To get sufficient amount of material pools of samples with similar concentrations (activities) of analytes were prepared. If sufficient amount of sample with high level of analyte of interest was available, sample was diluted with 0.9% NaCl solution to get lower values. Pools were tested for anti-HIV1/2, anti-HCV and *Treponema pallidum* antibodies, hepatitis B surface antigen (HBsAg). Pools with at least one positive marker were discarded. Pools with negative markers were frozen and stored at -20°C until the day of testing. On the day of testing samples were thawed for 1 hour and centrifuged for 10 min at 2500g to exclude precipitates. For split-sample testing pools of four (five) levels of concentration or activity were collected. After centrifugation samples were split for two instruments and measured in triplicate. Testing samples were included in daily routine batches randomly.

5.2. *In vitro* medical devices

5.2.1. Automated clinical chemistry analyzers

In order to collect more objective results and minimize the influence of the manufacturer IVD devices from different manufacturers were used in the study:

- Automated clinical chemistry analyzer OpeRA (former Bayer, now Siemens, Germany),
- Automated clinical chemistry analyzer Cobas Mira Plus (Roche Diagnostics, Switzerland),
- Automated analyzer Dimension RxL (former Dade Behring, now Siemens, Germany)
- Integrated clinical chemistry and immunochemistry system Architect ci8200 (Abbott, USA).

To keep the confidentiality it was avoided to use the names of instruments were it was possible. Experimental numbers were used in most of cases.

5.2.2. Calibration and control materials

Commercially available analyzer specific calibrators and calibrators from the independent companies were used: Bayer, Randox (Randox Laboratories Ltd., UK), Dade Behring and Abbott. For the measurement of activity of enzymes calculation factors provided by the reagent supplier were used.

For the QC measurements analyzer specific QC material was partly used provided by Bayer. Generally QC materials were from independent manufacturer.

- Lyophilized multiparameter commutable human serum based QC materials:
  - Human Control Serum Level 2 (Randox Laboratories Ltd., UK),
  - Human Control Serum Level 3 (Randox Laboratories Ltd, UK);
- Liquid multiparameter commutable human serum based QC materials:
  - Liquicheck Level 1 (Bio-Rad Laboratories Inc., JAV),
  - Liquicheck Level 2 (Bio-Rad Laboratories Inc., JAV),
  - Liquicheck Level 3 (Bio-Rad Laboratories Inc., JAV).

EQA samples were supplied by impartial EQA provider Labquality OY (Finland) and RIQAS (Randox International Quality Assessment Scheme, Randox Laboratories Ltd, UK). EQA samples provided by Labquality OY were lyophilized or liquid. In some programs reference materials as well as native and processed human serum samples were used. EQA samples from RIQAS were lyophilized human serum based.

5.3. Analytical methods and measurement procedures

ASAT activity was measured by α-ketoglutarate, Asp / NADH, photometry (IFCC/SCE without pyridoxal-5-phosphate) method, ALT activity – by Ala / NADH, photometry (IFCC/SCE without pyridoxal-5-phosphate) method. Reagents manufacturers: former Bayer, later Siemens, bioMerieux (France), Abbott. ALP activity was measured by IFCC compatible method (p-nitrophenylphosphate, AMP buffer / pNP, photometry). Reagents manufacturers: former Bayer, later Siemens, Abbott. GGT activity was measured by GLUCANA, γ-glutamil-3-carboxi-4-nitroanilide (Szasz modification) method. Reagents manufacturers: former Bayer, later Siemens, Abbott.

Concentration of glucose was measured by glucose oxidase / 4-aminoantipyrin method (former Bayer, Randox), later by reference hexokinase method (former Dade Behring, now Siemens, Abbott). Concentration of total protein was measured by Biureth method (former Bayer, now Siemens, and Abbott).Albumin concentration was measured by bromcresol green method (former Bayer, now Siemens, and Abbott). Total bilirubin concentration was measured by modified Jaffe method (Abbott, Randox) and Dimethyl Sulfoxide method (former Bayer, now Siemens).

5.4. Statistical analysis of data

For statistical analysis ‘MS Excel for Windows’ and ‘Statistica for Windows 6.0’ software packages were used. Basic QC statistics were calculated. Statistical significance was determined by using the Student’s t-Test. A p value of less than 0.05 was considered as significant.

For evaluation of results from split–sample testing software for method evaluation in clinical chemistry ’Method validator software’, version 1.1.10.0 (Philippe Marcuis, www.multiqc.com) was used together with ’Analyse–it for Microsoft Excel‘ (Analyse-it Software, Ltd, UK). Both softwares used Passing–Bablok regression analysis for linearity testing and determination of slope and intercept. The 95% confidence interval for the intercept A was used to test the hypothesis that A=0. This hypothesis was accepted if the confidence interval for A contains the value 0. If the hypothesis was

rejected, then it was concluded that A is significant different from 0 and both methods differ at least by a constant amount.

The 95% confidence interval for the slope B was used to test the hypothesis that B=1. This hypothesis was accepted if the confidence interval for B contains the value 1. If the hypothesis was rejected, then it was concluded that B is significant different from 1 and there is at least a proportional difference between the two methods.

Statistical evaluation of EQA results was performed by RIQAS and Labquality. Workload calculations were performed by Abbott GmbH & Co. KG (Germany).

6. Results

6.1. Investigation of analytical characteristics of most often used routine analytes

Set of 8 most often routinely performed analytes was chosen for experiments of comparisons: albumin, glucose, total bilirubin, total protein, ALT, AST, ALP and GGT. Two analytical instruments coded BIO001 and BIO002 were used. The same methods for analyte determination were used on both instruments, but reagents were from different manufacturers. BIO001 was an open system – reagents used were from independent producer. BIO002 was partly open system – reagents were from the same manufacturer as of system. 40 analytical measurement runs were carried out during 4 months. All analytes were measured 320 times on each instrument. Results are presented in table 1. Analytical performance data were compared to the analytical quality requirements based on biological variation. Evaluation of bias was based on long term EQA results. Expanded uncertainty was calculated.

It was found that results of ALT, albumin, total protein, GGT and ALP from instruments BIO001 and BIO002 were significantly different ($p<0.01$). Meanwhile it was no significant difference for AST, total bilirubin and glucose. It was found that analytical CV's for albumin, AST, total protein, glucose and ALP results on BIO001 and for AST and total protein on BIO002 exceeded desirable imprecision I – half of intra-individual biological variation of particular analyte. Analytical performance of listed analytes was considered to be dissatisfactory. Attention should be paid especially to the analytical performance data of AST and total protein, where $CV_{A1}>CV_{A2}>I$.

Calculations of analytical bias were based on EQA data from RIQAS because there were no uncertainty data of calibration materials available from the manufacturers. As an estimate of bias RMSDI expressed as number of SDI was used. Expression of RMSDI was calculated on 10 consequent SDI results covering 5 months of participation in EQA and including 4 months then experiment was carried out. Desirable quality specifications for RMSDI do not exist, that's why estimate of bias was also calculated and expressed in percent according to the formula:

$$Bias_{expected} = (S_2 \times RMSDI / X_2) \times 100.$$

For the calculation purposes output group of EQA participants was considered as homogenous and difference of variances in output group and within the laboratory as negligible. Bias estimates were calculated for BIO002 only because no EQA data for BIO001 were available.

It was shown that positive bias for AST and negative bias for total bilirubin exceeded desirable bias limit calculated from biological variation of the analytes.

Total allowable error was calculated according to the formula:

$$TE_A = Bias + 1{,}65CV_{A2.}$$

It was found TE_A(AST) > TE(AST) with both imprecision and bias exceeding desirable specification limits, and TE_A(total bilirubin) > TE(total bilirubin) exceeding limits bias only.

Expanded uncertainty for BIO002 results was calculated:

$$U = ((S_2)^2 + (RMSDI \times S_{EQA})^2)^{1/2}.$$

6.2. QC results

QC data analysis results are presented in table 2. It was found that long term analytical CV of albumin and total protein on both instruments, glucose on BIO002 and ALP on BIO001 exceeds desirable CV limits. For the instrument BIO001 control material from independent company was used while for BIO002 – from the reagents and instrument manufacturer. It was considered as inappropriate for evaluation and only very general considerations were done.

It was found that levels of albumin, total protein and ALP in BIO002 CSN material were in the pathological level, and all but glucose level in BIO001 CSN was in pathological level too. This finding identified that control materials predefined to be in normal levels of analytes actually were in pathological level and were not suitable for evaluation of analytical performance in the region of healthy subject.

EQA results for BIO002 only were available and trends for ALT (+1,15S), AST (+0,94S) and total bilirubin (–1,07S) did not agree with QC results or no shifts from expected mean were identified in QC results.

Table 1. Results of analytical characteristic investigation of the set of routine analytes

Analyte	Data from BIO001			Data from BIO002			p	Desirable imprecision, I, %	Bias		Desirable bias, %	Expanded uncertainty U, meas. units	Total error TE_A, %	Total allowable error TE, %
	X_1	S_1	CV_{A1}, %	X_2	S_2	CV_{A2}, %			RMSDI	%, expected				
ALT, U/L	51,70	4,37	8,45	47,23	4,34	9,18	<0,01	12,2	1,15	10,6	12	10	25,7	32,1
Albumin, g/L	44,94	1,79	**3,98**	42,76	0,64	1,48	<0,01	1,6	-0,79	1,17	1,3	2,7	3,8	3,9
ASAT, U/L	57,48	8,24	**14,33**	55,68	3,78	**6,79**	0,21	6,0	0,94	**6,38**	5,4	10	17,6	15,2
Total protein, g/L	62,20	1,64	**2,63**	61,26	0,95	**1,55**	<0,01	1,4	-0,44	0,68	1,2	2,35	3,2	3,4
Total bilirubin, µmol/l	22,44	2,60	11,57	22,59	2,77	12,27	0,81	12,8	-1,07	**13,3**	10,0	6,9	**33,5**	31,1
GGT, U/l	58,23	2,34	4,01	60,08	1,33	2,21	<0,01	6,9	-0,03	0,13	10,8	3	3,8	22,2
Glucose, mmo/l	5,73	0,17	2,96	5,76	0,16	2,82	0,48	2,9	-0,13	0,7	2,2	0,36	5,4	6,9
ALP, U/l	247,4	15,16	**6,13**	262,8	6,21	2,36	<0,01	3,2	-0,33	1,56	6,4	18	5,5	11,7

Table 2. QC data analysis results

Analyte	Data from BIO001								Data from BIO002							
	CSN				CSP				CSN				CSP			
	Expected mean	X	S	CV, %	Expected mean	X	S	CV, %	Expected mean	X	S	CV, %	Expected mean	X	S	CV, %
ALT, U/L	55	52,28	3,25	6,21	118	109,71	7,96	7,26	35	33,8	1,81	5,35	119	120,9	4,22	3,50
Albumin, g/L	43,5	45,41	0,96	2,12	30,3	31,03	0,69	2,22	34	34,32	0,79	2,30	26	25,53	0,68	2,65
ASAT, U/L	51	52,52	2,26	4,30	133	130,61	4,77	3,65	38	38,4	2,10	5,46	177	178	6,13	3,44
Total protein, g/L	58,9	59,66	2,28	3,82	45,4	42,83	1,04	2,44	56	57,37	1,59	2,78	46	45,62	1,01	2,21
Total bilirubin, µmol/l	27,7	24,29	1,46	6,02	83,2	88,29	5,73	6,49	8	7,91	0,64	8,09	86	88,33	5,57	6,31
GGT, U/l	51	52,31	2,70	5,17	n.d.	n.d.	n.d.	n.d.	33	33,3	1,05	3,15	100	97,09	2,79	2,87
Glucose, mmo/l	6,1	5,8	0,13	2,23	15,5	15,4	0,39	2,53	5,20	5,04	0,16	3,10	16,6	16,75	0,55	3,26
ALP, U/l	232	230,59	14,63	6,34	411	400,34	16,35	4,08	236	233,7	6,34	2,71	402	406,9	11,8	2,90

n.d. – no data (due to incommutable QC material)

6.3. Split-sample testing

Serum samples for split–sample testing were prepared according the procedure described in chapter 3.1. 20 samples for each were prepared to cover clinically significant intervals of analytes concentrations (activities). Results of split–sample testing are presented graphically in figures 1–7 in plots of differences and Passing–Bablok agreement between two different analyzers. The way to present results of split-sample testing as plots of differences and Passing–Bablok agreement found to be most convenient to analyze the differences in whole linearity range or in the range of clinical decision making. Passing-Bablok regression analysis graph visualizes character of the difference: proportional or constant.

There were 4 samples used for split–sample testing to simplify the procedure for the comparisons. Samples were collected in a way to cover most clinically significant regions of the linearity range. Results of 4 split–sample testing are presented in figures 8–14. 4 split–samples testing was found to be inadequate for albumin and glucose while for the rest of tests identical results were received as with 20 samples. We suggested to use five levels of split–samples instead of four. Later experiments were done with 5 levels of split–samples. We found split–sample testing to be most optimal then testing for identity of results received on separate IVD instruments at the same laboratory.

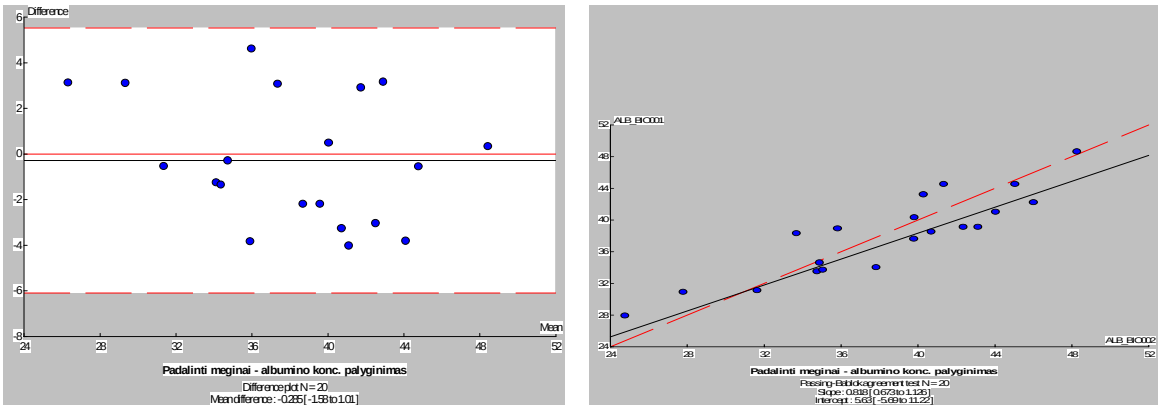


Figure 1. Plot of differences and Passing–Bablok agreement of albumin results on two different analyzers.

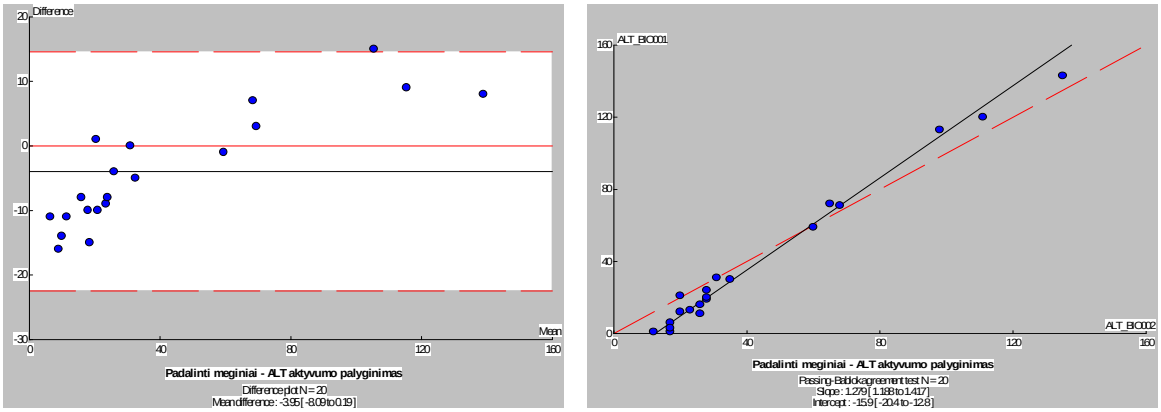


Figure 2. Plot of differences and Passing–Bablok agreement of ALT activity results on two different analyzers.

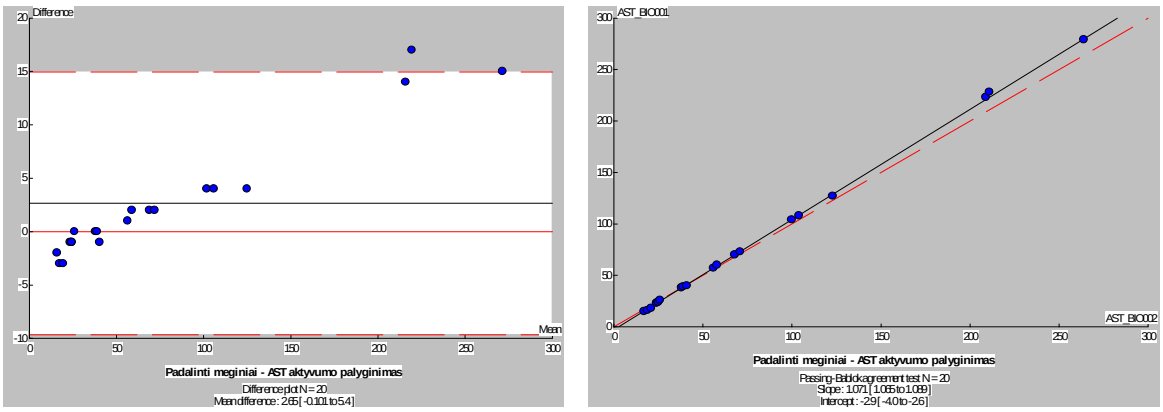


Figure 3. Plot of differences and Passing–Bablok agreement of AST activity results on two different analyzers.

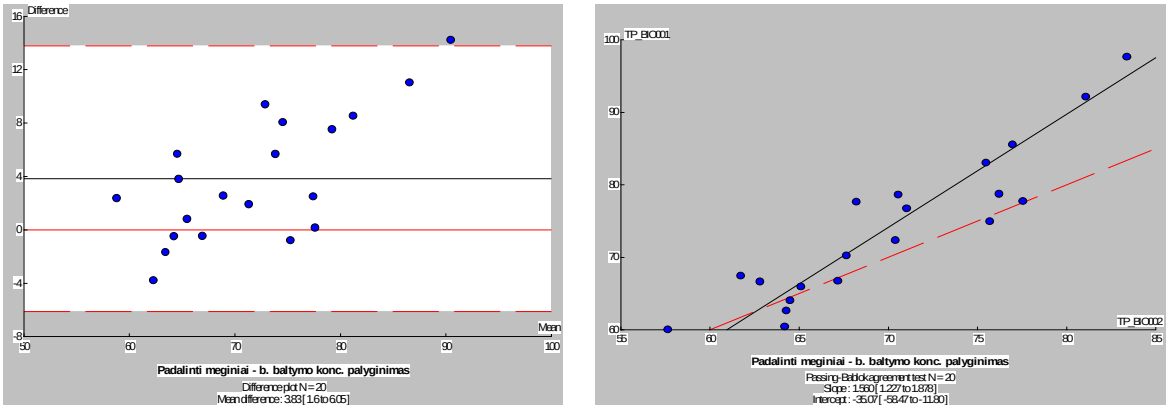


Figure 4. Plot of differences and Passing–Bablok agreement of total protein results on two different analyzers.

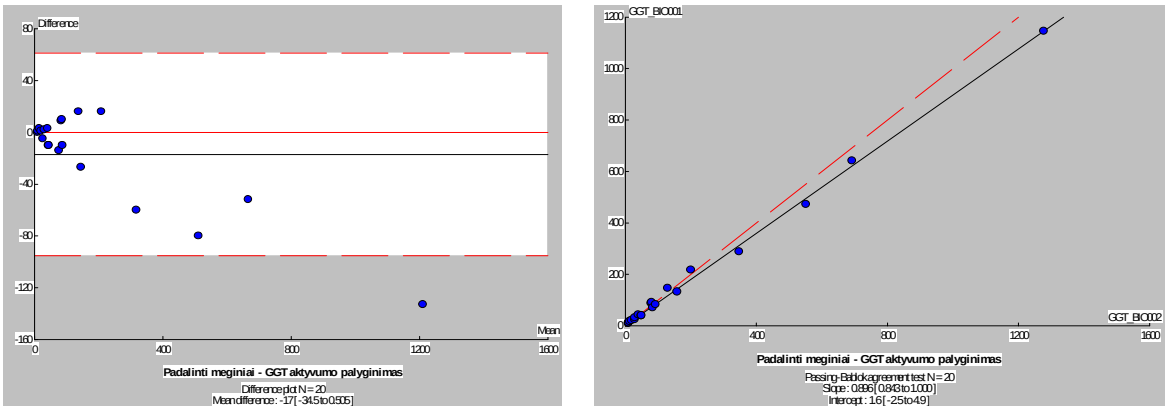


Figure 5. Plot of differences and Passing–Bablok agreement of GGT activity results on two different analyzers.

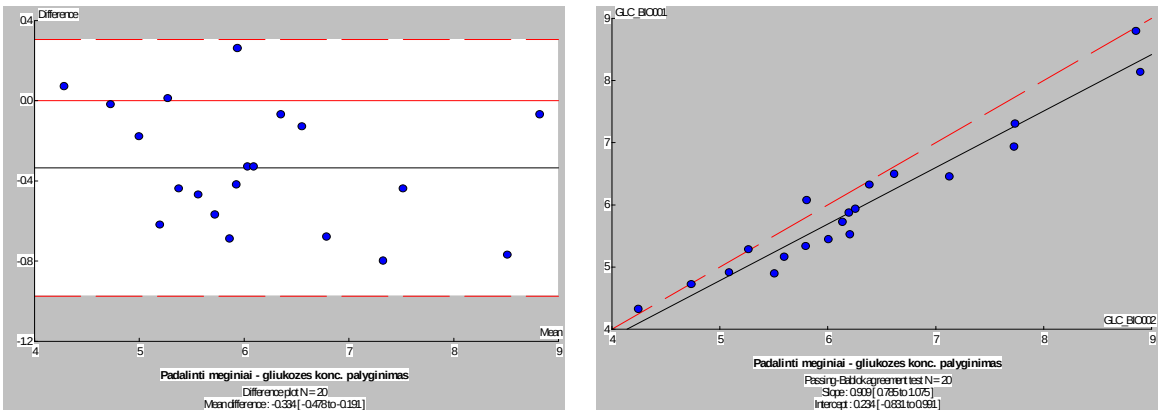
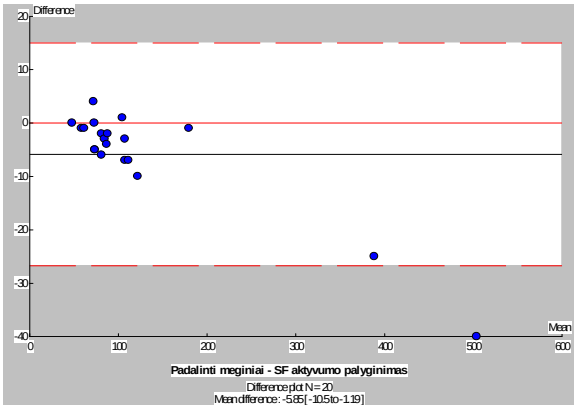


Figure 6. Plot of differences and Passing–Bablok agreement of glucose results on two different analyzers.



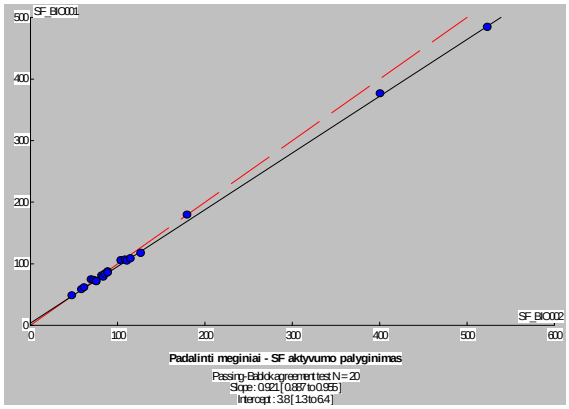


Figure 7. Plot of differences and Passing–Bablok agreement of ALP activity results on two different analyzers.

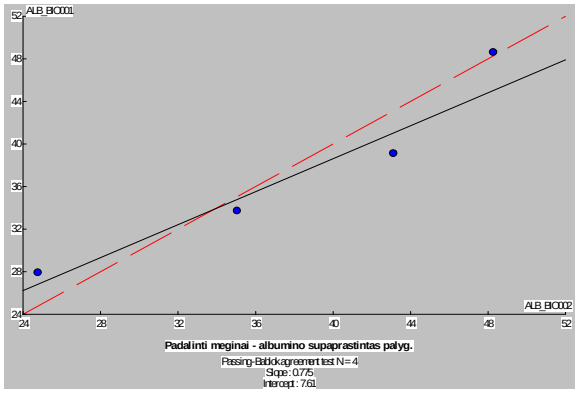


Figure 8. Passing–Bablok agreement of albumin results by split–sample testing

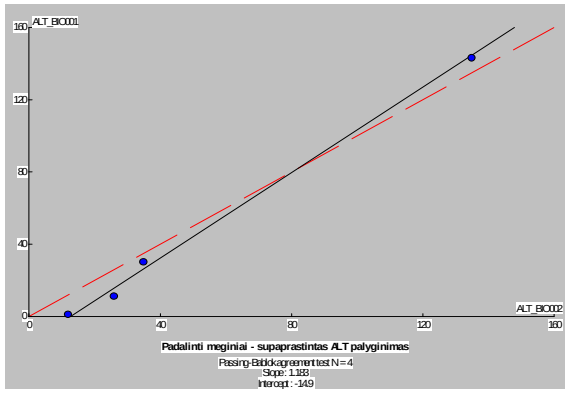


Figure 9. Passing–Bablok agreement of ALT results by split–sample testing

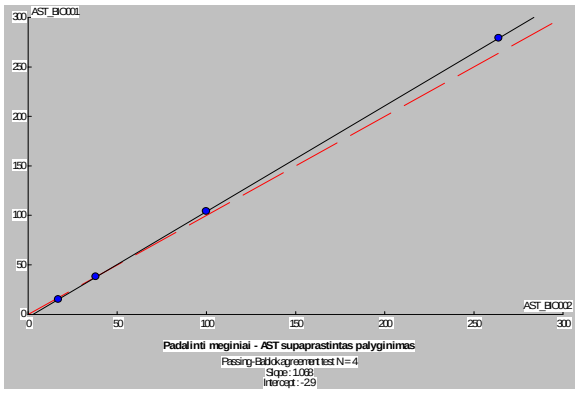


Figure 10. Passing–Bablok agreement of AST results by split–sample testing

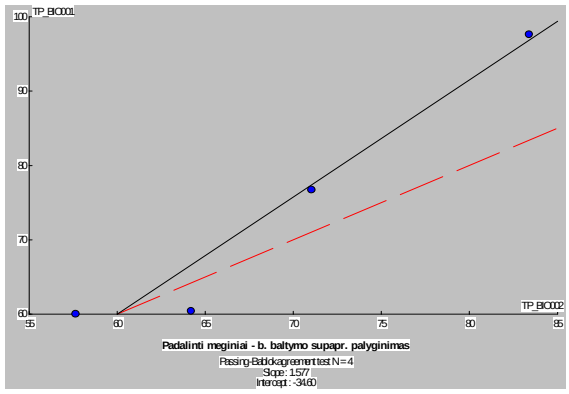


Figure 11. Passing–Bablok agreement of total protein results by split–sample testing

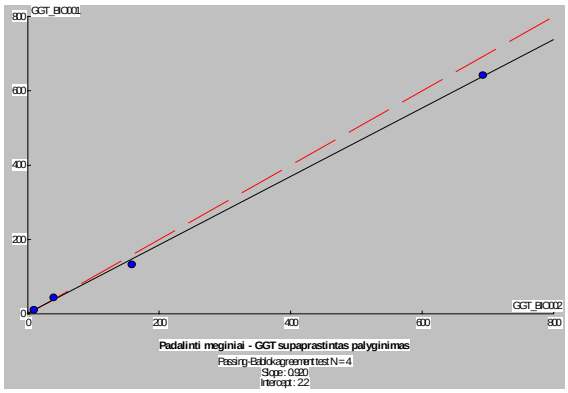


Figure 12. Passing–Bablok agreement of GGT results by simplified split–sample testing

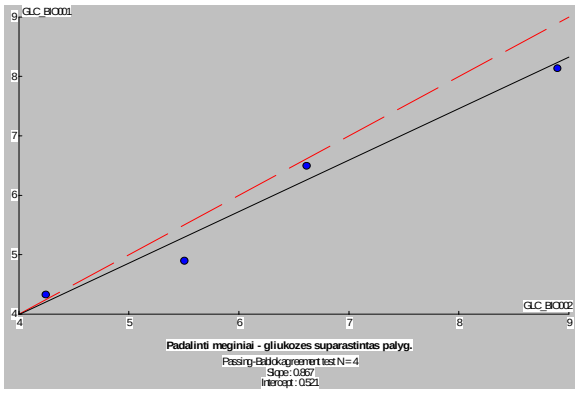


Figure 13. Passing–Bablok agreement of glucose results by simplified split–sample testing

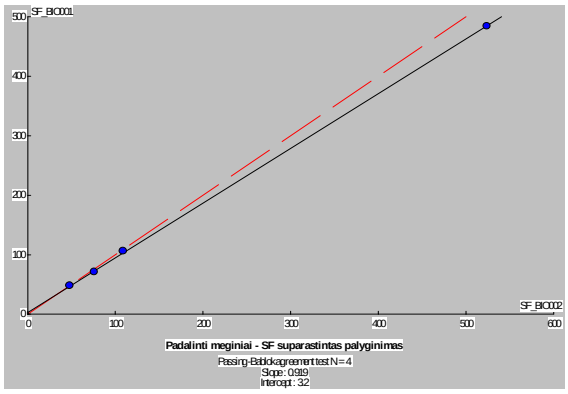


Figure 14. Passing–Bablok agreement of ALP results by split–sample testing

6.4. Process improvement

As a starting point for the evaluation of laboratory workload data of year 2005 was chosen. 1 109 369 test were performed in 5 laboratories at the Centre of Laboratory Diagnostics (CLD) during 2005.

Table 3. The structure and workload of the CLD in 2005.

Laboratory	Number of tests	Separate parts of laboratory
Laboratory of Biochemistry	750 815	POCT, radioimmunoassay
Laboratory of Hematology and Cytology	247 545	
Laboratory of Microbiology	34 698	Divisions of virology and molecular diagnostics
Laboratory of Clinical Immunology	15 027	
Blood Bank Laboratory	61 284	

To identify and analyze existing processes within the laboratory and improve workflow efficiency labor utilization, urgent request capability, turn around time (TAT) and to decrease error rates workflow analysis was performed by lean. A lot of 'waste' or non-value added activities were identified: tube passes 24 steps and information – 13 steps, manual work should be used at 37 steps before the result could be released to the customer (Figure 15). There were also found 9 IVD instruments and 8 different software types used for routine testing, no connection between instruments and LIS despite exiting advanced LIS at the laboratory. There was calculated mean time to STAT test release – 1hour 10 min at off peak time and 2 hour 20 min at peek time. Mean time to routine result release – 4 hours.

Using value stream mapping areas for process improvement were identified: laboratory work area consolidation (microbiology and immunochemistry), instruments (clinical chemistry and immunochemistry), more effective sample flow (less aliquots); more effective information flow (bar codes on samples and request forms combined with middleware solution); automation of pre-analytical processes.

The results of workload simulation analysis have shown that implementation of two identical integrated analytical instruments with clinical chemistry and immunochemistry tests in one platform will result in TAT decrease to 36 min and STAT to – 29.4 min after arrival to the laboratory during off peak and to 46 and 37 min during high peak time respectively. Theoretically 95 % of STAT clinical chemistry tests could be released during 26 min and 95 % of routine clinical chemistry tests – during 40 min. In high peak period 44 % of instrument capacity would be used.

As it is shown in Fig. 17 after lean implementation samples have to pass 13 steps and information – 3–4 steps.

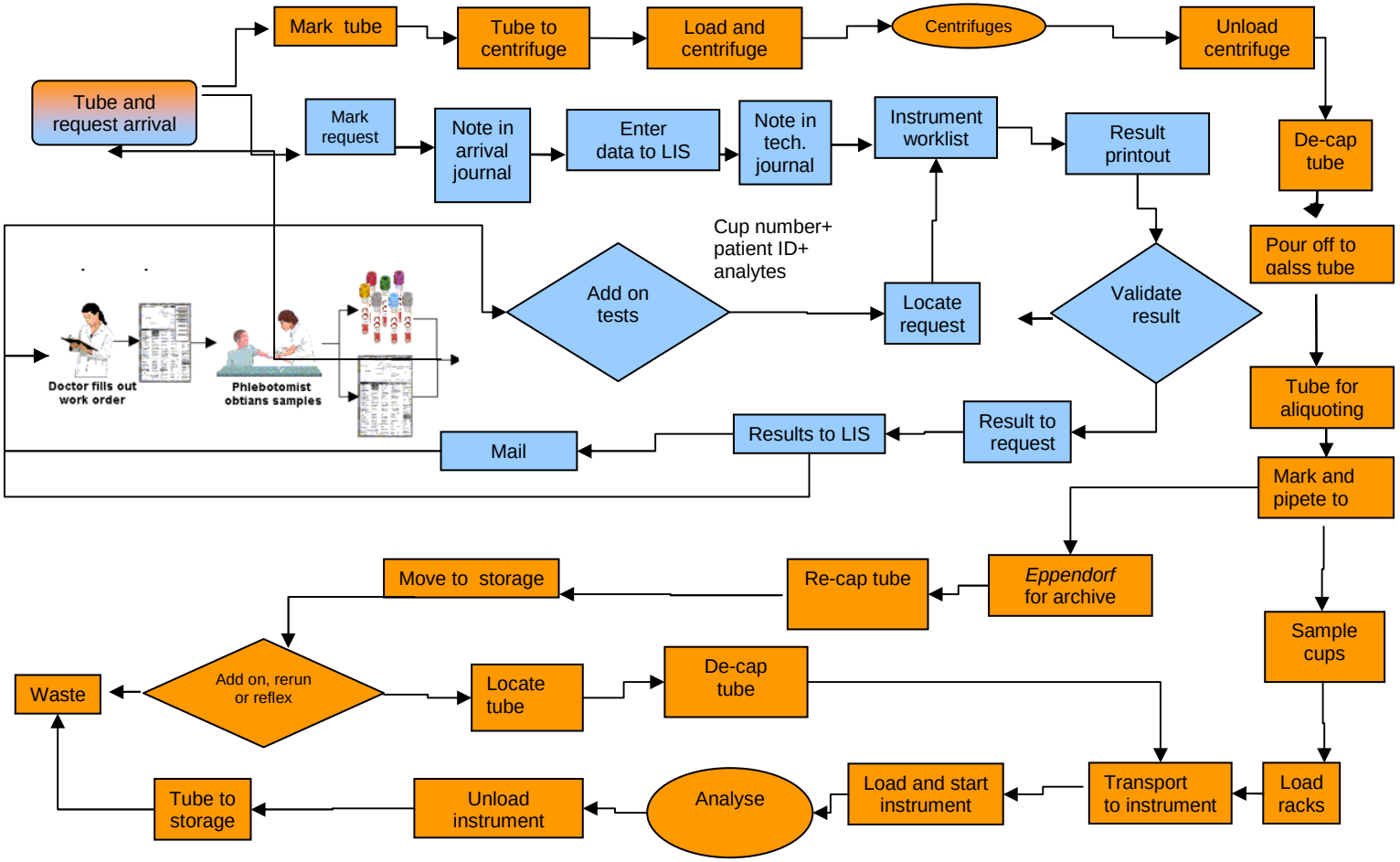
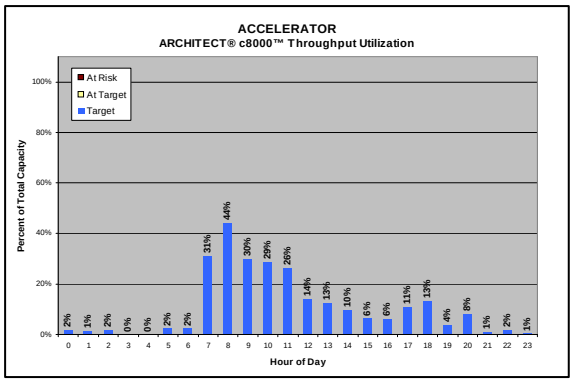
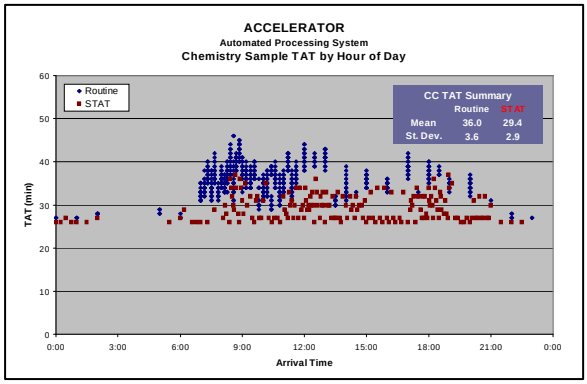


Figure 15. Information and sample flow in the laboratory of Biochemistry

Capacity Planning



TAT analysis



Efficiency

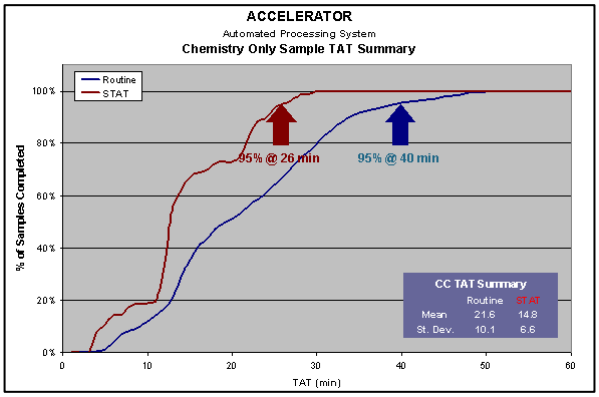


Figure 16. Results of workload simulation analysis

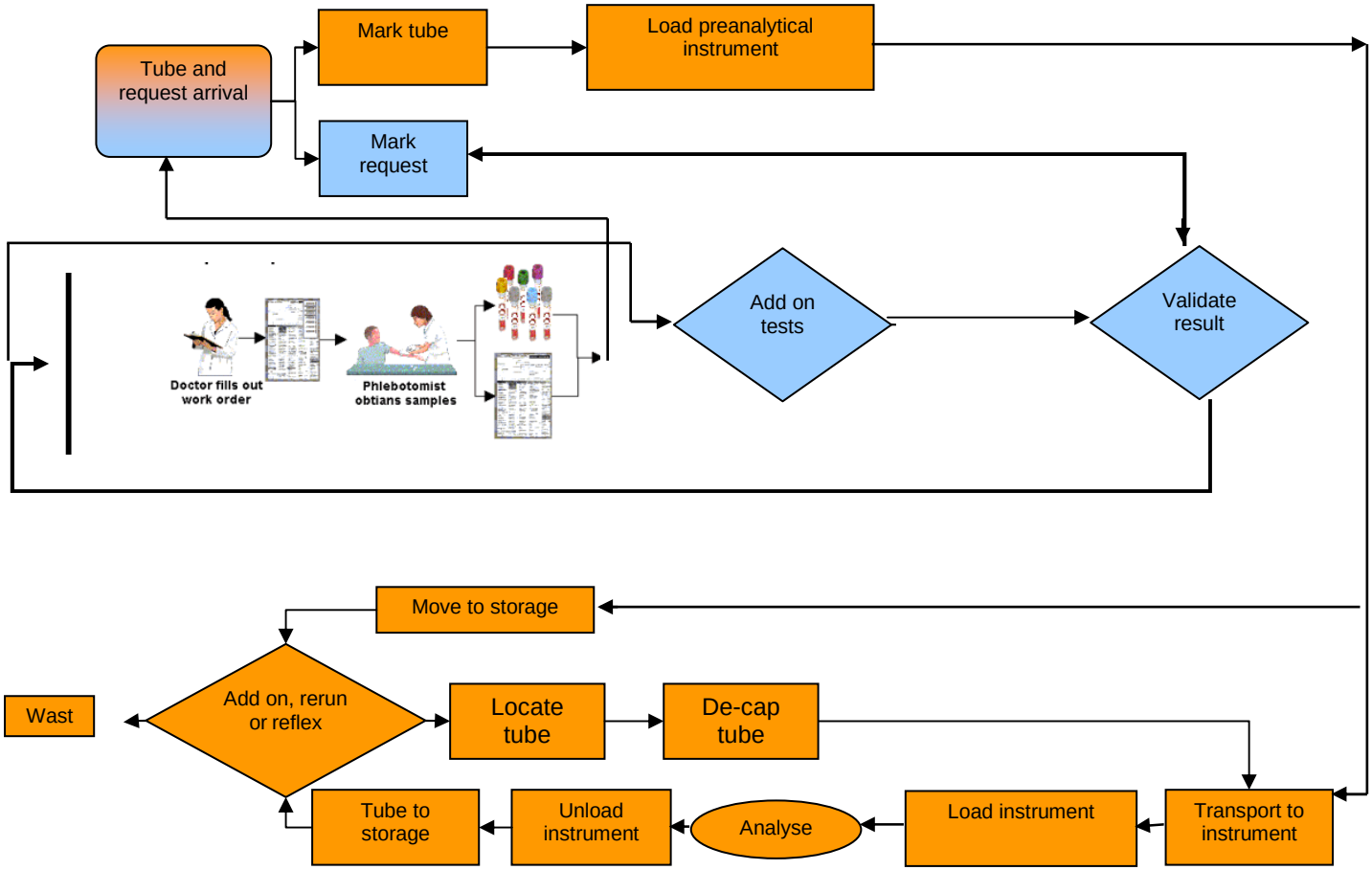


Figure 17. Information and sample flow in the laboratory of Biochemistry after lean

6.5. Analytical characteristics investigation of integrated analytical systems

After lean implementation the evaluation of analytical performance of the optimized laboratory was studied for 12 months by running 3 levels of QC daily 1–3 times each. All the tests were performed using reagents recommended by the manufacturer of the instruments. QC data were compared to the cumulative QC data from the laboratories using the QC material around the world. Data from instrument used before lean implementation was added to the comparisons. Cumulative QC data were calculated in collaboration with Bio–Rad Laboratories Inc. (USA). Data evaluation results are presented in Table 4.

Most of analytes after lean implementation have reached less inaccuracy: analytical CV's decreased for AST, ALP, GGT, total bilirubin and glucose, for total protein – remain stable and less when cumulative CV from different laboratories (except ALP).

Desirable analytical performance remained unreached for total protein mainly due to narrow interval of intra-individual biological variation 2.7 %. To reach the analytical goal $CV<0{,}5CV_I$ for total protein is a challenge, even when state of the art technology is used. The similar situation was for albumin in the lower normal level and pathologically low level.

Analytical CV of ALT increased within the limits of desirable imprecision. It should be pointed out that IFCC comparable method without pyridoxalphosphate was used despite the strong criticism for it. This measurement procedure remains in use by many laboratories in Lithuania even it is not standardized.

The was no significant difference found when comparing results on to systems by terms of basic statistics even for ALP which was remarkable due to instability of reagents.

Short term samples B and C (Labquality) were used for EQA with reference values during 15 months. Basically satisfactory results were received except ALT, AST and albumin. There were outliers received constantly in low level of both enzymes activities which resulted in strong negative bias in the low level region. Conversely all albumin results had constant positive bias of 6 g/L or 14.5 %.

Series of split–sample testing were performed for comparison of native samples results in 5 different levels. Data are presented graphically by Passing–Bablok regression analysis in Fig. 18–25. Near ideal agreement was received: slope of the regression lines of all tests was found 0.97-1.00 except ALP. ALP slope 0.863 demonstrated the proportional difference between ALP results in native samples on two identical analytical systems. It has proven effectiveness of split–sample testing, which covers all linearity range or the most clinically important levels.

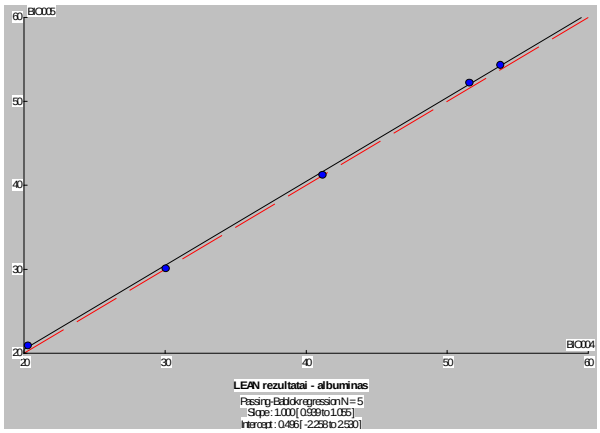


Figure 18. Passing–Bablok agreement of albumin results by split–sample testing after implementation of lean.

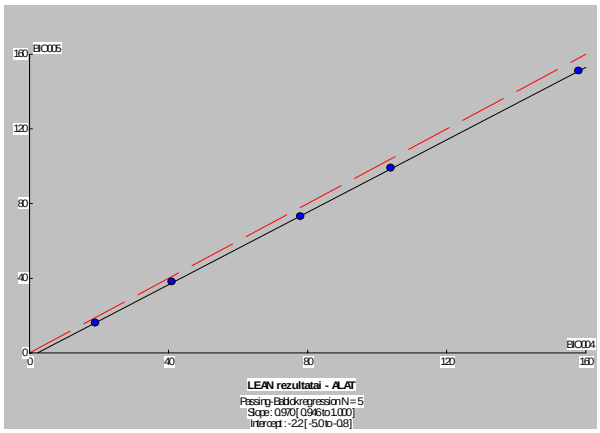


Figure 19. Passing–Bablok agreement of ALT results by split–sample testing after implementation of lean.

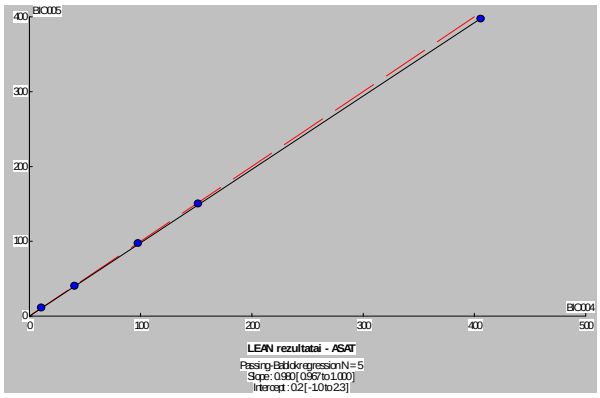


Figure 20. Passing–Bablok agreement of AST results by split–sample testing after implementation of lean.

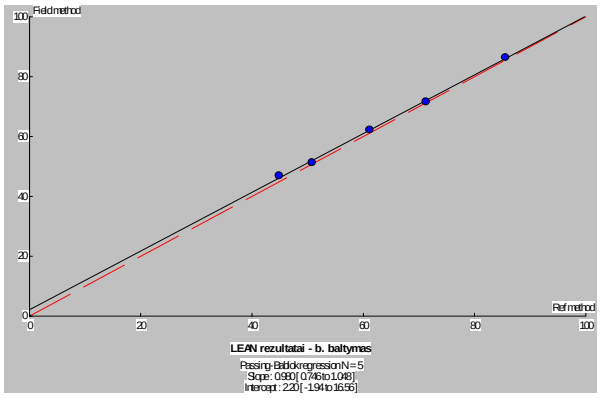


Figure 21. Passing–Bablok agreement of total protein results by split–sample testing after implementation of lean.

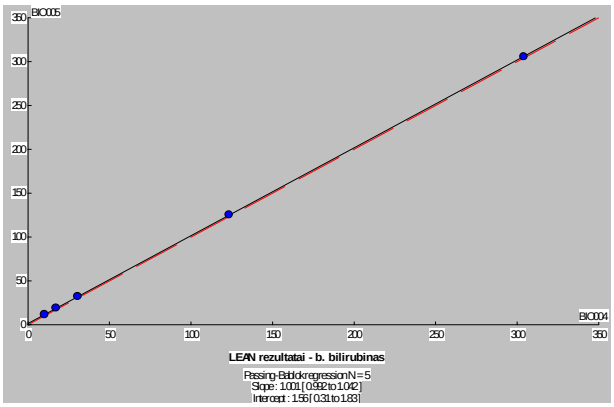


Figure 22. Passing–Bablok agreement of total bilirubin results by split–sample testing after implementation of lean.

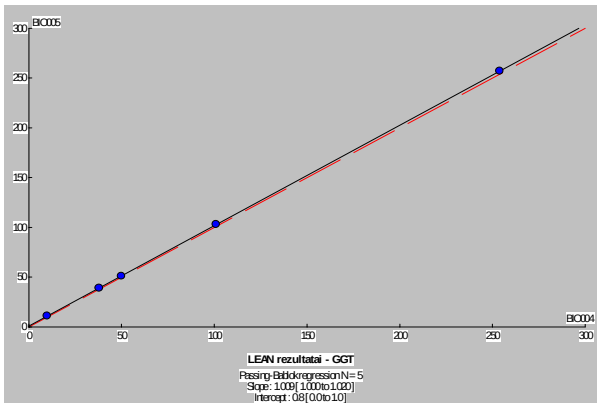


Figure 23. Passing–Bablok agreement of GGT results by split–sample testing after implementation of lean.

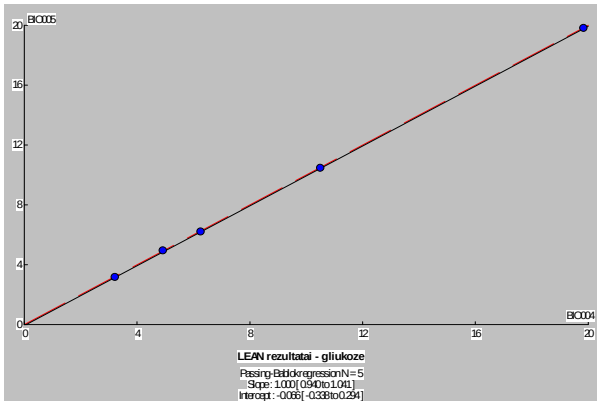


Figure 24. Passing–Bablok agreement of glucose results by split–sample testing after implementation of lean.

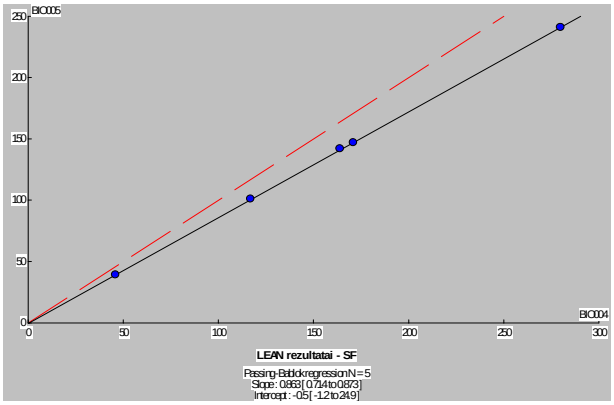


Figure 25. Passing–Bablok agreement of ALP results by split–sample testing after implementation of lean.

7. Conclusions

1. It was found that results of clinical chemistry tests of native samples could be significantly different when separate IVD instruments are used at the same laboratory. Results of five of eight tested analytes did not meet desirable quality requirements.
2. QC and EQA results of analytes used in the study represented important analytical characteristics of laboratory tests – analytical variation and bias. However it was considered insufficient for comparison of native sample results covering whole linearity range if separate instruments for the same analyte are in use at the same laboratory.
3. Proportional or constant differences in results of native sample testing have been described by split–sample tests covering the critical ranges for clinical decision making.
4. Process improvement by lean in Laboratory of Biochemistry of Vilnius University Hospital Santariškių klinikos had an impact to the total performance of the laboratory:
    a. Sample preparation and information flow automation resulted in decrease of manual work and human errors rate; knowledge and competence of skilled staff were switched to medical validation of results and total quality improvement at the laboratory.
    b. TAT for STAT samples decreased to 40–50 min and 95 % of STAT tests are released to the customer during 1 hour.
    c. Imprecision of most of studied analytes, expressed as analytical CV, after implementation of new analytical systems decreased: AST, ALP, GGT, glucose, total bilirubin.
5. Developed and tested model for quality assurance at the laboratory of clinical chemistry consist of:
    - internal QC based on concept of biological variation;
    - EQA schemes, where reference materials are used, or target values for analytes are assigned by reference measurement procedures;
    - split–sample testing for the evaluation of internal reproducibility within the laboratory;
    - process improvement by lean.

8. List of publications

1. Vitkus D. Quality management principals in laboratory of clinical chemistry – traditional and modern. Laboratorinė medicina 2009; 11(1): 26–32.

2. Vitkus D, Gogelienė L. Split-sample testing – part of quality assurance in laboratory of clinical chemistry. Laboratorinė medicina 2009; 11(2): 99–103.

3. Vitkus D, Coj A. Lean concept for quality improvement in clinical laboratories. Laboratorinė medicina 2009; 11(2): 93–8.

4. Huisman W, Horvath AR, Burnett D, Blaton V, Czikkely R, Vitkus D, et all. Accreditation of medical laboratories in the European Union. Clin Chem Lab Med 2007; 45(2): 268–275.

9. REZIUMĖ

Įvadas. Pagal Tarptautinės klinikinės chemijos ir laboratorinės medicinos federacijos (angl. *International Federation of Clinical Chemistry and Laboratory Medicine, IFCC)* apibrėžimą klinikinė chemija – tai disciplina, teikianti matavimų rezultatus ir stebėjimus, susijusius su liga, sveikatos priežiūra, ir šiuos duomenis perkelianti į bendrą ir specifinę informaciją apie pacientą [1]. Šiandien laboratorijos gali atlikti daugiau nei 1000 klinikinės chemijos tyrimų, kurių rezultatai, paprastai, lemia gydytojų priimamus sprendimus. Todėl labai svarbu užtikrinti jų tikslumą, glaudumą, pakartojamumą ir atitiktį, ypač jei tam pačiam asmeniui tie patys tyrimai atliekami skirtingais prietaisais ar skirtingais metodais. Šiam tikslui yra būtina efektyvi kokybės sistema ir kokybės vertinimo būdai, veiksmingi ankstyvo galimų klaidų nustatymo metodai.

Pasiūlyta įvairių būdų klinikinės chemijos laboratorijose atliekamų tyrimų kokybei užtikrinti. Šiam tikslui yra diegiami tarptautiniai etalonai, ieškoma informatyvesnių statistinio duomenų apdorojimo ir įvertinimo būdų, bandomi nauji išoriniai kokybės vertinimo modeliai. Šios priemonės pirmiausia skirtos pagerinti rezultatų atkuriamumą tyrimus atliekant skirtingose laboratorijose ir/ar skirtingais metodais. Tačiau didesnėse laboratorijose, ypač tose, kuriose yra nutolusių nuo centrinės laboratorijos padalinių, tiems patiems tyrimams atlikti gana dažnai naudojami tie patys metodai, bet skirtingi prietaisai. Net ir nedidelėse laboratorijose dažnai skiriasi prietaisai, naudojami dirbti dieną ir naktį. Tuomet tradicinių vidaus kokybės kontrolės metodų nepakanka, nes jie yra skirti tik konkrečiu analizatoriumi atliekamo konkretaus tyrimo kokybei įvertinti.

Lietuvos klinikinėse laboratorijose kokybės užtikrinimo ir vertinimo aspektai ir toliau nagrinėjami tik praktiniu lygiu, tam dažniausiai taikant senus ir mažai veiksmingus būdus. Pasikeitus laboratorinio darbo sąlygoms, pasigendama mokslinio požiūrio į analizės kokybės reikalavimus (kokybės tikslus). Įvairiose laboratorijose tie patys tyrimai atliekami skirtingais tyrimo metodais, naudojant skirtingus prietaisus, todėl pacientui keliaujant iš vienos gydymo įstaigos į kitą, neišvengiama rezultatų neatitikčių.

Lietuvoje nėra nacionalinės klinikinių laboratorijų išorinio kokybės vertinimo sistemos, todėl stokojama informacijos apie naudojamų metodų paplitimą, jų kokybinius rodiklius bei analizės rezultatų skirtumus.

Klinikinių laboratorijų darbe kokybės vertinimo bei užtikrinimo aspektų nagrinėjimas išlieka labai aktualia problema. Tai skatina ieškoti naujų analizės kokybės vertinimo modelių bei paklaidų prevencijos metodų, diegti mokslu pagrįstus analizės kokybės reikalavimus (kokybės tikslus).

Didėjant ekonominiam spaudimui ir griežtėjant užsakovų (gydytojų ir pacientų) reikalavimams, laboratorijos susiduria su užduotimi: maksimaliai kokybiškai atlikti kuo daugiau tyrimų per trumpą laiką su minimaliomis išlaidomis. Todėl mokslo pasiekimai turi būti diegiami jau ne tik analizės procese, bet ir organizuojant visą laboratorijos darbą, planuojant ir valdant išteklius, dirbant su užsakovais. Lietuvoje šia tema mokslo darbų dar nėra atlikta.

Darbo tikslas – ištirti tradicinių klinikinių biocheminių tyrimų kokybės kontrolės metodų efektyvumą naudojant natūralius mėginius, įvertinti analizės rezultatų, gautų skirtingaiss prietaisais ir/ar skirtingais tyrimo metodais, atitiktį ir pasiūlyti biocheminių tyrimų kokybės užtikrinimo modelį tyrimų rezultatų neatitiktims nustatyti ir sumažinti, racionaliai naudojant laboratorijos išteklius.

Uždaviniai:

1. Ištirti grupės dažniausiai atliekamų klinikinės chemijos tyrimų natūralių mėginių analizės rezultatų, gautų skirtingaiss prietaisais ir/ar skirtingais tyrimo metodais, atitiktį rekomenduojamiems kokybės tikslams.
2. Ištirti ir įvertinti tos pačios grupės dažniausiai atliekamų klinikinės chemijos tyrimų kokybės kontrolės mėginių analizės rezultatus, gautus skirtingais prietaisais ir palyginti juos su natūralių mėginių tyrimų rezultatais.
3. Išbandyti padalintų natūralių mėginių modelį, skirtingais prietaisais tiriamų analičių kokybei įvertinti.
4. Ištirti laboratorijos veiklą, pasirinkti koncepciją procesams gerinti, įvertinti procesų gerinimo įtaką laboratorijos veiklos organizavimui ir kokybinėms analizės charakteristikoms.
5. Sukurti nesudėtingą, tinkamą praktinėms laboratorijoms klinikinės chemijos tyrimų kokybės užtikrinimo modelį tyrimų rezultatų neatitiktims nustatyti ir sumažinti, racionaliai naudojant laboratorijos išteklius.

Mokslinė darbo reikšmė ir naujumas:

Europos Sąjungos direktyvose pateikiami griežti reikalavimai *in vitro* diagnostikos prietaisams, kurie turėtų būti įgyvendinti prieš pateikiant prietaisus į rinką. Pastarojo meto publikacijose rašoma apie nuolatinio budrumo, stebint bei įvertinant klinikiniams laboratoriniams tyrimams naudojamų prietaisų, reagentų, tyrimo metodų patikimumą bei diagnostinę vertę, svarbą. Tačiau tokie reikalavimai paprastai apsiriboja neatitikties konstatavimu, nepateikiant jokių rekomendacijų neatitikčiai pašalinti. Moksliniai diagnostinių sistemų tyrimai dažniausiai atliekami tik šių sistemų kūrimo ar ankstyvojo pritaikymo praktikoje stadijose.

Šiame darbe buvo ištirta ir įvertinta klinikinių biocheminių tyrimų kontrolinių ir natūralių mėginių analizės rezultatų, gautų naudojant skirtingus prietaisus ir/ar skirtingus tyrimo metodus, tarpusavio atitiktis.

Šiame darbe laboratorinių tyrimų kokybės klausimai nagrinėjami ir netradiciniu požiūriu – sutelkiant dėmesį ne tik į įprastą analizės kokybės užtikrinimą ir kontrolę, bet ir į procesų, vykstančių įvairiose laboratorijos vietose ir įvairiais tyrimo atlikimo etapais, optimizavimą. Pirmą kartą Lietuvoje kokybei klinikinėje laboratorijoje gerinti pritaikyta LEAN teorija – taupioji paslaugų ir gamybos procesų valdymo sistema.

Mokslo darbų apie klinikinių laboratorinių tyrimų kokybės vertinimą bei užtikrinimą, LEAN teorijos taikymą klinikinėse laboratorijose Lietuvoje nebuvo atlikta, todėl naujų analizės kokybės vertinimo modelių ir paklaidų prevencijos metodų paieška, mokslu pagrįstų analizės kokybės reikalavimų (kokybės tikslų) ir veiklos optimizavimo modelio diegimas pasižymi moksliniu naujumu.

Tyrimo metodai. Visiems eksperimentams, kuriuose buvo naudoti natūralūs kraujo serumo mėginiai, buvo parinkti rutininiams tyrimams paimto pacientų kraujo serumo mėginių likučiai be hemolizės ir lipemijos pėdsakų. Mėginių kaupiniai gauti maišant skirtingų pacientų, kurių pasirinktų analičių koncentracijos (aktyvumai) buvo artimi, mėginių likučius. Jei buvo galima gauti pakankamą kiekį serumo, kuriame yra didelė tiriamos analitės koncentracija (aktyvumas), serumas buvo skiedžiamas 0,9% NaCl tirpalu mažesnėms koncentracijoms (aktyvumams) gauti. Paruoštuose kaupiniuose buvo tirti antikūnai prieš žmogaus imunodeficito 1, 2 tipo, hepatito C virusų antigenus (ŽIV 1/2, anti-HCV), hepatito B paviršinis antigenas (HbsAg), antikūnai prieš *Treponema pallidum.* Kaupiniai, kuriuose buvo rastas bent vienas iš šių infekcijų žymenų, buvo sunaikinti, o tie kaupiniai, kuriuose visi tirti infekcijų žymenys buvo neigiami, homogeniškai išmaišyti ir laikyti užšaldyti (-20ºC) temperatūroje iki tyrimo dienos. Tyrimo dieną mėginiai 1 valandą atšildyti kambario temperatūroje ir centrifuguoti 10 min. 2500g siekiant pašalinti kaupinyje susidariusius precipitatus. Padalintų mėginių tyrimams buvo rinkti keturių skirtingų koncentracijų (aktyvumo) mėginiai, kurie buvo gaunami ir paruošiami taip pat, kaip kiti serumo mėginiai. Iš nucentrifuguotų kaupinių buvo ruošiami mėginiai skirtingiems analizatoriams ir kiekvienu iš jų tiriami trimis pakartojimais. Eksperimentinių mėginių tyrimai buvo atliekami kartu su pacientų mėginių tyrimais, eksperimentinius mėginius atsitiktiniu būdu įterpiant į rutininių tyrimų seriją tuo pačiu metu.

Atskiruose eksperimentų etapuose buvo naudoti skirtingi *in vitro* diagnostikos medicinos prietaisai: OpeRA, Cobas Mira Plus, Dimension RxL, Architect. Komercinės įvairių gamintojų specifinės analizatorių ir nepriklausomos kalibravimo medžiagos buvo naudotos kalibruoti analizatorius substratams nustatyti. Fermentų aktyvumui nustatyti naudoti gamintojo konkrečiam analizatoriui pateikti kalibravimo faktoriai. Vidaus kokybės kontrolei naudotos nepriklausomo gamintojo multiparametrinės liofilizuotos įvairiems analizatoriams tinkamos žmogaus kraujo serumo pagrindu paruoštos kontrolinės medžiagos. Išoriniam kokybės vertinimui naudotos Labquality OY (dalis su pamatinėmis medžiagomis) ir RIQAS programos.

Aspartataminotransferazės (ASAT) aktyvumui nustatyti naudotas α-ketoglutarato, Asp / NADH, fotometrijos (IFCC/SCE be piridoksal-5-fosfato) metodas, alaninaminotransferazės (ALAT) – Ala / NADH, fotometrijos (IFCC/SCE be piridoksal-5-fosfato) metodas. Šarminės fosfatazės aktyvumui nustatyti naudotas su IFCC rekomenduotu suderintas metodas (p-nitrofenilfosfatas, AMP buferis / pNP, fotometrija). GGT aktyvumas matuotas GLUCANA, γ-glutamil-3-karboksi-4-nitroanilido (Szasz modifikacija) metodu. Gliukozės koncentracija tirta gliukozės oksidazės / 4-amino antipirino metodu vėliau pamatiniu heksokinazės metodu. Bendrojo baltymo koncentracija tirta biureto metodu. Albumino koncentracija matuota bromkrezolio žaliojo metodu. Bendrasis bilirubinas tirtas modifikuotu Jaffe metodu ir dimetilsulfoksido metodu.

Statistinė duomenų analizė atlikta naudojant „MS Excel for Windows“ ir „Statistica for Windows 6.0“ programų paketus. Skaičiuoti įprastiniai statistiniai vidaus kokybės kontrolės duomenys, statistiškai palyginti gautų rezultatų skirtumai taikant Stjudento t kriterijų. Statistiškai reikšmingais laikyti skirtumai, jei $p<\alpha$, reikšmingumo lygmenimi pasirenkant $\alpha=0,05$. Padalintų mėginių tyrimų duomenims analizuoti naudota klinikinės chemijos tyrimų metodų vertinimo programa „Method

validator software“, versija 1.1.10.0 ir statistikos programa „Analyse–it for Microsoft Excel“. Darbo krūvio modeliavimo analizė atlikta Abbott GmbH & Co. KG, naudojant programą „Accelerator“.

Rezultatai. Palyginamieji tyrimai atlikti dviem skirtingais laboratorijoje naudotais analizatoriais. ALAT, albumino, bendrojo baltymo, GGT ir šarminės fosfatazės rezultatai statistiškai reikšmingai skyrėsi ($p<0,01$), esant reikšmingumo lygmeniui $\alpha=0,05$. ASAT, bendrojo baltymo ir gliukozės atvejais statistiškai reikšmingo skirtumo negauta. Apskaičiuotos variacijos koeficientų CV_{A1} ir CV_{A2} reikšmės lygintos su kokybės tikslu I, kuriuo išreiškiamas maksimalus priimtinas analizės netikslumas – pusė individo tiriamos analitės biologinės variacijos. Nustatyta, kad BIO001 analizatoriumi tirtų albumino, ASAT, bendrojo baltymo, gliukozės ir šarminės fosfatazės, o analizatoriumi BIO002 tirtų ASAT ir bendrojo baltymo variacijos koeficientai viršija I.

ASAT ir bendrojo bilirubino poslinkiai viršijo maksimalaus leistino poslinkio ribas. Tai rodo, kad laboratorijoje taikomi šių analičių tyrimų rezultatai sistemiškai nukrypsta nuo tikėtinų verčių, o ASAT būdingas teigiamas sistemingasis poslinkis (sistemingoji paklaida), bendrajam bilirubinui – neigiamas.

Nustatyta, kad ASAT ir bendrojo bilirubino TE_A viršijo didžiausią leistiną paklaidą. ASAT atveju tai nulėmė abu sandai – netikslumas ir poslinkis, bendrojo bilirubino atveju – poslinkio sandas.

Išoriniam kokybės vertinimui buvo pateikiami tik analizatoriaus BIO002 duomenys, kurie ALAT (+1,15S), ASAT (+0,94S), bendrojo bilirubino (–1,07S) atvejais visiškai neatitiko vidaus kokybės kontrolės rezultatų tendencijų, kadangi juose nuokrypio nuo tikėtinų reikšmių nestebėta. Padalintų mėginių tyrimai leido įvertinti viso tiesiškumo intervalo arba kliniškai svarbios jo dalies rezultatų tarpusavio atitikimą.

Atlikus srautų analizę, nustatyta, kad tyrimai laboratorijoje atliekami 9 analizatoriais, naudojamos 8 skirtingos kompiuterio programos, valdančios prietaisus, jie nėra sujungti į bendrą tinklą, nors veikia gerai išvystyta laboratorijos informacinė sistema.

Apskaičiuota, kad vidutinė skubaus tyrimo rezultato pateikimo užsakovui trukmė svyruoja vidutiniškai nuo 1 val. 10 min. mažiausios apkrovos metu iki 2 val. 20 min. esant didžiausiai apkrovai. Vidutinė rutininio tyrimo rezultato pateikimo užsakovui trukmė siekia apytiksliai 4 val.

Nustatytos procesų gerinimo kryptys: skirtingų laboratorijos sričių – mikrobiologijos ir imunochemijos sujungimas (konsolidacija), biochemijos ir imunochemijos instrumentų integravimas, informacijos srautų judėjimo efektyvumo didinimas įdiegiant mėginių brūkšninį kodavimą, sujungiant prietaisus į bendrą tinklą per tarpinę programą, preanalizinių procesų automatizavimas įdiegiant robotinę mėginių paruošimo sistemą.

Optimizavus procesą ir įdiegus dvi identiškas konsoliduotas analizines sistemas, jomis galima ištirti 96 % į laboratoriją patenkančių mėginių. Planiniai tyrimai vidutiniškai būtų atliekami per 36 min., o skubūs – per 29,4 min. nuo jų patekimo į laboratoriją, didžiausios apkrovos laiku – atitinkamai per 46 ir 37 min. 95 % skubių klinikinės chemijos tyrimų būtų galima atlikti per 26 min., 95 % planinių klinikinės chemijos tyrimų – per 40 min. Esant didžiausiai prietaisų apkrovai būtų

išnaudojama 44 % jų galimybių. Įdiegus LEAN koncepciją mėgintuvėlio kelias laboratorijoje sutrumpėjo iki 13 etapų, o informacijos – iki 3–4 etapų, daugumos nagrinėjamų analičių netikslumas, išreikštas variacijos koeficientu, pradėjus naudoti naujas analizės sistemas sumažėjo. Integruotų analizinių sistemų veikimo charakteristikoms įvertinti taip pat taikyti padalintų mėginių tyrimai. Visų analičių, išskyrus šarminės fosfatazės, gauti rezultatai artimi idealiems: regresijos kreivių nuolinkis svyruoja tarp 0,97 ir 1,00. Tačiau šarminės fosfatazės regresinės analizės tiesės nuolinkis tik 0,863 rodo ryškius rezultatų tarp dviejų identiškų analizinių sistemų proporcinius skirtumus.

Išvados

1. Nustatyta, kad klinikinės chemijos tyrimų natūralių mėginių analizės rezultatai, gauti naudojant skirtingus prietaisus toje pačioje laboratorijoje, gali būti statistiškai patikimai skirtingi. Penkių iš aštuonių tyrinėtų analičių rezultatai neatitiko rekomenduojamų kokybės tikslų.
2. Tyrinėtų klinikinės chemijos analičių vidaus kokybės kontrolės ir išorinio kokybės vertinimo mėginių rezultatai atspindėjo svarbias analizės proceso kokybines charakteristikas – variaciją ir poslinkį. Tiriant natūralius mėginius nustatyta, kad šių charakteristikų nepakanka rezultatų skirtumams tarp skirtingais prietaisais atliekamų tyrimų visame tiesiškumo intervale įvertinti.
3. Išbandyti padalintų natūralių mėginių tyrimai, apimantys kliniškai svarbiausius verčių intervalus, išryškino skirtingais prietaisais atliekamų tyrimų rezultatų skirtumus, atsirandančius dėl proporcinio arba pastovaus nuokrypio.
4. Pritaikius LEAN koncepciją optimizuoti Vilniaus universiteto ligoninės Santariškių klinikų Laboratorinės diagnostikos centro Biochemijos laboratorijos veiklos procesai turėjo svarbios įtakos laboratorijos veiklos kokybiniams rodikliams:
    a. Automatizavus preanalizinį mėginių paruošimą ir informacijos srautų tėkmę, sumažėjo rankinio darbo, tuo pačiu ir tikimybė atsirasti žmogaus klaidoms, kvalifikuotų ir kompetentingų darbuotojų žinios ir kompetencijos nukreiptos medicininiam rezultatų patvirtinimui ir laboratorijos veiklos kokybei gerinti;
    b. Skubių tyrimų rezultatų atidavimo laikas sutrumpėjo iki 40–50 min., o 95 % skubių tyrimų rezultatų užsakovui pateikiama vidutiniškai per 1 valandą;
    c. Daugumos nagrinėjamų analičių netikslumas, išreikštas variacijos koeficientu, pradėjus naudoti naujas analizės sistemas sumažėjo: aspartataminotransferazės (ASAT), bendrojo bilirubino, γ-gliutamiltransferazės (GGT), gliukozės, šarminės fosfatazės.
5. Sukurtas ir išbandytas kokybės užtikrinimo klinikinės chemijos laboratorijoje modelis susideda iš:
    - biologinės variacijos koncepcija pagrįstos vidaus kokybės kontrolės,
    - išorinio kokybės vertinimo, kuriame naudojamos pamatinės medžiagos arba tikrosios tiriamų analičių vertės nustatomos pamatiniais metodais,

- padalintų mėginių tyrimų, atliekamų atkuriamumui laboratorijoje įvertinti ir
- veiklos gerinimo, pritaikant LEAN vadybos koncepciją.

10. CURRICULUM VITAE

Dalius Vitkus was born in Utena, Lithuania on August 25, 1970.

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Education:
1989–1994 – Vilnius University, Faculty of Chemistry (Diploma, 1994)
1996 – Primary Specialization in Clinical Laboratory Diagnostics, Vilnius University, Faculty of Medicine (Certificate of Professional Qualification, 1996)
2005–2009 – doctoral studies in Vilnius University, Faculty of Medicine

Postgraduate training courses:
Laboratory diagnostics of Atherosclerosis, 1995; Center of Postgraduate training for medical specialists, Warsaw, Poland.
Preanalytical phase in patient care and hospital management, 1999; Florence, Italy.
Basic and clinical enzymology, 2000; Naples, Italy.
Quality management in laboratory, 2000; Vilnius University, Lithuania.
Workshop on the In Vitro Directive, 2003; Vilnius, Lithuania.
OECD Principals of Good Laboratory Practice and Compliance Monitoring“, 2003; Vilnius, Lithuania.
Accreditation criteria according EN 17025, 2003; Vilnius, Lithuania.
ISO 9000:2000 Training course for internal auditors of quality systems, 2003; Vilnius, Lithuania.
Laboratory quality management system (according LST EN ISO/IEC 17025:2003), 2004; Kaunas, Lithuania.
Laboratory tests for use by general practitioner, 2004; Vilnius University, Vilnius, Lithuania.
Training Course on Quality Assurance, 2004; Gdansk, Poland.
Quality assurance of laboratory measurements, 2004; Vilnius University, Vilnius, Lithuania.
Results of chemical analysis in laboratories, 2005; Center of Quality Management of Vilnius Gediminas Technical University, Vilnius, Lithuania.
Implementation of the concepts of measurement traceability and measurement uncertainty in the fields of environment, health and food sectors, 2005; Vilnius, Lithuania.
Training course on Medical Devices, 2006; Vilnius, Lithuania.
Diagnostic immunology, 2006; Vilnius University, Vilnius, Lithuania.
Medical laboratories – particular requirements for quality and competence ISO 15189, 2006; Vilnius, Lithuania

Membership in professional societies and organizations:

Member of American Association for Clinical Chemistry (since 1998)
Member of Lithuanian Society of Laboratory Medicine (since 1995)
Member of Working group on Accreditation and ISO/CEN of the European Federation of Clinical Chemistry and Laboratory Medicine (EFCC, former EC4) (Since 2005)
Corresponding member of IFCC Committee for Traceability in Laboratory Medicine (C-TLM), IFCC Committee on Reference System of Enzymes (C-RSE), IFCC Committee on Nomenclature, Properties and Units (SC/C-NPU) (Since 2005)
Board member of the Baltic Association for Laboratory Medicine (since 2007)

Approbation
Oral presentations:

1. Vitkus D. Process improvement – tool for quality management. 9th Baltic Congress on Laboratory Medicine (2008), Jurmala, Latvia

2. Vitkus D. Need of standardization on a national level: an example of Lithuanian EQA results. 8th Baltic Congress on Laboratory Medicine (2006), Vilnius, Lithuania.

3. Vitkus D. Clinical biochemistry: relationship between science and practice implementing quality requirements. Scientific Conference of Lithuanian Academy of Sciences "Laboratory medicine – usual and modern" (2008), Vilnius, Lithuania.

4. Vitkus D. Concept of biological variation in quality assessment. Scientific Conference of Kaunas Medical University and Lithuanian Society of Laboratory Medicine (2009), Kaunas, Lithuania.

5. Vitkus D. New biochemical tests in diagnostics of diseases. Conference of Klaipėda University and Lithuanian Society of Laboratory Medicine (2007), Klaipėda, Lithuania

6. Vitkus D. Implementation of quality system at the laboratories seeking attestation. Conference of Vilnius University and Lithuanian Society of Laboratory Medicine (2006), Šiauliai, Lithuania

7. Vitkus D. Laboratory diagnostics of multiple myeloma. Conference of Vilnius University and Lithuanian Society of Hematology (2006), Vilnius, Lithuania

Poster presentations:

1. Coj A, Vitkus D. New possibilities for national EQA schemes by cooperation with international EQA organiser for small country. 16th IFCC European Congress on Clinical Chemistry (2005), Glasgow, UK

2. Vitkus D, Coj A, Kučinskiene Z. Influence of major optical interferences on routinely performed clinical chemistry tests. 16th IFCC European Congress on Clinical Chemistry (2005), Glasgow, UK

3. Jurkevičiene J, Gogelienė L, Coj A, Vitkus D. Screening for subclinical hypothyroidism in a population of pregnant women in Lithuania. 16th IFCC European Congress on Clinical Chemistry (2005), Glasgow, UK

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