Designing a diagnostic total testing process as a base for supporting diagnostic stewardship

Cobbaert, C.; Albersen, A.; Zwiers, I.; Schippers, P.; Gillis, J.

Opinion Paper

Christa Cobbaert*, Arjan Albersen, Irna Zwiers, Pascal Schippers and Judith Gillis

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Abstract: To more comprehensively support clinical management of patients in our hospital, we redesigned the diagnostic Total Testing Process (TTP) from request to report. To that end, clinical needs were identified and a vision on Total Laboratory Automation (TLA) of the TTP was developed. The Delft Systems Engineering Approach was used for mapping a desirable laboratory testing process. The desirable "To Be" diagnostic process was tendered and the translation of a functional design into a specific TLA-configuration – compliant with the vision and the predefined functional design – was accomplished using a competitive dialogue tender variant (based on art. 29 of the EU guideline 2014/24). Realization of this high-end TLA-solution enabled a high-quality testing process with numerous improvements such as clear and supportive digital request forms, specimen consolidation, track and trace and non-conformity registration at the specimen level, better blood management (~40% less blood sampled), lean and in line processing with increased productivity (42% rise in test productivity per capita), and guaranteed **total** turn-around-times of medical tests (95% of TLA-rooted in line tests are reported <120 min). The approach taken for improving the *brain-to-brain* loop of medical testing, as fundament for better diagnostic stewardship, is explained.

Keywords: competitive dialogue variant; Delft Systems Approach; functional design; Total Laboratory Automation; Total Testing Process.

Introduction

The Total Testing Process (TTP) has recently been reappraised as "a set of interrelated or interacting activities that transform biologic patient sample materials into laboratory results and information to ultimately assure the most appropriate clinical outcome" [1]. Plebani and other key opinion leaders advocate that there are nowadays several reasons for counteracting the 20th century vision of the medical laboratory as a commodity, only focusing on cost reduction and economy of scale [2–9]. Also, in this era of precision medicine and digitalization lab professionals are facing "disruptive" changes. These trends were also addressed during the Strategic Conference of the European Federation of Laboratory Medicine (EFLM) in 2018: "*The end of Laboratory Medicine as we know it?*" [10]. Being the central hub of diagnostic healthcare information, medical laboratories are widely affected by innovations in biomarkers, technology, and IT. As healthcare demands evolve continuously, laboratory medicine has to adapt and to prepare for its future.

Currently automation has become a 'must have' for any medical laboratory. The current climate of decreasing reimbursements for medical tests has further increased the importance of automation and has pushed laboratories to optimize laboratory throughput and quality, and to keep up with increasing demands. Many medical labs worldwide are converting to Total Laboratory Automation (TLA), based on strong evidence that automation heightens profitability and improves quality, turn-around-times, and lab flexibility. TLA is defined as a multi-disciplinary strategy to optimize and capitalize on technologies in the laboratory that enable new and improved processes for the performance of highly repetitive tasks in the laboratory. TLA replaces human operators in the preanalytical, analytical, and postanalytical phases of testing by robotic devices. In our organization clinical needs were identified in the existing *brain-to-brain*

***Corresponding author: Christa Cobbaert**, PhD, EuSpLM, Professor in Clinical Chemistry and Laboratory Medicine, Department of Clinical Chemistry and Laboratory Medicine, Leiden University Medical Centre, Albinusdreef 2, Leiden 2300 RC, The Netherlands, E-mail: c.m.cobbaert@lumc.nl. https://orcid.org/0000-0003-3565-1404
Arjan Albersen, Pascal Schippers and Judith Gillis, Department of Clinical Chemistry and Laboratory Medicine, Leiden University Medical Centre, Leiden, The Netherlands
Irna Zwiers, CHIZ Interim Management and Coaching, Deventer, The Netherlands

loop testing processes via questionnaires, observations, repetitive complaints and notifications in the quality management system, and brainstorm sessions with clinicians, quality officers and lab professionals. Major clinical needs, defined as missing or inadequately performing components in the multi-phased diagnostic testing process, were the need for clinical request and decision support, the need for lab consolidation and operational excellence, the need to streamline the testing processes and advance workflow capabilities and the need to improve productivity at justified costs.

We here describe a Systems Engineering approach utilized in the Leiden academic hospital (Leiden, the Netherlands) to redesign the TTP and to reconfigure the underlying Lab Information Management System (LIMS) and the order management process in the Hospital Information System (HIS) for the sake of improving patient services in diagnostic-therapeutic pathways and for supporting clinical governance [3, 4, 8, 9]. In this manuscript the authors explain the approach taken for improving the *brain-to-brain* loop of medical testing [11] as a base for supporting diagnostic stewardship [3]. In the context of this report diagnostic stewardship is defined as a concept related to improving the process of ordering, testing, and reporting with the goal of decreasing unnecessary testing and treatment.

Redesigning the Total Testing Process

Vision on Laboratory Diagnostics

A **vision** on Laboratory Diagnostics was developed. The goal was to establish a four-pillar TLA change process that facilitates patient care and research and development. The four pillars considered to be essential were:

(1) Realizing hospital wide TTP and IT-process robotization and interoperability with
   a. An open automation solution that enables to interface any instrument to a common track, regardless of the vendor. Independence from a specific vendor allows the open automation system to transport specimens from different parts of the hospital to the 24/7 core lab, providing a single automation solution;
   b. Specimen consolidation and workflow integration for clinical chemistry, immunochemistry, hematology, coagulation, blood transfusion, immunology, microbiology, and pharmacy in order to simplify and standardize the TTP, improve quality and economic outcomes of lab diagnostics.
   c. Guaranteed turn-around times and no extra handling for emergency processing of specimens.

(2) Accomplishing a redesigned diagnostic TTP that facilitates
   a. Clinical care pathways with patient-centric approaches and lean hospital logistics;
   b. Overall optimization of lab diagnostics and test utilization;
   c. Direct connectivity between the wards/outpatient clinic to the central laboratory with automatic unloading on the track and robotized processing, also for other lab departments;
   d. Research and biobanking using the robotized central reception infrastructure.

(3) Empowering lab technicians and staff so that they become cross-trained and broadly employable across clinical chemistry, hematology, and coagulation.

(4) Maximizing process quality and return-on-investment of the financial assets by
   a. Reducing complexity through standardization and abolishing manual steps;
   b. Reducing waste e.g., via blood tube miniaturization;
   c. Guaranteeing track and trace of all primary and secondary specimens by robotizing the entire sample reception and sample preparation.
   d. Full robotization of diagnostic services (including pediatric tubes) and processing from test request to waste bin.

A Systems Engineering approach was utilized, a methodology well known in the industry. **Systems engineering** means to enable the realization of successful **systems** [12]. A **system** is defined as a collection of elements that is discernable within the total reality. These discernable elements have mutual relationships and relationships with other elements from the total reality. Systems engineering considers both the business and technical needs of **all** stakeholders with the goal of providing a quality product that meets the users' needs. In Leiden we used the Delft Systems Engineering Approach [12] which puts the redesigned TTP in the full context of the desirable healthcare services of our hospital and its related partners. The entire restructuring program was named "Build to Last" (Supplementary Figure 1).

Redesigning the pre-analytical and post-analytical phases

Rethinking the pre- and post-analytical processes was an essential part for improving the TTP and accomplishing

TLA. The establishment of a Central Phlebotomy Unit was a necessity to assure quality of the preanalytical phase [13, 14]. Pre- and postanalytical starting points compliant with the TTP requirements are summarized below:

- Blood collection tube consolidation and standardization for pediatric and adult specimens.
- Miniaturization of the blood sampling process.
- Tube consolidation.
- Minimalization of blood waste.
- Guaranteed max. waiting times for outpatients through optimization of the phlebotomy logistics with a patient flow management system (Ricoh Nederland BV, Den Bosch, the Netherlands).
- Facilitating electronically ordered (endocrine) function tests whereby requesting physicians can reserve a timeslot for their patient in the electronic agenda of the HIS. Function tests are entirely configured in the LIMS whereby all actions (including the IV catheter placement, medication intake and order, and time of blood draw) are fully traceable in the LIMS and reportable to the physician.
- Scheduled phlebotomy rounds for inpatients.
- Registration of actual phlebotomy time via WIFI-connected laptops and scanners assembled on the phlebotomy cars
- Non-compliance registration at the specimen level in the LIMS, with common non-compliances being predefined in a dropdown menu.
- Adding interpretative value and clinical decision support to the postanalytical phase by cross-trained staff who continuously interact with one another in a central cockpit on 1st, 2nd, and 3rd line authorization of test results and clinical interpretation.
- During the post-analytical review of test results the non-compliance registration button in the LIMS highlights in case of registered non-compliances. This enables the lab staff to take non-compliances into account when authorizing test results.

Starting points for the "To Be" diagnostic process

The lab specialist staff explicitly aimed to move from a compartmentalized, workstation-oriented approach toward a TLA-centric change, conformant to Delfts System Engineering, and enabling continuous reinforcement of TTP outcomes and perspectives [1–9]. To that end, process optimization and simplification of the entire brain-to-brain loop, with complete decompartmentalization of the former diagnostic processes from separate 24/7 units into one integrated process for patient care and for supporting clinical research, was strived for. The integrated diagnostic process should allow to connect preanalytical, analytical, and postanalytical modules and analyzers from different IVD-manufacturers to an open and flexible track system. The track system should be physically connectable to a robust, user friendly and flexible Pneumatic Tube System (PTS) that allows nearly instantaneous delivery and automatic unloading of specimens send from e.g., the Central Phlebotomy Unit (CPU) (located approximately 170 m from the lab facility) and critical wards, according to a *first-in first-out* principle (no distinction between emergency and regular specimens), which is highly relevant for guaranteed *total turnaround times* (i.e., the time from request to report). To operationalize the "To Be" diagnostic process a supportive, reconfigured LIMS/HIS and adapted prepre- and postpostanalytical phases were equally essential.

Functional (re)design of the desirable "To Be" Diagnostic Test Process

The starting points for the future Diagnostic Test Process were translated into an overall functional design that specified the characteristics and functionalities of the TTP, taking into account the desirable interactions and services with the other departments and wards in the hospital and with the outside world. It is demonstrated in Figure 1 how the main test process combines the core tasks for patient diagnostics and R&D (including biobanking), with common pre-analytical processing for multiple diagnostic departments (including microbiology, pharmacy, immunology).

Tender procedures

Because of the complexity and broadness of the Build to Last program, three European tenders (according to the 2014/24/EU Directive of the European Parliament and the Council of 26 February 2014 on public procurement and https://europadecentraal.nl/wp-content/uploads/2016/06/Notitie-implementatie-nieuwe-aanbestedingsrichtlijnen-in-de-Aanbestedingswet-juni-2016.pdf) were successively prepared and submitted during three subsequent years in the following order:

a. A Hematology Work Area which had to be connectable to the envisioned open track system;
b. A fully robotized central reception with *in line* Serum Work Area (SWA), Urine Work Area (UWA), and Coagulation Work Area (CWA) and robotized archiving, the tender being based on a competitive dialogue with IVD-applicants. See https://europadecentraal.nl/onder

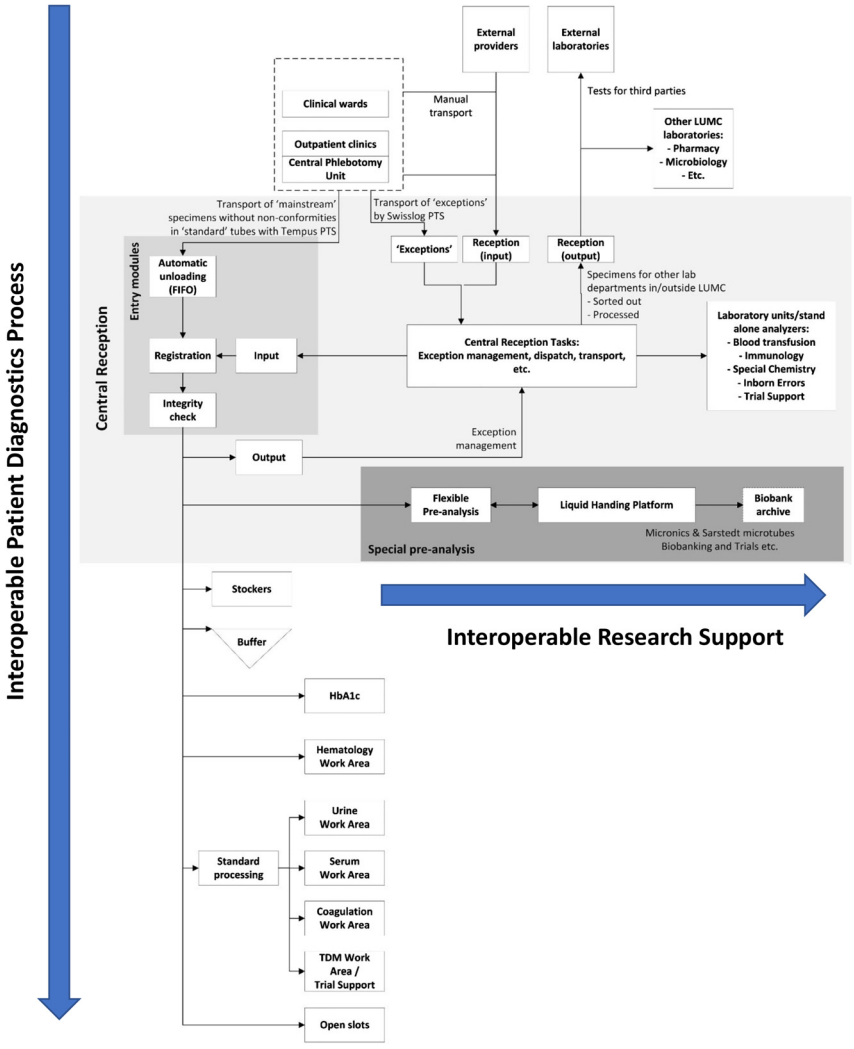


Figure 1: Functional design of the desirable robotized Diagnostic Total Testing Process with integrated Research Support for processing clinical trial and biobank specimens.

werp/aanbestedingen/aanbestedingsprocedures/concurrentiegerichte-dialoog/.

c. And a matching Pneumatic Tube System that allows *front-to-end* connectivity between Central Phlebotomy Unit or clinical wards and the Central Laboratory Reception.

The tender for the entirely robotized central reception and the *in line* Serum, Urine, and Coagulation Work Areas had the following characteristics:

a. Three hundred and ninety six absolute requirements (i.e., *knock out* criteria) regarding performance characteristics of the TTP, the IT – and hardware configurations and architecture, and the medical test quality and menu. With respect to the *fitness-for-purpose* of tests, the analytical quality was described in terms of precision, accuracy, analytical sensitivity, detection limits, interferences, robustness, and turn-around-time;
b. Ten interchangeable requirements which gave some flexibility and developmental opportunities to IVD-manufacturers;
c. Requirement of a detailed implementation plan in two phases, firstly to guarantee preparedness and adequate training of all technicians and medical staff during a predefined transition phase, and secondly, to assure full blown operations and continuity of all 24/7 lab activities from the pre-agreed Go Live date on;
d. A research alliance which allows to further develop the diagnostic test process requirements during the life-span of the TLA-based diagnostic lab.

Tendering a functional process, describing solely functional specifications and requirements and leaving open any concrete solutions, was experienced as innovative but risky. In order to find the best solutions, the contracting authority made use of a competitive dialogue variant (based on art. 29 of the EU guideline 2014/24). That variant allows a structured dialogue between contracting authority and potential inscribers according to well-defined rules. The contracting authority can use this procedure whenever it is not capable to define ahead the resources needed to

fulfill the required performance specifications for a successful system nor to oversee which technical, financial, and legal solutions are available on the (diagnostic) market (see also consideration 42 in the EU guideline 2014/24). This tender was awarded based on the feasibility to meet all absolute requirements within a reasonable time slot, combined with convincing rationale for adding value and a good quality-to-cost ratio (according to art. 67 par. 2 of EU guideline 2014/24).

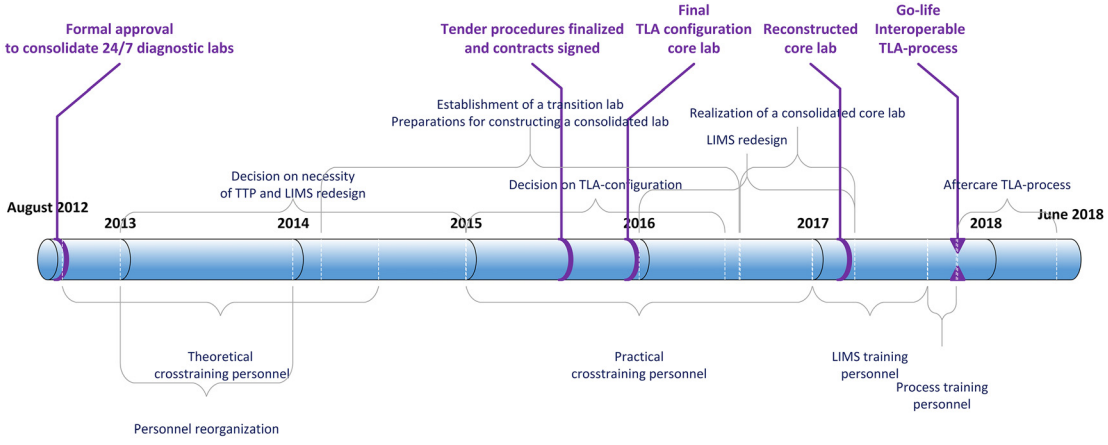
Tender outcomes: from Public Procurement to Awarding

The hematology work area was awarded to Sysmex Nederland BV (Etten-Leur, the Netherlands). Utilizing the competitive dialogue IVD-manufacturers collaborated together in order to find an integral solution that would fit the 396 knock-out criteria and other requirements of the second tender. Several IVD-companies participated in different combinations in the dialogue phase, taking into account the stringent procurement rules. The dialogue process was entirely guided by the purchasing department whereas clarifications regarding the desirable "To Be" diagnostic process were the responsibility of laboratory specialists. After the dialogue phase, the tender was awarded to the combination of Roche Diagnostics Nederland BV (Almere, the Netherlands), Sysmex/GLP Nederland BV (Etten-Leur, the Netherlands), and Stago BNL BV (Leiden, the Netherlands), with Roche taking the responsibility as lead manufacturer. The Pneumatic Tube System tender was awarded to TEMPUS 600 (Telecom, the Netherlands). Subsequently, a meticulous process of refining the TTP with all relevant stakeholders took place. Multiple sketches were needed in order to fit the robotized central reception, the track backbone, the modules, analyzers, work areas, and archives into the available core lab space. The final sketch is shown in Supplementary Figure 2.

Redesigning the LIMS and the test request process

To support the redesigned TTP, a harmonized LIMS with uniform architecture that enables interoperability of sample and data logistics across all local lab departments and guarantees complete sample *track and trace* for all LIMS-operating departments, is key. To accomplish this, a new LIMS was configured (GLIMS9 from MIPS Headquarters, Ghent, Belgium). The LIMS requirements are presented in Table 1.

Per test, we mapped the entire routing of specimens, from phlebotomy unit to archive, considering the starting



August 2012	Formal approval to consolidate 24/7 diagnostic labs
January 2013 – December 2014	Decision on necessity of TTP and LIMS redesign
March 2014 – July 2016	Establishment of a transition lab
March 2014 – July 2016	Preparations for constructing a consolidated lab
January 2015 – June 2016	Decision on TLA configuration
July 2015	Tender procedures finalized and contracts signed
December 2015	Final TLA configuration core lab
January 2016 – March 2017	LIMS redesign
August 2016 – March 2017	Realization of a consolidated core lab
February 2017	Reconstructed core lab
November 2017	Go-life interoperable TLA-process
November 2017 – December 2018	Aftercare TLA-process

September 2012 – June 2014	Theoretical crosstraining personnel
January 2013 – December 2013	Personnel reorganization
January 2015 – December 2016	Practical crosstraining personnel
January 2017 – August 2017	LIMS training personnel
September 2017 – October 2017	Process training personnel

Figure 2: Overview with timelines and milestones of the Leiden laboratory diagnostic change program.

Table 1: Predefined requirements for setting up a hospital wide interoperable LIMS.

Laboratory-specific setup requirements for the reconfigured LIMS are:
– A LIMS set-up according to the *Master-Slave* concept. This signifies that the LIMS is the Master, contains all information needed to enable the connectivity with the so-called '*slaves*' in the TLA-process, such as the modules for automated specimen receipt and processing, the automated analyzers, and the PTS- and track-systems, independent of the IVD- and other manufacturers involved.
– Middleware is not allowed unless its functionalities have obvious added value for patient diagnostics.
– The setup of the LIMS is in line with all process- and TLA-related starting points.
– Standardized, one-way routing of patient samples to the central reception of the lab department for all clinical and research samples.
– Registration of all samples in the LIMS upon arrival at the department and subsequently upon arrival in other laboratory (units or) departments where analyses take place, in order to obtain detailed track and trace of all samples.
– Every laboratory remains responsible for the specifications of its primary specimen collection, whereby the clinical chemistry department facilitates robotized primary sample processing and sample aliquoting in secondary tubes, based on information from the LIMS.
– Via the central reception the samples and/or aliquots are further distributed to other laboratory units and specimen banks according to ISO15189:2012 procedures.
Common LIMS-architecture requirements for **all LIMS-operating departments**:
– The LIMS set-up reflects the actual routing of samples and processes in the TTP chain along their trajectory through the hospital.
– The LIMS functionalities are used according to their intended use.
– There is uniformity in parameterization and use of standardized Mnemonics.
– There is a uniform process for medical test requests using a consensus-based lay-out and coding for all specimen labels.
– The test request is done according to a patient-centric approach with joint processing of all GLIMS-operating labs in the same lab order in case of multiple samples generated under one order.
– There is agreement regarding the uniform lay-out of labels and numbering of test orders and test samples.
– Every sample possesses a unique sample number.
– Aliquoting of material on the track is performed based on information in the LIMS, in accordance with the master-slave concept.
– Samples only get the status 'active' in the LIMS when they arrive on the department where the analysis will be performed.
– The basis of the LIMS configuration is resumed in an architecture guide.

LIMS, Lab Information Management System; TTP, Total Testing Process; TLA, Total Laboratory Automation.

points for an optimal and lean process. Per test the optimal trajectory was determined:

- Is the test handled via the track for centrifugation, decapping, aliquoting, recapping and sorting?
- Is the test performed on a track-connected analyzer?
- Is the test performed in another unit/laboratory, in other words, does this sample need to be distributed to another unit/laboratory?

Subsequently, processes were simplified. This resulted in typical flowcharts per specimen collection tube. An example for the EDTA-specimen workflow is demonstrated in Supplementary Figure 3.

Configuring the LIMS according to the Master-Slave concept

An entirely new aspect in the setup of the LIMS as master was the installation of an open, flexible track system from GLP Systems (distributed by Sysmex Inc, Etten-Leur, the Netherlands at that time) connected to multiple pre-analytical and post-analytical modules, and to analytical work areas. The track is controlled by middleware which is responsible for determining the fastest routes of the samples on the track. These trajectories are based on the information received from the LIMS and the availability of the modules/analyzers/archives connected to the track.

As demonstrated in Supplementary Figure 4, the LIMS as master is communicating with the track and track-modules as well as with the track connected analyzers and archives, whereas there is no direct communication between the track and the connected analyzers and archives. In order to get unique sample numbers for achieving track and trace of primary and secondary samples in the LIMS, the LIMS is made fully responsible for the logistics of the aliquoting. The connection between LIMS and track middleware was customized for our setting to meet this master-slave requirement.

Rethinking order management and result reporting

In close collaboration with the clinicians and other lab departments digital ordering in the HIS was revised and simplified, taking into account the needs of the clinicians:

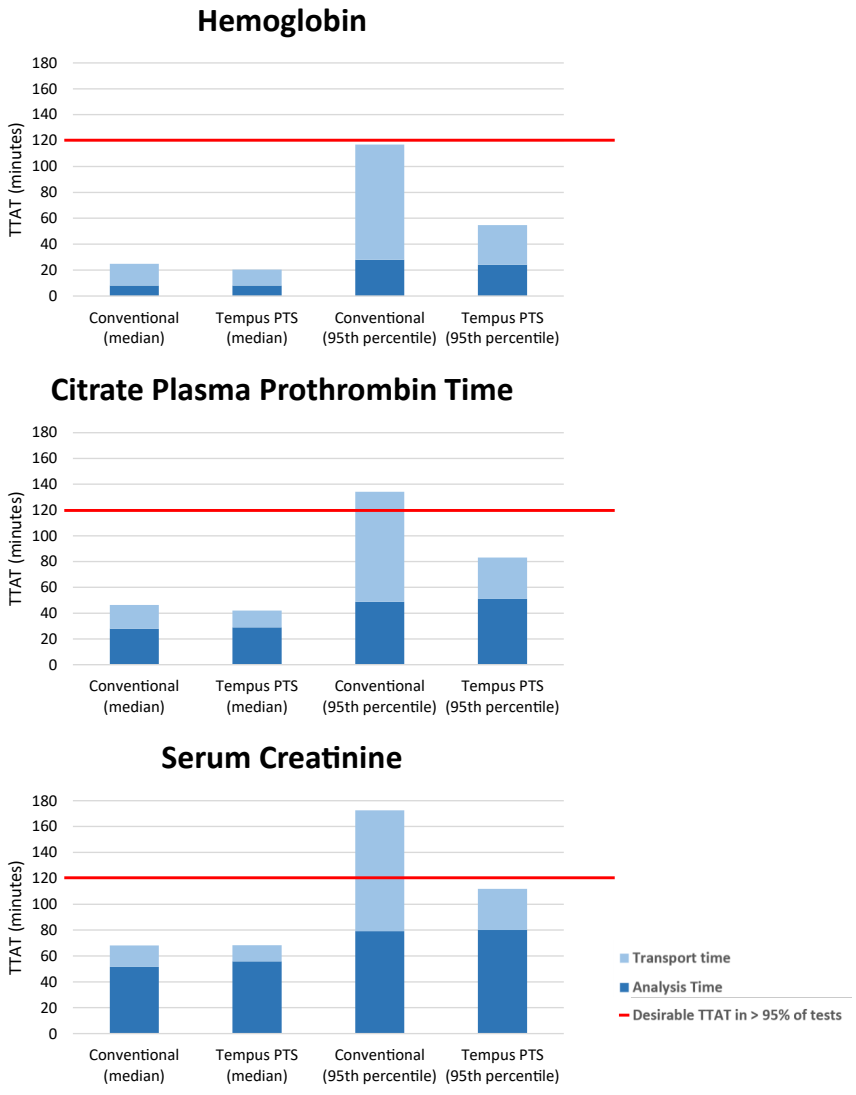


Figure 3: Total turn-around times (TTAT) (medians and 95th percenties) in the brain-to-brain loop for medical testing from requesting till reporting test results in the Hospital Information System (HIS), either by converntional transportation or transportation through a directly connected Tempus Pneumatic Tube System (PTS) with automatic unloading at the core laboratory. TTAT is divided in two parts; the analysis time is the time from arrival of the specimen in the core lab till reporting in the HIS. The TTATs are derived from a representative sample in 2019 encompassing the following number of specimens: for hemoglobin: conventional transport n = 179,499; PTS transport: n = 73,695; for PT: conventional transport: n = 47,793; PTS transport = 8,245; for serum creatinine: conventional transport: n = 181987, PTS transport n = 82268. The desirable TTAT is 120 minutes for > 95% of the specimens – see the red horizontal line).

- Simple and intuitive routing to a standard order management form where all routine diagnostic tests from all laboratories can be found;
- Working for all lab services in one order, an order being defined as a sample request done at a unique sampling time. As sampling of different body fluids (e.g., blood, urine) does not occur simultaneously, sampling of different materials results in different orders.
- Increasing the findability of tests by:
  - Functional grouping of tests (e.g., liver, kidney), sometimes one test can be found in multiple groups/tabs.
  - No separate listing of tests that are analyzed externally. Tests that have been externally analyzed are marked in the report, according to ISO 15189:2012 requirements.
  - Introduction of a new, undefined X-test on the order form so that the phlebotomists have the necessary information during blood withdrawal.

This resulted in **digital order request forms** for blood, for urine and for other body fluid types, and a separate order management form for ordering blood products. The order in which test results are reported was harmonized among regional hospitals.

Change management

Redesigning the TTP brought along substantial changes in tasks, responsibilities, and required skills of lab technicians. As robotics and automation eliminated repetitive (manual) tasks, these non-value adding tasks were

replaced by tasks that create added value for patient care, such as continuous confirmation and/or authorization of medical test results, continuous monitoring of turnaround times, and specific attention to complex specimens. To that end, all 24/7 lab technicians were cross-trained theoretically and practically in hematology, coagulation, and clinical chemistry, in order to meet the required skills demanded in their revised job descriptions. A training program was set up in three phases, consisting of a two year theoretical cross-training for core lab technicians, a practical cross-training on the new instrumentation and finally a total process training aimed at steering and monitoring the new Total Test Process. Forty lab technicians were involved. The entire "Build to Last" program was ~ a five year process. Major timelines and milestones of the program are summarized in Figure 3.

i. The theoretical cross-training encompassed the training of clinical chemistry lab technicians which had to become knowledgeable on haematology/coagulation/blood transfusion, and *vice versa*. The training consisted of weekly evening classes for 40 weeks per year during two years, concluded by 10-weekly examinations and yearly certifications. Skilled and qualified lab technicians in clinical chemistry respectively haematology/coagulation/blood transfusion were essential for running the new Total Test Process.
ii. The practical cross-training took place on the new equipment which was pre-installed in a transition lab for staff training and test validation.
iii. During the last two months before the Go Live, process trainings were given in the new, fully equipped, and consolidated lab. Main objective was to train technicians on the process oriented way of medical testing, instead of the former workstation oriented approach. The process trainings consisted of e-learnings, theoretical lessons, and practicing the total test process. Each core lab technician and staff member followed a four day process training, to familiarize with the new TTP, the reconfigured LIMS and the redefined tasks, authorizations and responsibilities. After four weeks everyone received a second four day process training.

In order to enable the practical training courses without compromising the 24/7 lab services, additional lab technicians and staff were appointed as well as a Project Leader responsible for the practical implementation of the TTP and the communication around it.

To prepare and accomplish the implementation of the new diagnostic TTP, a program and governance structure was put into place. See Supplementary Figure 5.

To anchor the new TLA-process and employees' tasks into the Quality Management System iProva (Infoland, Nieuwegein, the Netherlands) of the consolidated department, main and sub-processes were mapped in i-Process using process flowcharts, whereas the tasks, authorizations, and responsibilities of employees were summarized in RASCI tables which define who is Responsible-Accountable-Supporting-Consulting-or has to be Informed per (sub)process step (www.rascimethode.nl/en/about-us/rasci).

Structured communication as part of successful change management

Getting support and approval from the work floor and stakeholders regarding the realization of a new organization and TTP is a daunting task. Every employee or stakeholder experiences a transition from a former, well-known process "A" to a future, unknown process "B" in his/her own way. Besides the tangible and actual changes such as locations and working methods, but also quality- and IT-systems, the so-called 'rational upstream', major changes bring along either support or doubt, depending on the employees' norms and believes, personal characteristics, and motives, the so-called 'emotional downstream' [15, 16].

Achieving major changes requires change management and additional resources to organize the rational upstream properly and to consciously take into account and anticipate on the emotional downstream at the individual and team level. Dedicated coaching on change management was necessary, in order to channel the emotional downstream, triggered by different degrees of acceptance regarding the new way of working at different levels (LIMS-guided processes, automation, robotization, etc.) and the new culture.

Well-structured and consistent communication with all stakeholders of the TTP was of decisive importance both in and outside the lab. By redesigning the TTP, clinicians, residents, nurses, care managers, and researchers were affected and had to adapt their traditional working methods and behavior. Therefore, all stakeholders were timely, periodically and systematically informed during the entire Program about the upcoming TTP, LIMS- and HIS- changes with consequences for their daily practice. Internally, the digital availability of Standard Operating Procedures regarding the TLA-process in the Quality Management System as well as i-Process flowcharts and RASCI tables supported the process-oriented way of thinking and working of our lab technicians.

Discussion

Gone is the time that medical laboratories do well when they only produce the highest volume at the cheapest price [5–8]. Healthcare currently considers transitioning from a fee-for-service or capitated approach towards value-based healthcare, in which providers will be paid based on the amount of healthcare services they deliver. The "value" in value-based healthcare will be derived from measuring health outcomes against the cost of delivering the outcomes. To support this from the lab diagnostic site, TLA-centric approaches that enable operational excellence, timeliness, flexibility, and increased productivity across the entire diagnostic process should be put into place [6–9].

In 2012 the decision was made by the Leiden board of directors to merge the diagnostic labs of clinical chemistry, hematology, coagulation, and blood transfusion. A steering committee staffed with the department heads of the involved diagnostic labs was established to prepare the lab merging. One of the first steps was the assessment of the clinical needs in the existing clinical care processes. Major clinical gaps were the lack of a standardized *brain-to-brain* loop process for medical testing and the lack of IT – and process interoperability across lab disciplines (preventing exchange of sample specimens). This impeded cooperation between lab disciplines and hindered the establishment of a high quality diagnostic process. Because of this, doctors were inadequately supported on test requesting and interpretation in the prepre- and postpostanalytical phases of their test requests. However, there is ample evidence that insufficient guidance on test selection and interpretation may lead to diagnostic errors that can cause harm to patients by preventing or delaying the right diagnosis and/or appropriate treatment, providing unnecessary or harmful treatment, or resulting in psychological or financial repercussions. In the Report on Diagnostic Errors by the National Academy of Medicine in the United States it was concluded that improving the diagnostic process is not only essential, it also represents a moral, professional, and public health imperative [18].

To fulfill the current clinical needs in our hospital setting, the *brain-to-brain* diagnostic processes and services were reconsidered using a holistic approach based on Systems Engineering. With involvement of the other diagnostic disciplines, all five stages of the diagnostic test process were (re)designed and aligned towards a desirable, common, and standardized test process (see https://youtu.be/JI5daJUmyOs). Unique in our approach was the functional design of the TTP, tailored to the needs of the university hospital stakeholders. The desirable functionalities for both diagnostic and research services, the underlying IT-demands for the LIMS and HIS, and the requirements regarding test menu and test quality were described in tenders. Critical elements for enabling the translation of a functional design into the envisioned TLA-configuration were: 1) a tender procedure based on a competitive dialogue that facilitated IVD-manufacturers to jointly figure out the most optimal and dynamic TLA-solution throughout its lifecycle; 2) the reconfigurations of the underlying LIMS and HIS systems; 3) the concomitant redesign of the peri-analytical phase(s); and 4) the meticulous planning and integrative monitoring of all subprojects during the preparation, transition and final implementation phase via stringent program management, and structured communication. IVD-partnerships enabled front-to-end process robotization and interoperability as manufacturers of specimen tubes, next generation PTS and track systems, analyzers, pre- and postanalytical modules and the LIMS manufacturer developed joint solutions to realize the desirable TTP (Supplementary Figure 2). Major game changers were the Tempus 600 PTS with direct unloading and the flexible GLP track with connectivity to pre- and postanalytical modules for robotized specimen processing and archiving, and to work areas from different IVD-manufacturers. Further process developments during the TLA-lifecycle, such as advanced robotized processing of pediatric tubes and biobank specimens, are underway. We were positively surprised by the sharp learning curve of >95% of the lab technicians who were cross-trained and became rapidly familiar with the TTP in the integrated core lab. We encountered adaptation difficulties in a specific subgroup who was not used to LIMS-guided processes; this necessitated additional coaching.

Because of lab integration by means of a TLA-centric lab, multiple clinical needs were addressed. In Table 2 an oversight is presented of improved lab process metrics across the five diagnostic test phases seen from the perspective of the lab professional, the clinician, and the patient. In this era of cost containment the same volume of 24/7 diagnostic work can be done with 25% less workforces and a substantial productivity increase of the remaining lab personnel (number of tests processed per capita increased by 42% for TLA-supported in line testing), mainly due to streamlining, robotization and accomplishing interoperability of the prepre-, pre-, post- and postanalytical phases with the analytical processes. Our medical doctors experience major advantages from the guaranteed total turn-around times of medical test results, leading to complete availability of test results during consultations and ward visits. Doctors can now digitally order additional tests in archived left-over specimens without intervention of lab technicians. Add-on requests trigger automatic retrieval of the specimens from the archives and in

Table 2: Improved lab process metrics across the five diagnostic test phases seen from the perspective of the lab professional, the clinician and the patient.

	Diagnostic Total Testing Process redesign steps in the brain-to-brain loop of medical testing	Added value for laboratory professionals	Added value for clinicians	Added value for patients
Pre-preanalytical phase (LIMS and test request process)	Redesign of the digital request process in LIMS/HIS.		Clear and simplified request process with one request form per order for several lab disciplines (blood, urine, and other fluids forms, i.e., three forms instead of >20; blood product forms are excluded).[a] Intuitive test requesting because of functional grouping of tests, also for decentral tests Request forms include a search function. Possibility to order an undefined test in consultation with lab specialists, resulting in the necessary information during blood withdrawal (e.g., tube type and special pre-analytical conditions are part of the test application). A complete (endocrine) function test can be ordered with one test request, including the electronic reservation of a time slot at the central phlebotomy unit.	Clinicians are supported in their test requesting because of clear overview on the test menu, functional grouping of tests, tailored grouping of tests for specific clinical disciplines, test requests supported by embedded flowcharts according to clinical guidelines which support targeted requesting.
	Digital request form for blood products with clinical compulsory questionnaire according to national blood transfusion guideline.	Clinicians' compliance to provide essential clinical information. All clinical information is accessible for preventative antigen matching strategy and correct product specifications.	Clinicians are guided to order the right blood product, and the lab can safely select the right blood products.	Improved blood product safety
	Standardized barcode labels with information about tube and specimen type and blood volume.	Correct specimen type Less errors regarding wrong tube type (3 in 10,000 ordered tests).	Reduced number of delayed results due to e.g., redraws.	No extra phlebotomy because of an incorrect specimen type.
	Endocrine function test in one order with full track and trace.	Registration of preanalytical questions, time of draw, phlebotomist credentials, catheter flush (handling), time of administration of medicine are tracked in LIMS. Full track and trace.	Timely and complete function test reports.	Less repeats of function tests

Table 2: (continued)

	Diagnostic Total Testing Process redesign steps in the brain-to-brain loop of medical testing	Added value for laboratory professionals	Added value for clinicians	Added value for patients
Preanalytical phase	One central phlebotomy department	High quality venapuncture services delivered by skilled lab phlebotomists: 95% of serum/plasma samples have a hemolytic index <16 µmol/L free Hb both at the clinical wards and at the central outpatient clinic, compared to e.g., the ED where 5% of serum/plasma samples taken by nurses have a hemolytic index of >100 µmol/L. Guaranteed waiting times through optimization of phlebotomy logistics using a patient flow management system. Guaranteed phlebotomy TAT Centralised and harmonized phlebotomist competency training.	Higher efficiency of reportable test results because of improved overall quality of phlebotomy services. Venapuncture competency training for medical students who have to start their residencies.	More accurate and reportable results because of improved quality of the phlebotomy services.
	Customer Flow Management system	Optimize patient queue-time in line with predefined specifications. Prioritizing specific patient groups. Raised patient service level. Real-time and retrospective queue-time analyses. Staffing-by-demand. Optimal human resource (re)allocation for function testing and educational tasks without jeopardizing patient throughput. Monitoring phlebotomy productivity.		Prioritizing vulnerable patient groups
	Scheduled clinical/inpatient phlebotomy round	Scheduling of staff based on the amount of work per phlebotomy round.	Shorter TAT Results are known during doctors' visits so that MDs can directly anticipate on patient management and therapy. Time of rounds is determined in consultation with the clinicians, so most results are known during scheduled doctors' visits.	Shorter TAT and improved phlebotomy quality. Shorter period of hospital stay: reduced time period between phlebotomy and clinical consult.
	Tube consolidation and miniaturization of blood collection in adults.	Efficient use of disposables Improved blood waste management and less costs.	Better blood management	Lower blood volume drawn and less iatrogenic anemia;

Table 2: (continued)

Diagnostic Total Testing Process redesign steps in the brain-to-brain loop of medical testing	Added value for laboratory professionals	Added value for clinicians	Added value for patients
			per adult about 40% reduction in blood volume.
Miniaturization of venapuncture in pediatric patients (<12 years)		Pediatricians know that the lowest amount of blood volume is drawn.	Lower blood volume drawn and less iatrogenic anemia; 40% volume reduction.
The exact phlebotomy sampling time and the phlebotomist are registrated in the LIMS.	Insight in real transport times of specimens. Insight in phlebotomist's productivity and enabling personaLIMSed error management feedback.	Transparency about total turn-around-times in case of discussion due to full track and trace of the specimens' trajectories.	
Noncompliance (NC) registration of phlebotomy services in the LIMS.	Data analysis of preanalytical variables and insight in non-conformities and confounded test results due to hemolysis.		
Reduction in special transport conditions of specimens (e.g., less samples on ice).	Less manual work Reduced staffing at the central reception.	Less special precautions during specimen transport.	
Direct connectivity through a Tempus Pneumatic Tube System between central phlebotomy unit and the robotized central reception of the core laboratory, with automatic unloading of the samples on the preanalytical processing units.	Forty percent of tubes are processed automatically, without manual intervention. Reduced staffing at the central reception.	Shorter and guaranteed Total T urnaround Times (see Figure 2).	Shorter period of hospital stay: reduced time period between phlebotomy and clinical consult.
Central reception for most diagnostic laboratories within the hospital.[a]	Less samples arrive at the wrong reception.	Uniform routing of samples towards laboratories, from this central location the samples are further distributed to other diagnostic laboratories.	
All samples are registered in the LIMS upon arrival.	Improved Track and Trace of samples. Only the samples which are not processed via the Total Lab Automation (TLA)-track are registered manually in the LIMS.	Status of sample arrival is reported. Transparency in Track and Trace of samples routed via the TLA system.	
Temperature control and storage protection of samples designated for other diagnostic laboratories within the hospital.	Dedicated laboratory sample flows. Less loss of samples.		

Table 2: (continued)

	Diagnostic Total Testing Process redesign steps in the brain-to-brain loop of medical testing	Added value for laboratory professionals	Added value for clinicians	Added value for patients
	Unique primary, secondary, and tertiary sample numbers due to aliquoting procedure via LIMS.	Track and trace of mother, daughter tubes and aliquots.		
	Robotized pre-analytical processing of tubes	Standardized control on acceptance criteria (e.g., right specimen type, correct labelling of the tubes, …). Standardized and tailored 30′ clotting time for serum tubes based on actual phlebotomy time. In line centrifugation according to standardized centrifugation protocols. Automated decapping of tubes. Full track and trace on the entire pre-analytical processing of samples in the LIMS. Reduction of manual interventions to a minimum: from more than 30 manual steps to 3–5 steps in the robotized central reception. Less biosafety risks for lab staff due to robotization.		
Analytical phase	Real time sample processing with most tests being analyzed on a 24/7 basis, including endocrinology tests and tumor markers.	No separate batch analyses of lower volume tests and improved efficiency of lab staff resources. Substantial reduction in the number of telephone calls from clinicians to laboratory specialists for STAT analysis requests.	24/7 processing of lab tests leads to reduced TAT, allowing faster and completer clinical decision making both for clinical patients and outpatients directly during clinical rounds or consultations. Improved time management and efficiency of doctors who had to do a substantial number of phone consultations after receiving delayed, batched test results.	Full diagnostic services also beyond regular working hours. Shorter period of hospital stay: reduced time period between phlebotomy and clinical decision making.
	Fully robotized processing of samples (from registration on the TLA track to removal in the waste bins).	Limited staff is required for the sample analyses. Full track and trace of the analytical traject. Exact total turn-around time	Improved (T)TATs (see Figure 2)	Less blood redraws

Table 2: (continued)

	Diagnostic Total Testing Process redesign steps in the brain-to-brain loop of medical testing	Added value for laboratory professionals	Added value for clinicians	Added value for patients
		information can be generated. Nearly no complaints about sample losses due to lean processing and improved sample tracking.		
	Fully robotized processing of pediatric chemistry and hematology samples.	No human operator intervention during sample processing Full track and trace Real total turn-around time information Reduction in sample loss	Improved (T)TATs (see Figure 2)	Less blood redraws
	Minimal use of middleware	One standardized way of presenting data in the LIMS to the technical lab staff (e.g., patient results, QC, monitoring of process). Less training due to harmonized interfacing of labware and LIMS.		
	Cross-trained technicians	Enhanced cost-effectiveness due to broad coverage of lab services.	Patient-centric confirmation and authorization of test results.	
Postanalytical phase	Measurement of HIL-indices in all serum/plasma samples.	Based on thoroughly evaluated HIL-indices allowable interference budgets have been predefined. Test results with too much HIL-interference will automatically be blocked and reported with external comments why the results are not reported (e.g., result not reported because of >20% interference due to hemolysis).	Reporting medical test results that meet the allowable measurement uncertainty.	Reporting medical test results that meet the allowable measurement uncertainty.
	LIMS: Phlebotomy Noncompliance (NC) registration	Non-conformity flags are shown when reviewing and releasing test results. Lab staff and lab speciaLIMSts use this information for interpreting the results.	Reporting medical test results that meet the allowable measurement uncertainty.	Reporting medical test results that meet the allowable measurement uncertainty.
	Combined first, second and third level validation on one location by different functions within laboratory.	Lab staff is trained on the job in a joint cockpit setting for first, second and third line authorization of test results. Transparent and real time interaction and communication between lab specialists and lab technicians/lab staff. Laboratory specialists are visible and accessible for technicians.	Ultrapathology and special findings are timely reported and discussed with clinicians. The timeliness is tracked and traced.	

Table 2: (continued)

	Diagnostic Total Testing Process redesign steps in the brain-to-brain loop of medical testing	Added value for laboratory professionals	Added value for clinicians	Added value for patients
	Endocrine function test in one order	All the necessary information is available in the LIMS for correct interpretation and authorization.	Clear reporting and structuring of the results of function tests, including a conclusive interpretation of the function test, with standard texts predefined in the LIMS.	
	TLA-coupled archives for storage of left-over samples	Automated recapping of samples Automated withdrawal of samples after the storage time has passed. Automated retrieval of samples for batch testing on decentral, specialized units.		
Post-postanalytical phase	Add-on requests	Fully automated electronic add-on requesting in the HIS with automatic sample retrieval in the core laboratory. No manual intervention is needed in the LIMS.	Add-on tests can be electronically ordered by clinicians without intervention of the lab staff. No more paper forms or phone calls are needed. Short, guaranteed TTAT for add-on requests (average of 26 min (SD = 3, 6 min) from request till report for standard chemistry tests).	Less new blood draws
	Regionally harmonized report order		In this hospital region agreements have been made across lab staff for identical sequential grouping of test results. In case of SI-traceable test results, reference intervals and decision limits have been harmonized. Clinical residents who work during their training in different regional hospitals, can to some degree rely on a harmonized postpostanalytical phase in this region.	

[a]Includes the diagnostic laboratories: clinical chemistry and laboratory medicine, microbiology, pharmacy, special hematology and the HLA-transplantation laboratory. LIMS, Lab Information Management System; HIS, Hospital Information System; NC, Noncompliance; TLA, Total Laboratory Automation; HIL, hemolytic, icteric and lipemic (index); STAT, emergency processing.

line analysis of the extra tests. Add-on requests were previously major process disruptor for doctors and lab technicians, demanding an inconvenient and time-consuming request procedure. Patients also benefit from e.g., specimen tube miniaturization and improved blood management as the amount of blood drawn is nearly halved compared to the former situation. Finally, the quality of the TTP improved substantially, leading to significantly less complaints and disruptions caused by lost or inadequately transported specimens. **Total** turnaround times are demonstrated in Figure 3 for representative medical tests. More than 95% of the TLA-supported in-line tests are reported within 120 min, a predefined criterion for Total TurnAround Time (TTAT). Especially the direct connectivity between e.g., the Central Phlebotomy unit and the core lab brings along substantially reduced transport times of specimens, that are much more guaranteed. Our experiences are in line with the findings of other authors [17, 19, 20]. Beyond what has been accomplished, further process developments are desirable such as future interfacing of blood transfusion analyzers and robotized small molecule mass-spectrometers to the TLA-system.

Strengths of this report are related to the holistic approach taken for improving the *brain-to-brain* loop testing process, in order to make medical testing more effective and safe. The resultant major process improvements are shown in Table 2. Limitations are related to the fact that the degree to which the TLA-centric testing process reduces diagnostic errors in the prepre- and post-postanalytical phases has not been quantified yet.

We conclude that the redesigned TTP using a Systems Engineering approach enabled us to substantially improve diagnostic lab services through TLA-robotization from phlebotomy to waste bin, bringing along high *front-to-end* process quality, complete track and trace on specimens, non-conformity registration, and guaranteed Total Turn-Around-Times of in-line tests – thanks to direct connectivity with automated unloading and processing of specimens. Importantly, the resulting lab process metrics demonstrate the potential of interoperable TLA for continuously strengthening diagnostic stewardship by embedding test utilization and lab services as an integral part of the clinical care process.

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