Clinically Relevant Analytical Techniques, Organizational Concepts for Application and Future Perspectives of Point-of-Care Testing

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Nonstandard abbreviations:

Abstract

Applications of near-patient testing have developed rapidly during the last years. It offers quick test results and minimal preanalytical interference, having the potential to improve patient outcomes, even when still under scrutiny by laboratory and healthcare professionals. Near-patient diagnostics are currently also used increasingly in developing countries, due to the burden of inadequate healthcare services in resource-constrained settings.

This review describes the underlying emerging techniques that are based on advanced microfluidics and nanomaterials, device miniaturization, and multiplexing the detection mode. The organizational concepts for reasonable applications, contributing significantly to the future perspectives of this nascent diagnostic modality, are supplementary portrayed.

Content Table

1. Introduction

The name point-of-care testing (POCT) refers to the performance of biochemical, hematological, coagulation or molecular diagnostics tests at or near a patient. Applications of POCT in healthcare have been rapidly increasing during the last two decades. Patient-near testing is now implemented in various settings, from self-testing to outpatient clinics and, finally, to the intensive care unit. Near-patient testing offers the clinical advantage of quick test results and minimal preanalytical interference, having the potential to improve patient outcomes, although this is generally less well documented in clinical studies.
POCT is also being used more extensively in countries with limited resources, particularly for diagnostic purposes [Plebani 2014].

The POCT process is truly innovative in healthcare, since it offers new possibilities for prevention, diagnosis, and monitoring of diseased subjects. As Price and St. John [Price 2014] pointed out, while underlying analytical technologies hold some clever inventions, “genuine innovation can only come about if the invention is applied in a useful way” within the healthcare system to deliver an enhanced value for the patient. But it should be recognized that for POCT an additional principal catalyst for the innovation process is the patient himself, which reinforces the importance of POCT [Omachonu 2010].

Consequently, the benefits of a POCT process management are only to be reaped if cooperation with the core competences of the central laboratory exists [Bietenbeck 2014]. If there is complementary understanding between POCT specialists and laboratory experts, a reconfiguration of clinical pathways can significantly improve the overall patient outcome. A good example of this improvement is the self-testing of glucose or PT/INR by diabetics or patients under anticoagulation. These subjects use the self-monitoring to adjust treatment. There are already many studies available (as discussed in section **3.3.8.**), which show that a better disease management improves outcomes in a way that has not been possible before the advent of the respective POCT technologies [O´Kane 2014].
Innovation in healthcare means novel ways for care, being delivered to the patient. In the context of many health challenges in developing countries, it becomes apparent that POCT most likely offers such changes. The transforming effect of POCT can be verified by the fact that the increasing number of malaria tests has already reduced significantly inappropriate anti-malaria treatment during the last decade [Jani 2013].
The role of the central laboratory, however, is still very important, even when POCT is applied. Test results alone are useless [St. John 2014a and 2014b], as laboratory experts play an important clinical role for the support of the physicians as consultants in hospitals and for outpatient areas. They provide helpful advice for the interpretation of results, comment on pre- or postanalytical errors, recommend follow-up tests, and provide as POCT coordinators the quality management of the patient-near testing [Schimke 2006, Huckle 2008] (see also chapter **4.1.**).

What makes POCT so attractive globally, is that there has been a two-step paradigm shift occurring in the last decade:

1. POCT was originally a supplement of the central laboratory and defined as hospital bedside biochemical testing with a limited test portfolio. Now, POCT is often

used as the sole diagnostic approach in developing countries without a central laboratory infrastructure.

2. An additional shift arises from the insight that until today laboratory medicine focused on measuring a high number of parameters in the human body with sophisticated methodologies, whereas POCT analysis has a restricted number of parameters with robust devices for many subjects that are self-determined customers or indigent patients in developing countries.

The World Health Organization (WHO) demands that newly established POCT devices implicitly should meet the ‘‘ASSURED’’ criteria:

> **A**ffordable, **S**ensitive, **S**pecific, **U**ser-friendly, **R**apid and **R**obust, **E**quipment-free, and **D**elivered (to the enduser) [Peeling 2010, Pai 2012].

This catchy acronym was first coined at a WHO Special Programme for Research and Training in Tropical Diseases and was combined with the statement that POCT should always be done outside of laboratories and hospitals by non-laboratorians [Kettler 2004].

Thus, POCT is a type of sustaining technology, to be defined as “disruptive innovation”, a term first generated by Christensen *et al.* [Christensen 2009]. Besides genetic testing, promoted to the general public and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry for the rapid identification of bacteria and fungi, POCT was also identified as a disruptive innovation with the potential to offer healthcare solutions with new performance metrics [Nam 2015].

This review is dedicated to a description of the underlying analytical techniques, the concepts for reasonable application, and the perspectives of POCT. We aim also to portray the main drivers and motives of the dynamic evolution of the near-patient testing: developments of new analytical methodologies (molecular diagnostics, continuous monitoring, direct-to-consumer testing, etc.), changes in the clinical environment of the global healthcare systems, changes in regulatory affairs (concerning development of new devices and their clinical applications), and enhanced health awareness in the general population [Bietenbeck 2014].

But there are also several **limitations for the further evolution of POCT**.

- First, in the industrialized nations with central labs, the application of POCT is self-limiting and depends on the establishment of new and reliable parameters, which, in important clinical disciplines, remain elusive [Gubala 2012].
- Second, a global problem for the dissemination of POCT is that reimbursement systems often can't keep up with the technological changes in clinical diagnostics [Huckle, 2008] and, thus, hinder the further evolution.
- Third, further limitations for the development of novel POCT were caused by the market failure of non-invasive devices, having been under development for decades.

Huckle [Huckle 2015], interestingly, defined the diagnostic sample sources as “*invasive*” (whole blood), “*moderately invasive*” (capillary blood) or “*non-invasive, but sampled*” (urine, saliva, tears, etc). These categories were opposed to the real “*non-invasive and not sampled*” POCT, which means direct detection modes applied at the plane skin (electroporation, optical techniques). Apart from the newborn bilirubin

measurement, all of these diagnostics failed the market test. Additionally, "*non-invasive, but sampled*" POCT applications must be strongly challenged for preanalytical reasons [Huckle 2015].

2. Current Definition of POCT and Measurands

To define the context of POCT, it is essential to fully understand this type of laboratory testing. According to Bowman [Bowman 2000], it is necessary "to understand its breadth, encompassing varied sites, uses and technical options". Even today, however, the application fields of POCT are very dynamic. The technological and methodological evolution means that the given definition will change over time.

1. Laboratory testing of fluidic material from the human body in the immediate proximity to the patient;
2. Analyses outside a central laboratory or an emergency (STAT) laboratory;
3. No sample preparation, mostly whole or capillary blood as the patient material;
4. No pipetting steps;
5. »Ready-to-use« reagents, e.g. cassettes or »unit-use devices«;
6. Dedicated devices for performing single, not serial analyses;
7. Operations by non-laboratory personnel (physicians, caregivers, patients);
8. Very short turn-around-time (TAT), meaning from sample collection to result of measurement;
9. Immediate therapeutic actions, depending on analysis results.

In particular, the points 1, 6 and 9 are essential for the differentiation between central laboratory methods and POCT.

Additionally, the American National Academy for Clinical Biochemistry (NACB) specifies the hospital POCT (hPOCT) in the Laboratory Medicine Practice Guidelines [NACB 2007] as follows: "*Clinical laboratory testing conducted close to the site of patient care, typically by clinical personnel whose primary training is not in the clinical laboratory sciences or by patients (self testing). POCT refers to any testing performed outside of the traditional, core or central laboratory.*"

A selection of various metabolic, inflammation, organ-specific injury, hematological, hemostaseological, and drugs-of-abuse testing parameters, currently widely applied in the healthcare system by use of POCT methods, is given in **Table 1**.

Table 1 to be placed here.

3. Current Analytical Techniques and Clinical Application Fields

3.1. Analytical Devices

3.1.1. Test strips

These are highly simplified systems that apply ready-to-use reagents for single determinations. Test strips consist of porous matrices in which dried segments ("dry chemistry") are embedded onto a support element. The chemical reaction takes place once the reagent stick layer has been penetrated and soaked with the sample material (mostly capillary blood or urine) [Junker 2010, Gauglitz 2014]. One characteristic for these devices is that the sensors are integrated in the test strips and the detection can be performed by a simple visualization of a change in color induced by the sample. Otherwise, the strips are to be inserted in the reader instrument. It is characteristic for these systems that the calibration is replaced by an electronic or physical standard, which is measured whenever the reader is turned on.

3.1.2. Lateral-flow tests

A more complex POCT approach is the lateral-flow assay (LFA), also known as lateral flow immunochromatographic test. The carriers are also made of various porous materials, which transport the sample fluid (e.g., urine) by capillary forces. The recognition elements (antibodies, aptamers, scaffolds, anticalins), immobilized at the reaction area, interact with the target analyte during the migration process. This is followed by the transport of the immune complex to another area, where a second spotted binding partner captures the complex, thereby leading to a detectable color change.

3.1.3. Complex biosensor-based devices

Many POCT devices, which were developed in the last two decades, are based on biosensor technology. The schematized principle is portrayed in **Figure 1**. The instruments benefit from the fact that miniaturized biosensor systems can detect analytes by applying both biological and physicochemical detector components. The measurand in the biological fluid (e.g., whole blood, serum, plasma, urine, saliva, cerebrospinal fluid) interacts with the biological components of the recognition layer, immobilized on the solid-state surface of the sensor [Luppa 2011]. The biospecific interactions at the transducer surface are read out by use of either microgravimetrical, optical, or electrochemical methods. To give an example: glucose as analyte in plasma is biospecifically converted by glucoseoxidase in the presence of oxygen to gluconolactone and hydrogen peroxide, which is subsequently oxidized at the sensing electrode in order to produce 2 electrons/mol H_2O_2. This electron generation can easily be recorded amperometrically.

Figure 1 to be placed here.

3.1.4. Bench-top POCT analyzers

These POCT instruments are bigger than hand-held devices and use different analytical principles, which are derived from the standard repertoire of the central laboratory. Due to an ongoing miniaturization and information technology (IT) improvements, the size of these devices is best described by the term "bench-top". For clinical chemistry parameters, these analyzers use the traditional

spectrophotometric technique or reflectometry. They incorporate different test formats: test strips, reagent cassettes, or centrifugal disks. The latter technology is highly interesting, since centrifugal microfluidics [Strohmeier 2015] offer advantages over other microfluidic actuators: the pulse-free inertial liquid propulsion enables the application of closed centrifugal disks, which removes the need for an interface to external pumps or other drivers.
The blood cell-counting instruments mostly use the conventional hematological particle counting and are tailored for POCT needs. An exemption is the “dry hematology”, a centrifugally based hematology technology, which uses the principle of the quantitative buffy coat in conjunction with fluorescence [Erhaber 2013].
The immunosensor analyzers apply different antibody-based heterogeneous immunoassay techniques [Morgan 1996; Luppa 2001]. In particular, multi-channel devices, such as the Radiometer AQT90 (Kopenhagen, Denmark) or the Pathfast analyzer from Mitsubishi Chemical (Tokyo, Japan), are optimized for use at the POC. In particular, chemiluminescence-based systems offer highly sensitive analytics, but there are many on-site testing devices, which have progressed not beyond a prototype stage [Park 2014].

3.1.5. Lab-on-a Chip

Analytical device miniaturization for POCT developments can be achieved using the so-called Lab-on-a Chip (LOC) technology. The goal is to integrate several process steps into one reaction cell (chip): These steps are sample pretreatment, separation, detection and data processing [Pires 2014; Spindel 2014]. Such LOC platforms employ various detection modes within microfluidic devices. The underlying detection techniques are as follows:
Electrochemical detection, which measures changes in conductance or resistance/capacitance directly on the electrode´s surface; mechanical detection, which detects variations of the resonant frequency or surface stress of the (Quartz) sensor; and optical detection, which reports variations in light intensity, interference pattern or refractive index. Optical detection is the preferred solution for LOC devices, which is due to the nondestructive, sensitive, and real-time measuring mode and the ubiquity of opto-instrumentation [Pires 2014].

The microfluidic system platforms consist of capillary channels (maximum 50 × 400 µm) made of organic polymers or silica. The flow is usually controlled by capillary forces or by electroosmotic effects [Spindel 2014]. The plastics are thermoplastics or polymeric derivatives of polyacrylates, polystyrenes, polyethylenes and cycloolefin copolymers. These structural materials can be used to build LOC platforms by molding, embossing, etching, laser ablation or die cutting [Gubula 2012]. The optical, thermal, and chemical properties are to be optimized for each separate application mode, and for the surface functionalization for biomolecules or the attenuation of nonspecific adsorption phenomena.

The advances of the LOC concept, however, have not yet translated into much commercialization [St John 2014]. One notable exception is the iSTAT, based on the thick film technology (Abbott Laboratories, Abbott Park, IL, USA), which has already been on the in vitro diagnostics (IVD) market since the mid 1990s [Erickson 1993; Mock 1995]. Additionally, the one-step quantitative assay for prostate-specific antigen (PSA) in the format as FREND PSA from NanoEnTek Inc., Seoul, Korea can be given as example for a successful LOC application [Park 2013]. The LOC platform

consists of a disposable test cartridge and a compact automated fluorescence reader. The cartridge utilizes the micro-fluidics lateral flow technology, where the analyte in the blood sample forms immune complexes with fluorescent nanoparticles conjugated to anti-PSA while moving through the fluidics pathways. The quantification is done by the use of laser-induced fluorescence.

3.1.6. Microarrays

Microarrays are not yet the arena for POCT. Multiplexed analyses are, however, diagnostically relevant for near-patient testing. DNA- and protein-microarrays provide a new analytical tool for the simultaneous detection of multiple analytes in a single test format [Seidel 2008]. The advent of this technology for POCT applications is just around the corner. The affinity-based reactions of nucleic acids (hybridization with complementary single-stranded DNA/RNA molecules) and antibodies (immune complex formation with antigenic structures) are preferred for multiplexing in a quantitative mode. The analytical problem is the functionally reproducible, leach-proof and oriented immobilization of these recognition elements on an adequate solid-state surface. The readout of the detection signals by use of fluorescence, chemiluminescence, electrochemical, or evanescent techniques is state-of-the-art and poses no major sensitivity problems. Currently, many microarrays are already constructed as flow-through devices by applying sophisticated microfluidics. If automated systems for quantitative multiplexed analyses are available, a series of diagnostic applications, spanning from autoimmunity to infectious diseases, will pave the way for microarray-POCT.

3.1.7. POCT instrument categorization

Clinically relevant POCT analyzers, currently available on the IVD market, can be separated into six groups [Luppa 2011]. **Tables 2** and **3** provide the device categorization on the basis of the instruments´ practical use in POCT. The measuring mode and the underlying detection principle are mentioned together with examples for respective devices. Of course, these lists are not exhaustive.

Table 2 and Table 3 to be placed here.

3. 2. Analytical Techniques

The development of more and more miniaturized optics and electronics has brought to the construction of portable devices, capable to produce results as accurate as those provided by the main modern clinical laboratories [Ligler 2009; Jokerst 2009]. Such analytical techniques are based for example on electrochemical methods (i.e. electrophoresis, potentiometry, amperometry), optical transduction (i.e. spectrometry, refractometry), and chromatography (i.e. gas, liquid). Since the results obtained by using the different POCT devices are strictly related to the application, it is difficult to classify the better analytical technique to be selected. Therefore, some of them are in competition, but, in general, up to now, the electrochemical and optical based POCT are the leader choices [Luppa 2001; Gauglitz 2014; Setty 2014]. Some examples of the analytical techniques implied in the development of POCT devices are described in this section.

3.2.1. Mass-sensitive based devices

There are three main signal transduction methods available, based on mass-sensitive devices: quartz crystal microbalance (QCM), surface acoustic wave (SAW)-based devices, and microcantilevers.

- The quartz crystal of a QCM, covered by a metallic thin film, has a precise oscillation at its resonant frequency when an alternating voltage is applied. Every change at the surfaces of the sensor, caused by the interaction with the target analyte, perturbs the resonance of the quartz resulting in a frequency shift, which is related to the mass of the analyte. This system does not need a labeling procedure of the analyte giving the possibility of real-time measurements and it is extremely sensitive to the environmental surround, which results to be also the drawback of the QCM. For this reason it is common to have a reference system, which allows to discriminate the solely interaction with the target molecules [Ittarat 2013; Prakrankamanant 2014]. In order to overcome the high LODs reachable with QCM, several strategies have been applied such as, target amplification (applicable to DNA detection) with loop-mediated isothermal amplification (LAMP), which allows operating without dramatic increase of the temperature differently from the classic PCR; or nanoparticles labeling for sensitivity improvements through mass amplification [Salam 2013].
- SAW-based setups are micro-electromechanical systems (MEMS) based on vibrations such as QCM. SAWs, however, are limited to the surface of the sensor, decaying exponentially with distance into the bulk material [Thalhammer 2013]. The surface wave can be excited electrically by means of an interdigital transducer (IDT). The fundamental principle of SAW is based on having two ITDs, the input and the output, launching and receiving the waves, respectively [Hribšek 2010; Lange 2008]. The last generation SAW, suitable for POCT applications are the Love wave surface acoustic wave (LW-SAW) immunosensors, which allow an LOD in the nanomolar range. The goal to be reached by the LW-SAW is to minimize the acoustic losses, which occurs into the bulk of the substrate or into the liquid above the sensor surface. The sensitivity of the device can be increased, when the layer thickness is being optimized [Puiu 2013].
- The microcantilever is another example of a MEMS device, which consists of a miniaturized trampoline with an embedded piezoresistor in top of which the biosensing layer is immobilized. The specific target molecule interaction with the sensing area causes the cantilever bending, which can be monitored in different ways: electrical (i.e. capacitive), piezoresistive and optical [Mathew 2015; Gorelkin 2015]. Microcantilevers have found already some applications in POCT, since the bending structures have been integrated in microfluidics platforms [Ricciardi 2010; Pires 2014].

3.2.2. Electrochemical based devices

The electrochemical transduction-based systems include amperometry, potentiometry, conductometry modes [Thèvenot 1999; Ricci 2012; Monosik 2012; Holford 2012; Power 2013]. In some cases, measurands are electroactive and can be measured directly. In some others, in case the analytes are not electroactive, they are labeled with electroactive tags or with enzymes, which converts a silent molecule in an electroactive one. This last approach has also the advantage of signal amplification, even of several orders of magnitude [Gubala 2012]. In 2012 Ishige *et*

al. patented [Ishige 2012] a potentiometric sensor for possible application in POCT, based on the immobilization of an enzyme on the surface of the gold electrode, monitored in real time to measure the change of the surface potential. Recently, the state-of the-art of integrated electrochemical sensors for POCT applications has been reviewed [Ghafar-Zadeh 2015]. The authors subdivide the available devices in three major categories of miniaturized integrated devices, namely the implantable Wireless Bio-Sensors (WBSs), the wearable WBSs, and the handheld WBSs.

3.2.2.1. Amperometry

An amperometric biosensor is based on the measurements of the current flow between the working electrode and the reference one, which is induced by a redox reaction. The resulting current is monitored and correlated to the concentration of the electroactive analyte of interest, produced or consumed at the biocatalytic layer (stir-dependent responses) [Gessei 2014]. The main drawback of direct detection of certain analytes (i.e. NADH) in complex samples like biological fluids is the interference of others electroactive compounds, such as ascorbic acid, paracetamol, or uric acid, which render the sensor low selective. Azzouzi *et al.* [Azzouzi 2015] presented a novel amperometric biosensor based on gold nanoparticles anchored on reduced graphene oxide and L-lactate dehydrogenase (LDH) for L-lactate detection. Carbon nanotubes (CNT) are increasingly used for the improvement of amperometric biosensor transducers. Advantageous are high surface to volume ratio, extreme mechanical, chemical and thermal stability, fast electron transfer kinetics, and easy functionalization of CNT surfaces [Justino 2013]. In case when CNTs are coated within nanocomposites, e.g., with ferrocene as mediator, an enhanced electron transfer between immobilized enzymes/proteins, and the mediator/CNT adduct can be observed.

3.2.2.2. Potentiometry

Biosensors based on potentiometry take into account potential changes, which are logarithmically proportional to the specific ion activity, between two electrodes. In this case the reactants are at the equilibrium, neither consumed nor destroyed, therefore the biocatalytic layer does not undergo to concentration gradient formation (non stir-dependent responses). The Nernst equation can be used to define the concentration of the analyte of interest.
Related to potentiometric-based biosensors, different methodologies can be applied: transmembrane potential, field-effect transistor (FET), ion-selective field-effect transistor (ISFET), etc.

3.2.2.3. Conductometry and capacitance

In 1988, Bataillard *et al.* reported, how the antibody/antigen complex formation on the surface of an electrode causes changes in capacitance proportional to the size and concentration of the biolayer [Bataillard 1988; Holford 2012; Ma 2013]. In 2014 Barbosa *et al.* proposed a design and model of a capacitive touch screen to be used in a disposable probe-tip for urinary tract infection (UTI) detection for POCT applications. The bioreceptors are immobilized on a functionalized surface and the infectious agents present in urine, after specific interaction on the surface induce small capacitance variations that can be detected [Barbosa 2014].

3.2.3. Magnetic detection based devices

Magnetic particles have been employed in bioseparation since decades, but more

recently in bioassays. In fact, they can be used not only for preconcentrate and localize analytes, which can be pulled towards biorecognition elements, but also as labeling agents [Haun 2010].

Tamanaha *et al.* [Tamanaha 2008] and Llandro *et al.* [Llandro 2010] reviewed several methods, which have been developed for detecting magnetic particles in order to perform biological assays and molecular identification. Magnetic particles can be analyzed in different ways, such as:

- Direct detection (magnetic permeability, magnetic remanence, magneto-resistance, hall effect),
- indirect detection (micro-cantilever-based force amplified biological sensor, magnetic relaxation switches),
- frequency-dependent magnetometry (nuclear magnetic resonance) [Shao 2012],
- compact Bead Array Sensor System (cBASS), developed by the Naval Research Laboratory [Shandu 2010],
- solution phase methods such as superconducting quantum interference device-based detection. This technique offers their own set of advantages, such as the ability to use nanoparticles to label targets inside living cells.

3.2.4. Optical based devices

The optical transduction based systems can be subdivided in two more categories: spectroscopy (absorption, luminescence, Raman scattering) and refractometry (surface plasmon resonance, interferometry, optical resonance) [Gubala 2012; Gauglitz 2014].

3.2.4.1. Spectroscopy-based system

The reflectance photometry measuring principle is the most popular technique among the dipstick POCT devices. As an example, the Reflotron (Roche Diagnostics) allows the measurement of several parameters, such as bilirubin, cholesterol, creatinine or hemoglobin from whole blood, plasma or serum based on the colour change in the test strips at 567, 642, and 951 nm.

Fluorescence-based optical devices [Berrettoni 2014; Gervais 2009; Nagl 2008] are commonly employed due to their high level of sensitivity and low background noise; moreover, the use of light emitting diodes (LED), together with lenses, filters and waveguides integrated in a portable system paved the way for low-cost devices [Myers 2008].

There are a variety of fluorescent labels:

- Organic compounds that can be chosen in a wide range of the emission spectrum. They are commercially available with reactive groups, which easily react with protein lysine residues for labeling purposes [Wang 2014, Baldini 2009].
- Quantum dots (QD), which can overcome the limits of the organic fluorophores in terms of photostability, brightness and finely tunable sharp emission spectra [Zhang 2010; Yang 2010]. They are, however, more expensive and larger in size.
- QD-barcodes used for multiplexed immunosensors [Klostranec 2007] or for gene expression analysis [Eastman 2006], and also integrated in a possibly portable POCT device [Gao 2013].
- Fluorescent nanoparticles [Stranik 2007], where the fluorescence can be enhanced in case of the fluorophore is in intimate proximity of the metal

nanoparticles.

The fluorescence technique can be also applied with the Förster resonance energy transfer (FRET) [Varghese 2010; Tavares 2012]. Qin *et al.* [Qin 2003], using the FRET technique, developed a close-to-patient system for urinary albumin measurements, performing the assay in 12 minutes with 10 μL urine sample. With the Total Internal Reflection Fluorescence (TIRF), lower limit of detections (LOD) can be reached since only the fluorophores close to the transduction surface are excited, and therefore only those are involved in the interaction with the biorecognition elements. Rascher *et al.* [Rascher 2014] showed how this principle could be applied to a POCT device for procalcitonin quantification in 50-μL whole blood or plasma sample in less than 10 minutes. The analysis showed a good correlation with the reference measurement system Kryptor (BRAMHS, Berlin, Germany).
Another possibility for a spectroscopy-based system is the application of chemiluminescence/bioluminescence [Karsunke 2009] in which the luminescent emission is given while the target molecule interacts with the biorecognition element. This technique has the advantage that the instrumentation for excitation is not required. Thus, the background interference is - in principle - eliminated. Therefore, chemiluminescence/bioluminescence can be the alternative to reach lower LOD and are easier applicable in miniaturized devices [Roda 2003].
The Raman scattering itself is rarely presented as an analytical technique for POCT applications, since, even if the spectrum obtained for a molecule uniquely identify it as a sort of fingerprint of the molecule, it is a too weak phenomenon. In fact, Raman spectroscopy is a methodology found in central laboratories, using large volume samples, powerful lasers and precision optics [Myers 2008]. In POCT, a more suitable method is represented by the surface-enhanced Raman scattering (SERS) where, i.e. the introduction of nanoscale gaps onto the surface, or deposition of metallic nanoparticles (silver or gold) with different geometries (nanospheres, nanorods, nanourchins, etc.), has given a tremendous increase in the Raman scattering signal, even in small sample volumes. In 2014, Bonifacio *et al.* [Bonifacio 2014] presented a study on evaluation of SERS spectra of blood serum and plasma using various Ag and Au aqueous colloids, as SERS substrates.

3.2.4.2. Refractometry-based system

Even if the fluorescence-labeled systems are extensively used in optical POCT systems, they have some drawbacks, such as the costs for labeling procedure, possible changes in the affinity for the target molecules as a consequence of structure modifications, which occurred after the labeling, and moreover a possible photo-bleaching, which could limit the use of fluorescence for time-resolved monitoring of reaction kinetics. For these reasons, the direct, label-free optical detection is increasingly of interest for scientific community and the IVD industry [Gauglitz 2010].
Among the refractometry-based systems, optical resonance (i.e. guided-mode resonance [Kim 2010], whispering-gallery-mode (WGM) [Giannetti 2012; Foreman 2015]); interferometry (i.e. Bragg gratings [Sun 2014], Mach-Zehnder Interferometer [Sarkar 2014], Young interferometer [Wang 2012]), and surface plasmon resonance (SPR) are often used. The latter being the leading technology [Homola 2003].
The optical resonance phenomena in cavities occur in spheres, disc, ring, toroid, micro-bubble, etc. WGM resonators due to their high Q factors (> 10^7), small mode volumes and long storage lifetime for the trapped photon inside the cavity, guarantee a high light-matter interaction. These features make them a promising optical

platform for the development of high performance biosensors, to be applied for POCT. Their working principle is based on the morphological WGM dependence: any change in the external surface of the microsphere or in the inner wall of a micro-bubble, due to some chemical and/or biochemical bonding, causes a shift of the resonances and reduces the Q factor value of these microcavities. By measuring this shift, it is possible to obtain important information about the concentration of the analyte of interest [Soria 2011].

In general, the working principle of a biosensor, based on interferometry, is based on two paths into which the light is splitted. Since only one path is functionalized with the bioreceptors, specific for the target analyte, the other works as reference when the assay is performed. The activated path undergoes to a refractive index (RI) change after the interaction with the target molecule, while the reference path is responsible for the system sensitivity because it suffer for all the common interferences, such as non-specific adsorption, temperature fluctuations, etc., like the activated path.

The operating concept of SPR system is based on a thin-metal film (usually gold) deposited on a glass slide. The gold side, in top of which the bioreceptors are immobilized, is in contact with the fluid-sample containing the analyte of interest, while the glass side is in contact with a high-RI glass prism. When the incident light is running through the prism at a certain angle, electrons at the surface of the gold layer move because of the light excitation, and then a characteristic surface plasmon resonance band is formed. After the binding of the analyte to the bioreceptors in top of the surface, an increase of the concentration of the analyte occurs with a consequent change of the RI and then a shift of the SP band, which is measurable by the detector in a different amount of light reflected through the prism [Spindel 2014; Nguyen 2015]. SPR has the advantage of the label-free techniques, giving satisfying performances in terms of limit of detection (LOD), of the order of 10 pg/mL. Despite that, one challenge for SPR remains the interference on the detected signal of the non-specific bindings. Another advantage of this technique in general is that, since the angle of incidence is continuously monitored, the kinetics of binding events can be recorded in real-time, even if this information is not crucial for a POCT analysis. Jahanshahi *et al.* [Jahanshahi 2014] have proposed a SPR based system for a 10-minute detection of the anti-dengue virus in human serum samples, while Liu *et al.* [Liu 2015] showed preliminary results on a SPR biosensor-based smart phone platform. Both recent papers envision SPR as suitable analytical technique for POCT, even when portable/hand-held instruments are still not available.

3.3. Clinical Applications

Laboratory analyses support the diagnostic process in more than 50-60% of all diseases. Additionally, biochemical, hematological, and coagulation tests aid in health prevention and monitoring of disease progress. Thus, the clinical laboratory is essential for all physicians in direct contact with patients.
The application fields for POCT in hospitals and in outpatient areas have been defined more clearly during the last decade. POCT, however, is only helpful if the produced results lead to immediate therapeutic decisions [Nichols 2000]. Furthermore, it must be mentioned that in a series of POCT applications, evidence data are still unsatisfactory [Nichols 2007, Plebani 2014]. Even a recent systematic survey of the evidence of efficacy by Pecoraro *et al.* [Pecoraro 2014] showed that further studies are still required in order to define the real utility of POCT on clinical decision-making and on patient outcome.

In this section the attempt will be made to portray important facets of clinical problems for which POCT is helpful. **Figure 2** depicts the different operation sites for the various POCT devices, according to the categorization given in **Table 2** (see also section **3.1.7.**).

3.3.1 POCT in the emergency department

The application of POCT in the emergency department (ED) requires special emphasis. Here, the turn-around-time (TAT), i.e. the time between the collection of sample and recognized result, is fundamental for the discussion of application of POCT methods in hospitals with a central laboratory. A rapid analysis is not always combined with medical and economic advantages [Junker 2003]. Also Pena *et al.* [Pena 2014] pointed out that process improvements and new workflow models in the central laboratory can decrease the TAT of biochemical tests. The patient´s length of stay in the ED, however, can be reduced significantly, if a comprehensive metabolic panel POCT is applied. Jang *et al.* [Jang 2013] reported this finding in a randomized controlled study of more than 10,000 ED subjects. Also, another trial from Morgensen *et al.* [Morgensen 2011] showed that the time to clinical decision for bacterial infections in the ED can be reduced significantly by use of adequate POCT methods. The TAT can also be reduced by POCT when a pneumatic tubing transport system sends the samples into the central laboratory [Norgaard 2012].
However, this positive efficiency, when using near-patient tests, can only be accomplished if the process is linked to methodologies and quality management by the central laboratory [Di Serio 2003]. Integration of POCT in the ED requires a high level of integration and cooperation between all acting persons [Di Serio 2005, Casagrande 2010]. However, the benefits of a rapid TAT will only reach the ED if POCT is also adequately implemented in terms of a hospital POCT quality management system [Di Somma 2014]. The POCT coordination, guided by the central laboratory, should organize continuous education courses and periodically performed control measurements to increase the awareness of quality issues among the caregivers.

Another issue concerns overloaded EDs, thereby attesting the need for a rapid triage system for prioritizing patients at higher risk. As Soremekun *et al.* [Soremekun 2004] pointed out, near-patient measurements of metabolic markers, total hemoglobin, cardiac troponin, Brain-type Natriuretic Peptide (BNP), and lactate are a helpful

adjunct in the triage of patients with high-risk ED complaints.
POCT also has a clinical impact when used during critical care transport [Gruszecki 2003, Di Serio 2010].

3.3.2. Diagnosis and treatment of diabetes mellitus

Monitoring of blood glucose (reported as plasma glucose equivalent) [Wahl 2009] by use of POCT is widely recognized as an integral element of diabetes management in order to effectively control the levels of type 1 as well as type 2 patients. Continuous glucose monitoring (CGM) is a special exhaustive form of monitoring patients at risk for nocturnal hypoglycemic episodes, whereas the self-monitoring of blood glucose (SMBG) is intended to be used to obtain frequent measurements throughout the day at the patient´s home. Clinical, epidemiological, and economic evidence support that SMBG helps to avoid late complications [McGeoch 2007]. The standard DIN EN ISO 15197 (In Vitro Diagnostic Test Systems–Requirements for Blood Glucose Monitoring Systems for Self-Testing in Managing Diabetes Mellitus) specifies, in detail, the requirements for glucometer devices with regards to system performance, accuracy, and precision. A revision of the norm has further made these limits tighter for the minimum performance criteria. More than 95% of the respective device analytical results must fall within ± 15 mg/dL of the results of the manufacturer´s measurement procedure at glucose concentrations <100 mg/dL and within ±15% at concentrations >100 mg/dL. Recent studies of Freckmann *et al.* [Freckmann 2012] and Hasslacher *et al.* [Hasslacher 2013] showed that these minimum requirements were failed by a series of CE-marked glucometer devices, which are currently on the market. The responsible POCT coordinator should perform a standardized evaluation of instruments for SMBG before introducing them into the hospital environment [Solnica 2003, Kristensen 2003, Haeckel 2004, Petersmann 2013].

3.3.2.1. Tight glycemic control

Apart from diabetics, intensive-care unit (ICU) patients also benefit from a tight glycemic control (**TGC**). Even when the TGC is still controversially discussed due to conflicting study results [NICE-SUGAR Study group 2009, Wahl 2009], a glucose plasma level of 140-180 mg/dL is recommended in ICU patients [Kavanagh 2010]. Under such circumstances, where the glucose analysis in these patients is complicated by a high probability of the presence of interfering compounds in the circulation, the technical requirements have to be very high [Imhoff 2007]. Conventional glucose meters are less precise and accurate than the hexokinase/glucose-6-P-dehydrogenase method [Scott 2009], as specified in the ISO 15197. Particularly, the accuracy in the normo- and hypoglycemic range is often found to be insufficient [Wehmeier 2006, Weitgasser 1999]. Reduction of interferences, a tight correlation to the reference method, minimized interference of extreme hematocrit values, and a less than 15% of total allowable error tolerance is a clear claim [Karon 2010, Germagnoli 2009]. Currently, only the StatStrip (Nova Biomedical, Waltham, MA, USA) is in compliance with these criteria. Recently, the FDA enforced manufacturers of glucometers to specify the intended use for the respective meters [Klonoff 2014].
Also, alternative-site glucose measurement is often discussed. It seems that the subcutaneous adipose tissue can be used to establish TGC in ICU patients [Ellmerer 2006].

3.3.2.2. Continuous glucose monitoring

CGM can be seen as a tool for the management of diabetes in patients with hard-to-balance plasma glucose levels. A convergence of CGM and TGC is approaching [Miller 2007], where CGM should supply reliable data required to optimize insulin therapy and metabolic control [Koschinsky 2001]. Most systems are minimally invasive, such as the microdialysis systems, for which there is extensive clinical data. Also non-invasive monitoring technologies are on the market, which need a critical appraisal. Vashist [Vashist 2012, 2013] recently provides comprehensive reviews on available CGM systems and on non-invasive techniques.

CGM is postulated to also enable a diagnostic approach, such as in patients with early dysglycemia at a high risk of developing diabetes who might benefit from the application of CGM for 3-5 days [Soliman 2014].

Microdialysis systems analyze the glucose levels in the interstitial fluid of the subcutis [Baldini 2010], which is different in comparison to plasma levels. Therefore, devices for a direct intraarterial or intravenous measurement are under development. The initial results with the GluCath System (GluMetrics, Irvine, CA, USA) have already been published [Strasma 2015].

The continued discussion on technical issues concerning glucose analysis has contributed to the awareness of the special preanalytical problem of glycolysis. The inhibition of glycolysis in the specimen after blood collection is now performed more effectively, not only by addition of fluoride, but also by a citrate-buffer acidification, leading to more accurate and consistent results [Mikesh 2008, Gambino 2009, Yagmur 2012].

3.3.2.3. Hemoglobin A1c

The determination of hemoglobin A1c (HbA1c) is employed in the monitoring of diabetes therapy. HbA1ac has also proved itself as an essential metabolic component for diagnostic purposes. But the role of POCT for HbA1c in the management of diabetic patients is still questionable. There is no current evidence in clinical trial data that POCT is effective in the management of diabetes [Al-Ansary 2011]. Moreover, POCT devices for the determination of HbA1c do not generally meet the accepted performance criteria and are thus insufficient to meet the clinical need [Little 2011, Lenters-Westra 2014, Heinemann 2015]. This is due to the stringent analytical requirements for the accurate measurements of this measurand.

3.3.3. Markers for the diagnosis of cardiovascular diseases

Cardiovascular diseases are the most prominent causes for death. Most deaths are caused by coronary artery disease (CAD), with its acute form: acute coronary syndrome (ACS). The two main types of ACS are the instable angina and the acute myocardial infarction (AMI). The emergency diagnostic approach is based on three components: clinical symptoms, electrocardiogram and cardiac biochemical markers. It is clear that the TAT for this urgent diagnostic situation should be as rapid as possible [Yang 2006].

Two decades ago, the cardiac markers were CK, CK-MB_{mass} and myoglobin. Cardiac troponins I and T (cTnI, cTnT) have now become the undisputed cardiac markers, where the measurements of marker panels, including myoglobin, do not facilitate diagnosis of ACS [Di Serio 2007; Collinson 2013]. The analytical techniques, however, must ensure highly sensitive measurements. The quality gap between central laboratory and POCT methods continues to grow, since the latter find it hard

to achieve the internationally accepted criteria for highest sensitivity [Per Venge 2010; Lee-Lewandrowski 2011; Sandoval 2014; Lorley 2013]. cTn assays are classified according to whether they are able to measure the 99th percentile serum concentration of a reference population without CAD with imprecision coefficients of variation of less than 10% (to be guideline acceptable), 10-20% (to be clinically usable) or above 20% (to be not acceptable) [Per Venge 2013]. An extensive survey on the quantitative POCT devices, i.e. Triage, AQT90, iSTAT, Meritas, Pathfast, Stratus CS, h 232, Vidas, and RAMP, along with their analytical performance characteristics was recently assembled by Amundson and Apple [Amundson 2014]. Nonetheless, the determination of the significance of the use of POCT cardiac markers outside big hospitals with competitive central labs or in underdeveloped countries is still ongoing [Ryan 2009, Altintas 2014]. Potentially beneficial effects of POCT (e.g., length of stay) are to be considered individually and in the context of ED operations.

Emerging technologies for optimizing the analytical performance characteristics of near-patient cardiac tests can be envisioned for the future. Nanoparticles (comprising metal, semiconductors, or even organic compounds) significantly enhance the optical, (electro)chemical, or magnetic detector characteristics, which subsequently improves the analytical sensitivity of POCT immunoassays [Chan 2013]. Also, anti-fouling optimization strategies for the functionalized biosensor surface [Liu 2011], application of poly(dimethylsiloxane)-gold nanoparticles composite chips [Zhou 2010], and multiplex lab-on-a-nanobiochips [Floriano 2009] are of potential relevance.

sCD40 ligand, myeloperoxidase, ischemia-modified albumin, pregnancy-associated plasma protein A, placental growth factor, and fatty acid binding protein could be future ACS markers [Jaffe 2006]. Promising new data show that measuring copeptin (C-terminal part of vasopressin prohormone) could compensate for the lower sensitivity of POCT cTn assays when measured simultaneously for an early rule-out of an AMI [Vafaie 2015].

B-type natriuretic peptides (BNP, NT-proBNP) are serum parameters of chronic heart failure and are important in the ED when patients with acute dypnea (“shortness of breath”) are diagnosed. POCT devices are already in place in this setting [Peetz 2005; Anwaruddin 2006].

3.3.4. Markers for acute kidney injury and chronic kidney disease

ICU patients with acute cardiovascular and/or respiratory compromises are at risk for moderate or severe acute kidney injury (AKI). Often patients with AKI require hemodialysis, which is linked with a higher mortality rate. Until recently, there was a lack of biochemical markers for the early assessment of the risk for AKI. Chronic kidney disease (CKD) is characterized by a sustained reduction in glomerular filtration rate (GFR) due to structural or functional kidney abnormalities. CKD is associated with increased cardiovascular events, causing a high morbidity and mortality. Also, here, a rapid and accurate diagnosis by means of biochemical markers, except for the moderately informative parameters creatinine, urea and urinalysis, is missing. Today, developments and experimental trials have created a series of new and promising markers, which seem to have the potential to close the diagnostic gap for both diseases entities. Whether POCT or central laboratory methods will be in the forefront, remains open to debate and is subject for intensive

clinical trials.

The following biomarkers (tubular enzymes and proteins, indicating tissue leakage; inflammatory markers; cell arrest proteins) in serum/plasma and urine were identified to play a diagnostic role [Han, 2002; Wasung 2015]:

- AKI related biomarkers: Kidney Injury Molecule-1 (KIM-1), Neutrophil Gelatinase-Associated Lipocalin (NGAL), Tissue Inhibitor of metallo-proteinase 2 TIMP-2), and Insulin-like Growth Factor Binding Protein 7 (IGFBP7)
- CKD related biomarkers: NGAL, cystatin C, and FGF-23
- Candidate biomarkers for AKI: Myo-inositol oxygenase (MIOX) [Gaut 2014], Liver Fatty Acid Binding Protein (L-FABP), and IL-18 [Singhal 2014].

The recently launched device NephroCheck (Astute Medical, San Diego, CA, USA) is the first POCT instrument in this arena to quantify TIMP-2 and IGFBP7 in urine. Studies evaluating the combination TIMP-2 × IGFBP7 are currently underway. A first two-part multicenter observational study in critically ill patients showed that the combination of both markers is superior to existing markers and might provide additional information to clinicians [Kashani 2013]. A second study on patients after cardiac surgery further showed that the diagnostic POCT could identify subjects at increased risk for developing AKI only one day after surgery. At earlier time points the test was non-informative [Wetz 2015].

Other nephrological applications for POCT are:

- Monitoring the effect of hemodialyis by the measurements of nitrite and uric acid in sputum [Blicharz 2008];
- analysis of urinary albumin as an early marker of diabetic nephropathy by use of a fluorescence immunoassay [Qin 2003]; and
- rapid creatinine analysis to optimize clinical operations and patient disposition in the radiology department in order to prevent contract-induced AKI in subjects at risk [Skurup 2008; Lee-Lewandrowsky 2012; Naugler 2014].

3.3.5. Diagnosis and monitoring of blood gas and acid-base disturbances

Blood gas analysis (BGA) is mainly used in pulmonology and critical care medicine in order to evaluate the breath gas exchange processes, which take place across the alveolar-capillary membrane. The measurement of the (arterial) oxygen tension (paO2), carbon dioxide tension (paCO2) and acidity (pH) are crucial parameters for physicians and respiratory therapists when caring for patients with critical diseases or respiratory insufficiency.
Additional measured or calculated markers of BGA in arterial blood are: HCO_3^-, base excess (BE), oxygen saturation (saO_2), total oxygen-, and CO_2-concentrations (caO_2, $caCO_2$), lactate, hemoglobin, Na^+, K^+, Mg_{ion}^{++}, Ca_{ion}^{++} and of oxy-, carboxy- and methemoglobin [Boehmke 2004; Köhler 2006].

BGA is also used to evaluate acid-base disturbances. An acid-base equilibrium is fundamental for maintaining all life processes. To quantify potential acid-base disturbances, there are different theoretical approaches: the physiological, the base excess, and the physicochemical approach. The latter is known as the Stewart method [Rehm 2004; Lang 2007; Berend 2014]. Hemodynamic shock/hypoperfusion, resuscitation, and metabolic acidosis are life-threatening situations for ICU patients. Therefore, a prompt diagnostic evaluation is mandatory [Englehart 2006; Chalwla

2008]. The metabolic marker compound lactate plays a pivotal role in this evaluation. It should always be measured within the BGA, when acidosis can be assumed [Rossi 2004; Gunnerson 2006; Martin 2012].

BGA is performed nearly exclusively in the ICU by use of POCT analyzers, which is due to the instability of the heparinized blood samples that have to be analyzed within 15-30 min after arterial or capillary puncture [Luppa 2012]. The analyzers are mostly benchtop instruments (see **Table 2**), although handhelds, such as the iSTAT or the new Epoc system [Stotler 2013], are also in use.

3.3.6. Diagnosis of acute and chronic microbial infections

LFAs in the POCT format for the detection of pathogens (bacteria and viruses) were introduced already in the 1990s. The test systems for HIV, malaria, group A streptococci, pneumococci, and other pathogens are now more technically mature and widespread. However, these simple-to-perform POCT methods can only be applied successfully based on the fulfillment of the following mandatory requirements:

Tests are to be performed by trained users and a stringent quality management is established. Additionally – this is partly in contrast to the application of other patient-near testing scenarios – the seriousness of the infection and the epidemiological background of the contamination should be reviewed. Stürenburg and Junker [Stürenburg 2009] gave a sophisticated overview on currently available POCT LFAs; Moore [Moore 2013] additionally systematically reviewed the paucity of currently published data on the role of POCT in infection control. A study from Cohen-Bacrie *et al.* [Cohen-Bacrie 2011] showed that POCT can be effective in the ED when decisions regarding hospitalization or dismissal are made. The high negative predictive value of LFA enabled nearly three times more patients without infection to be discharged in comparison to conventional microbiological procedure. This, together with a rapid determination of inflammation markers [Pfäfflin 2009], makes it easier for clinicians in the ED to effectively manage the outbreaks of pathogens. Novel analytical attempts to improve microbial antigen detection by means of POCT have been made by several research groups. Exemplarily, Chin *et al.* [Chin 2011] established a so-called “mChip”, which is a mobile microfluidic chip for the immunoassay detection of two HIV and syphilis antigens. Breslauer *et al.* [Breslauer 2009] established a mobile phone based clinical microscope that can be applied adequately in resource-limited regions with a high burden of tuberculosis. Imaging of *Mycobacterium tuberculosis*-infected sputum samples was impressively performed by use of fluorescence detection using LED excitation (see **Figure 3**). Wang *et al.* [Wang 2013] reviewed the role of nanotechnology and microfluidics for POCT of tuberculosis.

Microbiological nucleic acid testing (NAT) promises rapid and reliable diagnosis of infectious diseases. In contrast to LFA, real-time nucleic acid amplification-based POCT methods have been constrained by a lack of test formats that are accurate and have low complexity.

Simple-to-use NAT devices provide the physician a rapid diagnostic tool to immediately initiate effective treatment and/or stringent isolation. However, apart from analytical difficulties to identify microbial/viral gene sequences, practical issues around using more complex POCT devices and handling of swabs or smears from affected patients compromise the feasibility of NAT POCT in the daily clinical routine.

Existing technologies for nucleic acid amplification are the polymerase chain reaction (PCR) and a series of isothermal amplification strategies. These are:

- Nucleic Acid Sequence Base Amplification (NASBA),
- Helicase Dependent Amplification (HDA) [Goldmeyer 2007],
- Recombinase Polymerase Amplification (RPA) [Piepenburg 2006],
- Loop Mediated Isothermal Amplification (LAMP),
- Strand Displacement Amplification (SDA),
- Rolling Circle Amplification (RCA) and others.

The main advantage of isothermal amplification strategies is the drastic reduction in analytical process time in comparison to PCR techniques [Craw 2012].

Cepheid (Sunnyvale, CA, USA) paved the way for extensive POCT applications during the last decade by providing the GeneXpert, a cartridge-based fully automated NAT technology. It extracts, concentrates, amplifies (by real-time PCR), and identifies targeted nucleic acid sequences in the bacterial/viral genome and provides results from unprocessed swabs, smears or sputum samples in less than 2 hours. Using advanced microfluidics, all aspects of the testing process are handled within the cartridge. The modularly scalable GeneXpert device platform fully integrates and automates the molecular biology processes. There are already a series of feasibility studies concerning a meaningful implementation of the device as POCT in clinical routine settings. Goldenberg *et al.* [Goldenberg 2014] described the testing for *Clostridium difficile* in two hospital settings, whereas Brenwald *et al.* [Brenwald 2010], and Parcell *et al.* [Parcell 2014] evaluated the system for the rapid identification of patients with methicillin-resistant *Staphylococcus aureus* (MRSA).
Another interesting approach is the Biofire FilmArray (BioMerieux, Marcy l'Etoile, France), a multiplex PCR system that integrates sample preparation, amplification, detection and analysis. The multiplexing PCR enables the simultaneous testing of different sets of pathogens (bacteria, viruses, yeast, parasites). The system employs three Food and Drug Administration (FDA)-cleared panels that test for more than a hundred pathogens. However, the instrument is not suitable for POCT, when there is paucity of reliably trained users [Gray 2012].
A rapid, easy-to-perform POCT device was recently launched by Alere, i.e. the Alere I *Influenza A* and *B* virus detection instrument, based on the rapid isothermal RPA reaction.

However, POCT-ready NAT diagnostics has yet to be achieved. There is a lack of observational studies using the described NAT systems that can thoroughly compare the POCT results with the conventionally performed culture and identification repertoire in the microbiological lab. Dark *et al.* [Dark 2009] further advised performing clinical effectiveness studies to prove cost- and patient benefit-efficiency prior to a general recommendation of this technology. Another unsolved problem is the significance of NAT technologies to determine antibiotic resistances at the respective bacterial gene level.

3.3.7. Diagnosis and monitoring of hematological diseases

By far, the near-patient testing of hematology parameters is not as common used in POCT as other parameters, such as cardiac markers etc. However, the need for basic information of the complete blood cell count allows rapid clinical decisions to be made, particularly in oncological ambulances. But the determinations of hemoglobin

(Hb) and CD4+ lymphocytes, as well as the malaria screening are also relevant medical issues.

There are two types of POCT devices for hematological analyses, i.e. bench-top analyzers (type 3) and quantitative hand-held devices (type 2). The bench-top systems (e.g., PocH-100i from Sysmex, Kobe, Japan) provide a complete blood cell count (CBC) with erythrocyte indices and either a 5-part white cell differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) or a partial 3-part differential. The hand-held devices enbable measurement of total Hb concentration, detection of *Plasmodium* spp. or quantification of CD4+ lymphocytes [Briggs 2012). A new development is the Hemocue WBC system, Hemocue America, Brea, CA, USA) for a partial 3-part differential. This automatic cell counting is performed by a hemolyzing agent, which lyses the red cells in a microcuvette and a staining dye. Thereafter, the stained white cells are counted by image analysis.

A different technological approach is presented by the QBC Star analyzer from Drucker Diagnostics (Port Matilda, PA, USA), which employs the so-called dry hematology [Erhabor 2013]. The core element of the device is a unique blood collection tube, which is internally coated with all necessary stains and reagents, and is filled with 65 μL of blood. The different cell components separate into layers during centrifugation of the tube due to their varying densities.

The internally coated tube also contains a precision float, which stretches out the different cell (thrombocytes, lymphocytes, monocytes, granulocytes) layers to make these small bands more easily measurable. Besides the measurement of the hematocrit, the specific density of the float further allows the direct measurement of the Hb concentration in the erythrocytes (mean corpuscular Hb concentration, MCHC).

The determination of the clinically relevant Hb concentration, together with the check of saO2 and pulse rate, is very often performed by non-invasive methods. The underlying principles of this are multiwavelength cooximetry and occlusion spectroscopy [Kim 2014]. Due to possibly interfering atypical Hb species (e.g., met-Hb), clinicians should be cautious when making therapeutic decisions based only on these instruments. But, the capillary-based Hb measurement can also be error-prone. Type 2 devices should be used with caution in critically ill patients, who may have peripheral hypoperfusion or tissue edemas. Erroneous results may be recorded [Seguin 2010]. However, type 3 devices should also be implemented into a strict quality assessment regime as described in section **4.4**. Additionally it should be mentioned that there are also international guidelines for POCT in hematology, which also have a special reference to the CBC [Briggs 2008; Briggs 2008a].

3.3.8. Diagnosis and monitoring of coagulation disorders

Hemostaseological testing can be classified as *humoral coagulation testing* and *analysis of thrombocyte function* [Perry 2010, Spannagl 2010, Curtis 2012]. Most prominent in the hospital, but also in the home care sector, is the monitoring of the International Normalized Ratio (INR) for patients under vitamin K antagonists (warfarin, marcumar). There are different analytical principles for the determination of the prothrombin time.

The following principles are realized in the respective POCT devices:

- Mechanical detection of the clot formation: Light reflectance from metal particles in a magnetic field and recording of movements of blood in capillary tubes.

- Electrochemical monitoring of thrombin generation by use of a recombinant human thromboplastin, which cleaves a synthetic fibrinogen peptide (electrocyme TH). The amount of cleaved o-phenylendiamine can be recorded by amperometric signaling.

Theoretically, the home testing of INR has an advantage of close monitoring that allows the patient to adjust the dosage of coumarin [Braun 2008]. However, the clinical studies on medical and economic issues concerning self-testing are conflicting [Matchar 2010; Lippi 2011; Siebenhofer 2014].
The activated clotting time (ACT) is mainly used to monitor the anticoagulation status with unfractionated heparin during cardiopulmonary bypass in patients undergoing cardiac surgery. Reliably performed ACT measurements reduce postoperative complications and the requirements for the transfusion of blood products [Nydegger 2006].
The D-dimer test enables the rapid exclusion of deep venous thrombosis in subjects with a low to moderate clinical suspicion for this coagulation disorder. Interestingly, the POCT instruments use immunoassay techniques to analyze this measurand, with the availablility of qualitative as well as quantitative methods [Geersin 2010].

Viscoelastic platelet function testing is a successful new application form for POCT in the perioperative setting. These tests aid anesthesiologists in diagnosis and treatment of acquired coagulopathies.
Thrombelastography (TEG) and Rotation Thrombelastometry (ROTEM) are POCT-ready instruments that provide both cellular and humoral information on the dynamics of the fibrin clot formation, clot stabilization, and fibrinolysis. Since the thrombelastogram reflects the *in vivo* hemostasis situation, the major application is to monitor complex major surgeries and trauma bleedings [Rhee 2010]. Several studies verify a significant reduction in necessary allogeneic erythrocyte and thrombocyte concentrates [Ak, 2009; Goodnough 2012].

Direct thrombocyte function tests are also available in the POCT format, but their handling requires specially trained personnel. The PFA-100 Analyzer (Siemens Healthcare Diagnostics, Eschborn, Germany) is an *ex-vivo* bleeding time analyzer and measures the closure time (i.e. the time to cessation of flow) of citrated blood aspirated through a central aperture of a membrane. The test is performed under high shear flow conditions similar to the physiologic environment in which platelets normally function. The test is very sensitive for the presence of aspirin. Also, the impedance thrombocyte aggregometer Multiplate (Roche Diagnostics, Mannheim, Germany) identifies patients with apparent aspirin or P2Y12 receptor antagonist (clopidogrel, prasugrel, ticagrelor) resistance. The underlying physical principle is that activated thrombocytes, in a cuvette, coat the surfaces of two electrodes of the analyzer, which are positioned in the cuvette at a determined distance between them. The initiated aggregation can be detected by the increase in electrical impedance, generated by multiple layers of aggregated platelets at the electrode surfaces [Paniccia 2015]. The cardiological management of patients at high risk of a major adverse cardiac event after coronary stenting or in the event of an ACS has high impact on the patient outcome [Levi 2015]. An adequate platelet aggregation inhibition regime is mandatory. Approximately 20% of patients do not respond adequately to clopidogrel after cardiac catheterization. Conversely, the risk of major bleeding is 2-3 times greater in patients who are high responders to P2Y12 receptor antagonists.

A new system is based upon the adhesion and aggregation of platelets onto a plate covered by polystyrene, using whole blood exposed to high shear. The original “Cone and Plate(let) Analyser (CPA)” device has now become a commercial instrument (IMPACT, Diamed, Switzerland), while the clinical evaluations are still pending.
An optical aggregometry system is the VerifyNow device (Accriva Diagnostics, San Diego, CA, USA), which is based on the principle of increase in light transmission as sample platelets aggregate to test fibrinogen-coated beads.
Other thrombocyte function analyzers are the HemoSTATUS (Medtronic, Parker, CO, USA), the Plateletworks (Helena Laboratories, Beaumont, TX, USA) and the TEG Platelet Mapping system (Haemoscope, Niles, IL, USA).

3.3.9. Miscellaneous

A reasonable application of rapid testing technology is the intraoperative immunoassay determination of intact parathyroid hormone. Serial measurements during the surgery procedure allow an optimization of the surgical management of hyperthyroidism [Sokoll 2004]. The determinations of various parameters for the evaluation of male and female fertility (pregnancy test (hCG); LH/FSH; sperm count; etc.) are also well established. A series of other POCT developments, such as cortisol determination for the evaluation of stress disorders [Kaushik 2014], cancer diagnostics [Soper 2006] or IgE driven allergy detection [Ono 2003], are highly speculative and clinically questionable.

4. Organizational Concepts and Quality Management of POCT

4.1. Organizational Concepts

In order to analyze the overall process time for clinical chemistry testing the concept of the brain-to-brain loop was created. The brain of the physician, who is treating the patient, first selects adequate laboratory tests to confirm a diagnosis. Blood is taken from the subject and transported to the laboratory. In the laboratory follow intermediary preanalytical, analytical and postanalytical steps before the test result is transmitted to the ordering physician. He finally has to interpret the findings and to initiate the adequate therapeutic action on the patient. This holistic concept has been termed "brain-to-brain loop" by Lundberg as early as 1981 [Plebani 2011, Lundberg 1981]. The time period needed to perform these steps is known as turn-around-time (TAT) [Steindel 2001, Breil 2011]. As the name implies, POCT is conducted at close proximity to the patients and reduces sample transportation time to a minimum. Therefore, POCT can produce faster results in comparison to testing in a central laboratory, especially due to the time taken in transportation of samples.

Time is a pivotal factor in almost all clinical settings and a short TAT is one of the highest priorities for treating physicians [Steindel 2001, Loeffert 2014, Kilgore 1998, Casagranda 2010]. A meta-analysis of several clinical trials on rapid testing, however, was found to be ambiguous concerning a possible medical benefit [Pecoraro 2014].
There are areas and disease categories where rapid results are of uttermost

importance. The treatment of sepsis at an early stage by antibiotic treatment critically improves the chances of survival in patients. Even differences as small as one hour significantly influence the outcome [Dellinger 2013, Ferrer 2009, Kumar 2006]. Therefore, there has been tremendous research into POCT applications pertaining to the detection of sepsis [Pfafflin 2009] or the identification of infectious pathogens [Niemz 2011] at a very early stage. Similarly, the benefits of thrombolytic treatment to ischemic stroke patients are greater if the treatment is started earlier [Lees 2010]. Moreover, POCT can reduce the TAT for preliminary laboratory analysis before treatment [Walter 2011]. For the acute coronary syndrome, the laboratory analysis should be concluded in less than 30 minutes [DeLuca 2004, Storrow 2007], the aim that has been realized in many commercial POCT devices [Chan 2013].

However, the introduction of POCT systems is only one of the several options to reduce TAT in a hospital setting. Improved workflow models, better pneumatic tube systems and other organizational changes have also been demonstrated to reduce the TAT of the central laboratory [DiSomma 2013, Kilgore 1998, Stotler 2012, Suchsland 2014]. The coexistence of central laboratory and POCT services in a hospital does not necessarily imply conflicts. There are, in fact, complementary synergies. Both organization units are procedurally important for optimal patient diagnostics and care, provided that a POCT coordination office ensures that both complement each other [Bietenbeck 2014].

4.2. Organizational Framework

The successful establishment of POCT requires close coordination of different players in a hospital. Therapists together with caregivers conduct the tests, while the pharmacy needs to distribute reagents and other consumables, and the department of medical engineering has to service the POCT systems. The laboratory professionals are usually responsible for fulfilling the regulatory requirements and for the quality management. This multidisciplinary group is brought together in the form of a POCT coordination unit, which is a steering group dedicated to the development of organization-wide clinical governance [Lewandrowski 2011, OKelly 2013, Nichols 2007, ISO22870]. It decides the parameters offered as POCT and selects the appropriate devices after evaluation, taking into account the clinical need, analytical performance, technical feasibility and economic impact. The POCT coordination is also responsible for the internal and external quality assurance of POCT measurements. This includes the authority to demand corrective actions including the withdrawal of POCT service in case of failures [Junker 2010, Gramz 2013, OKelly 2013]. ´

Although the POCT coordination establishes the strategy, the day-to-day work is carried out by the coordinator, who is usually recruited from the central laboratory based on the core competencies of laboratory analyses and quality management. He assists the POCT operators in the troubleshooting of errors and problems to ensure continuous workflows apart from supervising the proper execution of quality controls in compliance with relevant national regulative guidelines. His on-site inspections ensure a safe working environment, good hygiene and proper storage conditions for reagents, especially with regard to temperature and humidity [Richard 2014, Lewandrowski 2011]. Moreover, he implements protocols to prohibit the accidental use of reagents beyond their expiration date [Plebani 2009].

4.3. Training of POCT Operators

The person who conducts a POCT measurement usually has no background in laboratory medicine, even in professional medical environments. This leads to errors in POCT that are often operator- rather than instrument-related [Nobels 2004, Plebani 2009, OK´ane 2011, Nichols 2011, Howerton 2005, Ehrmeyer 2007, Meier2005, OKane 2014]. Common errors include the failure of operators to undertake basic instrument preparation, maintenance and quality control steps, non-adherence to standard test procedures and use of outdated reagents. This substantiates the need for numerous guidelines and policies requiring the formal training of POCT operator in order to reduce the errors and ensure patient safety [Nichols 2007, GMA 2015, ISO22870]. For example, the ISO 22870:2006 standard "Point-of-care testing (POCT) - Requirements for quality and competence" puts great emphasis on operators' qualifications. It stresses the appointment of a manager for the theoretical and practical training of all personnel before they are declared competent for POCT [ISO22870, Gregory 2009]. This is valid not only for hospital environments, but also for outpatient clinics, except for the home care use.

The POCT training program should promote the theoretical understanding and practical operation of the measurement system apart from the knowledge of clinical applications and limitations. Preanalytical and analytical procedures, such as patient identification and preparation, specimen collection, handling and processing, should be reliably conducted. The test results need to be recorded correctly with the identification of results falling outside the predefined reference range limits. The training program should also include quality control and assurance, instrument maintenance, function checks, problem-solving, effective reagent storage, disinfectants actions and waste disposal [Price 1999].

As the error frequency varies significantly between different POC tests [O´Kane 2011], the extent of training required to minimize/obviate errors is closely connected to the sophistication of the device. The existing test systems guide the operator to perform the tests correctly, flag critical results and lock the system in case of inadequate quality control assessments [Ehrmeyer 2011]. Such "safety-by-design" improvements can critically reduce the errors and may limit the need for extensive training on POCT devices, as provided by many vendors at present.

Although the need for operator training has been clearly established, the best methodology is still under debate. However, there is a need for persistent training to ensure a long-term effect [Liikanen 2013], and the continuous support from the central laboratory [Lehto 2011, Sanchez-Margalet 2005]. Several means of education, such as face-to-face teaching, training manuals, posters and computer programs, have been successfully employed for POCT training and operator (re)certification [Shephard 2009, Sanchez-Margalet 2005, Lehto 2011, Cantero 2015]. Moreover, the availability of internet-based software (eLearning) has further extended the educational outreach to POCT operators in remote locations [Knapp 2011].

4.4. Quality Assurance and Risk Management

Many guidelines and recommendations have been proposed by CLSI, ISO, and national accreditation bodies, how to deal with POCT. These include QMS14-A ("Quality Management System: Leadership and Management Roles and Responsibilities; Approved Guideline"), POCT 07A ("Quality Management – Approaches to reducing errors 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") [Ehrmeyer 2004, Hänecke 2004, Schimke 2009]

The internal quality control procedures check whether the measured result of a device is within the predetermined and accepted ranges of the target value by applying dedicated quality control samples. However, many POCT devices employ discrete and disposable testing unit. Therefore, unlike the batch-based processing in central laboratories, the performance of a single test gives no information about further accuracy [Gill 2010]. As a result, many instruments perform in-built electronic checks that assess the electronic performance of the device prior to analysis [Westgard 2001], the quality controls are additionally to be performed in predefined time periods [Nichols 2003, Demers 2004, Pearson 2006].

In external quality assessment schemes (EQAS), control samples with unknown analyte concentration are distributed to all participating laboratories. The results are then transferred back and evaluated by the EQAS provider, which enables the identification of sources of errors. Similarly, educational material and information exchange also improve the quality of POCT testing of individual participants [Bukve 2015]. Moreover, the comparison of results across different devices and measurement methodologies further facilitates the comparison of laboratory results, thereby providing an estimate of the device performance [Aslan 2014, Miller 2006]. The control samples need to be specially modified for prolonged stability without any compromising effect of storage and shipping. Inbuilt quality checks of the POCT-device might recognize that the sample is not native and therefore reject the control material. Additional problems can also occur: The sample matrix can influence POCT analyzer processes, causing erroneous results. Stavelin *et al.* [Stavelin 2013] present a solution for an EQAS evaluation in situations in which no commutable control samples are available. Nevertheless external quality assurance schemes for POCT are claimed by the national authorities and constitute one of several criteria for the evaluation of POCT devices [Lehe 2012].

POCT and central laboratory methods, measuring the same analyte, often coexist in hospitals, which enables the assessment of agreement via inter-method comparison [Nilsson 2014]. Several methods have been proposed for estimating the correlation [Shermock 2011], among them the kappa interrater statistics seems to quantify the amount of agreement between two methods adequately and enables a straightforward implementation in hospital settings [DIN58964]. It must kept in mind, however, that the testing different methodologies (POCT and central laboratory) can be influenced by different sources of error [Pereira 2015, King 2013].

The POCT coordination is responsible for the establishment of a risk-based quality control plan to mitigate and prevent errors, which needs to be tailored to the particular combination of measuring system, laboratory setting and clinical application of the test [EP23A2011, Nichols 2011a]. The EP23 risk assessment

guideline enables the POCT coordination to perform a quality control process based on risk and enables the responsible subjects to gather the essential information, performing the adjusted risk assessment, creating an individual quality control plan, and reviewing the plan for its effectiveness. Moreover, Cantero *et al.* [Cantero 2015] recommend the use of quality indicators, such as the percentages per month of POCT samples without results, insufficient sample volume in POCT, parameters with unacceptable results in EQAS of POCT, and parameters with imprecision's higher than selected target in the internal quality control of POCT.

4.5. Information Technology Systems for POCT

Central oversight and management of decentralized POCT devices has been made possible by appropriate information technology (IT) systems [Dyer 2001, Clarke 2007, Lewandrowski 2011, Jones 2014], which encompasses not only hardware and software, but also accompanying procedures such as data transfer, operational features and additional supportive functions. First example was the Remote Automated Laboratory System (RALS) technology [Menke 2007].

Modern POCT devices offer several data exchange interfaces to connect to the hospital network. A fixed cable is often the easiest choice for stationary tests, whereas the mobile devices might benefit from wireless connections such as Wi-Fi or Bluetooth. But data protection and a continuous connection are harder to guarantee with these protocols, which substantiate the need for docking stations with wired connection in order to exchange the network data that is saved in the mobile device only. Furthermore, there is a demand for an integrated robust barcode reader, which allows rapid and reliable identification of patients and operators [Snyder 2010]. The upcoming use of smartphones in medicine is also called mobile health ("mHealth"). There is a wide range of envisaged medical applications, such as POCT, treatment, or ambient assisted living. Moreover, there is a new dimension in sight, when mobile devices collect individual patient data from POCT devices and compare the result against large data sets, which are retrievable via the internet. This would provide therapeutic recommendations for the individual patient, but could also alert the community about imminent epidemics, which might be an attractive approach in the third world [Chin 2013]. On the other hand, mHealth becomes a challenge for the regulatory authorities, being responsible for ensuring the quality and effectiveness of diagnostic procedures. Consequently, the FDA has already introduced first rules for mobile health technologies [Cortez 2014].

A common syntax for the bidirectional communication is the POCT01-A2 standard [POCT01-A2], which in turn draws on the existing Health Level Seven International (HL7) standard for the electronic exchange, integration, and retrieval of health information [Byrdy 2003]. Contrary to proprietary protocols, POCT01-A2 allows cost-effective multivendor connectivity, which facilitates the transmission of at least the test result, the patient particulars, the time of measurement and the device operator. Further, this data has to be forwarded to the laboratory information management system to maintain all laboratory results at one single place.

Modern POCT IT supports not only the data exchange, but also day-to-day operations, thereby enabling the POCT coordinator to supervise all POCT processes, in terms of handling problems, quality control violations and workflow interruptions in

real-time in order to ensure patient safety. There should be an option to initiate maintenance actions, such washing cycles, recalibration procedures, remotely. If an analytical problem cannot be solved remotely, transmitted error logs might facilitate the service technician to prepare for his on-site visit.

As quality assurance is a key aspect in decentralized POCT, the compliance of quality control measurements have to be constantly supervised by the POCT coordinator in accordance with the respective laboratory guidelines. A device has to be locked, if these controls have not been performed or evaluated as being outside of the acceptable range. Similarly, the user's access to the devices should be allowed or denied based on their training and performance. Delta checks or more advanced algorithms can mark the results that need special attention, which assist in the interpretation of normal ranges. Some POCT software even push this information to the POCT device in order to warn the operator directly. Although the software support for POCT quality assurance does not reduce errors directly, it can result in significant savings [Salka 2003].

Apart from these core features, there is the need for additional supportive functions that are closely linked to POCT. However, depending on the overall IT infrastructure of the hospital, it might be more efficient to meet these requirements using dedicated software that covers POCT as well as other functions such as remote education. Assess to POCT devices can be certified, based on successful completion of such online training courses. Therefore, every time a user completes a course successfully, this information should be transferred to the actual POCT software. As POCT devices are distributed across the entire hospital, the reagents and other consumables should also be distributed accordingly. Moreover, there is a need for developing interfaces and data transfer to the hospital's purchasing department, which would result in reliable and cost-effective supplies. Similarly, external and internal accounting could also be benefitted from such data exchange with POCT.

5. Future Perspectives – Analytical and Healthcare Trends

5.1. Analytical Trends

Novel enabling technologies will considerably enhance the applications of POCT. However, the adoption trajectories depend largely on whether the new POCT concepts satisfy unmet clinical needs or fit with the special healthcare situations in different developing countries. The novel analytical technologies will include alternative biological detection elements and highly sensitive signal technologies, such as optical or magnetic detection modes.
Novel IT applications will pave the way for a more "personalized" POCT, whereas smartphone-based near-patient devices will open new horizons in wireless health [Komatireddy 2012].
The concept of a **micro total analysis systems** (μ-TAS) by integrating planar chip technology with separation techniques on the chip in the 1990s [Manz 1990 and 1992], paved the way for miniaturization and further development of microfluidics

[Bazydlo 2012]. A second revolutionizing step, however, was to transform this concept of μ-TAS to microfluidic paper-based analytical devices (μ-PAD) [Martinez 2010] that offer special advantages in developing countries due to inexpensive and easy-to-use diagnostic applications. Furthermore, technological developments by applying nanomaterials can be justifiably claimed for the near future.

A further optimization of **immunoassay formats** in terms of speed, sensitivity, and specificity will also be a future-oriented trend. Sakamoto *et al.* [Sakamoto 2014] recently showed that magnetically prompted sandwich immunoreactions, by use of functionalized fluorescent magnetic beads, allow significantly accelerated assay times. The polymer-coated microbeads consists of a conglomeration of ferrite particles via strong magnetic forces to fluorescent dye complexes with high fluorescence intensities.
Rissin *et al.* [Rissin 2010] reported an immunoassay format to detect serum proteins at subfemtomolar concentrations. An array of 50 fL-sized wells is able to isolate and detect single enzyme-labeled microbeads. This commercialized “single-molecule array” readily lends itself to a future adaptation for a series of low-concentrated meaurands.
A reasonable estimation of the technology trends for high-sensitive immunoassays is given by Gordon and Michel [Gordon 2012]. Pros and cons for LFAs, optical and electrochemical biosensors, field-effect transistors, and giant magnetoresistive techniques are portrayed as next-generation POCT methods.

The use of **aptamers** as alternative biorecognition elements is already well established. The hybridization of specific aptamers with a DNA-invertase conjugate is another prospective development. The aptamers, bound to magnetic beads, release the invertase when the specific analyte binds to the aptamer. The liberated invertase in solution then catalyzes the hydrolysis of sucrose into glucose, which is easily quantified by a glucometer [Xiang 2011, Song 2014]. Although specificity is ensured for this assay format, the complexity of this kind of reaction limits its usability in the POCT format.

As discussed previously the **establishment of new and reliable parameters** is also pivotal for the future perspectives of POCT in diagnostics. There is a high clinical need for better and rapid available markers for acute kidney injury, multiplex pathogen detection in sepsis, imminent aneurysm rupture of the thoracic or abdominal aorta, for preeclampsia, and acute stroke [Pullagurla 2015]. All of these acute diseases need an early diagnostic approach by using new, clinically proved parameters. The adaptation to POCT will be a minor challenge.
Rapid identifications of pathogens, responsible for a series of epidemic infectious diseases in resource-limited areas, is being demanded by many physicians. When diagnosed, an adequate antibiotic treatment can lower morbidity and mortality, and prevent further spreading of the pathogen.
Also, in sports medicine, there is a demand for new parameters, which allow an early indication of skeletal muscle injuries. The optimization of training in high-performance athletes and the discrimination between acute traumatic and chronic degenerative muscle injuries will be a rewarding object of interest for new muscle-related metabolic markers, which should be developed initially as POCT.
Oncology markers, such as free circulating tumor DNA, protein or microRNA tumor markers in serum, or even circulating tumor cells (CTC) are often described in the scientific literature as new possible fields for POCT developments. But, these claims

are not scientifically justified as specified below.

1. No immediate therapeutic decision will be made out of an oncologic POCT result. Oncologic treatment has become a multidisciplinary task, where decisions are mainly made in the so-called tumor board. All diagnostic findings (radiology and laboratory) must be thoroughly gathered and assessed prior to action.
2. Oncologic near-patient tests for developing countries also make little sense when the infrastructure for conservative, surgical or radiation therapy does not allow for an adequate treatment.
3. All biochemical, cellular and molecular markers in oncology patients are to be interpreted with caution due to the genetic instability of various tumor entities. It is necessary to prevent the unnecessary anxiety or false reassurance. As already mentioned: A test result alone is useless As laboratory experts are needed for the meaningful interpretation of results in terms of consistency, but also in the context of other clinical and radiological findings.

Nevertheless, the detection of novel blood biomarkers (proteins, nucleic acids, cells) from a single drop of capillary blood remains an exciting analytical challenge for molecular technologies [Song 2014].

5.2. Trends in Healthcare

The POCT systems' market in Europe has an annual turnover of more than 3.5 billion Euros, with the home care sector (mostly diabetes care) accounting for a major market share. During the last decade, the market size for POCT grew constantly by more than 10%, which can be partly explained by the new trend towards quantified-self measurements by laypersons. As promoted by pharmacies and pharmaceutical services, an increasing demand for direct-to-consumer (DCT) testing is currently underway in the industrialized nations, where the subject is no longer a patient but a consumer. Moreover, concerns about health have become integral parts of normal life. The "Quantified Self" movement mirrors this new normality. Healthy individuals measure many aspects of their daily life to gain new insights from this data and reach self-defined goals [Swan 2009]. These analyses rely on measurements from activity trackers, smart watches or wrist-bands. However, there is a growing demand to also include biochemical and physiological markers [Pearson 2011]. Due to their ease of use, POCT seems to be pre-designated to fulfill this need. Also the requests for genetic testing are growing exponentially, leading to the development of this uncontrolled, healthcare-parallel market. The testing process chain: patient – doctor – laboratory – doctor – patient is shortened to patient –laboratory – patient [Orth 2015]. This conceals many dangers for the patient, such as poor control of appropriateness and preanalytical requirements, as well as test panels, which are based on unsupported scientific data [Lippi 2011]. Additionally, the interpretation of tests results is complicated [Orth 2015]. In a professional medical setting, anamnesis and clinical examination usually precedes the ordering of clinical chemistry tests. The appropriate selection of the tests ensures their high pretest probability. In unselected individuals with very low disease prevalence, a single test is bound to produce meaningless or even harmful results in spite of good sensitivity and specificity. Therefore, new data mining algorithms try to aggregate multiple self-tracking data streams for a meaningful analysis [Swan 2013]. If they succeed, they might indeed

have a big impact on medicine.

On the other side, it can be expected that informed and autonomous consumers, who want to optimize their physical health and empower fitness, might decrease the rate of metabolic sickness (diabetes, CVD, obesity) in the population. Additionally, all kinds of ambient assisted living will profit from novel DCT developments. In aging populations, it might not be sufficient to provide access to laboratory tests only through physicians. For example, dosage has to be regularly adjusted to kidney function for many drugs. Pharmacists might be able to test for creatinine with a POCT device to check that therapy does not need to be adjusted [Geerts 2013]. Other areas of use are risk assessment, monitoring of health outcomes for patients with chronic diseases, or the detection of common diseases. In this regard, Japan has allowed its pharmacies to offer HbA1c-testing [Abel 2015]. Similarly, a pilot program in the US offered onsite HIV testing [Weidle 2014].

Resource-limited countries will increase the use of cost-effective POCT. Therefore, the efforts to develop inexpensive POCT method and device solutions should be strengthened. These methods include low-cost paper or textile-based chips (μ -PAD). Apart from all described clinical applications, POCT platforms for the rapid diagnosis of acute and chronic microbial infections (as described in 3.3.6) are critically important for high burden countries. HIV, *Mycobacterium tuberculosis*, Ebola, Lassa and Dengue viruses are only a few examples for pathogens, for which near-patient testing, including drug resistance evaluation, is highly desired [Abel 2015].

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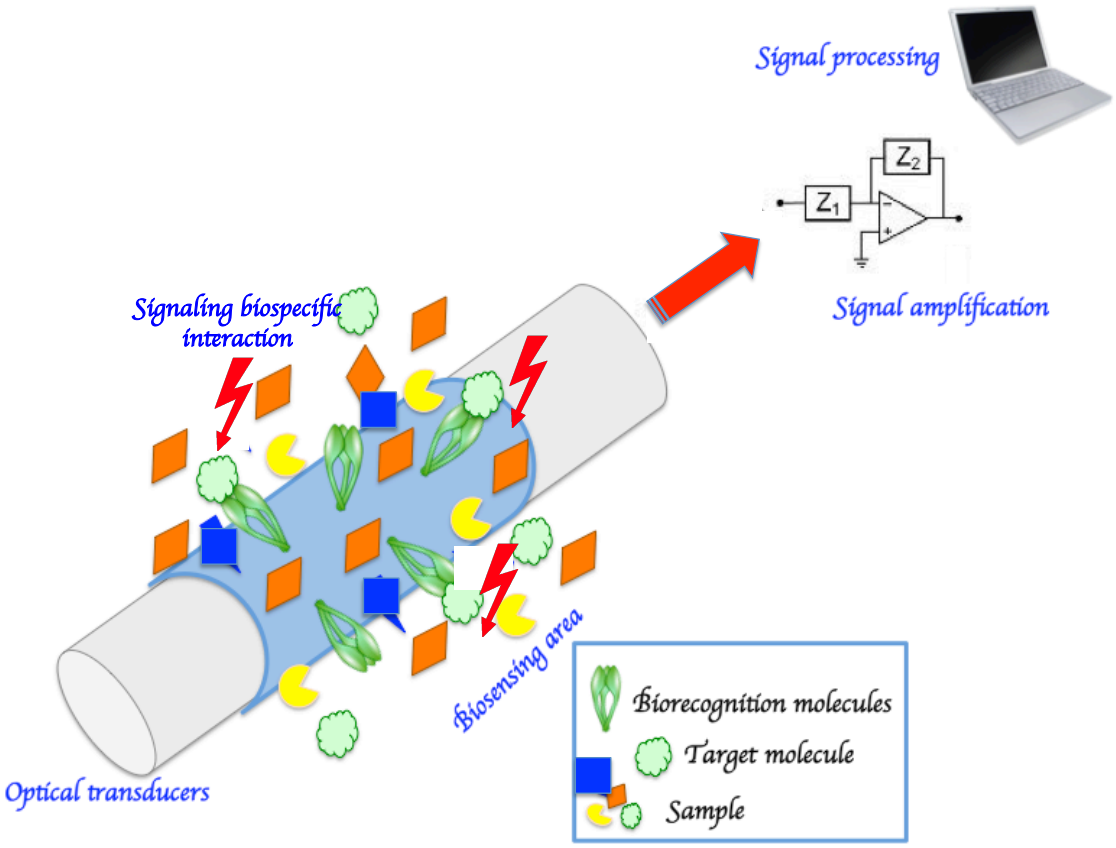

Fig. 1. Schematized principle of the biosensor technology.

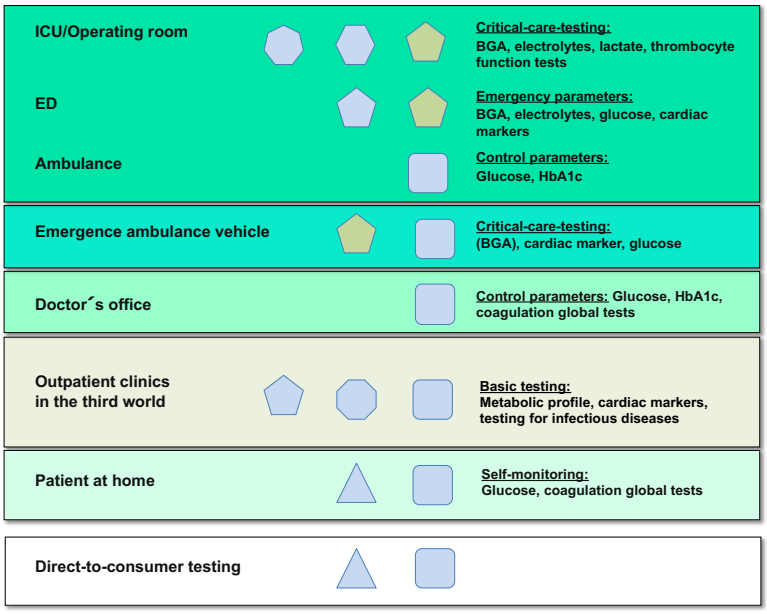

Fig. 2. Overview of the different operation sites for the application of POCT.

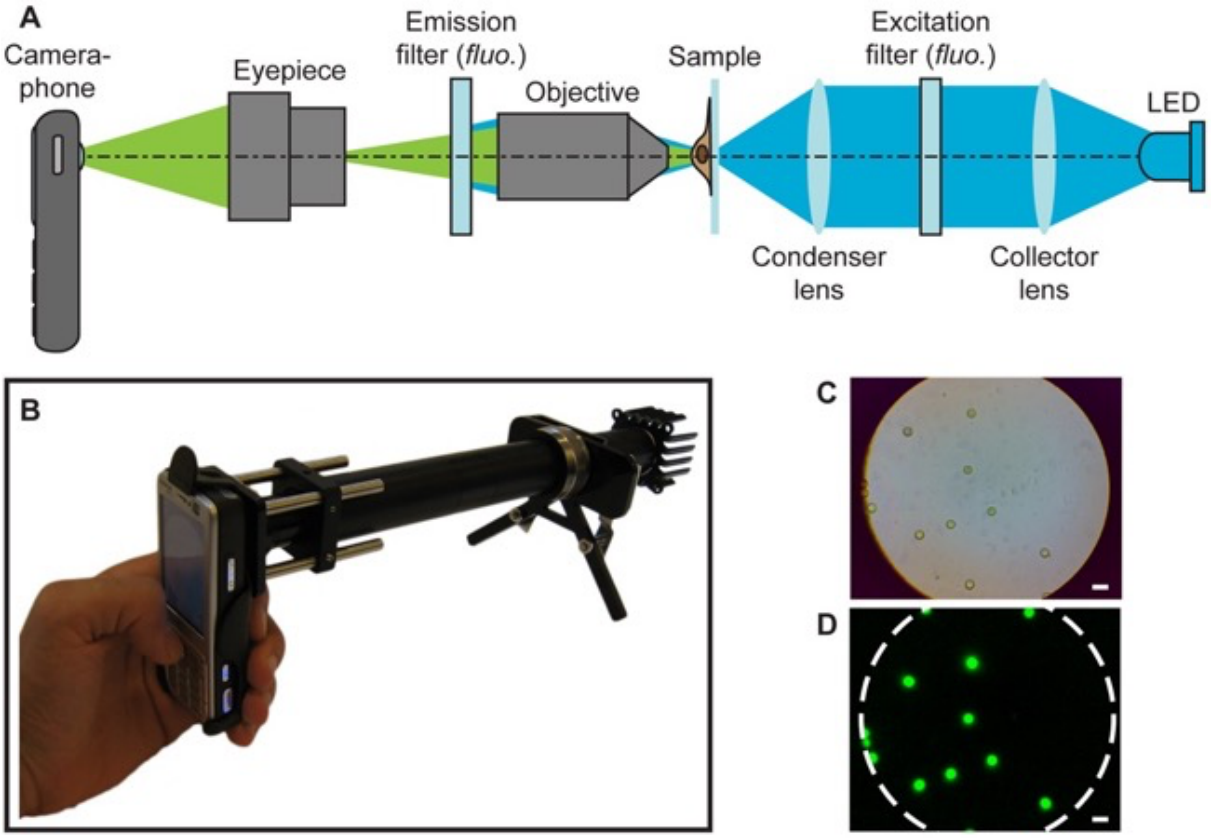

Fig. 3. Mobile phone microscopy according to Breslauer et al. (Breslauer et al., 2009) (doi:http://dx.doi.org/10.1371/journal.pone.0006320.g001). a) Mobile phone microscopy optical layout fluorescence imaging. b) A current prototype, with filters and LED installed. d) Fluorescent images of beads shown in c).

Table 1: Clinical relevant or evolving parameters to be analyzed by use of POCT devices

Metabolic parameters		Inflammation markers and infectious agents		Organ-specific injury markers		Hematological parameters	Humoral and cellular coagulation markers	Drugs-of-abuse detection	Miscell-aneous
Small metabolites	Enzymes	Humoral inflammation markers	Serological markers	Heart	Kidney Urogenital tract				
Glucose	ALAT/ASAT	CRP	HIV	cTNT/cTnI	Urine stick (pH, protein, glucose, ketones, bilirubin, urobilinogen, nitrite, leukocytes, erythrocytes)	Total Hb	Prothrombin time (PT, INR),	Li	hCG (pregnancy testing)
HbA1c	GGT	SAA	Infectious mononucleosis	(NT-pro)-BNP	Microalbuminuria	CO-oximetry	Activated partial thromboplastin time (aPTT)	Alcohol	LH and FSH (fertility check)
Creatinine/Urea Uric acid	CHE	YKL-40	Chlamydia trachomatis, Trichomonas vaginalis,	Myoglobin	Cystatin C	Differential cell count: Erythrocytes, granulocytes, lymphocytes, monocytes, thrombocytes	Activated clotting-time (ACT)	Amphetamines	Sperm count (fertility check)
Biliriubin	CK	Il-6	*Plasmodium falciparum* and *vivax*	CK-MB mass	TIMP-2	CD4+	D-Dimer	Barbiturates, benzodiazepines	Cortisol
Chol/TG LDL/HDL	Alkaline phosphatase	IL-8	*Influenza A* and *B*	Copeptin	IGFBP7	CTC (?)	Viscoelastic and measurements of thrombocyte function	Cannabinoids	
Electrolytes (Na, K, Cl, Ca, Mg)	Alpha-Amylase	PCT	*Steptococcus A* and *B*	sCD40 ligand	NGAL	Parasite detection (e.g., malaria)	Aggregometric measurements of thrombocyte function	Cocaine	
Lactate			*Clostridium difficile*	Ischemia-modified albumin	KIM-1		In-vitro bleeding time	Methadone	
Ammonia			Allergen-specific IgE	Pregnancy-associ-ated plasma protein A (PAPP-A)	L-FABP			Opiates	
BGA: pH, pO2, pCO2, HCO3-, BE			Antibodies against mutated citrullinated vimentin (anti-MCV)	Placental growth factor (PlGF)	FGF-23				

Table 2: Categorization of POCT devices according to the underlying technological principles

TYPE	Name	Description	Principles	Examples for applications
1	Qualitative strip-based methods	These qualitative tests discriminate between plus/minus results and are mostly strip-based. The signaling is often performed by simple visualization or by optical detection modes performed by use of a simple readout device.	The detection principles span from chemical indicator reactions to immunological reactions, such as immunochromatography (performed as lateral flow assays, LFA). The strips are made of a porous matrix mixed with dried reagents onto a carrier element. The sample is deposited onto the matrix and starts the reaction while penetrating and soaking the stick layer.	Applications are urinary pregnancy testing, detection of blood in stool, urine dipstick analyses, detection of infectious agents in swab material
2	Unit-use analyzers	All these systems use unit-use test strips and whole blood obtained by finger prick making them most convenient for the patient. These test strips are one-use articles.	Simplest form of a quantitative POCT device. Detection modalities: optical or electrochemical or micromechanical (coagulation), with analyses taking place on the respective test strips. The reader is used to read out the strips, where the reaction has already taken place.	Glucometers for both home and the hospital POCT stations. ¶ Vitamin K-antagonist therapy monitoring by use of INR POCT devices. ¶
3	Benchtop analyzers	These instruments are generally more complex than the unit-use machines and use different analytical principles. ¶	1. Spectrophotometric substrate and enzyme activity measurement ¶ 2. Hematological particle counting ¶ 3. Immunoassay ¶	Spectrophotometry/reflectrometry is usually applied for clinical chemistry parameters. The analyzers use different test formats: E.g. centrifugal disks, test strips or cassette analyzers. Haematological multichannel analyzers use conventional techniques, but are tailored for POCT needs. Immunological multichannel devices are also tailored for the special POCT applications. They use antibody-based immunoassay methodologies.
3a	Benchtop blood gas analyzers (BGA) with CO-oximetry	These instruments are highly complex instruments for the measurement of various blood gas parameters inclusive CO-oximetry together with an electrochemical module for the analysis of electrolytes and metabolites	The CO-oximetry is a diode array multiwavelength spectrophotometry and analyzes the typical absorption spectra of the various haemoglobin (Hb) species. Many companies on the market have sophisticated oximetry units on board of their BGAs, having no counterpart in the central laboratory. Due to the fact that Hb species are found only inside the erythrocytes, some systems use a cell lysis step prior to the spectrophotometry step, whereas others eliminate the erythrocyte-caused light scattering by applying matrix-assisted algorithms.	The blood gas analyzers (BGA) use either potentiometric/amperometric or optical sensors for pH, pO2 and pCO2. Additional ion-sensitive electrodes for the measurement of electrolytes (Na+, K+, Caion++, Mg++) and other substrates (glucose, lactate, creatinine) are implemented. The analysis of the various Hb species by use of the CO-oximetry is performed in order to distinguish O2-Hb (oxy-Hb) from other Hb species and to determine the O2-Hb-satura-tion: the percentage of O2-Hb compared to the total amount of Hb, including CO-Hb, O2-Hb, desoxygenated Hb (HHb with Fe2+), and Met-Hb (HHb with Fe3+).
4	Haemostasiological coagulation analyzers	These POCT compatible machines show high complexity. Although they are valid for use in POCT, only qualified personnel, such as trained technical assistants should operate them.	The combined analysis of plasma clotting, thrombocyte function and fibrinolysis is termed viscoelastic coagulation tests.	Systems for the determination of global humoral coagulation parameter, such as aPTT or PT/INR. Systems for the determination of thrombocyte function parameters: thrombelastometry, in vitro bleeding time, optical aggregometry.
5	Continuous (glucose) monitoring	The most common example here is continuous glucose monitoring. Such analyzing and application systems are already available commercially. They are likely to replace the invasive, intravenous electrode by the minimally invasive location of a microdialysis catheter in subcutaneous tissue.	The systems using microdialysis are measuring low-molecular analytes by use of the same methodology as used for single measurements. Other non-invasive methods, such as microporation or optical techniques in direct transcutaneous measurement of metabolic parameters, are at least unlikely to prevail.	There are many systems available for continuous glucose monitoring. Other metabolites such as lactate or glycerol or blood gas monitoring systems are still in their infancy.
6	Molecular biology-based devices for the detection of infectious agents	Molecular biology-based POCT devices for the detection of infectious agents	1. Qualitative test strips to detect infectious pathogens. The basic principle in most systems is immunochromatography (LFA). ¶ 2. There are devices using molecular biological methods (mostly the polymerase chain reaction, (qRT)-PCR), but also isothermal amplification techniques for POCT applications.	Infectious agents are bacteria, bacterial toxins and viruses. LFA measure specific microbial antigen (or more rarely, antibodies against bacterial/viral antigens) in the patient sample (urine, swab, whole blood), whereas with molecular diagnostics either specific DNA or RNA sequences are to be detected. ¶

Table 3: (Non-comprehensive) examples for POCT devices to be used in clinical settings. IMPORTANT NOTE: Due to the enormous numbers of different systems and manufacturers, it is impossible to list POCT devices for whole blood glucose (WBG), other qualitative strip-based POCT methods (e.g. pregnancy testing) and lateral flow assays for the detection of infectious agents.

CT parameters	**Devices for applications**	**Company**
A1c	**Afinion POC HbA1c Analyzer**	Alere (Waltham, MA, USA)
	D-100	Bio-Rad (Hercules, CA, USA)
	InnovaStar	DiaSys (Holzheim, Germany)
	Quo-Lab	EKF Diagnostics (Barleben, Germany)
	cobas b 101	Roche Diagnostics (Mannheim, Germany)
	DCA Vantage	Siemens Healthcare Diagnostics (Eschborn, Germany)
nical chemistry rameters	**Piccolo express**	Abaxis (Union City, CA, USA)
	Triage Meter Pro, Afinion AS100, Cholestech LDX	Alere
	Spotchem EZ SP-4430, BA PA-4140, D-Concept	Arkray (Nakagyo-ku, Kyoto, Japan)
	Smart 700/340, Cube	Eurolyser Diagnostica (Salzburg, Austria)
	c 111	Roche Diagnostics
	Dri-Chem NX500	Fujifilm (Minato, Japan)
	Labgeo PT10	Samsung (Daegu, South Korea)
ine stick and sediment	**Urisys 1100**	Roche Diagnostics
	Clinitek Status+	Siemens Healthcare Diagnostics
	URiSCAN Optima II	YD Diagnostics (Kyunggi-Do, South Korea)
matological parameters	**QBC STAR Dry Hematology Analyzer**	Drucker Diagnostics (Port Matilda, PA, USA)
	HemoSpeed	EKF Diagnostics
	Hemocue WBC system	Hemocue America (Brea, CA, USA)
	Micros CRP, 60	Horiba Medical (Irvine, CA, USA)
	Labgeo HC10	Samsung
	PocH-100i	Sysmex (Kobe, Japan)
munoassay analytes	**iSTAT**	Abbott (Abbott Park, IL, USA)
	Triage, **Heart Check System**	Alere
	m16	Edan (Nanshan Shenzhen, China)
	Pathfast	LSI Medience Corporation (formerly Mitsubishi Chemical) (Tokyo, Japan)
	FREND system	NanoEnTek (Guro-gu, South Korea)
	Minicare I-20	Philips (Amsterdam, The Netherlands)
	AQT90	Radiometer (Copenhagen, Denmark)
	ReLIA mini	ReLIA Diagnostics (San Francisco, CA, USA)
	RAMP Reader	Response Biomedical (Vancouver, BC, Canada)
	Labgeo IB10	Samsung
	MICT	MagnaBioScience (San Diego, CA, USA)
	Evidence MULTISTAT	Randox Laboratories (Crumlin, UK)
	Stratus CS 200	Siemens Healthcare Diagnostics
	Getein 1100	Getein Biotech (Nanjing, China)
	Astute140 (NephroCheck)	Astute Medical (San Diego, CA, USA)
	Meritas POC Analyzer	Trinity Biotech (Bray, Co Wicklow, Ireland)
ood gas analysis (BGA)	**AVOXimeter 4000**	Accriva Diagnostics (representing ITC and Accumetrics, San Diego, CA, USA)
	Epoc	Alere
	i15	Edan (Nanshan Shenzhen, China)
	GEM Premier 3500, 4000	Instrumentation Laboratory (Bedford, MA, USA)
	Irma TRUpoint	ITC Medical (San Francisco, CA, USA)
	EasyBloodGas, EasyStat	Medica Corp. (Bedford, MA, USA)
	Stat Profile Critical Care Xpress, Stat Profile Prime	Nova Biomedical (Waltham, MA, USA)
	OPTI CCA-TS2, OPTI R	OPTI Medical Systems (Roswell, GA, USA)
	ABL5, ABL800 FLEX, ABL80 FLEX, ABL90 FLEX	Radiometer
	cobas b 123, cobas b 221	Roche Diagnostics
	Rapidlab 800, 248/348EX, 1200, Rapidpoint 400/405	Siemens Healthcare Diagnostics
agulation testing	***Humoral coagulation parameters:***	
	Hemochron Jr. Signature+, Elite	Accriva Diagnostics
	INRatio2	Alere
	Cascade POC, Abrazo	Helena (Beaumont, TX, USA)
	CoaguChek CS Pro, Plus	Roche Diagnostics
	Xprecia Stride	Siemens Healthcare Diagnostics