This is a non-final version of an article published in final form in:

Bietenbeck, Andreas, Ralf Junker, and Peter B. Luppa. "Central laboratory service and Point-of-Care Testing in Germany—from conflicting notions to complementary understandings." *Point of Care* 14.1 (2015): 1-11.

http://www.poctjournal.com/

Central Laboratory Service and Point-of-Care Testing in Germany – From Conflicting Notions to Complementary Understandings

Andreas Bietenbeck[1], Ralf Junker[2], and Peter B. Luppa[1]

[1] Institute of Clinical Chemistry and Pathobiochemistry, Klinikum rechts der Isar der Technischen Universität München, Munich, Germany

[2] Institute of Clinical Chemistry, Universitätsklinikum Schleswig-Holstein, Kiel, Germany

*** Corresponding author:**

Prof. Dr. Peter B. Luppa
Institute of Clinical Chemistry and Pathobiochemistry,
Klinikum rechts der Isar der TU München
Ismaninger Str. 22, D-81675 Munich, Germany
Phone: +49-89-4140-4759, fax: +49-89-4140-4875
Email luppa@klinchem.med.tum.de

Central Laboratory Service and Point-of-Care Testing – From Conflicting Notions to Complementary Understandings

Tables

Table 1: Main categories of POCT applications

POCT category	Users	Application
Hospital	Multiple users	Diagnosis and monitoring of (intensive care) patients
Outpatient	Multiple users	Diagnosis of patients
Self-testing	Single patient	Monitoring of patient
Qualified self-testing*	Single consumer	Health care customer
Disaster/military testing**	Multiple users	Triage for victims

* POCT in pharmacies, malls, fitness centers, etc. Over-the-Counter (OTC) and Direct-to-Consumer (DCT) testing.

** POCT is able to facilitate triage decisions in emergency and disaster settings.

Table 2: List of the most prominent parameters, performed by POCT [2]:

Clinical application	**Parameter**
Blood gases, acid-base balance	pH, pO2, pCO2, sO2, CO-oxymetry, HCO3-, Base Excess
Electrolytes	Na+, K+, Cl-, Ca++ion, Mg++ion
Diabetes mellitus markers	Plasma glucose, HbA1c
Hematology	Total Hemoglobin, HK, RBC, WBC, full blood count with leucocyte differential, reticulocytes, CD4+ T-lymphocytes
Hemostaseology	aPTT, INR, ACT, D-Dimer, viscoelastic thrombocyte function tests, ex-vivo bleeding time
Cardiac markers	cTnT, cTnI, (NT-pro)-BNP, myoglobin, CKMBmass, fatty acid-binding protein
Acute phase proteins	CRP in serum, calprotectin in faeces
Therapeutic Drug Monitoring/ Drugs of Abuse	Therapeutic drugs, alcohol, amphetamines, barbiturates, benzodiacepins, cannaboids, cocain, methadone, opiates, phencyclidin
Fertility (mostly urinary parameters)	hCG, LH, FSH, estrogens, sperm count
Urinary Diagnostics	Urinary sticks (Glucose, protein, bilirubin, urobilinogen, nitrite, leucocytes, erythrocytes, bacteria), microalbumin
Stool Diagnostics	Blood detection
Metabolites	Cholesterol, triglycerides, creatinine, BUN, uric acid, total bilirubin, lactate, NH3
Enzymes	LDH, Amylase, aP, CK, AST, ALT, GGT,
Infectious agents (bacteria, parasites)	Chlamydia trachomatis, Trichomonas vaginalis, Plasmodium spp., Streptococcus A and B
Infectious agents (viruses)	HIV, Influenca A and B, infectious mononucleosis
Allergy testing/autoantibody detection	Allergene-specific IgE, Anti-CCP, anti-MCV (mutated citrullinated vimentin)

Table 3: Key processes and workflows are the basis of the organizational structure of the POCT coordination

Tasks	**Requirements**	**Activities**
Administration and training of POCT users	Minimum elements of competency and handling training are:	Routine performance of the patient tests, Recording and reporting of test results, Internal and external QC recording, Instrument maintenance and function checks.
Management of instruments and reagents	IT-supported monitoring of the status of all decentralized POC devices	
Quality control and risk management	Maintenance of quality assurance can easily be achieved by:	Compliance of QC measurements, QC lock-out features, Adaptation of QC operations, Safeguarding of every individual device, Retrospective QC review and report.

Table 4: Summary of costs, receipts, and possible savings by applying POCT methods

	Costs	**Receipts**	**Possible savings**
Hospital setting	Additional costs for POCT units, reagents, operation	No additional receipts, reimbursement with the daily hospital rate or the G-DRG revenue	Possible if central laboratory will be sourced out totally or in part.
Medical practice	Additional costs for POCT units, reagents, operation	Additional payment for POCT, but slightly higher than for conventional analyses.	No possible savings.
Home care	Additional costs for POCT units, reagents, operation	No additional receipts.	Lower frequency of medical consultations.

Figure 1: Conceptual framework for innovation in healthcare
Click here to download high resolution image

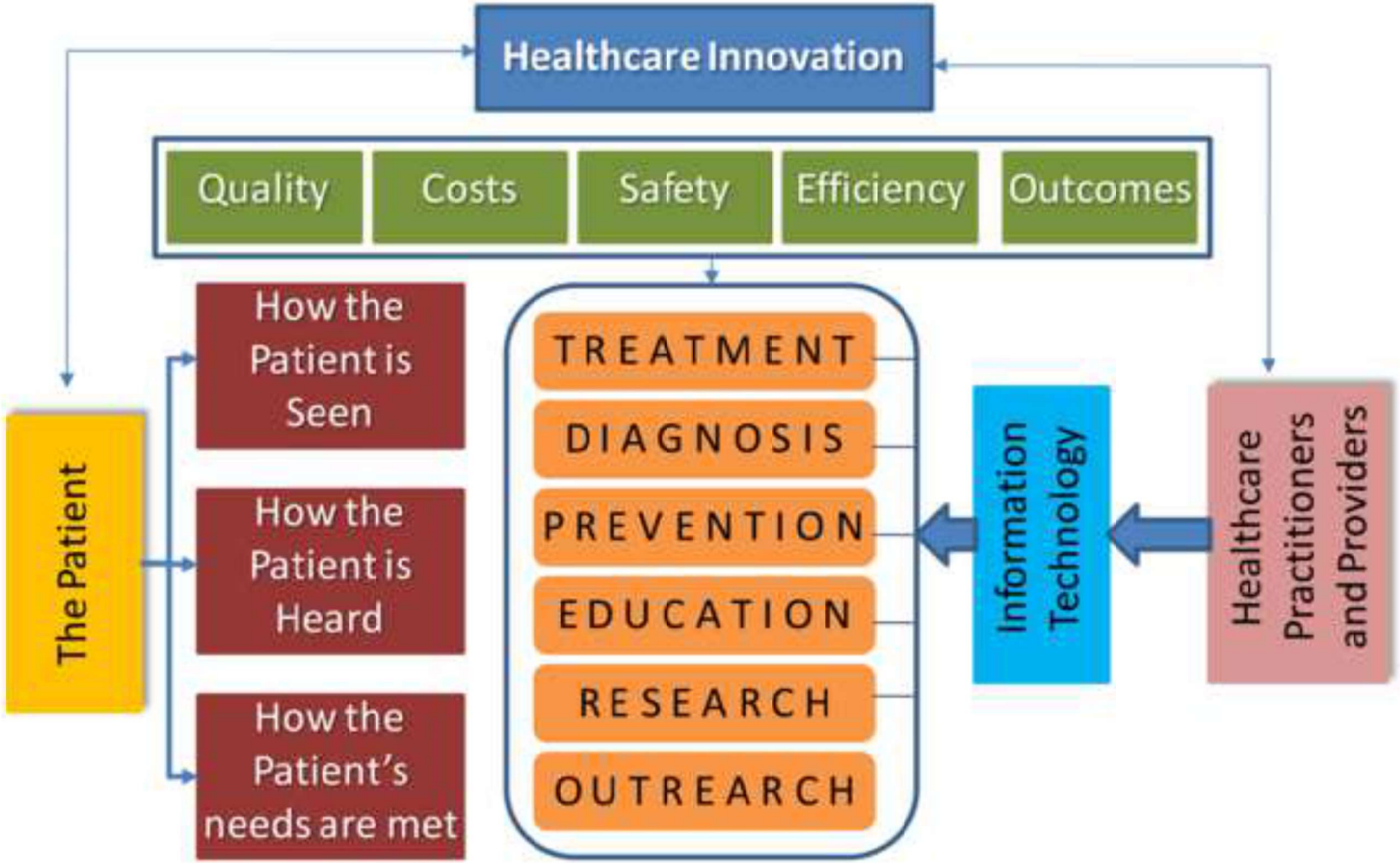


Figure 2: Total number of POCT publications

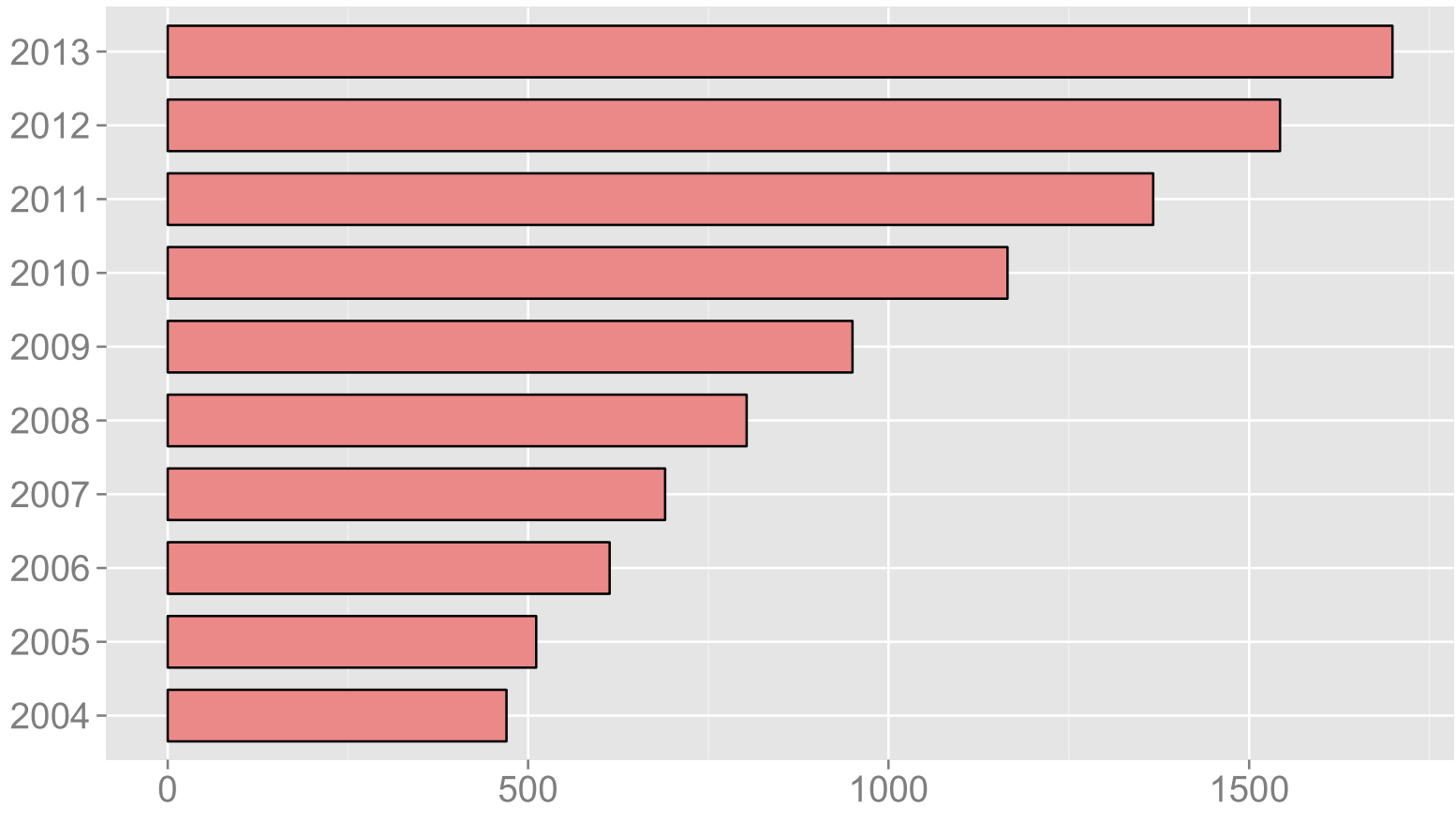


Figure 3: Tasks of the hospital POCT coordination

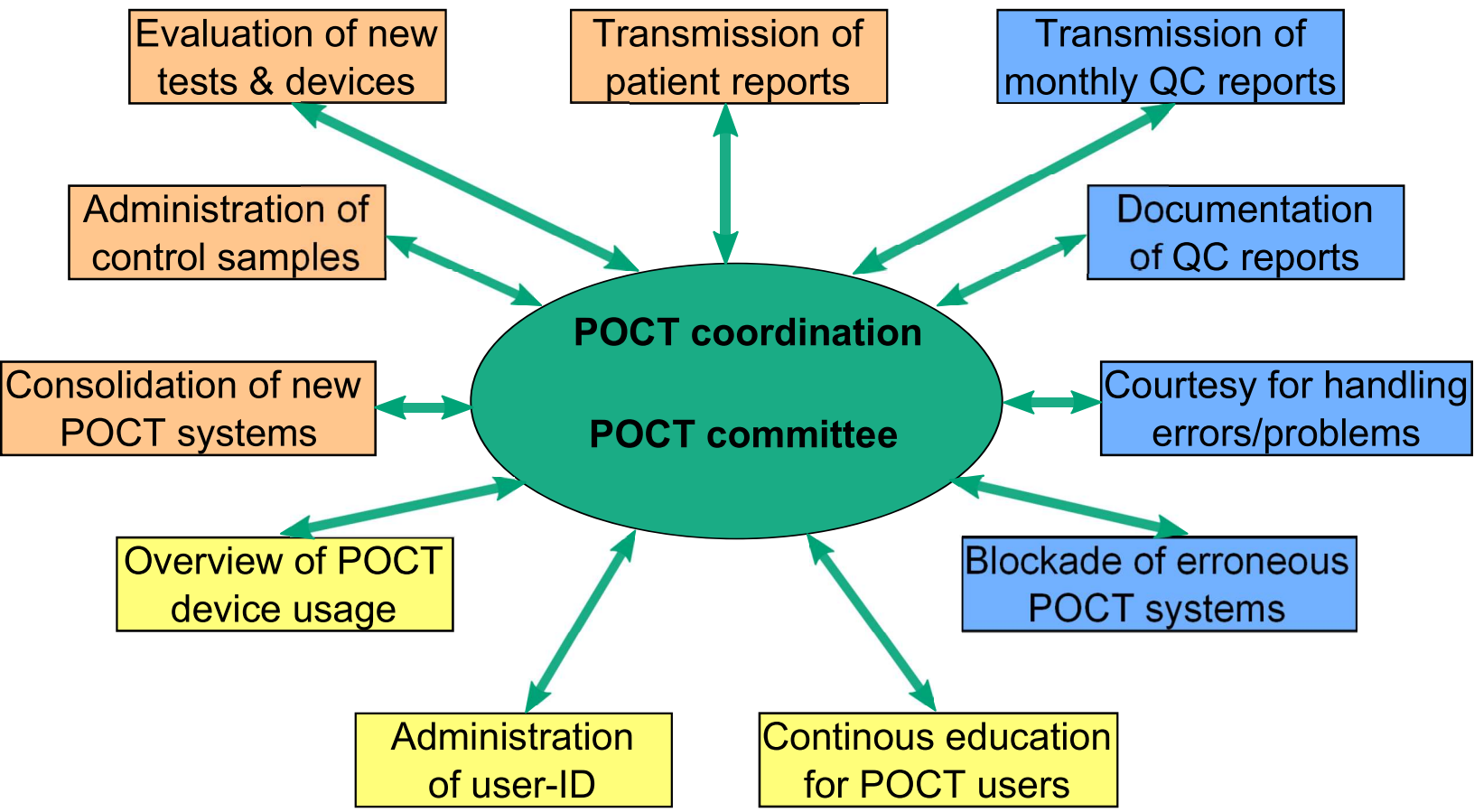
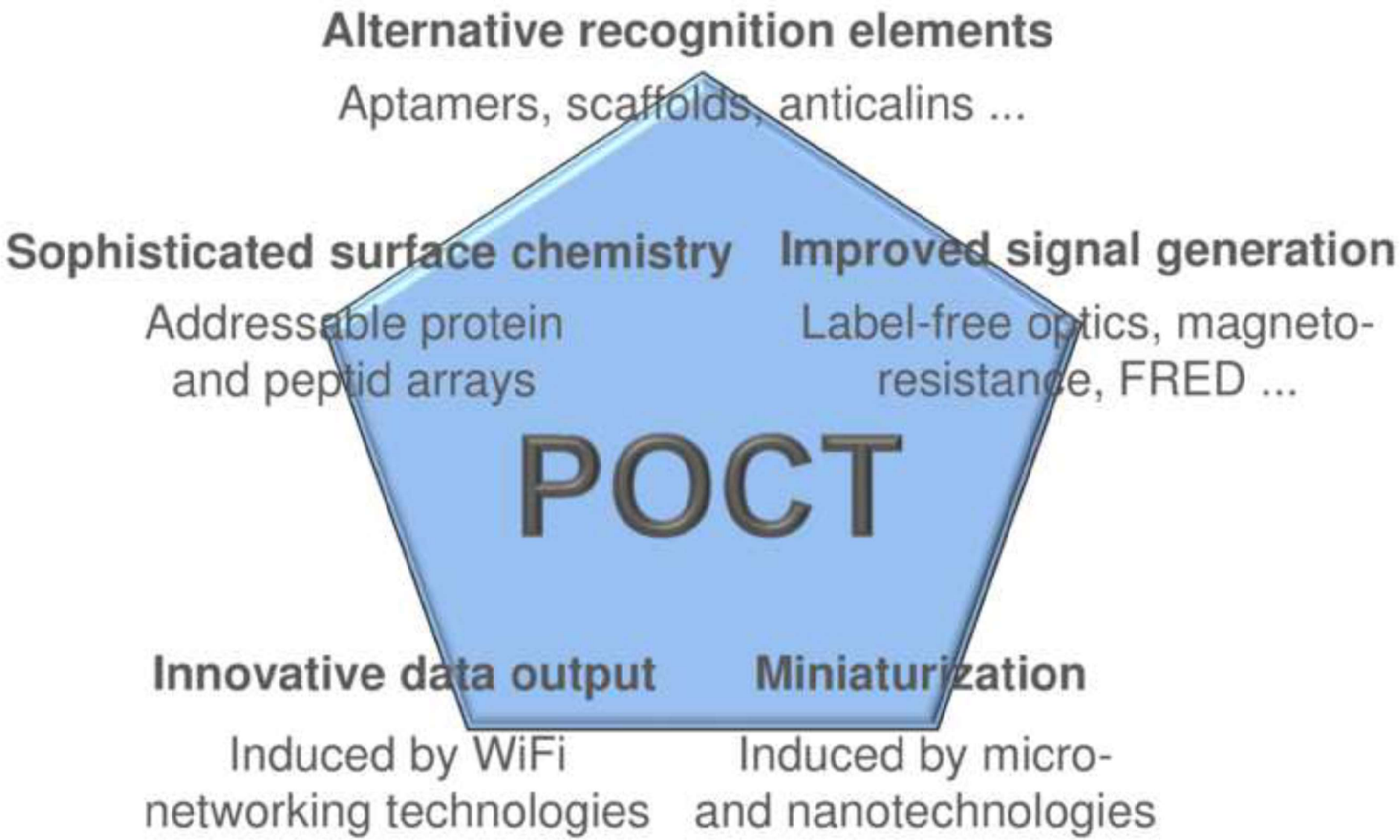


Figure 4: Technology drivers for new POCT developments
Click here to download high resolution image



LWW Copyright Transfer and Disclosure Form

Click here to download LWW Copyright Transfer and Disclosure Form: Unbenannt2.pdf

LWW Copyright Transfer and Disclosure Form: Luppa
Click here to download LWW Copyright Transfer and Disclosure Form: Unbenannt1.pdf

LWW Copyright Transfer and Disclosure Form

Click here to download LWW Copyright Transfer and Disclosure Form: Junker POCT Copyright Transfer unterschrieben-1.pdf

Introduction

From a historical aspect, the development of clinical chemistry has been a process of continuous centralization and improvement in efficiency and quality. Clinical analytics has moved from uroscopy at the patient's bed towards large medical laboratories, frequently not even located in the same hospital where the patient was treated. These laboratories are characterized by a high degree of automation and a designated workforce. Economics of scale has paved the way for reliable, fast and affordable laboratory diagnoses.

The move away from direct patient contact, however, has not remained unchallenged. Technical and analytical advances in a variety of miniaturization and detection methods [1] recently facilitated a trend towards decentralized point-of-care testing (POCT) devices. POCT encompasses proximity to the patient testing outside the central or satellite laboratory, no sample preparation or pipetting, ready-to-use reagents, dedicated analytical instruments, ease of use and rapidly available results that lead to diagnosis or immediate treatment [2]. With how quickly the applications of POCT are evolving, definitions have varied greatly and are likely to be modified even more so in the future [3,4].

Price and St. John critically commented [5], recently, that laboratory medicine in general lacks innovation. They rely on a definition of healthcare innovation, given by Omachonu and Einspruch: „*Introduction of a new concept, idea, service, process, or product aimed at improving treatment, diagnosis, education, outreach, prevention and research, and with the long term goals of improving quality, safety, outcomes, efficiency and costs.*“ [6]. In this context, it should be noted that successful innovation must focus on i) how the

patient is seen, ii) how the patient is heard, and iii) how the patient's needs are met. In the general perception, innovative POCT is directed towards the patient´s needs and leads to higher satisfaction [7]. This is in contrast to the negative public opinion regarding laboratory medicine as a whole. Innovation in healthcare has to do with radical changes in the way that care is delivered. The variety of POCT technologies – besides the ongoing IT achievements – most likely offers such changes. Three examples for POCT driven innovation processes are set out below.

- The first example of an innovative process is the use POCT to reduce the length of stay in the Emergency Room (ER). Here POCT addresses key aspirations of medical treatment: a more patient centered approach to care plus an improved clinical outcome by accelerating clinical decisions. POCT may lead to a reduction in the length of hospitalization and a reduced number of hospital admissions.
- A second example for innovation by POCT is the "Test, Treat, and Track-Program" of the WHO, fighting malaria in the third world [8]. In order to scale up malaria testing and link it to treatment and disease surveillance, POCT is being perceived as a successful professional attempt to solve this medical problem.
- A third well-known area of application where POCT has significantly improved treatment and patient satisfaction is self-monitoring of blood glucose levels for diabetics [9] The home-care approach avoids frequent clinical consultations. Recently developed devices, which allow a continuous measurement of glucose concentrations [10] prove that the innovative process has not ended but that improvements are still possible.

In the hospital, both POCT and the central lab are important for optimal functioning of the diagnostic processes. They complement each other, provided that quality assurance of POCT is integrated into the overall quality management system of the central lab [11]. Vice versa, POCT is a stimulus for lab managers to rethink how they can improve services from the central lab. The long standing paradigm, of hospital labs to provide resistance to POCT, has shifted towards managing it. Thus performing testing close to the patient´s bed by non-laboratorians would benefit the patient while not compromising quality [12,13]. It is the inherent interest of laboratory medicine to connect the processes of biochemical molecular analytics and microsystems technology with the discovery of novel biomarkers for use in clinical applications.

As evidenced by the rising number of publications within the last ten years, novel POCT technologies [1,14,15] have experienced a vibrant evolution, in terms of technological developments and new clinical applications.

It is anticipated that the global market for POCT will continue to grow considerably in the near future. Drivers of POCT are [4]:

- Changes in analytical, microfluidic and interfacing methodology
- Changes in the clinical environmental and economic needs of the healthcare system, greater access in healthcare niches (e.g. assisted ambient living)
- Changes in the commercial environment
- Changes in the regulatory environment
- Increasing patient/consumer engagement and health awareness.

The increased availability of POCT data in the hospital setting will necessitate modified clinical processes and new algorithms on how to use the diagnostic information provided by POCT [16].

In developed countries there will emerge new or expanding sectors for deployment of POCT, besides the classical healthcare inpatient and outpatient areas: pharmacies, shopping malls, fitness centers and ambient assisted living areas. The main categories of POCT applications are depicted in Table 1. The aim of this review is to portray important facets of hospital POCT (hPOCT) and to identify fruitful interdependencies with the traditional laboratory medicine in the face of future developments in the global healthcare systems.

Clinical Issues

hPOCT has been well established in most developed countries. In the context that a central lab is on-site, the advantages and disadvantages of hPOCT will be portrayed in this chapter. Important topics regarding hPOCT include available parameters, sampling issues, turn-around-times, analytical quality and potential errors and possible medical benefits [17].

The occurrence of hPOCT in various countries worldwide was significantly different in the past, but is now more and more akin. In Europe, larger hospitals with central laboratory services always offer POCT as well.

Available Parameters

In the late 60ies of the last century, blood gas analyzers were the first POCT devices being placed at the point-of-need and run by physicians and caregivers [18]. The precipi-

tating factor was the pre-analytical problem with the unstable parameters pO2, pCO2 and pH, as well as the clinical need for rapid analysis. The second POCT method being used widely in hospitals was the measurement of blood glucose. Today this parameter is still the most frequently applied analyte worldwide [19].

In the last decade, the spectrum of available measurements has grown considerably. Table 2 lists most prominent parameters performed by POCT [2]:

A new class of parameters available on POCT platforms is the detection of nucleic acids of infectious agents. These platforms currently integrate sample preparation, nucleic acid amplification (PCR or novel isothermal amplification protocols) and detection [20]. For instance, the Cepheid Xpert MRSA assay has been able to identify MRSA from various samples in approximately one hour of processing time, with minimal hands-on-time and with high accuracy [21].

Other POCT devices are not limited to the assessment of a single infectious disease. Multiplex assays search for the presence of nucleic acids from multiple bacteria, fungi and antibiotic resistance genes [22]. However, as NAT cannot distinguish between dead and viable microbes, these tests cannot easily be equated with traditional blood culture [23].

POCT devices often differ in matrix and measuring method from the central laboratory. For example blood gas analyzers typically have a direct ion selective electrode whereas automated analyzers in a central laboratory operate with an indirect ion-selective electrode technology. Therefore different factors interfere with the measurement [24,25]. As the

diverging results impact clinical assessments [26], a careful consideration between laboratory services, central lab vs. POCT, is mandatory for the individual hospital situation.

The management of the central lab always has to consider the three pivotal points: Quality, Service and Costs [12]. Meeting these criteria is always the goal for diagnostic disciplines. Thus, it is not appropriate to apply the whole POCT parameter spectrum in a hospital setting. The sophisticated analytical quality [27] and the competent consultation service provided by the central lab, will always contribute significantly to clinical outcome.

Sampling Issues

Concerning the sampling procedures of patient blood or other body fluids, POCT has decisive advantages over central lab testing. Unstable parameters can be handled without the precautions that are needed for time-consuming transportation to the central lab. Obviously, this applies only for rapid analysis after blood drawing. The second most crucial aspect is the small sample volume (mostly capillary fingerstick) needed for POCT. It is due to a lack of innovation that the central lab still needs high volumes of blood, even if only a limited number of parameters are analyzed. This is a problem particularly for neonates and small children. The requirement of frequent testing and phlebotomy also poses a substantial risk for adults in developing anemia, as a result of the cumulative blood loss [28]. Additionally, capillary fingerstick collection is convenient for the patient. There are yet also disadvantages: Measurements in capillary blood are not readily comparable to measurements in venous blood [29]. Also preanalytical issues should be taken

into account: Unwashed hands or squeezing of the finger are frequently seen faults and can easily lead to erroneous results [30]. Thirdly, the time for the blood collection is also crucial for the operational procedures of caregivers. Bedside glucose testing, using capillary blood, takes significantly less time than it does to collect an adequate specimen to be sent to the laboratory [31]. This fact should also be taken into account when considering the implementation of POCT in a hospital. It is, however, self-evident that for more complex test requests of multiple biochemical parameters, a venous sample of 5 – 10 mL is still mandatory.

Sampling for POCT can have an impact on infection control. Because during sampling patient and device are in close proximity to each other, contamination with blood occurs often. In their study, Louie et al. discovered blood contamination on approximately one third of all examined blood glucose meters [32]. Other groups found contamination of test strips from open vials [33]. However, when confined to a high-containment facility POCT devices reduce sample transportation and therefore limit exposure [34].

Turn-Around-Times

Time is a pivotal factor in clinical settings, most of all in the ER. The state-of-the-art management of critical patients depends on effective diagnostic processes. Clinicians demand rapidly performed and reported laboratory test results [35,36]. This is referred to as short turn-around-time (TAT). Unfortunately, the definition of TAT is still a matter of debate, since starting and end points of the testing process can be differently defined [36,37]. The starting point may alternatively be the ordering or the collection time, end points

may be the time of reporting, interpretation of the result or the immediate therapeutic action. In general, it is mandatory to reduce the diagnostic period of action in order to optimize patient care and to ensure stringent continuous workflows in the ER, OR and other hospital areas, such as the ICU [38]. Transformations of modified diagnostic processes into the existing hospital procedures should be evaluated in every setting [39,40]. Interventions such as workflow changes, increased staffing or the installation of pneumatic tube systems can shorten the TAT in a central laboratory [41]. An emergency department was able to reduce median overall door-to-result TAT for troponin testing from 117 to 60 minutes through process improvement and the implementation of a new workflow model [42]. Newer pneumatic tube systems can transport single samples without additional packing and directly into the bulk loader of a laboratory automation system, further reducing TAT [43]. Nørgaard et al [44] showed, however, that even when a pneumatic blood sample tube transporting system is used for a rapid transfer of patient specimens to the central laboratory, CRP measurements by use of POCT are able to shorten the TAT by more than half. It is evident that vital parameters, such as blood gases, glucose or cardiac markers, should be made available within an optimized TAT, either through the central laboratory or with POCT devices in cases where organization or distance do not allow the laboratory to ensure an adequate TAT [45]. The TAT often varies depending on the day of a week or the time of a day. Different times are needed for different laboratory tests. Therefore a careful comparison of POCT and central laboratory TAT has to consider these factors [45].

The call for ever faster results has to be critically evaluated. No benefits of a shorter TAT may be deduced for parameters, such as allergen-specific IgE or humoral tumor mark-

ers. In these diagnostic areas the use of POCT is most questionable, since no immediate clinical actions are obligatory. [46].

Analytic Quality and Potential Errors

According to the Technical Specification by the International Organization for Standardization (ISO/TS 22367), a laboratory error is a "failure of planned action to be completed as intended, or use a wrong plan to achieve an aim, occurring at any part of the laboratory cycle, from ordering examinations to reporting results and appropriately interpreting and reacting to them" [47]. This patient-centered definition examines all errors in the brain-to-brain loop from the selection of a laboratory test to the transmission of the result to the ordering physician [48]. Varying definitions and methods impair a comparison of the frequency of errors. In one study, only 225 errors occurred in 407,704 (0.00055%) POCT applications [49]. Another large study reported however, that 205 out of 5,154 (4.0%) tests could not be conducted with POCT devices and had to be transferred to the central laboratory [50]. Reported overall error frequencies for central laboratories range from 0.006% to 0.00012% of results [51].

The error types in POCT differ from tests conducted in a central laboratory. The first failure might occur when tests are ordered inappropriately. A meta-analysis found that 20.6% and 44.8% of all tests across different settings were over- and underutilized, respectively [52]. Professionals from a central laboratory might contribute to the continuous education of doctors who routinely order the tests and help to improve ordering patterns. Most studies detected the majority of errors in a central laboratory in the pre-analytical phase [53,54]. These errors included incorrect or insufficient samples, erroneous sample

conditions, incorrect identification and mistakes in sample handling and transport, leading to 56-68.2% of total errors [53]. All problems with regard to transport, especially, are substantially reduced in the pre-analytical phase of POCT. One study found only 32% of all errors are in this phase [49].

Automation, standardization, internal and external quality controls as well as better trained personnel has led to a dramatic reduction in analytical errors in the central laboratory [47]. It accounts for only 7 - 13.3% of the total error [53]. In most cases the analytical quality of POCT is not as high as the methods used in the central laboratory [55]. Moreover, POCT often lacks dedicated personnel. Therefore, operator incompetence is one of the leading sources of errors [55]. For example users were unable to authenticate themselves, minor maintenance procedures could not be performed [49] and manufacturers' instructions were disregarded [56]. Overall, 65.3% of POCT errors fall to the analytic phase [49].

To assess the impact of errors on patient care, a recent study distinguished actual from potential harm. 75.1% of 658 failures did not result in any change in patient management and no actual adverse clinical outcome was observed. However, 67.9% of all errors were graded as potentially leading to a significant adverse clinical outcome [57]. The fact that relatively few potential severe errors lead to actual harm indicates that effective countermeasures mitigate the impact of laboratory errors. It has been speculated, that these countermeasures might be affected when a physician acts quickly on POCT results [56].

Potential Medical Benefits

Measurable medical benefits of POCT were investigated in a series of clinical trials. The results were ambiguous, which may have to do with the heterogeneous clinical settings investigated in the studies. Pecoraro et al [58] performed a metanalysis of 84 studies for five POCT parameter groups: neonatal bilirubin, procalcitonin, intra-operative parathyroid hormone, troponin and blood gas analysis. The authors found that, although POCT has the potential to provide beneficial patient outcomes, further studies may be required, especially for defining its real utility on clinical decision making. Other extensive studies were conducted to examine whether the introduction of POCT shortens the length of stay for patients in emergency departments [40]. The results were inconsistent, and while some studies reported indeed a reduction [50, 59] others found no difference [60] or even an increase in the length of stay [61].

Collinson et al [62] ascertained that a combination of POCT and structured decision making reduces the length of hospital stay. Mortality was found equivalent in 263 consecutive selected patients with suspected acute coronary syndrome (ACS), tested for cardinal troponin T (cTnT) either with POCT or with a central lab method. The authors also found no difference in the length of stay. In the pre-specified early discharge group, however, there was a significant reduction in the overall hospital stay in those randomized to POCT. Also, Renaud et al [63] assessed the impact of a POC measurement of cTnI on the time for anti-ischemic therapy for patients with suspected non-ST-segment elevation ACS (NSTE-ACS). 860 patients in the ER were randomly allocated to POCT or central lab testing. They concluded that POCT for cTnI might be clinically relevant for patients with a suspicion of NSTE-ACS, particularly for high-risk patients with a low sus-

picion of ACS. Per Venge et al [64] found, however, that current POCT cTnI assays are less sensitive for outcome prediction of patients with myocardial injury. Therefore, the clinical judgment of patients with suspected ACS should not solely rely on results from POCT methods, which still are compromised by analytical insufficiencies. Deficiencies of the clinical process management also mitigate possible advantages of POCT. Ryan et al [61] pointed out in a randomized trial, evaluating 2,000 patients in four US ER settings, that at one site, POCT decreased time to admission, whereas at another, the near-patient testing even increased time to discharge. Effects of POCT on patient throughput and outcome should be considered in the full context of ER operations. This effect was already seen in a pioneer publication of Nichols et al [65] in 2000. The authors concluded that although hPOCT has the potential to provide benefits, merely moving testing from a central laboratory to the medical unit does not guarantee improved patient outcomes.

Another area of successful application of hPOCT methods is the management of bleeding trauma patients [66,67]. These subjects are particularly in need of coagulation tests because of the complex coagulopathies that can develop from substantial hemorrhage. Effective implementation of the viscoelastic technology, such as thrombelastography (TEG) or rotational thromboelastometry (ROTEM), had significant effects on the amount of administered fresh frozen plasma, as well as erythrocyte- and thrombocyte concentrates in massively transfused patients. Thus, POCT coagulation devices, detecting the thrombocyte functionality, are rapidly becoming standard of care in trauma centers. A handling problem, however, remains for these viscoelastic methods: The device complexity imposes high demands on the users. Therefore bigger hospitals run these analyses in close cooperation with coworkers from the central lab.

POCT facilitated faster clinical decision making, especially for senior staff [59]. Actions were taken earlier with POCT when the diagnosis was mainly based on laboratory findings [63,68]. To avoid bottlenecks, all relevant tests have to be transferred to POCT devices [69]. The length of stay in an emergency department depends on many other factors besides faster results [70]. Thus, systematic changes in patient management are required. This underlines that only a tight partnership between the central lab and the clinical settings where POCT is performed facilitates substantial clinical benefits. On the other hand, it is well established that a rapid initialization of treatment leads to better results in conditions like sepsis [71], stroke [72] and acute myocardial infarction [73].

In 2007, the National Academy of Clinical Biochemistry (NACB) developed evidence-based Laboratory Medicine Practice Guidelines for hPOCT [74]. These guidelines systematically reviewed the scientific literature relating POCT to clinical outcomes and offered recommendations to improve the clinical utility of POCT. The authors advised against overutilization or inappropriate usage of hPOCT, whose results can be misleading and increase healthcare costs. The evaluation of the NACB is still useful to clinicians considering the addition of POCT, questioning current practices in POCT, and seeking evidence-based support for POCT in clinical management. Until today, their recommendations for a series of biochemical tests were valid: Coagulation POC tests, as well as blood gas and plasma glucose measurements, are clearly evidence-based methods that are able to improve the clinical outcome. For the POCT application of cardiac markers in 2007, the authors stated no evidence for an improved patient outcome. They gave, however, the additional statement that with improved analytical methods for cardiac

markers, evidence will likely be presented in the future. For renal function parameters, no evidence for improved patient outcomes could be found.

Organization Related Issues

hPOCT Coordination

The available analytical spectrum and the abilities of a comprehensive networking of decentralized positioned POCT systems have made it possible to develop new approaches to laboratory medicine services. The cooperation of laboratory professionals with clinicians and caregivers leads to complementary insights on both sides. The project to implement POCT in a hospital, however, needs suitable management structures with clearly defined areas of responsibilities [75,76].

In the last decade, it has been shown for hospitals implementing POCT that it is essential to set up a new organizational body, the POCT committee, bringing together all hospital groups dealing with POCT: central lab, clinics, pharmacy, administration and the department of medical engineering. Managed by the central laboratory this executive group is committed to fulfilling the regulations for quality management and improving the whole process [77]. The POCT committee is the right place for actively fulfilling the spirit of partnership and should meet at least once a year. It is important that clinical POCT users have participation in decision-making. POCT users and central lab have to meet several analytical and organizational challenges for a joint diagnostic service [11].

The head of the POCT committee should be the POCT coordinator with clearly laid out responsibilities. Standard troubleshooting and maintenance procedures for the performance of POCT should be defined by the coordinator after consultation with the clinical users. Here the POCT coordinator, being a central lab coworker, is a key player since laboratory analyses are his core competency. The users should also be placed in an important role in resolving routine QC failures.

POCT data management middleware enables the coordinator not only to check the QC of all connected devices, but also the actions of POCT users. Handling problems, QC violations and workflow interruptions are supervised in nearly real-time and can be eliminated reliably, thus, ensuring patient safety.

Quality assurance is a key aspect in decentralized POCT and requires appropriate tools to manage the process. A powerful and flexible data management middleware bridges the gap to both the Laboratory and Hospital Information Systems [11]. This connectivity allows reliable documentation of the POCT results, optimization of quality assurance, and proper calculation of cost-effectiveness. It achieves high quality and efficiency for the hPOCT service [11].

The tasks of the POCT coordinator are depicted in Figure 3.

The organizational structure of the POCT coordination inside a hospital can successfully be built by implementation of the following key processes and workflows, which are depicted in table 3:

Administration and Training of POCT Users

In many European countries, identification of POCT users is mandatory. The operator´s ID is important for documenting that only authorized subjects perform POCT - the authorization being received on the basis of qualification and/or experience. A personal recertification is to be planned every 24 months of duty. The POCT server software should be able to manage all approved users within a hospital or a hospital group, and to allocate them on a hospital-wide basis to individual instruments and/or tests. The system should have the ability, again from one central point, to remove the authority of an individual operator from carrying out a particular test (e.g. if the operator's certificates are no longer valid) or re-authorize him (e.g. after having certificates renewed) [78]. Appropriate IT systems are again the key factor to such operator management issues [79].

Training issues: For developing competency of POCT users, the regulatory requirements of many countries provide initial training and reassessments, either (semi)-annually or every other year.

Minimum elements of competency and handling training are:

i. Routine performance of patient tests, including patient identification and preparation, specimen collection, handling and processing (preanalytical and analytical issues).
ii. Recording and reporting of test results (postanalytical issues).
iii. Internal and external QC recording and preventive maintenance records.
iv. Instrument maintenance and function checks and problem-solving skills.

The partnership between POCT and the central lab is best demonstrated in this context by the provision of support for the education of personnel. Training courses may be provided by the vendor of the different POCT devices, either solely or in cooperation with certified POCT coordination trainers.

Quality Assessment and Risk Management

Surveillance of QC measurements is one of the most important tasks to be carried out by the POCT coordinator. Since the purpose of QC is to ensure the reliability of the POCT results, it has to be performed prior to patient testing by the caregivers who perform the analysis, and it must be checked for acceptability prior to performing patient testing. A sophisticated IT QC system, allocated to the POCT coordinator, has to achieve the following key requirements for the maintenance of quality assurance:

- Compliance of QC measurements on a regular basis in accordance with laboratory guidelines,
- QC lock-out feature within the device preventing analyses if QC has not been performed or evaluated as being within the acceptable range,
- Adaptation of QC operations with shift patterns or testing routines,
- Safeguarding that individual device set-ups maintain the highest level of quality assurance without disturbance of hospital workflows,
- Retrospective QC review, performed periodically, combined with consultation with the clinical personnel.

The EP-23 document from CLSI [80] provides checklists based on *risk management* for both central laboratories and POCT to develop quality control plans tailored to the particular combination of measuring system, laboratory setting, and clinical application of

the test. The POCT coordinator should establish such a risk management plan to mitigate and prevent errors. The plan should describe the comprehensive process of specified activities in order to control the quality of POCT and to ensure that intended purposes are met. All efforts are meant to prevent failures and to detect nonconformities that may occur before incorrect results are reported and clinical action is triggered.

C*omprehensive quality assurance* of hPOCT should consider all quality management rules, defined by CLSI and ISO, as well as quality rules given by local accreditation bodies. QMS14-A (Quality Management System: Leadership and Management Roles and Responsibilities; Approved Guideline), POCT 07A (Quality Management – Approaches to reducing errors at the Point-of-Care), EN ISO 15189 (Medical laboratories — Particular requirements for quality and competence) and ISO 22870 (Point-of-care testing (POCT) - Requirements for quality and competence) provide the theoretical background of the relevant procedures.

Internal and external QC protocols are conducted to prevent errors in the analytical phase and to validate the accuracy of the devices. It is the rationale of quality assurance that all QC samples are treated wherever possible like patient samples. Internal QC validates the performance of a device by use of defined performance criteria and applies the analysis of defined (commercially available) control materials, which are manually processed in the same way as patient samples. The results have to be confirmed to be within predetermined and accepted ranges of the target values. Modern blood gas analyzers with higher complexity often apply automated QC sequences.

Apart from this traditional type of internal QC, electronic built-in checks are often found in POCT analyzers, which assess the electronic performance of the device prior to the analysis [81]. Procedural or built-in controls for certain tests can also be found. The applicability of the latter QC tests, however, has to be reviewed with regard to conformity with the respective national guidelines.

In some European countries, and in the US, a calibration verification and linearity materials are additionally in use to complete the quality assurance. These materials may be used for compliance with regulatory agencies' standards/requirements, verification of the parameter´s measurement range, and demonstration of assay performance and of analyzer-to-analyzer comparability.

Comparability of laboratory results is one of the fundamental goals of laboratory medicine [82] but is still not satisfactorily solved. POCT and central laboratory methods that measure the same analyte often coexist in a hospital. This problem needs to be thoroughly addressed. A thoroughly performed intermethod comparison and interpretation of the agreement level, using the Cohen kappa coefficient [83,84], is a practical approach to this problem.

External QC validates the accuracy of the devices within an organizational unit. The assessment can also be performed with other POCT users dealing with the same instrument family. Due to the independence of the control material from the device manufacturer, external QC measurements allows the POCT coordination to validate the performance of the whole instrument pool over a period of time [85].

The matrix of external QC samples, however, often poses problems for POCT analyzers [86]. Examples are blood gas analysis and measurement of plasma glucose. In the latter case, a suitable control material for a variety of POCT devices (with different methodologies) is not commercially available. An evaluation may currently only be performed on the so-called consensus value model (mean value from the received results depending on the method in use). The glucose-6-P-dehydrogenase-hexokinase reference method value is not applicable as the target value [87].

To address quality issues in laboratory medicine, different countries in the EU and the US have developed similar approaches. The paradigm is that there should be no quality difference between POCT and conventional laboratory diagnostics. To implement this requirement in the hospital, POCT coordination is mandatory. The national quality assessment scheme of Germany for POCT should serve as an example. The 2008 directive of the German Medical Association on the quality assurance of tests in laboratory medicine (RiliBÄK 2008 [88]) does not stipulate any special regulations for POCT in comparison to those for a medical laboratory, the only exception being the unit-use systems. Part A of the RiliBÄK is dedicated to quality management and contains fundamental requirements for quality assurance, such as the preparation of a quality handbook. Part B1 contains the specific requirements for the quality assurance of a series of quantitative laboratory tests. Most hPOCT methods are included in this list. There are also rules concerning the daily internal and quarterly external quality controls.

It has been argued that the responsibility for assuring the quality of a POCT result rests with the manufacturer [89]. Intriguingly, the specific causes of errors differ significantly between devices [49]. A manufacturer can implement integral controls and calibrators and

sophisticated algorithms that are inaccessible to the operator. This transfer of human intelligence to automated machinery is termed "autonomation" [89]. Automated quality control is not new in central laboratories. Only a few test procedures, however, possess such a tightly integrated automated QC.

Management of Instruments and Connectivity

IT connectivity should enable the POCT coordinator to monitor the status of all decentralized POC instruments and to lock and unlock them from a central site. Modern IT connectivity systems allow remote communication with several bidirectional connected device types in order to perform maintenance actions (washing cycles, recalibrations etc

Modern POCT devices are designed for connection to a POCT server and often possess bi-directional communication capabilities. The POCT01-A2 standard [90] is generally accepted by major IVD companies as an adequate interface to link the POCT instruments with hospital IT systems. Bidirectional connectivity implies that results and additional information can be uploaded from the device to the data manager, and also that (calibration) data and commands can be downloaded or even that remote access to the device is possible.

Making the choice between wired and wireless IT technologies is often a difficult task within the hospital. Explicit concerns about the security of patient data must be taken into considerations.

As POCT devices are distributed across the whole hospital, so are reagents. Therefore, a quality management for POCT has to ensure that reagents and other consumables are

readily available at each device. However, the storage conditions must not exceed predefined limits especially with regard to temperature and humidity [91]. Of course, no reagent may be used beyond its expiration date [55].

Reagent management can easily be achieved via the IT system by the consumption statistics from all decentralized POCT instruments. A collaboration of the POCT coordinator with reagent suppliers and clinical settings is important.

Economics Related Issues

Economic Effectiveness

Economic considerations and cost-effectiveness analyses concerning the use of hPOCT were made by a series of authors [28,75,92,93]. It should be emphasized that economic issues greatly depend on the individual settings. In general, cost effectiveness is the result of *costs* (expenditure on personal and material, overhead etc.), *receipts*, and the possibilities of *savings*. Regarding these factors, the assessment of costs and benefits of POCT has to be evaluated separately, for each of the different areas of use. Moreover, cost-effectiveness of POCT not only depends on direct costs for measuring a parameter, but also on the consequences of quickly knowing the measurement results. They must be evaluated from an objective medical point of view.

One example from a study, performed by Howanitz and Jones [92], should portray this situation: Analytical costs per glucose test were found to be lower for central laboratory glucose testing than for POCT, which, in turn, was highly variable and dependent on

volume. It must be considered that hPOCT has a higher cost-per-test due to the manual nature of single measurements, whilst it offers the potential of substantial savings through enabling rapid delivery of results and reduction of facility costs [93].

Costs

The generally given statement that POCT procedures are markedly more expensive than conventional laboratory tests should be reconsidered. Components of total costs are expenditures on materials and personnel, reagents, water and electricity, overhead, etc. Apart from the greater costs for the instruments and reagents, additional working hours are needed. This has to be reflected in the number of jobs in the hospital or practice. In particular for POCT, components such as an IT network or additional logistics (separate blood sample collection, delivery of reagents etc.) are sometimes neglected.

Hortin [28] pointed out that labor is the major expense, and the controversy regarding relative costs of POCT arise, in part, from whether labor costs represent allocation of personnel time or actual changes in the number of paid hours resulting from POCT. hPOCT and central laboratory testing are not equivalent processes; a comprehensive comparison of both requires consideration of quality of care as well as cost. Usually, the addition of easy to perform POCT processes to a nursing unit has no impact on the number of staff or hours worked if the number of analyses per day does not exceed the number of beds by more than three times (authors' personal experience). Therefore, it could be argued that it does not represent a labor cost, but rather a change in productivity. Such arguments, however, must be seen in light of largely unchanged fixed costs in the cen-

tral laboratory and of the substantial and not increasable workload of caregivers in many critical hospital sites. An expansion of an existing hPOCT service needs therefore a critical appraisal. Table 4 shows a summary of costs, receipts, and possible savings.

Receipts and Savings

Reimbursement regulations differ largely between the European countries. E.g., the inpatient reimbursement policy in Germany is as follows: for POCT and laboratory analyses, receipts can be earned for individual measurements and reimbursed with the daily hospital rate or the German Diagnosis Related Groups (G-DRG) revenue. There is no additional payment for laboratory analyses and especially not for the use of POCT instruments.

For the outpatient sector, the medical account system allows in principle fees for laboratory and POCT analyses. Payments for POCT, however, are only slightly higher than for conventional analyses and reflects the real costs only in rare cases [94,95]. The low utilization of POCT among general practitioners may be explained thereby. This particularly applies to basic services with low reimbursement rates, which may nevertheless be essential for operating the practice in specialized areas. Beside direct payments, receipts can be increased by a higher number of treated patients per time due to more quickly available laboratory results and other aspects.

The potential of economic and organizational improvements should always be considered, e.g., by optimizing the time course of work in the central laboratory or in the outpatient clinic. This comprehensive approach was applied by Adams at al. when they calculated overall costs for different clinical pathways for testing and treatment of chlamydia

and gonorrhea [96]. They predicted the highest savings for a rapid pathway that makes use of NAT POCT testing. On the other hand, payment in medical practices largely depends on services delivered, so that the individual POCT analysis is charged for accordingly.

Economic considerations are also relevant at a higher level. If screening with laboratory tests could reduce the use of expensive imaging procedures, this might lead to overall savings in the health system—but also to a reduction in the revenue in other diagnostic disciplines as well. In a hospital setting, the fixed costs in the laboratory are often largely unchanged. For self-monitoring in the home setting, it should be taken into account that costs for medical consultations can be reduced [75].

Future Developments and Applications of POCT

At present, novel analytical principles and instruments can be envisioned for the near future, including alternative biological detection elements, sophisticated applications of optical signal technologies and new dedicated protein microarrays [15]. This process will be encouraged additionally through innovations from the IT industry. The analytical drivers are depicted in Figure 4.

In particular, the extraordinary opportunities of multiplexed **micro total analysis systems (μTAS)** will change the future of laboratory testing [97]. Establishment of these μTAS will revolutionize the diagnostics of infectious diseases in resource-limited countries of the third world (due to the fact that they are not depending on a hospital laboratory infrastructure).

Device miniaturization and modern microfluidics lead to the **Lab-on-a Chip (LOC)** concept [98,99]. The development of such affinity based systems is a driving force of the rapidly growing nanotechnology industry which involves microfluidics, microelectronics and analytical chemistry in a multidisciplinary way [100].

A variety of academic proof-of-concept studies have shown the potential of LOC systems compared to central laboratory tests [101]. There are, however, until today no conclusive POCT applications since translating concepts into commercial devices has proved difficult mainly due to high production costs [13]. In the future a conceivable area of application of LOC techniques could be the multiplexed detection of nucleic acids for diagnosing infectious diseases.

An emerging new mode of analysis should also to be mentioned here, even when this development is already in clinical use: **Continuous monitoring**, by use of microdialysis techniques. The most prominent example is glucose monitoring (CGM) allowing frequent glucose measurements. Thus, glucose level trends in poorly controlled diabetic patients can be monitored in nearly real time. CGM provides information about shifting glucose levels (mainly measured in the interstitial fluid **[102]**) during 24 h. In particular the detection of hyperglycemic excursions as well as asymptomatic nocturnal hypoglycemia may improve management of glucose levels in these patients **[103]**. A CGM mode using non-invasive methods (e.g. Raman spectroscopy) is still in its infancy **[104]**.

This technical progress may considerably change the application modalities of POCT in a hospital. The adoption trajectories, however, cannot be foreseen, but depend largely on whether new POCT concepts satisfy unmet clinical needs. It is obvious that the diag-

nosis of infectious diseases might be the pivotal area of such new applications. There are a series of clinical data already available that show the potential of these devices for infection control purposes [105].

References

1. Gubala V, Harris LF, Ricco AJ, Tan MX, Williams DE. Point of care diagnostics: status and future. *Analytical chemistry.* 2011;84(2):487-515.
2. Luppa PB, Schlebusch H. *POCT - Patientennahe Labordiagnostik.* 2. Aufl. 2012 ed. Berlin, Heidelberg: Springer; 2012.
3. Nichols JH. *Laboratory Medicine Practice Guidelines Evidence-Based Practice for Point-of-Care Testing.* The National Academy of Clinical Biochemistry;2007.
4. Bowman C. Point of Care Testing Toolkit.
5. Price CP, St John A. Innovation in healthcare. The challenge for laboratory medicine. *Clinica chimica acta; international journal of clinical chemistry.* Jan 1 2014;427:71-78.
6. Omachonu VK, Einspruch NG. Innovation in healthcare delivery systems: A conceptual framework. *The Innovation Journal: The Public Sector Innovation Journal.* 2010;15(1):2.
7. Crocker B, Lewandrowski EL, Lewandrowski N, Gregory K, Lewandrowski K. Patient satisfaction with point-of-care laboratory testing: report of a quality improvement program in an ambulatory practice of an academic medical center. *Clinica chimica acta; international journal of clinical chemistry.* Sep 23 2013;424:8-11.
8. T3: Test. Treat. Track initiative. 2014; http://www.who.int/malaria/areas/test_treat_track/en/. Accessed 2014-11-11.
9. Polonsky WH, Fisher L, Schikman CH, et al. Structured Self-Monitoring of Blood Glucose Significantly Reduces A1C Levels in Poorly Controlled, Noninsulin-Treated Type 2 Diabetes: Results from the Structured Testing Program study. *Diabetes care.* February 1, 2011 2011;34(2):262-267.
10. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study G, Tamborlane WV, Beck RW, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med.* 2008/10// 2008;359(14):1464-1476.
11. Diesel D, Gsoell C, Slaat EH. Point-of-Care Testing (POCT): key factors to ensure efficiency and high quality. *Clinical Lab International* May 2004.
12. Dilts TJ. Point-of-care Testing: A Step to the Future. *BD Diagnostics - Preanalytical Systems, LabNotes.* 1998;8(1):1-4.
13. St John A, Price CP. Existing and Emerging Technologies for Point-of-Care Testing. *The Clinical biochemist. Reviews / Australian Association of Clinical Biochemists.* Aug 2014;35(3):155-167.
14. Gauglitz G. Point-of-Care Platforms. *Annual review of analytical chemistry.* Jun 12 2014;7(1):297-315.
15. Luppa PB, Müller C, Schlichtiger A, Schlebusch H. Point-of-care testing (POCT): Current techniques and future perspectives. *TrAC Trends in Analytical Chemistry.* 6// 2011;30(6):887-898.
16. Jani IV, Peter TF. How point-of-care testing could drive innovation in global health. *The New England journal of medicine.* 2013;368(24):2319-2324.
17. Schimke I, Griesmacher A, Schimke E, Müller MM. Patientennahe Sofortdiagnostik (Point-of-Care Testing; POCT) im Krankenhaus—Ja oder Nein. *Intensivmedizin und Notfallmedizin.* 2006;43(2):143-155.
18. Severinghaus JW. MEASUREMENTS OF BLOOD GASES: Po2 AND Pco2*. *Annals of the New York Academy of Sciences.* 1968;148(1):115-132.
19. Yoo E-H, Lee S-Y. Glucose biosensors: an overview of use in clinical practice. *Sensors.* 2010;10(5):4558-4576.

20. Niemz A, Ferguson TM, Boyle DS. Point-of-care nucleic acid testing for infectious diseases. *Trends Biotechnol.* May 2011;29(5):240-250.
21. Rossney AS, Herra CM, Brennan GI, Morgan PM, O'Connell B. Evaluation of the Xpert Methicillin-Resistant Staphylococcus aureus (MRSA) Assay Using the GeneXpert Real-Time PCR Platform for Rapid Detection of MRSA from Screening Specimens. *Journal of clinical microbiology.* October 1, 2008 2008;46(10):3285-3290.
22. Altun O, Almuhayawi M, Ullberg M, Ozenci V. Clinical evaluation of the FilmArray blood culture identification panel in identification of bacteria and yeasts from positive blood culture bottles. *Journal of clinical microbiology.* Dec 2013;51(12):4130-4136.
23. Afshari A, Schrenzel J, Ieven M, Harbarth S. Bench-to-bedside review: Rapid molecular diagnostics for bloodstream infection - a new frontier? *Crit Care.* May 2012;16(3):222.
24. King RI, Mackay RJ, Florkowski CM, Lynn AM. Electrolytes in sick neonates - which sodium is the right answer? *Archives of disease in childhood. Fetal and neonatal edition.* Jan 2013;98(1):F74-76.
25. Jain A, Subhan I, Joshi M. Comparison of the point-of-care blood gas analyzer versus the laboratory auto-analyzer for the measurement of electrolytes. *Int J Emerg Med.* 2009/06/01 2009;2(2):117-120.
26. Morimatsu H, Rocktäschel J, Bellomo R, Uchino S, Goldsmith D, Gutteridge G. Comparison of Point-of-Care Versus Central Laboratory Measurement of Electrolyte Concentrations on Calculations of the Anion Gap and the Strong Ion Difference. *Anesthesiology.* 2003;98(5):1077-1084.
27. Jones BA, Bekeris LG, Nakhleh RE, Walsh MK, Valenstein PN. Physician Satisfaction With Clinical Laboratory Services: A College of American Pathologists Q-Probes Study of 138 Institutions. *Archives of pathology & laboratory medicine.* 2009/01/01 2009;133(1):38-43.
28. Hortin GL. Does Point-Of-Care Testing Save Money or Cost More? *Lab Medicine.* 2005;36(8):465-467.
29. Colagiuri S, Sandbæk A, Carstensen B, et al. Comparability of venous and capillary glucose measurements in blood. *Diabetic Medicine.* 2003;20(11):953-956.
30. Hortensius J, Slingerland RJ, Kleefstra N, et al. Self-Monitoring of Blood Glucose: The Use of the First or the Second Drop of Blood. *Diabetes care.* March 1, 2011 2011;34(3):556-560.
31. Moultrie C, Hortin G, Randolph V. Comparative costs and labor efficiency of bedside versus central laboratory glucose testing. *Clinical chemistry.* Jun 1997;43(S):162.
32. Louie RF, Lau MJ, Lee JH, Tang Z, Kost GJ. Multicenter Study of the Prevalence of Blood Contamination on Point-of-Care Glucose Meters and Recommendations for Controlling Contamination. *Point of care.* 2005;4(4):158-163.
33. Ng R, Koo S, Johnston R. Multicenter evaluation of bacterial contamination of glucose test strips. *Clinica Chimica Acta.* 10/9/ 2012;413(19–20):1485-1487.
34. Hill CE, Burd EM, Kraft CS, et al. Laboratory Test Support for Ebola Patients Within a High-Containment Facility. *Lab Medicine.* July 1, 2014 2014;45(3):e109-e111.
35. Löffert S, Damerau M. Die Bedeutung der Labordiagnostik für die Krankenhausversorgung. 2014.
36. Steindel SJ, Howanitz PJ. Physician Satisfaction and Emergency Department Laboratory Test Turnaround Time. *Archives of pathology & laboratory medicine.* 2001/07/01 2001;125(7):863-871.
37. Breil B, Fritz F, Thiemann V, Dugas M. Mapping turnaround times (TAT) to a generic timeline: a systematic review of TAT definitions in clinical domains. *BMC medical informatics and decision making.* 2011;11(1):34.
38. Norgaard B, Mogensen C. Blood sample tube transporting system versus point of care technology in an emergency department; effect on time from collection to reporting? A

randomised trial. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine.* 2012;20(1):71.
39. Kilgore ML, Steindel SJ, Smith JA. Evaluating stat testing options in an academic health center: therapeutic turnaround time and staff satisfaction. *Clin Chem.* Aug 1998;44(8 Pt 1):1597-1603.
40. Di Somma S, Magrini L, Travaglino F, et al. Opinion paper on innovative approach of biomarkers for infectious diseases and sepsis management in the emergency department. *Clinical Chemistry and Laboratory Medicine.* Vol 512013:1167.
41. Stotler BA, Kratz A. Determination of Turnaround Time in the Clinical Laboratory: "Accessioning-to-Result" Time Does Not Always Accurately Reflect Laboratory Performance. *American journal of clinical pathology.* November 1, 2012 2012;138(5):724-729.
42. Pena ME. Decreasing Troponin Turnaround Time in the Emergency Department Using the Central Laboratory: A Process Improvement Study. *Clinical biochemistry.* (0).
43. Suchsland J, Greiser A, Streichert T, et al. Evaluation of a fast single sample pneumatic tube system. Deutschen Kongress der Laboratoriumsmedizin; 2014; Mannheim.
44. Nørgaard B, Mogensen CB. Blood sample tube transporting system versus point of care technology in an emergency department; effect on time from collection to reporting? A randomised trial. *Scandinavian journal of trauma, resuscitation and emergency medicine.* 2012;20:71.
45. Casagranda I. Point-of-care testing in critical care: the clinician's point of view. *Clinical chemistry and laboratory medicine : CCLM / FESCC.* Jul 2010;48(7):931-934.
46. Schluter B, Junker R. POLITIK-Medizinreport: Labordiagnostik-Schneller ist nicht immer besser. *Deutsches Arzteblatt-Arztliche Mitteilungen-Ausgabe A.* 2003;100(3):87-89.
47. Plebani M. The detection and prevention of errors in laboratory medicine. *Ann Clin Biochem.* Mar 2010;47(Pt 2):101-110.
48. Lundberg GD. Acting on significant laboratory results. *JAMA.* May 1981;245(17):1762-1763.
49. O'Kane MJ, McManus P, McGowan N, Lynch PL. Quality error rates in point-of-care testing. *Clinical chemistry.* Sep 2011;57(9):1267-1271.
50. Jang JY, Shin SD, Lee EJ, Park CB, Song KJ, Singer AJ. Use of a comprehensive metabolic panel point-of-care test to reduce length of stay in the emergency department: a randomized controlled trial. *Annals of emergency medicine.* Feb 2013;61(2):145-151.
51. Bonini P, Plebani M, Ceriotti F, Rubboli F. Errors in laboratory medicine. *Clinical chemistry.* May 2002;48(5):691-698.
52. Zhi M, Ding EL, Theisen-Toupal J, Whelan J, Arnaout R. The landscape of inappropriate laboratory testing: a 15-year meta-analysis. *PloS one.* 2013;8(11):e78962.
53. Kalra J. Medical errors: impact on clinical laboratories and other critical areas. *Clin Biochem.* Dec 2004;37(12):1052-1062.
54. Carraro P, Plebani M. Errors in a Stat Laboratory: Types and Frequencies 10 Years Later. *Clinical chemistry.* July 1, 2007 2007;53(7):1338-1342.
55. Plebani M. Does POCT reduce the risk of error in laboratory testing? *Clinica chimica acta; international journal of clinical chemistry.* Jun 2009;404(1):59-64.
56. Meier FA, Jones BA. Point-of-care testing error: sources and amplifiers, taxonomy, prevention strategies, and detection monitors. *Archives of Pathology and Laboratory Medicine.* 2005;129(10):1262-1267.
57. O'Kane M. The reporting, classification and grading of quality failures in the medical laboratory. *Clinica chimica acta; international journal of clinical chemistry.* Jun 2009;404(1):28-31.
58. Pecoraro V, Germagnoli L, Banfi G. Point-of-care testing: where is the evidence? A systematic survey. *Clinical chemistry and laboratory medicine : CCLM / FESCC.* Mar 2014;52(3):313-324.

59. Asha SE, Chan AC, Walter E, et al. Impact from point-of-care devices on emergency department patient processing times compared with central laboratory testing of blood samples: a randomised controlled trial and cost-effectiveness analysis. *Emergency medicine journal : EMJ.* Jun 7 2013.
60. Kendall J, Reeves B, Clancy M. Point of care testing: randomised controlled trial of clinical outcome. *Bmj.* Apr 1998;316(7137):1052-1057.
61. Ryan RJ, Lindsell CJ, Hollander JE, et al. A multicenter randomized controlled trial comparing central laboratory and point-of-care cardiac marker testing strategies: the Disposition Impacted by Serial Point of Care Markers in Acute Coronary Syndromes (DISPO-ACS) trial. *Annals of emergency medicine.* Mar 2009;53(3):321-328.
62. Collinson P, John C, Lynch S, et al. A prospective randomized controlled trial of point-of-care testing on the coronary care unit. *Annals of clinical biochemistry.* 2004;41(5):397-404.
63. Renaud B, Maison P, Ngako A, et al. Impact of point-of-care testing in the emergency department evaluation and treatment of patients with suspected acute coronary syndromes. *Acad Emerg Med.* Mar 2008;15(3):216-224.
64. Venge P, Öhberg C, Flodin M, Lindahl B. Early and late outcome prediction of death in the emergency room setting by point-of-care and laboratory assays of cardiac troponin I. *American heart journal.* 11// 2010;160(5):835-841.
65. Nichols JH, Kickler TS, Dyer KL, et al. Clinical Outcomes of Point-of-Care Testing in the Interventional Radiology and Invasive Cardiology Setting. *Clinical chemistry.* April 1, 2000 2000;46(4):543-550.
66. Shore-Lesserson L, Manspeizer HE, DePerio M, Francis S, Vela-Cantos F, Ergin MA. Thromboelastography-Guided Transfusion Algorithm Reduces Transfusions in Complex Cardiac Surgery. *Anesthesia & Analgesia.* 1999;88(2):312-319 310.1213/00000539-199902000-199900016.
67. Goodnough LT, Hill CC. Use of point-of-care testing for plasma therapy. *Transfusion.* 2012;52:56S-64S.
68. Mogensen CB, Borch A, Brandslund I, others. Point of care technology or standard laboratory service in an emergency department: is there a difference in time to action? A randomised trial. *Scandinavian journal of trauma, resuscitation and emergency medicine.* 2011;19(1):1-6.
69. Walter S, Kostopoulos P, Haass A, et al. Point-of-care laboratory halves door-to-therapy-decision time in acute stroke. *Ann Neurol.* Mar 2011;69(3):581-586.
70. Lee-Lewandrowski E, Corboy D, Lewandrowski K, Sinclair J, McDermot S, Benzer TI. Implementation of a point-of-care satellite laboratory in the emergency department of an academic medical center. Impact on test turnaround time and patient emergency department length of stay. *Arch Pathol Lab Med.* Apr 2003;127(4):456-460.
71. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med.* Feb 2013;39(2):165-228.
72. Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet.* May 2010;375(9727):1695-1703.
73. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. *Circulation.* Mar 16 2004;109(10):1223-1225.
74. Nichols JH, Christenson RH, Clarke W, et al. Executive summary. The National Academy of Clinical Biochemistry Laboratory Medicine Practice Guideline: evidence-based practice for point-of-care

testing. *Clinica chimica acta; international journal of clinical chemistry.* Apr 2007;379(1-2):14-28; discussion 29-30.
75. Junker R, Schlebusch H, Luppa PB. Point-of-Care Testing in Hospitals and Primary Care. *Dtsch Arztebl International.* August 20, 2010 2010;107(33):561-567.
76. Gramz J, Koerte P, Stein D. Managing the Challenges in Point-Of-Care Testing: An Ecosystem Approach. *Point of care.* 2013;12(2):76-79 10.1097/POC.1090b1013e3182685e3182633.
77. Lewandrowski K, Gregory K, Macmillan D. Assuring quality in point-of-care testing: evolution of technologies, informatics, and program management. *Archives of pathology & laboratory medicine.* Nov 2011;135(11):1405-1414.
78. Baker GA. Managing Point-of-Care Testing Challenges Requires Savvy Electronic Tools. *Point of care.* 2013;12(2):69-70 10.1097/POC.1090b1013e318265e318166.
79. Jones RG, Johnson OA, Batstone G. Informatics and the clinical laboratory. *The Clinical biochemist. Reviews / Australian Association of Clinical Biochemists.* Aug 2014;35(3):177-192.
80. (CLSI) CaLSI. Laboratory Quality Control Based on Risk Management; Approved Guideline. *CLSI document EP-23A*. Wayne, PA: Clinical and Laboratory Standards Institute (CLSI); 2011.
81. Westgard JO. Electronic quality control, the total testing process, and the total quality control system. *Clinica Chimica Acta.* 5// 2001;307(1–2):45-48.
82. Miller WG, Myers GL, Rej R. Why Commutability Matters. *Clinical chemistry.* April 1, 2006 2006;52(4):553-554.
83. Cohen J. Weighted kappa: nominal scale agreement with provision for scaled disagreement or partial credit. *Psychological bulletin.* Oct 1968;70(4):213-220.
84. Cohen J. A Coefficient of Agreement for Nominal Scales. *Educational and Psychological Measurement.* April 1, 1960 1960;20(1):37-46.
85. Gill JP WL. Quality control and quality assurance in point-of-care testing. In: Price CP SJA, Kricka LJ, ed. *Point-of-care testing.* . 3rd edition ed. Washington DC: AACC Press; 2010.
86. Stavelin A, Petersen PH, Solvik UO, Sandberg S. External quality assessment of point-of-care methods: model for combined assessment of method bias and single-participant performance by the use of native patient samples and noncommutable control materials. *Clinical chemistry.* Feb 2013;59(2):363-371.
87. Petersmann A, Luppa P, Michelsen A, Sonntag O, Nauck M. Gemeinsame Stellungnahme zur Situation der Bewertung von Ringversuchen für Glucose mittels Systemen f\xfcr die patientennahe Sofortdiagnostik (POCT)/Joint statement on the situation of external quality control for glucose in POCT systems. *Laboratoriumsmedizin.* Vol 362012:165.
88. Richtlinie der Bundesärztekammer zur Qualitätssicherung laboratoriumsmedizinischer Untersuchungen. *Dtsch Arztebl International.* September 27, 2013 2013;110(39):1822.
89. Ehrmeyer SS, Laessig RH. Point-of-care testing, medical error, and patient safety: a 2007 assessment. *Clinical chemistry and laboratory medicine : CCLM / FESCC.* 2007;45(6):766-773.
90. (CLSI) CaLSI. Point-of-Care Connectivity; Approved Standard - Second Edition. *CLSI document POCT01-A2*. Wayne, PA: Clinical and Laboratory Standards Institute (CLSI); 2006.
91. Richard LF, William FJ, Corbin CM, John VH, Gerald KJ. Vulnerability of point-of-care test reagents and instruments to environmental stresses: implications for health professionals and developers. *Clinical Chemistry and Laboratory Medicine.* Vol 522014:325.
92. Howanitz PJ, Jones BA. Comparative Analytical Costs of Central Laboratory Glucose and Bedside Glucose Testing: A College of American Pathologists Q-Probes Study. *Archives of Pathology & Laboratory Medicine.* 2004/07/01 2004;128(7):739-745.
93. St John A, Price CP. Economic Evidence and Point-of-Care Testing. *The Clinical Biochemist Reviews.* 2013;34(2):61.
94. *Gebührenordnung für Ärzte.* Deutscher Ärzte-Verlag; 2001.

95. Bundesvereinigung K. Einheitlicher Bewertungsmaßstab (EBM). 2009.
96. Adams EJ, Ehrlich A, Turner KME, et al. Mapping patient pathways and estimating resource use for point of care versus standard testing and treatment of chlamydia and gonorrhoea in genitourinary medicine clinics in the UK. *BMJ Open.* July 1, 2014 2014;4(7).
97. Komatireddy R, Topol EJ. Medicine unplugged: the future of laboratory medicine. *Clinical chemistry.* Dec 2012;58(12):1644-1647.
98. Pires NMM, Dong T, Hanke U, Hoivik N. Recent Developments in Optical Detection Technologies in Lab-on-a-Chip Devices for Biosensing Applications. *Sensors.* 2014;14(8):15458-15479.
99. Luppa PB, Sokoll LJ, Chan DW. Immunosensors—principles and applications to clinical chemistry. *Clinica Chimica Acta.* 12// 2001;314(1–2):1-26.
100. Altintas Z, Fakanya WM, Tothill IE. Cardiovascular disease detection using bio-sensing techniques. *Talanta.* 10/1/ 2014;128(0):177-186.
101. Chin CD, Linder V, Sia SK. Lab-on-a-chip devices for global health: Past studies and future opportunities. *Lab on a chip.* 2007;7(1):41-57.
102. Vashist SK. Continuous Glucose Monitoring Systems: A Review. *Diagnostics.* 2013;3(4):385-412.
103. Soliman A, DeSanctis V, Yassin M, Elalaily R, Eldarsy N. *Continuous glucose monitoring system and new era of early diagnosis of diabetes in high risk groups.* Vol 182014.
104. Vashist SK. Non-invasive glucose monitoring technology in diabetes management: A review. *Analytica Chimica Acta.* 10/31/ 2012;750(0):16-27.
105. Moore C. Point-of-care tests for infection control: should rapid testing be in the laboratory or at the front line? *The Journal of hospital infection.* Sep 2013;85(1):1-7.

Figure legends:

Figure 1: Conceptual framework for innovation in healthcare [6] (with permission of "The Innovation Journal")

Figure 2: Total number of POCT publications in PubMed from 2004 until 2013
(Search terms were: POCT OR point-of-care OR point-of-care testing OR bedside testing OP near-patient testing AND 20xy [DP])

Figure 3: Tasks of the hospital POCT coordination

Figure 4: Technology drivers for new POCT developments