



National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Lab-on-a-chip devices for clinical diagnostics

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Measuring into a new dimension



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Colophon

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Abstract

Lab-on-a-chip devices for clinical diagnostics

Measuring into a new dimension

A lab-on-a-chip (LOC) is an automated miniaturized laboratory system used for different clinical applications inside and outside the hospital. Examples of applications include measurements of blood gases, blood glucose, and cholesterol or counting the number of HIV cells. The RIVM has described the current state of the art with respect to LOCs for clinical applications, including an overview of products currently on the market or expected to enter the market soon. Research has shown that LOC-based applications are developing rapidly and that their number will increase in the near future. This investigation was performed at the request of the Dutch Health Care Inspectorate.

It is foreseen that the use of LOC will have several advantages compared to the current test methods. Most important ones concern fast diagnostics at the location where diagnosis is needed (*point of care*) and small amounts of samples and materials required to perform tests. However, attention for quality management aspects regarding calibration and maintenance of the device, and training and education of the user is necessary. This way, the benefits of LOC applications will not compromise quality of health care and patient safety.

The use of LOC applications will contribute to the current trend of more self-reliance in health care, because general practitioners can perform tests immediately or even the patients themselves can do the test. Furthermore, LOC technology will contribute to the development of treatments specified to the patient's needs (*personalized medicine*). The use of LOC applications by health care professionals will increase if they are involved in the design and development of new devices that meet their needs.

This report presents also the technology used in LOC applications, microfluidics. This technology provides the possibility to manipulate and handle fluids on microscale.

Keywords: lab-on-a-chip, microfluidics, diffusion, point of care, quality management

Rapport in het kort

Lab-on-a-chip apparatuur voor klinische diagnostiek

Meten in een nieuwe dimensie

Een *lab-on-a-chip* (LOC) is een miniatuur laboratoriumsysteem dat binnen en buiten het ziekenhuis voor verschillende medische doeleinden wordt gebruikt. Voorbeelden zijn het bepalen van bloedwaarden, het bloedglucose- en cholesterolgehalte of het aantal HIV-cellen. Het RIVM heeft de *state of the art* van dergelijke LOC's beschreven, inclusief een overzicht van producten die op de markt zijn of binnenkort verwacht worden. Hieruit blijkt dat deze producten sterk in ontwikkeling zijn en het aanbod in de nabije toekomst verder zal toenemen. Het onderzoek is uitgevoerd in opdracht van de Inspectie voor de Gezondheidszorg (IGZ).

Naar verwachting levert het gebruik van LOC's voordelen op ten opzichte van de huidige testwijze in klinisch diagnostische laboratoria. De belangrijkste zijn dat ze het mogelijk maken om op locaties waar dit direct gewenst is snel een diagnose te stellen (*point-of-care*), en dat er minder monsters en materialen nodig zijn om de tests uit te voeren. Wel is aandacht nodig voor kwaliteitsmanagementaspecten, zoals meetafwijkingen corrigeren (kalibratie), onderhoud van de apparatuur en scholing van de gebruiker. Op die manier gaan de voordelen van LOC's niet ten koste van de kwaliteit van de zorg en de patiëntveiligheid.

Het gebruik van LOC's draagt bij aan de huidige trend van meer zelfredzaamheid in de gezondheidszorg, doordat huisartsen zelf tests kunnen uitvoeren of mensen dat thuis kunnen doen. Daarnaast draagt het bij aan de ontwikkeling van behandelingsvormen die meer op de individuele patiënt zijn geënt (*personalized medicine*). De kans dat zorgprofessionals LOC's gaan gebruiken neemt toe als zij de ontwikkelaars van LOC's kunnen laten weten hoe ze nog beter aansluiten bij hun behoeften.

Dit onderzoek beschrijft ook de technologie die gebruikt wordt bij de LOC's, microfluidica. Deze technologie maakt het mogelijk om vloeistoffen op microschaal te gebruiken en manipuleren.

Trefwoorden: *lab-on-a-chip*, microfluidica, diffusie, *point-of-care*, kwaliteitsmanagement

Contents

Summary–9

1 Introduction– 11

1.1 Background–11

1.2 Aim–11

2 Methodology–13

2.1 Literature search–13

2.2 Manufacturers and products–13

2.3 Interviews–13

3 State of the art of microfluidic-based LOC devices – 15

3.1 General–15

3.2 Current LOC applications–15

3.3 Device substrate materials–15

3.4 Microfluidic unit operations–16

3.5 Microfluidic platforms–18

3.6 Diagnostic targets–20

3.7 Detection principles–22

3.8 LOC technologies–23

4 Future perspective–27

4.1 Design aspects–27

4.2 Technology trends–28

4.3 Impact on health care–31

Acknowledgements–35

References–37

Annex I: Overview of companies and LOC devices–43

Summary

A lab-on-a-chip (LOC) is a device of several square millimetres to centimetres that comprises several analytical steps. Making use of microfluidics — the technology to control and handle small volumes of liquids — analytical processes are miniaturized to enhance mobility and efficiency. This makes LOC applications suitable for clinical diagnostics and 'near-patient' or 'point-of-care' (POC) testing. In many ways, the features of LOC devices fulfil the requirements for a POC diagnostic device: low consumption of reagents and sample, miniaturization of device and fast turn-around time for analysis.

This report describes the state of the art with respect to LOC devices and applications for clinical diagnostics. It also discusses the impact of the introduction of LOC devices on health care and its diffusion outside the central laboratory, with emphasis placed on quality management for the use of these devices.

By performing a literature review combined with key opinion-leader interviews we identified many LOC devices and microfluidic techniques. For the manufacture of LOC devices, various materials can be used. The most common device substrates are silicon, glass, polymers such as polydimethylsiloxane, and paper. Each dedicated microfluidic platform also contains sets of microfluidic elements, performing basic fluidic unit operations. These basic operations have to be able to transport fluids, storage of reagents and preparation of the sample. Microfluidic unit operations can be combined in different microfluidic platforms, such as lateral flow tests, linear actuated devices and surface acoustic waves. LOC can be used for the detection of proteins, nucleic acids, cells, pathogens, metabolites and other small molecules. The technologies implemented to measure the parameters can vary between chemical analysis, immunoassay-based tests or flow cytometry.

For the further development of LOCs, the miniaturization and integration of diagnostic tests are important aspects to consider. Improving robustness and reliability without compromising sensitivity is a focus point in their development, as is creating new and reliable interfaces. Measuring multiple parameters in one test is an important trend, as is designing cell-on-chip or even organ-on-chip platforms that mimic the physiological aspects of diseases. In addition, the use of nanotechnology can make devices smaller and more sensitive when measuring analytes. Furthermore, LOC devices have a potential to leverage next-generation companion diagnostics for personalized (stratified) medicine.

Diffusion of LOC devices outside the central laboratory of a hospital may decrease costs and reduce the turnaround time of analysis. The quality of the analyses, however, needs to be reliable, which poses challenges for future applications.

1 Introduction

1.1 Background

A lab-on-a-chip (LOC) is a device that integrates several analytical functions on a single chip only a few square millimetres up to centimetres in size. LOC devices can perform the same functions as their full-scale counterparts. Processes, normally carried out in a laboratory, are miniaturized on a single chip in order to enhance efficiency and mobility as well as reduce sample and reagent volumes (Chin *et al.*, 2012).

The concept of LOC is based on microfluidics. Microfluidics is the technology of manipulating and controlling fluids and particles at micron and submicron dimensions and the technology associated with the development of methods and devices to undertake such operations (Whitesides, 2006). Using building blocks to form microfluidic platforms enables the implementation of assay miniaturization. Such platforms, characterized by fluidic channels and chambers, will enable the miniaturization, integration, automation and parallelization, as in performing multiple tests at the same time, of (bio)chemical processes (Streets & Huang, 2013). Microfluidic-based LOC devices are particularly useful for applications in drug discovery, life sciences, ecology and clinical (in vitro) diagnostics (Mark *et al.*, 2010). However, some platforms used for gene expression and sequencing, such as microarray, do not comply with this definition of a generic microfluidic platform. These systems will not be discussed in this report.

The largest LOC market segment, which is clinical diagnostics, can be divided between point-of-care (POC) testing (i.e., a diagnostic test performed near the patients without needing a clinical laboratory) and central laboratory-based testing (i.e., diagnostic laboratory in a hospital). Clinical diagnostics ranges from relatively simple immunochromatographic strips, similar to pregnancy tests, to highly complex systems requiring external machinery and expert training for their handling. Clinical diagnostic applications also include detecting nucleotides and peptides that are considered early indicators of disease.

In many ways, the features of LOC devices fulfil the requirements for a POC diagnostic device: low consumption of reagents and sample, miniaturization of device and fast turn-around time for analysis. It is a versatile technology that enables the miniaturization of complex fluid handling and integrated detection.

1.2 Aim

The first aim of the study is to describe the state of the art with respect to LOC devices used for clinical diagnostic applications. Furthermore, an overview of products on the market will be given. Products that are currently being developed and are expected to enter the market within three to five years, will be indicated. The second aim is to discuss the impact of the introduction of LOC devices on health care and its diffusion outside the central laboratory, with emphasis placed on quality management for the use of these devices. This report is not intended to provide a comprehensive overview of LOC devices. By reviewing different LOC systems, the various technological possibilities of LOC are illustrated.

2 Methodology

2.1 Literature search

Potentially relevant scientific literature (e.g., review articles) published up to 1 July 2013 was identified using PubMed (US Library of Medicine) with the following search terms: 'lab on a chip', 'microfluidics', 'point of care', 'near patient', 'central laboratory', 'diagnostic', 'diagnosis'. Synonyms and truncated search terms, such as 'diagnostic*' and 'microfluidic*', were used to broaden the search for additional literature.

The citations were screened for inclusion using titles and abstracts in English. Full text articles were obtained and the bibliographies of these journal articles were reviewed to identify additional relevant publications. In addition, an Internet search with similar search terms was used to find supplementary information.

2.2 Manufacturers and products

Manufacturers and products were identified using Internet searches, the Technology Networks' website, which provided information for the life sciences community (www.technologynetworks.com), journal articles and the exhibition event at the Dutch MicroNanoConference 2012 (10-11 December 2012, Ede, The Netherlands).

2.3 Interviews

RIVM's professional network was used to select key opinion leaders in the field of LOC devices in the Netherlands. An important resource was NanoNextNL. NanoNextNL is a consortium of more than one hundred companies, universities, knowledge institutes and university medical centres which is aimed at research into micro and nanotechnology. Projects within NanoNextNL are clustered according to ten different themes. Within the theme 'Nanomedicine', two programme directors who lead the relevant programmes 'Nanofluidics for lab-on-a-chip' and 'Integrated microsystems for biosensing' were identified and interviewed. In addition, professionals from universities, hospitals and companies were also interviewed. Another resource was the Dutch National Platform Nanomedicine. This platform aims to bring stakeholders together to exchange knowledge and vision on scientific, social and policy developments. Suggestions of opinion leaders to interview professionals not yet identified were taken into account. A total of seven key opinion leaders were interviewed. Interviews were recorded and transcribed.

3 State of the art of microfluidic-based LOC devices

3.1 General

Within the field of LOCs, a milestone was set in 1979, when a miniaturized gas chromatograph was realized on a silicon wafer (Terry *et al.*, 1979). The first high-pressure liquid chromatography column microfluidic device was published by Manz in 1990 (Manz *et al.*, 1990). By the end of the 1980s and the beginning of the 1990s, several microfluidic structures, such as microvalves and micropumps, had been realized by silicon micromachining, thus providing the basis for the automation of complex liquid handling protocols by microfluidic integration. This marked the advent of the emerging field of LOC devices, which were referred to as micro total analysis system (μ TAS) (Harrison *et al.*, 1992). At the same time, much simpler, yet very successful microfluidic analysis systems based on wettable fleeces, such as a piece of fabric or paper, emerged. First came very simple dipsticks for things such as pH measurement based on a single fleece that paved way for more complex test strips known as lateral-flow tests in the late 1980s. These products are still on the market and include test strips for cardiac markers, pregnancy and drug abuse. Among the devices that completely automated a biochemical analysis by microfluidic integration in one miniature piece of hardware, the test strips became the first devices that obtained a remarkable market share and still remain one of the few microfluidic systems which are sold in high numbers (Mark *et al.*, 2010).

3.2 Current LOC applications

An inventory has been compiled of the current LOC applications. The complete overview is presented in Annex I. It comprises 75 companies with 154 devices on the market and 33 devices under development. Many of these applications concern devices for blood glucose and electrolytes analysis, HIV diagnostics and determination of cardiac markers. The leading companies in the LOC diagnostics market are Abbott, Alere, Arkray, Bayer, LifeScan, Menarini Diagnostics, Roche and Siemens.

3.3 Device substrate materials

The main issues in the manufacturing techniques for microfluidic devices usually lie in the area of forming microfluidic channels, which are micro/nanostructures. Various materials are used for the manufacture of microfluidic channels.

3.3.1 Silicon

Historically, microfluidic channels were patterned directly into silicon (Manz *et al.*, 1990). In general, the advantages of using silicon as a structural material include its good mechanical properties, excellent chemical resistance, well-characterized processing techniques and the capability of integrating control/sensing circuitry.

3.3.2 Glass

Glass substrate is also used due to its excellent optical transparency and ease of electro-osmotic flow. One of the most successful examples of using glass as a substrate material in LOC applications is the capillary electrophoresis chip, which is manufactured using glass etching and fusion bonding techniques. The optical

transparency is required for most LOC devices that use optical detection (Harrison *et al.*, 1992).

3.3.3 *Polymers*

Nowadays, polymers or plastics have become popular materials due to their low cost, ease of manufacture, and favourable biochemical reliability and compatibility. Polymers are promising materials in LOC applications because they can be used for mass production using casting, hot embossing¹, injection-moulding² and soft lithography techniques. This mass-production capability allows the commercialization of disposable LOCs. The workhorse material has been polydimethylsiloxane (Klapperich, 2009). Polydimethylsiloxane is an inexpensive, clear elastomeric polymer with rubbery mechanical properties at room temperature. Polydimethylsiloxane is mixed in small batches, poured onto moulds with micro-scale features and cured at moderate temperatures for minutes to hours. Cast microfluidics can be cut into shapes easily. Open polydimethylsiloxane channels are closed by adhering the channel-bearing component to a glass slide or a second, flat piece of polydimethylsiloxane. Inlets and outlets can be formed easily by using punch tools. Another way of using polydimethylsiloxane for creating channels and moulds is by soft lithography. The soft lithography method is used to transfer a thin, molecular pattern onto a surface (Duffy *et al.*, 1999; Effenhauser *et al.*, 1997). This can be done by microstamping, stencil patterning, and microfluidic patterning. Furthermore, 3D structures can be created using multilayer lithography, whereby layers of material are sequentially added and patterned to build microfluidic systems containing valves and pumps entirely out of polymeric material (Naito *et al.*, 2012; Unger *et al.*, 2000). Other thermoplastics and new polymeric materials, including derivatives of polyacrylate, polystyrene, polyethylene and cyclo olefin (co)polymers, can be utilized for microfluidic-based LOC devices (Kuo & Chiu, 2011).

3.3.4 *Paper*

Recently, the manufacturing of paper-based LOCs has been introduced, allowing an even cheaper and more simplified method for manufacturing LOC devices (Martinez *et al.*, 2007; Martinez *et al.*, 2010). Paper-based LOC devices, commonly referred to as microfluidic paper-based analytical devices (μ PADs), often have the ability to analyse a single liquid sample for multiple analytes. They are more functional than traditional dipstick type paper tests. This functionality is achieved by creating pathways or channels for flow within paper sheets, allowing the formation of distinct regions that can be functionalized with chemical indicators.

3.4 **Microfluidic unit operations**

Similar to the platforms in the application-specific integrated circuit industry in microelectronics, which provide elements and processes to make electronic circuitries, a dedicated microfluidic platform comprises a set of microfluidic elements. These elements have to be able to perform the basic fluidic unit operations required within a given application area (Haeberle & Zengerle, 2007). Such basic fluidic unit operations are described in the following paragraphs.

¹ Hot embossing refers to a stamping process whereby microstructural features from a hot mould insert (master) are transferred on to a thermoplastic substrate.

² In injection moulding, the material is injected and fills the cavity at high temperature.

3.4.1 *Pumping and valving*

Microfluidic analytical systems require micropumps and microvalves enabling precise control of sample, buffer, and reagent flow and delivery. Microvalves are sometimes regarded as a part of micropumps. Micropumps and microvalves are necessary for many next-generation LOC devices that integrate features such as sample separation, complex assays that include incubation, mixing, or separation steps and more quantitative outputs. Several mechanisms have been suggested for transporting the fluids in microfluidic systems and they can be categorised in displacement and dynamic pumping. Displacement pumps exert pressure forces on the fluid through one or more moving boundaries. Micropumps can be based on reciprocating or rotary actuations or may have piezoelectric, peristaltic, (thermo)pneumatic, electrostatic and electromagnetic moving units to displace fluids (Noh *et al.*, 2011).

3.4.2 *Mixing*

Sample dilution, resuspension of dried reagents, and reaction of multiple reagents in LOC devices often require rapid and efficient mixing. However, mixing in microfluidic platforms is difficult because flow is laminar and mixing is dominated by diffusion unless special measures are taken. Efficient micro-mixing can be achieved through a number of active and passive mixing mechanisms (Lee *et al.*, 2011a). In active mixing, external driving forces such as acoustic waves, magnetic beads coupled with moving permanent magnets, or actuated air bubbles enhance the mixing of samples. In passive mixing, liquids are driven through microstructures designed to increase the contact area between different streams and to speed up diffusive or induce chaotic mixing.

3.4.3 *Separation*

The beginning of modern microfluidic and LOC devices is closely linked to separations of (bio)chemical substances, in particular using electrophoresis. Separation is important for LOC devices because it increases the target purity by removing interfering agents prior to detection. Separation methods include capillary electrophoresis, dielectrophoresis, isoelectric focusing, liquid (electro)chromatography, size-based filtration, magnetic fields, acoustic waves, optical tweezers, and various combinations of flow, diffusion, and sedimentation-based phenomena (Gubala *et al.*, 2012).

3.4.4 *Reagent storage*

For practical LOC devices, it is necessary to store reagents for extended periods on or in the device. Reagent, e.g. enzymes or antibodies, can be stored in a wet or dry state. The latter is often preferred in those cases where drying does not cause total and unrecoverable loss of activity, because reagents that are successfully dried typically exhibit improved stability relative to those stored wet (Weigl *et al.*, 2008).

On-chip storage of dry reagents is well-developed. Lateral flow assay strips are dry and include reagents, typically at least one type of antibody and often two, and other reagents as well. Glucose sensors include dried glucose oxidase and electron-transfer catalysts. There is not, however, a single best process for freeze-drying, lyophilizing, or otherwise depositing and drying reagents in a form from which they are readily reconstituted. The addition of sugars, e.g. trehalose, is a widely utilized method to improve reagent stability and retention of activity (Weigl *et al.*, 2008).

Large fluid volumes require off-chip storage, but small volumes can be stored within the device with appropriate sealing and release methods. Blister pack technology, well-developed by the pharmaceutical industry, has been reported as a component of LOC systems (Jokerst *et al.*, 2008). Caution must be exercised when implementing liquid storage using polymer films, many of which have significant permeability to water vapour. Polydimethylsiloxane is among the worst in this regard. Some fluorocarbons and cyclic olefin (co)polymers are better, and most polymers can be rendered impermeable by vacuum deposition of a thin film of metal such as aluminium (Gubala *et al.*, 2012).

3.4.5 *Sample preparation*

Sample preparation, a necessary analytical step, is important in achieving adequate sensitivity and specificity in any detection platform. This is especially important in the case of complex matrices, such as blood, saliva, and interstitial fluid. Sample preparation encompasses sample concentration, diffusion, filtration, purification and fractionation of analytes from analytically noisy background matrices. Although large numbers of LOC devices accommodate unprocessed blood samples, the range of assays that can be performed is limited by the lack of well-developed on-chip sample preparation methodologies (Kim *et al.*, 2009).

3.5 **Microfluidic platforms**

A microfluidic platform provides a set of fluidic unit operations which are designed for easy combination within a well-defined manufacturing technology. An overview of several microfluidic platforms that have been developed up to now is given in the following section (reviewed by Mark *et al.*, 2010). Examples of some microfluidic platforms are given (see also Annex I).

3.5.1 *Lateral flow tests*

In lateral flow tests, also known as test strips, the liquids are driven by capillary forces. Liquid movement is controlled by the wettability and feature size of the porous or microstructured substrate. All required chemicals are pre-stored within the strip. Typically, the readout of a test is done optically and is often implemented as colour change of the detection area that can be seen by the naked eye. A common example of this type of test is the pregnancy test strip.

3.5.2 *Linear-actuated devices*

Linear-actuated devices control liquid movement by mechanical displacement of liquid, e.g. by a plunger. Liquid control is mostly limited to a one-dimensional liquid flow in a linear fashion without branches or alternative fluid pathways. Typically, liquid calibrants and reaction buffers are pre-stored in pouches. One example of the linear-actuated device is the i-STAT® analyzer (Abbott Point of Care Inc, USA). With this portable hand-held analyser, several blood parameters, such as electrolytes and coagulation, can be measured using different disposable cartridges. The blood sample is introduced into the cartridge and placed inside the analyser. First, calibrant solution is released to provide a baseline and thereafter the sample is pushed into the measuring chamber, which displaces the calibrant solution. Blood parameters are then determined and results are displayed by the analyser.

3.5.3 *Pressure-driven laminar flow*

A pressure-driven laminar flow platform is characterized by liquid transport mechanisms based on pressure gradients, usually leading to hydrodynamically stable laminar flow profiles in microchannels. There is a broad range of different implementations in terms of using external or internal pressure sources such as syringes, pumps or micropumps, gas expansion principles, pneumatic displacement of membranes, etc. The samples and reagents are processed by injecting them into chip inlets either batch-wise or in a continuous mode.

3.5.4 *Microfluidic large-scale integration*

Microfluidic large-scale integration describes a microfluidic channel circuitry with chip-integrated microvalves based on flexible membranes between a liquid-guiding layer and a pneumatic control-channel layer. The microvalves are closed or open corresponding to the pneumatic pressure applied to the control-channels. Just by combining several microvalves, more complex units such as micropumps, mixers, multiplexers, etc., can be built up with hundreds of units on a single chip.

3.5.5 *Segmented flow microfluidics*

Segmented flow microfluidics describes the principle of using small liquid plugs and/or droplets immersed in a second immiscible continuous phase (gas or liquid) as stable micro-confinements within closed microfluidic channels. Those micro-confinements are in the picolitre to microlitre volume range. They can be transported by pressure gradients and can be merged, split, sorted and processed without any dispersion in microfluidic channels.

3.5.6 *Centrifugal microfluidics*

All processes in centrifugal microfluidics are controlled by rotating a microstructured substrate. This provides several relevant forces for liquid transport; centrifugal force, capillary force, Coriolis force and Euler force (Figure 3.1). Assays are implemented as a sequence of liquid operations arranged from radially inward positions to radially outward positions. Spinning CD-like fluidic disks transport samples and reagents by the interplay of the abovementioned forces. Fluids can be pumped towards the rim of the disk at a wide range of flow rates through control of the spin speed, channel dimensions and surface energy, and various geometric details, with temporary capillary 'stop valves' opened to fluid passage simply by increasing rotational velocity (Zoval *et al.*, 2010). Microfluidic unit operations include metering, switching, aliquoting, etc., and can be used for processes such as DNA extraction or plasma separation.

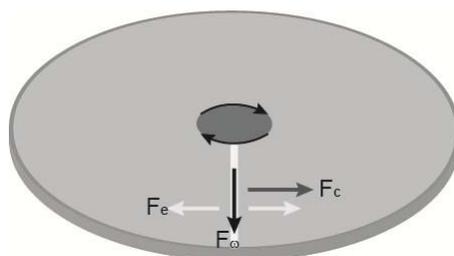


Figure 3.1 Schematic overview of relevant forces for centrifugal microfluidics.

When Newton's laws of motion are transformed to a uniformly rotating frame of reference, the Coriolis (F_c) and centrifugal forces (F_ω) appear. Both forces are

proportional to the mass of the object. The Coriolis force is proportional to the rotation rate and the centrifugal force is proportional to its square. The Coriolis force acts in a direction perpendicular to the rotation axis and to the velocity of the body in the rotating frame and is proportional to the object's speed in the rotating frame. The centrifugal force acts outwards in the radial direction and is proportional to the distance of the body from the axis of the rotating frame. These additional forces are termed inertial forces. They allow the application of Newton's laws to a rotating system. For a non-uniformly rotating reference frame, when there is variation in rotation speed, the Euler force (F_e) appears.

3.5.7 *Electrokinetics*

In electrokinetics platforms microfluidic unit operations are controlled by electric fields acting on electric charges, or electric field gradients acting on electric dipoles. Several electrokinetic effects such as electro-osmosis, electrophoresis, dielectrophoresis and polarization superimpose each other and can be used in the same LOC, dependent on buffers and/or sample. For instance, for the transport of a liquid bulk electro-osmosis can be used, while other effects can be used to separate different molecules or particles from the bulk liquid. An example of this platform is the microfluidic electrophoresis chip used for DNA/RNA analysis on the Bioanalyser developed by Agilent Technologies.

3.5.8 *Electrowetting*

Electrowetting platforms use droplets immersed in a second immiscible continuous phase (gas or liquid) as stable micro-confinements. The droplets reside on a hydrophobic surface that contains a one or two-dimensional array of individually addressable electrodes. The voltage between a droplet and the electrode underneath the droplet defines its wetting behaviour. By changing voltages between neighbouring electrodes, droplets can be generated, transported, split, merged and processed. Figure 3.2 illustrates these principles for a single droplet of water in air and for an oil droplet in water. These unit operations are freely programmable for each individual droplet by the end-user, enabling online control of an assay.

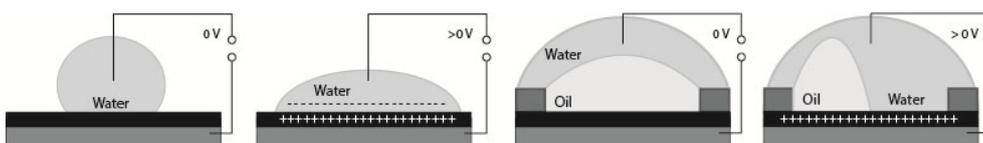


Figure 3.2 Electrowetting principles.

3.5.9 *Surface acoustic waves*

The surface acoustic-waves platform uses droplets residing on a hydrophobic surface in a gaseous environment (air). The microfluidic unit operations are mainly controlled by acoustic shock waves travelling on the surface of the solid support. These shock waves are generated by surrounding sonotrodes, defining the droplet manipulation area.

3.6 **Diagnostic targets**

3.6.1 *Proteins*

Current LOC devices utilize immunoassay technology, including antigen-antibody binding. These assays target disease-specific protein markers, such as glycosylated haemoglobin (HbA1c) for diabetes, C-reactive protein (CRP) for inflammation

indicating cardiovascular disease, D-dimer for thrombosis, and troponin I or T for cardiac damage, prostate-specific antigen for prostate cancer, bacterial and viral infection-related markers such as human immunodeficiency virus (HIV), influenza, chlamydia, and hepatitis (Gubala *et al.*, 2012).

The best-known protein-detection device, the pregnancy test kit, measures the pregnancy hormone human chorionic gonadotropin. The test's key component is the lateral flow strip. Currently, Bio-Alternative Medical Devices Ltd (UK) is developing a next-generation pregnancy test utilizing a technology for reading and quantifying traditional chromatography-based lateral flow immunoassay tests. The design incorporates novel sensors, diagnostics, display, and power management capabilities.

3.6.2 *Metabolites and other small molecules*

Metabolites are products of chemical processes that generate energy, nutrients or wastes. Because of the similarities in their physiological transport and detection approaches for LOC assays, they are grouped together with blood ions (Na^+ , K^+ , Cl^- , etc.) and small-molecule organic substances, including non-protein hormones, e.g. epinephrine and cortisol. Levels of these molecules are often diagnostic indicators of disease (Luppa *et al.*, 2011). The current panel of metabolites most often targeted by POC diagnostics are glucose, cholesterol, triglycerides, creatinine, lactate, ammonia, and urea (Gubala *et al.*, 2012).

The best-known metabolite, glucose, enables the diagnosis and management of diabetes mellitus. Glucose biosensors account for approximately 85% of the entire biosensor market (Wang, 2008). Diabetic complications are controllable with tight regulation of glucose levels. Most diabetic patients now regulate their condition at home using hand-held blood glucose meters that analyse a small capillary blood sample.

A prominent and one of the early LOC devices for blood analysis is the i-STAT® system (Abbott Point of Care Inc, USA), see also paragraph 3.5.2. This hand-held system carries out different analyses (depending on which cartridge is loaded) ranging from ions, carbohydrates (glucose and lactate), blood gases (pO_2 and pCO_2) to peptides (brain natriuretic peptide), proteins (thrombin) and other blood indicators such as haematocrit. Analytes are detected at clinically relevant levels in 65 μl whole blood samples within two minutes (Erickson & Wilding, 1993). The cartridge contains a fluidic system for sample distribution to different thin-film electrodes measuring analytes via conductivity or ion-selective electrode potentiometry, depending on the analyte type.

3.6.3 *Nucleic acids*

Nucleic acid diagnostics, often referred to as molecular diagnostics, measure DNA or various types of RNA in order to assay particular genomic or genetic details of a patient or to assay nucleic acid sequences unique to invading pathogens. Polymerase chain reaction (PCR) and numerous other methods of selectively copying ('amplifying') preselected nucleic acid sequences are often part of such assays (Gubala *et al.*, 2012). These tests are one of the most challenging assays to develop due to additional steps required for sample pre-treatment (e.g. cell sorting, isolation, lysis and nucleic acid extraction), signal amplification, and target contamination and instability (Chin *et al.*, 2007).

3.6.4 *Cells*

The identification and enumeration of specific (human) cells in blood and other samples is a rapidly expanding field in POC diagnostics. In addition to basic blood cell counting, it has been widely recognized that POC cell assay-based devices could implement diagnostic and prognostic testing for infectious

diseases, cancers, inflammatory responses and haematological parameters (Chin *et al.*, 2007; Toner & Irimia, 2005).

3.6.5 *Pathogens*

Bacteria, viruses and parasites are important analytical targets, particularly those that cause infectious diseases (Clerc & Greub, 2010; Foudeh *et al.*, 2012). Rapid identification of the causative pathogen of an infection can reduce treatment costs, reduce suffering, help systems against spreading of disease, and save lives. Because species and strain identification is required, pathogens are often diagnosed using nucleic acid identification. In some cases, immunoassays are utilized for the diagnosis via the specific antibodies that are present in an infected host.

3.7 **Detection principles**

The detection principles for sensors on microfluidic-based LOC devices are classified into several types, including optical, electrochemical, magnetic and mass sensitive methods. The trend in the development of detectors has been to pursue two key qualities: sensitivity and selectivity, aiming to minimize the numbers of false negatives and false positives.

3.7.1 *Optical detection*

Conventional optical detection methods, including absorbance, fluorescence and chemiluminescence, have all been applied in LOC devices. Miniaturizing devices that use optical detection is generally difficult because of the expensive hardware it requires. Furthermore, due to the shorter optical paths through the sample, sensitivity is reduced and increased noise from non-specific adsorption to the walls of the chamber can be caused by a lower surface-to-volume ratio (Myers & Lee, 2008). To address these issues, many integrated optical systems are being explored in which new techniques are integrated onto the microfluidic device to reduce costs and increase sensitivity.

3.7.2 *Electrochemical detection*

Electrochemical detection methods can be divided into three types of measurements, namely amperometric, potentiometric, and impedimetric measurements. The most commonly used biosensors are amperometric ones. Typically, they generate current in proportion to the concentration of the detected analyte, used for instance in glucose assays. Potentiometric detection examines the difference in potential between two reference electrodes separated by a selective permeable membrane. Impedimetric biosensors operate by measuring the change in impedance caused by changes in resistance at the sensor (Mohammed & Desmulliez, 2011). Depending on the target analyte, all three detection methods can be used by the modern version of the i-STAT® system. (Chin *et al.*, 2007).

3.7.3 *Magnetic detection*

Magnetic particles can be used to concentrate and localize analytes. Moreover, they can be used as labelling technology for detection without the requirements of fluorescent dyes. Stimulated by advances in memory devices, magnetic particle detection technology has evolved rapidly, the most promising and sensitive methods now using the giant magnetoresistance (GMR) effect, with detectors based on so-called spin valves or magnetic tunnel junction methods (Gubala *et al.*, 2012).

Philips Research (the Netherlands) reported the development of a compact biosensor platform to detect biomolecules with superparamagnetic particles labels using GMR sensors. The silicon detection chip is packaged in a disposable cartridge that integrates electrical connections for readout and fluidic subsystem. Recently, sensitive detection of amplified DNA on this system was reported using a miniaturized detection platform suitable for POC application (Koets *et al.*, 2009).

3.7.4 *Mass sensitive detection*

Mass sensitive detection entails the recognition of molecules based on their mass. The detector gives a response that is proportional to the mass of the molecules or materials. Mechanical transducers for POC applications oscillate or resonate. These include micro- and nanocantilevers (Waggoner & Craighead, 2007) as well as various acoustic wave devices such as the quartz-crystal microbalance and a range of the surface acoustic wave family (Rocha-Gaso *et al.*, 2009). Operating characteristics such as frequency and signal attenuation for piezoelectric devices are affected by the mass and mechanical properties of molecules and materials linked to their oscillating surfaces.

3.8 **LOC technologies**

3.8.1 *Chemical analysis*

Chemical analysis of samples is mostly done using chromatographic separation techniques, such as high performance liquid chromatography with ultraviolet detection or mass spectrometry detection, or gas chromatography with mass spectrometry detection. As stated in the introduction, one of the first LOC applications to be developed was the μ TAS (Harrison *et al.*, 1992; Manz *et al.*, 1990). Using this system, chemicals were separated for analysis with capillary electrophoresis (Harrison *et al.*, 1992). The sample is electro-osmotically transported and metered inside the chip, then separated via capillary electrophoresis and analysed by fluorescence detection (Mark *et al.*, 2010). Zhang *et al.* (2007) described a method for the detection of morphine and codeine in human urine using electrochemical detection as well. A polydimethylsiloxane microchip with electrochemical detection was developed for rapid separation and detection of trace amounts of these two compounds. It was found that morphine and codeine were well separated within 140 s. Compared with the conventional methods, the presented method had several advantages such as lower instrument cost, less reagent consumption and shorter analysis time (Zhang *et al.*, 2007).

More recently, chemical analysis technology for LOC purposes is being implemented for the detection of, among many others, blood gasses, electrolyte analyses and lactate determination (Lin *et al.*, 2011).

3.8.2 *Immunoassay-based technologies*

Immunoassay-based technologies are mostly used for detection of specific protein biomarkers for disease or infection. These immunoassays comprise the binding of a specific antibody to a unique site on a target biomarker (antigen). The generation of a signal resulting from antigen capture is predominantly realized by some type of label on a secondary reaction antibody. There are many different types of antibody labels and selection is dependent on the specific detection methodology. These include fluorescent labels, enzymes for catalysis of colour changing/redox reactions, paramagnetic particles (inductance/magnetic field based measurement) and metallic colloids as surface

enhanced Raman spectroscopy probes (Mohammed *et al.*, 2011). Commercial antibody-based POC devices have most commonly used traditional lateral flow technology. One basic example, as previously mentioned, is the pregnancy test to detect the hormone human chorionic gonadotropin. A simple colour reaction shows if the protein is present in the urine sample. Immunofiltration is another application of an antibody-based detection method. The sample is filtrated through porous membranes containing immobilized antibodies that can detect the analyte of interest (Gubala *et al.*, 2012). This principle is applied in the NyoCard and Afineon systems from Axis-Shield to identify CRP and HbA1c, among other things.

Currently, steps are being taken to increase the sensitivity of immune-based assays. An approach has been developed that combines the single molecule sensitivity of enzyme-linked immunosorbent assay (ELISA) with microscopic bead encoding techniques to provide highly sensitive, multiplexed detection of proteins (Rissin *et al.*, 2013).

3.8.3 DNA/RNA-based technologies

Miniaturized nucleic acid amplification systems are essential for the development of genetic marker-based POC diagnostics (Park *et al.*, 2011).

PCR is a process for amplifying short regions of interest in DNA using an enzyme-based method. With the use of repeated cycling steps of denaturation, annealing and elongation for DNA replication, millions of copies can be created. Improvements in thermal cycling speed, instrument size, and reaction volume are necessary for POC applications. The bulky instrumentation and large reaction volume required in conventional benchtop thermal cyclers lead to large thermal mass, which reduces the temperature transition speed and reaction efficiency. These shortcomings can be addressed through miniaturization (Park *et al.*, 2011) in a so-called microPCR system. This refers to a microfluidic chip with microlitre or nanolitre volume size chambers for the execution of single or multiple PCRs. These systems can be classified in two major principles, the static chamber PCR and flow-through PCR. In static chamber PCR, the temperature of the chamber containing the sample and PCR reagent is cycled and, in flow-through PCR, the reagent travels through different chambers with various temperatures (Ahmad & Hashsham, 2012).

Before the PCR steps can take place most of the time, nucleic acids need to be extracted and purified from the sample. Many current methods for lysing cells that are used can be divided into four groups. (1) Mechanical lysis employs cellular contact forces to crush or burst the cells. One method for mechanical lysis is to force the cell through a filter with openings too small for a whole cell to pass through, thus shearing the cell membrane. Walls may even include sharp 'microknives', causing cell rupture and release of cell content. Another basic method is simply to burst the cells by deforming the cell to the point that the membrane bursts. One such method uses a polydimethylsiloxane membrane to crush cells and break their membranes. (2) Thermal lysis uses high temperatures to disrupt the cell membrane. (3) Chemical lysis uses a chemical buffer, such as sodium dodecyl sulphate, or enzymes to break down the cell membrane. (4) Electrical lysis induces cell membrane porosity with a low-strength electric field or complete lysis of the cells with a stronger field (Kim *et al.*, 2009). After lysis the nucleic acids can be extracted using different extraction techniques, which can be categorized as different methods; silica-based surface affinity, electrostatic interaction, nanoporous membrane filtration, and functionalized microparticles (Kim *et al.*, 2009; Sista *et al.*, 2008). Integrated microsystems that simultaneously implement cell sorting, cell lysis and DNA purification steps have been developed and used (Chen *et al.*, 2007).

However, with new methods, DNA detection can take place with the raw samples. Recently, Manage *et al.* (2013) described the use of an in-gel PCR cassette with multi-target and multi-sample detection. The cassette contains capillary reaction units and is configured in a format for testing simultaneously up to 16 patients for two or more targets. It accommodates different sample types on the same cassette, has integrated positive and negative controls, and allows flexibility for multiple geometries. PCR reagents in the cassette are desiccated to allow storage at room temperature with rehydration by raw sample at the time of testing. The sample is introduced to the cassette via a transfer pipette simply by capillary force. DNA amplification is done in a portable instrument for PCR thermal cycling with fluorescence detection of amplified products. This platform allows multiparameter clinical testing with a pre-assembled cassette that requires only the introduction of a raw sample (Manage *et al.*, 2013).

Nucleic-acid-based LOC technologies can be used for identification of pathogens (Foudeh *et al.*, 2012), but may also be of use in personalized medicine (van de Stolpe *et al.*, 2011) (section 4.3.2).

3.8.4 Flow cytometry

Flow cytometry has become a very powerful tool for cell-based assays. It is routinely used in diagnostics to quantify (counting), isolate and examine cells (e.g. different subtypes of lymphocytes) according to their size, granularity and expression of specific surface antigens (Lenshof & Laurell, 2010). There are three key components of a typical flow cytometer, the first being a fluidic mechanism that causes all of the cells in a suspension to line-up in a single file as they flow down a channel. The second key component is a set of detectors (such as lasers of different wavelengths) that can probe individual particles, along with the fluid stream, flowing past the detector and obtain information (such as whether a given cell has taken a particular fluorescent dye) that indicates one or more specific properties of the cell. This information, along with the known velocity of the cell travelling down the channel, can then be taken advantage of by the third key component of the flow cytometer to steer target cells to specific downstream collection chambers. Although conventional state-of-the-art flow cytometers can measure and subsequently sort particles based on a combination of as many as ten parameters and/or achieve throughputs as high as ~10,000 cells per second, they do suffer from serious drawbacks. Besides requiring expert operators, they also require large volumes of sheath fluid (~1 l of sheath fluid per 1 ml of sample) and high performance pumping systems to operate, thereby making them non-portable and expensive for routine diagnostic procedures in the clinical setting. In addition, modern fluorescence-activated cell sorters are usually expensive.

To overcome these limitations, much effort has been put into the development of microfluidic flow cytometry. Miniature versions of flow cytometers can replace conventional glass capillary-based systems with microfluidic chips that employ integrated optics and hydrodynamic or electrokinetic-based flow-switching systems for collecting cells of interest. Examples of commercial benchtop flow cytometers are the Agilent 2100 Bioanalyzer® (Agilent Technologies Inc, USA) and the Cyflow® Space (Partec GmbH, Germany). Portable flow cytometers are the CyFlow® miniPOC (Partec GmbH, Germany) and the Alere Pima CD4 Analyser (Alere Inc, USA).

4 Future perspective

4.1 Design aspects

The first and probably most important consideration in developing new POC applications is that there should be a demand for the specific device. Development of POC-systems which are expected to be used infrequently will not have a positive cost-benefit ratio, meaning the system will be expensive compared to similar measurements in the clinical laboratory. The development and production costs of a new test can be very high, as indicated by one of the opinion leaders. There needs to be certainty that the test is actually measuring the marker it is designed for and both its sensitivity and selectivity have to be adequate for the intended use. The costs per test have to be low compared to conventional methods in order for the test to be performed routinely and fit into applicable pricing and reimbursement policies for that region (Gervais *et al.*, 2011).

4.1.1 *Miniaturization & integration*

The miniaturization and integration of diagnostic tests into LOC devices have increased their usefulness for POC applications. The degree of integration of microfluidic technology in POC applications can vary from having a disposable chip used with peripheral equipment (pumps, reader, etc.) to having all functions needed for processing and analysing a sample and reporting the results on a chip. For the development and use of LOC devices, several application-specific requirements should be taken into account. For POC, the main selection criteria are portability, time to result and costs per test (Gervais *et al.*, 2011; Mark *et al.*, 2010). The size and weight of the device need to be minimal, since they affect the portability and energy consumption of the read-out device. A hand-held device with low energy consumption is ideal for near-patient use. The time to results should be between seconds and minutes, as devices are often used at the patient's side and timely results are required. Fully automated LOC devices would be ideal; the device can analyse the sample, calibrate the result, record and transmit encrypted data wirelessly to an electronic health record.

The ability to measure multiple parameters from one sample would be an advantage, as would be the small volume of sample that is needed in such a case. Compared to the conventional benchtop systems that typically use microlitres or millilitres, microfluidic systems only require nanolitre or picolitre volumes to fill the channels. This not only reduces the costs of the reagents involved, it also means that diagnostic tests can still be performed efficiently when only limited amounts of the sample are available, which is ideal for POC applications (Robinson & Dittrich, 2013).

4.1.2 *Interfaces*

A mechanical interface is unavoidable between microfluidics and the read-out device in order to connect channels and tubing for the transport of liquids. Since outcome may be distorted by leakage, dirt or dust, an interface can be a source of technical problems. Overall performance of the instrument may be hampered by the interface (Schumacher *et al.*, 2012) requiring the device to be intrinsically safe. Prevention of sample contamination or misinterpretation of the results is an important aspect to consider in the development of devices. The interface of the device should be designed to be user-friendly, so that use of the

device by personnel with limited training should produce reliable and reproducible results.

The read-out module of a LOC device might be replaced by a high-resolution camera of a consumer product, such as a smart phone. This not only decreases the costs, but also allows for diagnosis in (remote) specialized laboratories (Martinez *et al.*, 2008; Mudanyali *et al.*, 2012; Stedtfeld *et al.*, 2012).

An example of such a device is the Gene-Z for screening genetic markers (Stedtfeld *et al.*, 2012). Using a disposable, valveless polymer microfluidic chip containing four arrays of 15 reaction wells each with dehydrated primers for isothermal amplification, the Gene-Z enables simultaneous analysis of four samples, each for multiple genetic markers in parallel, requiring only a single pipetting step per sample for dispensing. Read-out is done by a smart phone camera. Another example has been developed by Mudanyali *et al.* (2012). This device uses the camera of a smart phone and combines this with various lateral flow immuno-chromatographic assays.

4.2 Technology trends

4.2.1 *Droplet-based and digital microfluidics*

Droplet-based microfluidics deals with the generation, manipulation, and application of droplets with dimensions, in the range of several micrometres to hundreds of micrometres in diameter (femtolitre to nanolitre in volume) in microfluidic devices (Zeng *et al.*, 2011). Compared with conventional systems such as microtiter plates, the sample size can be decreased more than a 1,000-fold, even for complex assays such as PCR (Beer *et al.*, 2008; Schaerli *et al.*, 2009). Further use of droplets is made in digital microfluidics, which constitutes a discrete droplet manipulation technique by electrowetting, see also paragraph 3.5.8 (Pollack *et al.*, 2011). Microfluidic processing is performed on unit-sized packets of fluid which are transported, stored, mixed, reacted, and analysed in a discrete manner using a set of standard basic instructions.

4.2.2 *Multiplexing*

Detecting multiple analytes in a single test is an important trend. Many recent POC developments are in multi-analyte tests or panels, including cancer markers, cardiac death and infectious disease. Testing for infectious agents in a blood sample is a particularly important feature of POC application. It could be a screening test to start treatment of the disease, since laboratory culture-based analysis requires hours to days for organism growth, with the results sometimes arriving too late for a patient with a bloodstream infection that leads to septic shock and death.

Monitoring cancer treatment efficacy or checking for recurrence usually requires tracking multiple biomarkers. The determination of cancer markers in serum and saliva using quantum dot bioconjugate labels has been reported (Jokerst *et al.*, 2009).

Sexually transmitted infectious diseases are a challenge in both low-resource and developed environments. A single LOC device that includes the most common of the sexually transmitted diseases will save time and money, and rapid results can help reduce the spread of these diseases by ensuring patients know their status and treatment can be initiated before patients leave the clinic or hospital (Chin *et al.*, 2007; Manage *et al.*, 2013).

4.2.3 *Cell-on-a-chip*

Microfluidic technology allows the development of devices on which cells can be cultured. Using a microformat, cell behaviour such as differentiation, migration and apoptosis can be studied in real-time. Especially in the field of toxicology testing and drug discovery, cell-based sensor arrays are potentially useful for studying the effects of drugs and cell-external stimuli interactions (El-Said *et al.*, 2009). El-Said *et al.* (2009) have demonstrated a method in which living immobilized HeLa cancer cells are cultured onto a on gold-patterned silicon substrate. The cells, when cultured under the condition that the cells were adhered and incubated for 2 days on the chip, exhibited a quasi-reversible voltammetric response. Using this technique and the anticancer drugs hydroxyurea and cyclophosphamide as models, the ability of the cell-based chip to monitor the effect on the cell viability using the voltammetric methods was tested.

The results demonstrated that the cell-based chip design is useful not only as a substrate for the culture of HeLa cells, but also as an electrode for measuring cellular electrochemical properties and permits the assessment of cell viability (El-Said *et al.*, 2009). More recently and for similar purposes, a microfluidic device consisting of five parallel microchambers with integrated read-out grid for screening the anti-proliferative activity of drugs in vascular smooth muscle cells was presented (Rodriguez-Rodriguez *et al.*, 2012). Again, this type of device demonstrated good performance in the evaluation of the anti-proliferative activity of drugs.

Using cell culture on a microfluidic LOC device makes it possible to mimic the flow of fluid across the cells and study the transport and uptake of compounds, as takes place in the blood brain barrier. In a recently developed LOC, the barrier function is modulated both mechanically, by exposure to fluid shear stress, and biochemically, by stimulation with tumour necrosis factor alpha (TNF- α), in one single device. This realistic microfluidic platform of the blood brain barrier is suited to studying barrier function in detail and evaluating drug passage in order finally to gain greater insight into the treatment of diseases related to the blood brain barrier (Griep *et al.*, 2013).

Using cells on a chip enables researchers to study cell function in detail and come up with devices that mimic complete organ systems, as will be discussed in the next section.

4.2.4 *Organ-on-a-chip*

An organ-on-a-chip can replicate the physiologic aspects of diseases. It combines an artificially engineered, physiologically realistic cell culture microenvironment with the potential for parallelization and increased throughput (van der Meer & van den Berg, 2012).

Researchers at Harvard University have shown that a lung-on-a-chip can mimic a life-threatening lung condition (Huh *et al.*, 2012). The lung-on-a-chip device is a clear, flexible thumb-sized block of polymer perforated by two channels separated by a thin membrane. Air flows through one channel, which is lined with human lung cells. A nutrient-rich liquid that acts as a blood substitute flows through the other channel, which is lined with blood vessel cells. A vacuum applied to the chip moves the channels to recreate the way human lung tissue physically expands and contracts when breathing. This on-chip disease model revealed that mechanical forces associated with physiological breathing motion play a crucial role in the development of increased vascular leakage that leads to pulmonary oedema, and that circulating immune cells are not required for the development of this disease.

Recently, the institute also developed a human gut-on-a-chip (Kim *et al.*, 2012). The central channel of the device, which is lined with human cells, can be subjected to wavelike movements that mimic the movement of the intestines during digestion. In the chip, the cells form finger-like structures known as villi that are important for absorption of nutrients and other compounds. These structures do not form well when cells are cultured in a dish. In addition, common intestinal bacteria (e.g., *Lactobacillus rhamnosus*) can be successfully co-cultured for extended periods (>1 week) on the luminal surface of the cultured epithelium without compromising epithelial cell viability.

These organ-like chips enable researchers to study human cells in a more 'realistic' environment and to test how they respond to drugs and toxins. The devices could improve the speed and success of drug discovery, reduce animal testing and contribute to the development of novel disease models.

By connecting the microfluidic versions of the heart (Agarwal *et al.*, 2013), intestine (Kim *et al.*, 2012), kidney (Jang & Suh, 2010), liver (Lee *et al.*, 2013), lung (Huh *et al.*, 2012), muscle (Grosberg *et al.*, 2012), blood-brain-barrier (Griep *et al.*, 2013) and more, perhaps using integrated vasculature (Schimek *et al.*, 2013), researchers are potentially able to develop an integrated 'human-on-chip' and move a step closer to mimicking the whole human response.

4.2.5 *Nanotechnology*

Nanotechnology is important for the further development of LOC devices. The use of nanomaterials brings in a series of advantages in the design of new or the improvement of existing LOC platforms, for instance as building blocks of smaller devices. Nanomaterials are being used in microfluidic platforms as detectors, tools for microreactors and other things (Medina-Sanchez *et al.*, 2012). A broad range of nanomaterials can be used, including quantum dots, nanotubes, nanowires, gold nanoparticles and magnetic nanoparticles. The use of nanoparticles, for instance, can increase the surface to volume ratio, which contributes to a higher sensitivity of detection of the specific target.

Nanoparticles can also be used for labelling purposes. Quantum dots are the most common nanoparticles used as labelling platforms in microfluidics. They could be attached to antibodies, oligonucleotides or peptides. Magnetic nanoparticles are also used as labels in magnetoresistive sensors, but may have an additional function as a molecule transport controller in order to pre-concentrate the sample on the detector chamber (Medina-Sanchez *et al.*, 2012).

Miniaturization of the LOC device will also involve nanofluidics. Nanofluidics is often defined as the study and application of fluid flow in and around nanosized objects (Eijkel & van den Berg, 2005). Incorporation of nanopores and nanochannels in LOC devices holds great promise for new analytical applications. At this scale, forces and phenomena are present which are negligible or absent in larger microchannels (Kovarik & Jacobson, 2009). For example, in nanochannels molecules can be controlled by charge, because of their electrostatic interaction with the electrical double layer, a shielding layer that is naturally created within the liquid near a charged surface. Furthermore, filtration and sieving based on size can be achieved, as the length scales of biomolecules and synthetic nanometre-sized objects are similar (Schoch *et al.*, 2008).

Overall, nanotechnology is considered an enabling technology that advances the development and improvement of LOC devices.

4.2.6 *Near-future LOC applications*

Many of the technology trends are implemented in newly developed LOCs. One of the LOC devices that is expected to enter the market soon concerns the measurement of CD4 T cells (a type of white blood cell) which is used for

monitoring disease progression in HIV infected patients. The gold standard method for counting CD4 cells is via flow cytometry. This usually takes quite a long time, requires large equipment and is performed in a hospital setting. Several companies are currently developing and validating their POC/LOC methods to count CD4 cells, such as Daktari Diagnostics, MBio Diagnostics and Zyomyx. Daktari Diagnostics, for instance, is developing a portable CD4 cell counting system that makes use of microfluidic cell chromatography to separate the cells and electrochemical detection to identify CD4 cells (<http://www.daktaridx.com/products/>). Zyomyx is developing a CD4 count test that is mainly aimed at its use in remote areas and developing countries with a high disease burden (<http://www.zyomyx.com/products/>). Especially in developing countries and remote areas, the diagnosis and monitoring of HIV is difficult because of the lack of resources and the great distance people need to travel for clinical support. Therefore, Zyomyx aims to market a low-cost LOC application that can be used by everyone. In contrast to all POC applications for HIV diagnostics that use CD4 cell count, Wave 80 Biosciences is working on an EOSCAPE HIV-1 RNA Test to measure viral load in blood for acute diagnosis of HIV infection and for early infant diagnosis (<http://www.wave80.com/products/index.php>).

Another LOC application is the one for troponin I testing for cardiovascular disease. Troponin I is already an established marker, specifically for myocardial infarction, and its measurement is regularly done in the central laboratory. But this assay is difficult to transfer to a near-patient system while maintaining sensitivity. LOC applications for measuring troponin I are currently being developed and validated. One company that is working on this system is Nanomix Inc. They have developed a system that determines the levels of troponin I in the whole blood of patients (<http://www.nano.com/emergency-medicine.html>). Recently, clinical trials have been started to assess its usefulness in the clinic.

4.3 Impact on health care

4.3.1 *Inside and outside hospital*

Microfluidics technology has the potential to enhance development of POC devices and thereby provides the decentralization of medical testing (Yager *et al.*, 2006). Some of the LOC devices for clinical diagnostics allow for POC applications, such as for the monitoring of regular metabolic parameters, e.g. glucose. The earliest POC tests detected glucose and were based on tablets containing the test reagents. Subsequent technological innovation led to the development of dipstick devices that evolved to become self-contained lateral flow tests (e.g., for cardiac disease, HIV-1, pregnancy) for which only the addition of a sample is necessary. More recently, POC devices integrating both disposable microelectronic and microfluidic components have been developed (Sia & Kricka, 2008).

Inside the central laboratory of a hospital, LOC devices are less frequently used. As stated by one of the key opinion leaders, these laboratories are usually equipped with conventional, large analysers for clinical diagnostics, which decreases the need for LOC applications. In the hospital, however, LOC devices are of use for near-patient care. In the Netherlands, the majority of hospitals have POC devices for blood glucose testing, followed by POC tests for blood gases (Roszek *et al.*, 2013). In general, POC tests as identified were used in different departments, e.g. intensive care unit, internal medicine, pulmonary

medicine, the emergency department and cardiology. One rationale for POC testing is that it may streamline health care. It offers opportunities for decentralized and sustainable health care. However, to realize a decentralized health care system, the organization of the entire health care system needs to be adapted.

One of the interviewees depicted how LOC can have a positive influence on turnaround time in health care. LOC technology might provide the ability to increase the speeds of certain analyses, regardless of whether the LOC is used as a POC test or in the clinical laboratory. In addition, rapid testing is expected to lead to rapid intervention (Price & Kricka, 2007). Studies have shown an improved turnaround time with the implementation of POC testing compared with central laboratory testing (Koehler *et al.*, 2013; Lee *et al.*, 2011b). The use of POC devices in the emergency department slightly reduced disposition decision time for only a moderate increase in costs (Asha *et al.*, 2013). However, evidence for better clinical outcomes due to an improved turnaround time is limited (Zydron *et al.*, 2011).

Hospitals are not the only place LOCs are used for near patient care. Devices are also used by general practitioners and remote caretakers. Previously it was shown that in the practices of general practitioners POC tests, such as blood glucose and urine nitrite tests, were used on a daily basis by 95% of the respondents (de Vries *et al.*, 2012; Hofland, 2010). POC devices used outside the hospital can improve health care in terms of a quick and easy diagnostic decision and rapid treatment. As several opinion leaders indicated, POC tests can guide a general practitioner or doctor in the clinical decision-making process. One such example is the use of CRP testing in lower respiratory tract infections by the general practitioner. In a trial using this test, it was shown that there was a significant decrease in antibiotic prescriptions for lower respiratory tract infections without compromising on the patients' recovery and satisfaction with care (Cals *et al.*, 2009, interview). Another example concerns a POC test for detection of D-dimer in deep venous thrombosis. Using this test in combination with regular clinical decision-making reduced the need for referral of patients with suspected thrombosis to secondary care (Geersing *et al.*, 2009). In general, POC tests can therefore provide important information and guide patient management by either confirming or excluding the diagnosis and possible subsequent treatment.

Health care practitioners are not the only ones that will make use of LOC applications. Due to recent developments, LOC devices will become more easily available to patients at home as well. As discussed in the RIVM report about eHealth, safe application of LOC devices requires that patients are physically and mentally able to handle the technology (Ossebaard *et al.*, 2012). The patient should be motivated to use the technology correctly, follow instructions and be well-trained. To decrease costs, future research regarding the read-out platform for LOC devices is more directed towards using existing portable devices such as smart phones or tablets, since these devices are already being widely used. As stated before, this might decrease costs, but it also allows monitoring at remote locations. Examples of such technologies are given in section 4.1.2.

Not only in urban settings, but also in remote settings and developing countries, LOC have the potential to enable the rapid and portable diagnosis of a range of conditions. A considerable part of the burden of disease in the developed world is caused by non-communicable diseases: cardiovascular disease, cancer, respiratory disease, and neuropsychiatric conditions are some of the more

significant diseases. By contrast, in the developing world, while non-communicable diseases are prevalent, a significant burden of disease is attributed to infectious diseases, many of which can be treated and prevented. Major infectious diseases, according to the burden presented by the disease, include HIV/AIDS, tuberculosis, malaria, diarrhoeal diseases and lower respiratory infections. The ability to provide health care in remote areas and developing countries, where resources are limited and people need to travel long distances for health care support, may improve overall health. Though LOCs may offer opportunities in these regions, the health care systems in Western countries may also benefit from their application.

Improved diagnostics may lead to early treatment and, in turn, investments in diagnostics and prevention can be more cost-effective than treatment (Chin *et al.*, 2011; Chin *et al.*, 2007; Yager *et al.*, 2006). As a proof-of-principle for future studies, Chin *et al.* (2011) demonstrated the use of a LOC device for the detection of both HIV and syphilis in Rwanda and showed implementation of this test was cost-effective.

4.3.2 *Personalized medicine*

Trends toward a tighter link between diagnostics and therapeutics, and more frequent monitoring are motivating the development of microfluidic systems. Linking diagnostics and therapeutics is fundamental to personalized medicine, using specific information about the individual patient to create a more effective, targeted therapeutic approach (Kim, 2013). The ability of LOC to control the micro-environment (e.g., create stable biochemical gradients) opens up the potential for more personalized diagnosis and treatment. LOC enables companion diagnostics. In companion diagnostics, the assay provides a tool to specify therapy for an individual patient. For instance, in cancer diagnostics the characterization of circulating tumour cells can help in selecting the proper medication. Novel anti-cancer treatments are directed to specific targets in molecular pathways causing growth and expansion of the tumour. Assessment of whether or not a specific drug target is present in tumour cells may therefore be very important to determining which treatment a patient needs to receive (van de Stolpe *et al.*, 2011). Also, in prognosis or treatment efficacy monitoring, LOC applications have a great opportunity.

Novel applications of nanotechnology such as nanopores and magnetic nanobeads are maturing as the next generation of genomic sequencing. The next generation of genomic sequencing will increase sequencing throughput, speed and accuracy, and will lead to a reduction in sample size (Branton *et al.*, 2008). Information on the personal genome will facilitate personalized medicine, strongly influencing future health care provision.

4.3.3 *Quality management*

Diffusion of LOC devices outside the central laboratory of a hospital may decrease costs and reduce turnaround time. But new risks regarding diffusion of LOC use will arise and should be dealt with. To maintain good and safe use of LOC devices, it is important to check quality aspects regularly. Furthermore, the device should be safe to use and user-friendly so that analysis can be done by non-technical medically trained personnel or even the patient himself. This poses some issues concerning the quality management of the LOC devices for (remote) health care practitioners. When used in the hospital, quality management of in-vitro diagnostic devices, i.e. maintaining quality standards of the devices and their use, is the responsibility of the central laboratory (Roszek *et al.*, 2013).

The impact of a growing number of POC applications in the hospital will shift the responsibility of the central laboratory as a testing facility to more quality management tasks in order to assure and maintain the diagnostic quality of POC tests. It is increasingly recognized that quality management and patient safety will need greater attention to ensure a high quality of health care. As health care professionals such as nurses will be performing more POC tests, they need (extra) training to become (or remain) qualified. Trends towards decentralized health care and personalized medicine may ensure the importance in the future of LOC for POC testing.

With LOC usage outside the hospital, e.g. by general practitioners, attention should be given to quality control measures as well, such as training the health care professional, calibration and maintenance of the devices (de Vries *et al.*, 2012). Awareness of the importance of these issues is growing. In the guidelines '*Handboek voor diagnostische verrichtingen*' by the Dutch College of General Practitioners, attention is given to POC devices.

In addition, the Netherlands Society for Clinical Chemistry and Laboratory Medicine (NVKC) has published a guidance document on the use of POC tests in primary care (Kleinveld *et al.*, 2012). Several recommendations include the collaboration and monitoring of POC in primary care by a central laboratory of the hospital as one way to implement quality control measures. By consulting the central laboratory, a suitable selection of possible LOC devices for POC use, such as in the medical practices of general practitioners, could be made. When used, agreements on calibration and maintenance by the central laboratory and general practitioners' medical practices need to be set up to ensure quality. In the case of the Jeroen Bosch Hospital ('s-Hertogenbosch, the Netherlands), all information on certified personnel, patient measurements and devices is logged in a secured electronic file. To ensure correct use, personnel can only operate the device when they are qualified via practical training. Results of the measurements are immediately stored in the patient's file. As stated by one of the interviewees, the hospital has implemented a similar quality management system for use in primary care as well

([http://www.jeroenboschziekenhuis.nl/Publicaties/114241/POCT-\(Point-of-Care-Testing\)\)](http://www.jeroenboschziekenhuis.nl/Publicaties/114241/POCT-(Point-of-Care-Testing)))). All systems are connected and the central laboratory provides all services, including inventory management, troubleshooting and remote quality control. Not many hospitals and general practitioner practices in the Netherlands employ this type of quality management yet, although this could change as the awareness is growing. Other interviewees announced that a similar system will be implemented to enhance quality management of POC applications in the Maastricht area in the near future.

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Annex I: Overview of companies and LOC devices

Company	Country	Name of device/chip/system	M/D ¹	Application
Abaxis Inc	USA	Piccolo® Xpress	M	blood analysis
Abbott Diabetes Care Inc	USA	FreeStyle Lite®	M	blood glucose
Abbott Diabetes Care Inc	USA	FreeStyle Freedom Lite®	M	blood glucose
Abbott Diabetes Care Inc	USA	FreeStyle InsuLinx	M	blood glucose
Abbott Diabetes Care Inc	USA	Precision Xtra®	M	blood glucose and ketone
Abbott Diabetes Care Inc	USA	Precision Xceed Pro	M	blood glucose and beta-ketone (hospital setting)
Abbott Point of Care Inc	USA	i-STAT®	M	cardiac markers, blood gases, electrolyte analyses, lactate, coagulation, haematology
Abbott Point of Care Inc	USA	i-STAT® 1 Wireless	M	cardiac markers, blood gases, electrolyte analyses, lactate, coagulation, haematology
Achira Labs Pvt Ltd	India	ACHIRA 2000	M	thyroid disorders, infertility
Advanced Liquid Logic	USA	-	D	HIV diagnostics / CD4 count
Agilent Technologies Inc	USA	2100 Bioanalyzer	M	nucleic acids, proteins and cells
Akonni Biosystems Inc	USA	TruDiagnosis®	M	DNA, RNA, and antibody-based testing
Alere Inc	USA	Alere Pima™ CD4 Analyser	M	HIV diagnostics / CD4 count
Alere Inc	USA	NAT System	D	HIV diagnostics / CD4 count
Alere Inc	USA	Alere Cholestech LDX® System	M	cholesterol, blood glucose, liver enzymes
Alere Inc	USA	Alere™ Heart Check System	M	B-type natriuretic peptide
Alere Inc	USA	Alere Triage® MeterPro	M	BNP, CK-MB, D-dimer, myoglobin, NGAL, troponin I, PLGF
Alere Inc	USA	Alere™ INRatio® / INRatio® 2 PT / INR Monitor	M	Anticoagulation
Arkray Global Business Inc	Japan	GLUCOCARD 01	M	blood glucose
Arkray Global Business Inc	Japan	GLUCOCARD 01-mini	M	blood glucose
Arkray Global Business Inc	Japan	GLUCOCARD 01-mini plus	M	blood glucose
Arkray Global Business Inc	Japan	GLUCOCARD X-METER GT-1910	M	blood glucose
Arkray Global Business Inc	Japan	GLUCOCARD X-mini	M	blood glucose
Arkray Global Business Inc	Japan	GLUCOCARD X-mini plus	M	blood glucose
Arkray Global Business Inc	Japan	GLUCOCARD Σ	M	blood glucose
Arkray Global Business Inc	Japan	GLUCOCARD Σ-mini	M	blood glucose
Atonomics A/S	Denmark	Atolyzer	D	cardiovascular disease, prostate cancer
Axis-Shield plc	UK	Afineon	M	CRP, HbA1c, ACR, lipid
Axis-Shield plc	UK	NyoCard	M	CRP, HbA1c, D-dimer, U-albumine
Bayer Diabetes Care	Switzerland	CONTOUR® XT	M	blood glucose
Bayer Diabetes Care	Switzerland	CONTOUR® NEXT USB	M	blood glucose
Bayer Diabetes Care	Switzerland	CONTOUR® USB	M	blood glucose
Bayer Diabetes Care	Switzerland	CONTOUR® Link	M	blood glucose
Bayer Diabetes Care	Switzerland	CONTOUR®	M	blood glucose
Bayer Diabetes Care	Switzerland	BREEZE®2	M	blood glucose
Bayer Healthcare, Diabetes Care	USA	A1CNow+®	M	HbA1c (professional use)
Bayer Healthcare, Diabetes Care	USA	A1CNow+® SELF CHECK	M	HbA1c
BD Biosciences	USA	CD4 Point of Care Technology	D	HIV diagnostics / CD4 count
BD Biosciences	USA	BD FACSCount™ System	M	HIV diagnostics / CD4 count
BD Biosciences	USA	BD FACSCalibur™ System	M	HIV diagnostics / CD4 count (research use); benchtop analyser
BD Biosciences	USA	BD FACSCanto™ II System	M	HIV diagnostics / CD4 count; benchtop analyser
Beurer GmbH	Germany	GL 32	M	blood glucose
Beurer GmbH	Germany	GL 40	M	blood glucose
Beurer GmbH	Germany	GL 44	M	blood glucose

Company	Country	Name of device/chip/system	M/D ¹	Application
Beurer GmbH	Germany	GL 50	M	blood glucose
Bio-Alternative Medical Devices Ltd	UK	Blood coagulation monitor	D	blood coagulation
Bio-Alternative Medical Devices Ltd	UK	Digital strip reader	D	pregnancy test
Biocartis SA	Switzerland	Dynamic Multi-Analyte Technology	M	nucleic acid and protein-based biomarkers
Biochemical Systems International Srl	Italy	multiCare IN	M	blood glucose, cholesterol, triglycerides
Biochemical Systems International Srl	Italy	BlueCare	M	blood glucose
Biochemical Systems International Srl	Italy	Glucoval	M	blood glucose
BioFire Diagnostics Inc	USA	FilmArray®	M	automated analysis on FirmArray™ instrument (multiplex PCR)
Bioident Technologies Inc	USA	-	D	optoelectronic technology
Bioptik Technology Inc	Taiwan	EasyMate® G	M	blood glucose
Bioptik Technology Inc	Taiwan	EasyMate® GCU	M	blood glucose, cholesterol, uric acid
Bioptik Technology Inc	Taiwan	EasyTouch® GU	M	blood glucose, uric acid
Bioptik Technology Inc	Taiwan	EasyTouch® GCU	M	blood glucose, cholesterol, uric acid
Bio-Rad Laboratories Inc	USA	Genie Fast HIV 1/2 Assay	M	anti-HIV1/2 Ab
Bio-Rad Laboratories Inc	USA	in2it™ A1C	M	boronate affinity chromatography
Biosurfit SA	Portugal	spinit®	D	blood tests, CRP test
Burnet Institute	Australia	Semi-quantitative CD4 Test	D	HIV diagnostics / CD4 count
Cardinal Health	USA	Cardiac STATus™ Test	M	hand-held cardiac marker bedside test
Cepheid	USA	GeneXpert System®	M	pathogen / biomarker detection
Clearbridge BioLoc Pte Ltd	Singapore	AssayQuest™	D	ELISA
Daktari Diagnostics	USA	Daktari™ CD4 Counter	D	HIV diagnostics / CD4 count
Diagnosis Sp. z o.o.	Poland	DIAGOMAT	M	blood glucose
Diagnostic Chips LLC	USA	-	D	hand-held flow cytometer
Diagnostics For All	USA	-	D	instrument-free test based on paper
Diagnostics for the Real World Ltd	UK	SAMBA	D	HIV diagnostics / CD4 count
DiagnoSwiss SA	Switzerland	immuDrop™	M	generic system for the detection of biomarkers
DiagnoSwiss SA	Switzerland	immuSpeed™	M	generic system for the detection of biomarkers
DNA Electronics	UK	Genalysis®	D	single nucleotide polymorphisms; microchip-based technology
EKF Diagnostics Holdings plc	UK	Lactate Scout+	M	lactate
Epocal Inc (Alere)	Canada	epoc™	M	blood chemistry
Eurolab Lambda SA	Slovak Republic	HumanSens plus	M	blood glucose, cholesterol, uric acid
F. Hofmann-La Roche Ltd	Switzerland	Accu-Chek® Aviva	M	blood glucose
F. Hofmann-La Roche Ltd	Switzerland	Accu-Chek® Aviva Nano	M	blood glucose
F. Hofmann-La Roche Ltd	Switzerland	Accu-Chek® Performa	M	blood glucose
F. Hofmann-La Roche Ltd	Switzerland	Accu-Chek® Performa Nano	M	blood glucose
F. Hofmann-La Roche Ltd	Switzerland	Accu-Chek Active®	M	blood glucose
F. Hofmann-La Roche Ltd	Switzerland	Accu-Chek® Compact Plus	M	blood glucose
F. Hofmann-La Roche Ltd	Switzerland	Accu-Chek® Mobile	M	blood glucose
F. Hofmann-La Roche Ltd	Switzerland	Accu-Chek® Inform	M	blood glucose (hospital setting)
F. Hofmann-La Roche Ltd	Switzerland	Accu-Chek® Inform II	M	blood glucose (hospital setting), wireless communication
F. Hofmann-La Roche Ltd	Switzerland	Accutrend® Plus	M	blood glucose, cholesterol, triglycerides, lactate
F. Hofmann-La Roche Ltd	Switzerland	CoaguChek® XS	M	PT/INR value (home)
F. Hofmann-La Roche Ltd	Switzerland	CoaguChek® XS Plus	M	PT/INR value (physician's practice)
F. Hofmann-La Roche Ltd	Switzerland	CoaguChek® XS Pro	M	PT/INR value (high throughput anticoagulation centre & hospital setting)
F. Hofmann-La Roche Ltd	Switzerland	cobas b 123 POC	M	blood gases
F. Hofmann-La Roche Ltd	Switzerland	cobas h 232	M	troponin T, CK-MB, myoglobin, D-dimer, NT-proBNP

Company	Country	Name of device/chip/system	M/D ¹	Application
FluimediX / MEMSflow ApS	Denmark	NanoCycler™	D	warfarin metabolism; near patient DNA-based testing
Focus Diagnostics Inc	USA	3M™ Integrated Cycler	M	pathogen detection (real-time PCR)
Genefluidics Inc	USA	Asklepios	D	proteins, nucleic acids and small molecules (research use)
Gyros AB	Sweden	Gyrolab xP & Bioaffy® CDs	M	protein quantification
Helena Laboratories	USA	Cascade POC Analyzer	M	haemostasis assays
Hologic Inc	USA	TLiIQ® System	M	fetal fibronectin test
Innovative Biosensors Inc	USA	BioFlash-Dx™	M	pathogen detection
IQuum Inc	USA	Liat™ Analyser	D	HIV diagnostics / CD4 count
Kernel Int'l Corp	Taiwan	MultiCheck™ ET-321	M	blood glucose, cholesterol, Hb
Kernel Int'l Corp	Taiwan	MultiCheck™ ET-301	M	blood glucose, cholesterol, uric acid
Kernel Int'l Corp	Taiwan	MultiCheck™ ET-222	M	blood glucose, Hb
Kernel Int'l Corp	Taiwan	MultiCheck™ ET-202	M	blood glucose, Hb
Kernel Int'l Corp	Taiwan	MultiCheck™ ET-201	M	blood glucose, uric acid
Kernel Int'l Corp	Taiwan	MultiCheck™ ET-102	M	cholesterol
Kernel Int'l Corp	Taiwan	MultiCheck™ ET-101	M	blood glucose
LabNow Inc	USA	-	D	infectious diseases, cardiovascular disease, cancer
LeukoDx Ltd	Israel	-	D	HIV / AIDS, sepsis, urinary tract infections
LifeScan Inc	USA	OneTouch® Ultra®2	M	blood glucose
LifeScan Inc	USA	OneTouch® UltraMini®	M	blood glucose
LifeScan Inc	USA	OneTouch® UltraSmart®	M	blood glucose
LifeScan Inc	USA	OneTouch® Verio™IQ	M	blood glucose
LifeScan Inc	USA	OneTouch® Verio™Pro	M	blood glucose
Macherey-Nagel GmbH & Co KG	Germany	URYXXON® Relax	M	Urine analysis
Macherey-Nagel GmbH & Co KG	Germany	URYXXON® 500	M	Urine analysis
MBio Diagnostics	USA	MBio™ Diagnostics CD4 System	D	HIV diagnostics / CD4 count
MBio Diagnostics	USA	MBio™ Array System	D	multiple immunoassays; infectious diseases applications
Magna Diagnostics GmbH	Germany	MAZER™	D	technology based on magnetic nanoparticles
Medimate BV	Netherlands	Medimate Multireader®	M	bipolar disorder, chronic kidney disease, heart failure
Menarini Diagnostics	Italy	Glucocard Memory 2	M	blood glucose
Menarini Diagnostics	Italy	Glucocard Memory PC	M	blood glucose
Menarini Diagnostics	Italy	GlucoMen® Lx	M	blood glucose & ketone
Menarini Diagnostics	Italy	GlucoMen® Lx Plus	M	blood glucose
Menarini Diagnostics	Italy	GlucoMen® Gm	M	blood glucose
Menarini Diagnostics	Italy	Glucocard Xmeter	M	blood glucose
Menarini Diagnostics	Italy	StatStrip™	M	blood glucose (hospital setting)
Menarini Diagnostics	Italy	Aution MICRO	M	urine analysis
Micronics Inc	USA	ABORhCard®	M	blood type identification
Micronics Inc	USA	PanNAT™	M	single and/or multiplexed nucleic acid amplification assay
Molecular Vision Ltd	UK	-	D	cardiovascular disease, kidney disease
MycroLab Diagnostics Pty Ltd	Australia	Micro®Card	D	complete assay process on-card
Nanomix Inc	USA	Sensation™ technology	D	troponin I
Nanomix Inc	USA	Nanomix Asthma Management System	D	asthma; carbon nanotube electronic detection platform
Nipro Diagnostics Inc	USA	TRUEresult®	M	blood glucose
Nipro Diagnostics Inc	USA	TRUEresult® Twist	M	blood glucose
Nipro Diagnostics Inc	USA	TRUEbalance™	M	blood glucose
Nipro Diagnostics Inc	USA	TRUEone®	M	blood glucose
Opko Health Inc	USA	4Kscore™	M	kallikrein biomarkers
Partec GmbH	Germany	CyFlow® miniPOC	M	HIV diagnostics / CD4 count
Partec GmbH	Germany	CyFlow® Space	M	HIV diagnostics / CD4 count (benchtop analyser)

Company	Country	Name of device/chip/system	M/D ¹	Application
Philips Healthcare	Netherlands	Minicare	D	cardiac damage
Radiometer Medical	Denmark	AQT90 FLEX	M	cardiac biomarkers
Radiometer Medical	Denmark	ABL90 FLEX	M	blood gases
Randox Laboratories Ltd	UK	Evidence Investigator	M	cardiac/cerebral biomarker (troponin I/brain-derived neurotrophic factor, glial fibrillary acidic protein, interleukin-6)
Raindance Technologies Inc	USA	RainDrop™ Digital PCR System	M	droplet-based PCR
Raindance Technologies Inc	USA	RDT 1000	M	droplet-based PCR; fully automated low-to medium-throughput targeted sequencing system
Raindance Technologies Inc	USA	ThunderStorm™ System	M	droplet-based PCR; fully automated high-throughput targeted sequencing system
Response Biomedical Corporation	Canada	RAMP	M	cardiac biomarkers (troponin I, NT-proBNP)
Rheonix Inc	UK	Rheonix CARD® Consumable	D	HPV detection, warfarin dosing, sepsis, waterborne pathogens
Siemens AG	Germany	DCA Vantage™ Analyzer	M	HbA1c
Siemens AG	Germany	Stratus CS Acute Care Diagnostic System	M	cardiac biomarkers
Siemens AG	Germany	CLINITEK Status®+ Analyzer	M	urine analysis
Siemens AG	Germany	RAPIDChem® 744/754	M	serum, plasma, whole blood and urine
Siemens AG	Germany	RAPIDPoint500® Blood Gas Analyzers	M	blood gases, electrolytes, blood glucose, lactate, CO oximetry, neonatal total bilirubin, total haemoglobin
Siemens AG	Germany	RAPIDPoint400/405	M	blood gases, electrolytes, blood glucose, haematocrit, CO oximetry, neonatal total bilirubin
Siemens AG	Germany	RAPIDPoint340/350	M	blood gases, electrolytes
SpinChip Diagnostics AS	Norway	-	D	blood analyses; proteins, cells, DNA/RNA, nutrients, drugs
STmicroelectronics	Switzerland	In-Check™ platform	M	PCR micro-reactor
TearLab Corporation	USA	TearLab™ Osmolarity System	M	dry eye disease, ocular allergy
Taidoc Technology Corporation	Taiwan	TD-4116	M	blood glucose
Taidoc Technology Corporation	Taiwan	TD-4230	M	blood glucose
Taidoc Technology Corporation	Taiwan	TD-4227A	M	blood glucose
Taidoc Technology Corporation	Taiwan	TD-4231	M	blood glucose
Taidoc Technology Corporation	Taiwan	TD-4235	M	blood glucose
Taidoc Technology Corporation	Taiwan	TD-4253	M	blood glucose
Taidoc Technology Corporation	Taiwan	TD-4255	M	blood glucose
Taidoc Technology Corporation	Taiwan	TD-4234	M	blood glucose
Taidoc Technology Corporation	Taiwan	TD-4275	M	blood glucose
Taidoc Technology Corporation	Taiwan	TD-4276	M	blood glucose
Taidoc Technology Corporation	Taiwan	TD-4267	M	blood glucose
Taidoc Technology Corporation	Taiwan	TD-4269	M	blood glucose
Taidoc Technology Corporation	Taiwan	TD-4280	M	blood glucose
Taidoc Technology Corporation	Taiwan	TD-4285	M	blood glucose
Taidoc Technology Corporation	Taiwan	TD-4287	M	blood glucose
Taidoc Technology Corporation	Taiwan	TD-4277	M	blood glucose
Taidoc Technology Corporation	Taiwan	TD-4257A	M	blood glucose
Taidoc Technology Corporation	Taiwan	TD-4257B	M	blood glucose
Taidoc Technology Corporation	Taiwan	TD-4279	M	blood glucose
Taidoc Technology Corporation	Taiwan	TD-4268	M	blood glucose
Taidoc Technology Corporation	Taiwan	TD-4266	M	blood glucose
Taidoc Technology Corporation	Taiwan	TD-4140	M	blood glucose
TREND Pharma GmbH	Germany	TESTAmed® GlucoCheck Plus	M	blood glucose
TREND Pharma GmbH	Germany	TESTAmed® GlucoCheck Advance	M	blood glucose
Vital Diagnostics	Australia	Eon™ One	M	serum, plasma, whole blood (HbA1c), urine

Company	Country	Name of device/chip/system	M/D ¹	Application
Vital Diagnostics	Australia	Eon™ 100	M	serum, plasma, whole blood (HbA1c), urine
Vital Diagnostics	Australia	Eon™ 300	M	serum, plasma, whole blood (HbA1c), urine
Vivacta Ltd	UK	-	D	endocrine imbalances, infections, sepsis, stroke; piezo film technology
Wave 80 Biosciences	USA	EOSCAPE-HIV™ HIV Rapid RNA Assay System	D	HIV diagnostics / CD4 count
Zyomyx	USA	Zyomyx CD4 Test	D	HIV diagnostics / CD4 count

¹ M/D: on the market / under development

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Photo:
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